HK J Paediatr (new series) 2003;**8**:341-345

Helicobacter Pylori Eradication in Children with Ranitidine Bismuth Citrate – Based Triple Therapy Given for 4 Days versus 7 Days: A Prospective Randomised Study

YH ***TAM,*** JDY ***SIHOE,*** KH ***LEE,*** CK ***YEUNG***

Abstract *Helicobacter pylori* infection is common in paediatric population. The overall prevalence varies from 10% in developed countries to 80% in developing countries at the age of 10. The association of this infection with gastritis, peptic ulcerations and gastric cancer has warranted guidelines on the treatment of this infection in children. ***Aim of study:*** To determine an effective eradication regimen for *H. pylori* in children with the shortest duration to promote compliance. ***Patients and methods:*** We conducted a prospective randomised study comparing ranitidine bismuth citrate (RBC) – based triple therapy given for 4 days vs 7 days in 200 children with mean age 12.5 years (92 boys, 108 girls). *H. pylori* infection was diagnosed by ^{13}C-urea breath test (^{13}C-UBT). Children with body weight >40 kg received amoxicillin 1 g bid plus clarithromycin 500 mg bid plus RBC 400 mg bid. Dosages of antibiotics were reduced by half in those patients with body weight less than 40 kg while that of RBC remained the same. Outcome measures included success of eradication determined by repeat ^{13}C-UBT in 6 weeks, drugs adverse effects and patients' compliance. ***Results:*** Ninety-three (46.5%) and 107 (53.5%) of children were randomised to receive 7-day and 4-day regimen respectively. All 200 children completed the prescribed treatment according to the protocol. 89.2% of children who had received treatment for 7 days showed successful eradication comparing with 78.5% in those who received treatment only for 4 days (p-value <0.05). There was no statistical difference in terms of side effects between the two regimens. ***Conclusions:*** RBC-based triple therapy is an effective and well tolerated treatment for eradication of *H. pylori* in children. Seven days of treatment is the shortest duration to ensure effective eradication with the currently available therapeutic agents.

Key words Children; Eradication; *Helicobacter pylori*

Introduction

Helicobacter pylori infection is a worldwide medical issue in paediatric population. Cross-sectional studies suggest that the infection is usually acquired in early childhood.[1-3] The major risk factor for acquiring the infection is poor socioeconomic conditions during childhood.[4,5] In developing countries, up to 70-80% of children are infected by the age of 10 in contrast to the overall prevalence of less than 10% in children living in the developed world.[6,7] However, the prevalence can significantly increase up to 50% in those socially deprived children in developed countries.[4] As in adults, *H. pylori* infection is associated with chronic gastritis and peptic ulcerations in children.[8,9] Long term healing of ulcer disease can be achieved following eradication of the infection. The association of *H. pylori* infection with gastric carcinoma and the fact that *H. pylori* has been classified as a group I carcinogen by the World Health Organization[10,11] has raised serious concerns and questions about the management of this infection in children. It remains a contentious issue whether it is cost-effective to eradicate *H. pylori* in every infected child based on the

Division of Paediatric Surgery, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, N.T., Hong Kong, China

YH **TAM** （譚煜謙） *FRCS, FHKAM(Surgery)*
JDY **SIHOE** （司徒達燕） *MRCS(Edin)*
KH **LEE** （李劍雄） *FRCS, FHKAM(Surgery)*
CK **YEUNG** （楊重光） *MD, FRCS, FHKAM(Surgery)*

Correspondence to: Dr YH **TAM**

Received August 6, 2003

potential risk of progression to gastric carcinoma in adult life.[9,12,13] While further research works are pending to clarify the current controversies, guidelines on the treatment of this infection in children are warranted. However, data from the literature remains insufficient as controlled trials with adequate patient numbers are scarce and results from different studies are inconsistent. In children compliance is of particular concern, as paediatric patients will not tolerate a prolonged course of treatment. It is the aim of this study to determine a short but effective therapeutic regimen for eradication of *H. pylori* in children.

Methodology

Patients

From 1997 to 2000, 232 consecutive children, aged 7 to 15 years, were diagnosed to have *H. pylori* infection using ^{13}C-urea breath test (^{13}C-UBT). These included children presenting to the Paediatric Surgical clinic of the Prince of Wales Hospital with gastrointestinal symptoms warranting investigation for *H. pylori* infection and asymptomatic children found to be *H. pylori*-infected in an epidemiological study conducted by the same unit, whose parents strongly requested for *H. pylori* eradication therapy. Informed consent to enter into the therapeutic trial was obtained from parents of 200 children. There were 92 boys and 108 girls with a mean age of 12.5 years.

^{13}C-urea Breath Test

All the children had a 4-hour fast and received test meal with glucose polymer solution. Baseline breath sample was collected. ^{13}C-urea was then given at the dosage of 50 mg for those with body weight <50 kg or 75 mg for body weight >50 kg. Another breath samples were collected at 30 minutes after. Samples were analyzed by isotope ratio mass spectrometer and positive result was defined by a value of 3.5 delta over baseline.

Randomisation and Treatment Protocol

The 200 children were prospectively randomised by computer to receive either a one-week or 4-day *H. pylori* eradication regimen. The treatment consisted of three therapeutic agents. Children with body weight >40 kg received ranitidine-bismuth-citrate (RBC) 400 mg bid, amoxicillin 1 g bid and clarithromycin 500 mg bid. For children with body weight less than 40 kg the dosages of amoxicillin and clarithromycin were reduced by half while that of RBC remained the same.

Parental Counselling and Phone Interview

A senior paediatric surgeon prior to the commencement of treatment interviewed the parents of all the 200 children. The importance of drug compliance, all possible drug adverse effects, as well as the unproven benefits of eradication of *H. pylori* in asymptomatic children were very carefully explained. Informed consent for recruitment into the study and randomisation was obtained. A dedicated research nurse was present during the parental counselling and informed consent, and would be responsible to phone all the parents during and at the end of the treatment so as to ensure good drug compliance and that every single side effect be well documented.

Evaluation of Treatment Success

All 200 children had a repeat ^{13}C-UBT six weeks after the completion of treatment to evaluate the eradication rates in both treatment groups.

Results

Ninety-three out of 200 children (46.5%) were randomised to receive one-week regimen while 107 (53.5%) received 4-day regimen. All 200 children completed the prescribed treatment according to the protocol. Of the 107 children randomised to receive 4-day regimen, 84 (78.5%) were found to have successful eradication of *H. pylori* as demonstrated by the negative results of ^{13}C-UBT. Eighty-three out of 93 (89.2%) who had received one-week regimen showed successful eradication. The difference of the two treatment groups were statistically significant (p-value=0.041). There was no difference between males and females in the eradication rates in both treatment groups (Table 1).

On direct questioning during phone interview, 49 of the 200 children (24.5%) described to suffer from one or more side effects which included loose bowel motions (18%), dyspepsia (19.5%), headache (9%), mild skin rash (1%). All the side effects were mild and self-resolving and all children completed the treatment. It was also noted that 66.5% of the patients noticed blackening of stool as a result of the intake of bismuth compound. The one-week and 4-day regimen accounted for 44.7% and 55.3% of the overall side effects respectively. There was no statistical difference in terms of side effects between the two groups (p-value=0.48) (Table 2).

Table 1 Results of eradication

	7-day regimen	4-day regimen
No. of children receiving the regimen	93	107
No. of children with successful eradication	83 (89.2%)	84 (78.5%)
No. of children with failed eradication	10 (10.8%)	23 (21.5%)

p-value=0.041

Table 2 Drugs adverse effects

	7-day regimen	4-day regimen	
Loose bowel motions	17.2%	18.7%	NS
Dyspepsia	18.3%	20.5%	NS
Headache	8.6%	9.3%	NS
Skin rash	1%	0.9%	NS
Blackening of stool	68%	62%	NS

NS=no statistically significant difference

Discussion

Epidemiological studies have shown clear evidence that *H. pylori* infection is primarily acquired in childhood.[1-3] The fact has shifted the focus of investigation from adults to children. However, to date the knowledge about this infection in children remains limited. The mode of acquisition, the natural history of the infection, the relationship between infection and symptoms, are still poorly understood. In adults, the combination of a proton-pump inhibitor (PPI) plus two of the following antibiotics: clarithromycin, amoxicillin and metronidazole, has been advocated as the first-line eradication therapy in several consensus conferences and meta-analysis has shown an eradication rate of 80% on intention-to-treat analyses.[14-17] However, data in the literature is insufficient to determine the ideal treatment for children because randomised controlled trials are scarce and most of the reports consist of open case series. Oderda et al has recently published a systematic review of *H. pylori* eradication regimens in children.[18] From 1987 to 2000 only 30 full articles and 16 abstracts were found involving 870 and 1552 children respectively, compared with over 1000 treatment arms that have been studied in adult population in last decade.

In early reports on treatment of *H. pylori* infection in children, dual therapy with or without bismuth salts was shown to have an eradication rates varying from 43% to 80%.[19-23] However such regimens were usually given for 4 to 8 weeks. The long duration of treatment and the strong taste of ammonia associated with liquid bismuth invariably resulted in poor compliance in children. The experience of bismuth-based triple therapy was reported by Cucchiara et al[24] and Walsh et al[25] in 30 and 22 patients with an eradication rate of 75% and 95% respectively. Suboptimal drug compliance accounts for the discrepancy of the two reports. In the late nineties, antisecretory agent-based triple therapy including a proton-pump inhibitor and two antibiotics was reported in several open trials in children. Eradication rates varied from 63% to 92%.[26-29] Besides the inconsistency of the results, the drug durations were different and the patient numbers were small in most of the series. Recently, Gottrand et al[30] has published their results of a prospective randomised study on the efficacy of omeprazole plus amoxicillin and clarithromycin given for one week in children. Eradication rate for such regimen was 74.6% in intention-to-treat analysis in 63 children. All these results suggest that antisecretory agent-based triple therapy given in one week in children probably has similar efficacy as in adults. However, there are still uncertainties in interpreting the data in the literature. Firstly, the series of studied children are usually small because most of the trials were conducted in developed countries where the prevalence of infection is low and only very few are randomised studies. Secondly, unreliable drug compliance which happens commonly in children adds extra difficulties in analyzing the efficacy of different treatment protocols. In our study design, we increased the sample size by recruiting both symptomatic and asymptomatic children who had been shown to be *H. pylori*-infected in previous epidemiological study. Parents had been counseled about the unproven benefits of *H. pylori* eradication in asymptomatic children and informed consent was obtained. ^{13}C-UBT test has been proven to be accurate

in diagnosing *H. pylori* infection in children and evaluating the success of eradication after treatment.[31] Its use promoted the acceptance of this study by the patients and their parents. In this study drug compliance was ensured by two measures: 1) Before treatment the parents were interviewed by a senior paediatric surgeon about the importance of completion of treatment and the potential drug adverse effects. 2) The parents were interviewed on phone by our research nurse during the treatment period and at the completion for further counselling and monitoring of compliance. With such measures, all children completed the treatment according to our protocol.

Meta-analyses suggest that ranitidine bismuth citrate (RBC) when used in conjunction with two antibiotics works equally well as proton pump inhibitor-based triple therapy.[17,32] Some studies have shown that RBC- based triple therapy may be less influenced by the antibiotic resistance than their PPI-based counterparts.[33,34] Although data of RBC-based therapy in children is scarce, its components of ranitidine and bismuth have been widely used in paediatric population before. In our study, an eradication rate of 89.2% was achieved when RBC plus amoxicillin and clarithromycin were given to children for 7 days. The result corresponds very well to adult series. More side effects were documented in this study than the data in the literature and were most probably a result of direct questioning on the phone interview. Although they were usually mild and well tolerated in children, this signifies that no treatment protocols are without risk and further studies are required to better define indications for eradication treatment for *H. pylori*-infected children. The common finding of blackening of stool as a result of bismuth compound emphasises the importance that both the parents and patients should be warned about this prior to commencement of treatment.

This prospective randomised study in 200 children with optimal compliance allows us to conclude that ranitidine bismuth citrate plus amoxicillin plus clarithromycin given for one week is an effective and safe regimen to eradicate *H. pylori* infection in children. Efficacy drops significantly when the therapeutic agents are given for less than a week. The simple way of administration and short treatment duration promotes compliance in paediatric population. It should never be overemphasised that good compliance is the key for successful treatment and this depends on both an appropriate therapeutic regimen and adequate parental counselling by enthusiastic clinicians.

References

1. Cullen DJ, Collins BJ, Christiansen KJ, et al. When is *Helicobacter pylori* infection acquired? Gut 1993;34:1681-2.
2. Banatvala N, Mayo K, Megraud F, Jennings R, Deeks JJ, Feldman RA. The cohort effect and *Helicobacter pylori*. J Infect Dis 1993; 168:219-21.
3. Parsonnet J, Blaser MJ, Perez-Perez GI, Hargrett-Bean N, Tauxe RV. Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. Gastroenterology 1992;102:41-6.
4. Fiedorek SC, Malaty HM, Evans DL, et al. Factors influencing the epidemiology of *Helicobacter pylori* infection in children. Pediatrics 1991;88:578-82.
5. McCallion WA, Murray LJ, Bailie AG, Dalzell AM, O'Reilly DP, Bamford KB. *Helicobacter pylori* infection in children: relation with current household living conditions. Gut 1996;39: 18-21.
6. Perez-Perez GI, Taylor DN, Bodhidatta L, et al. Seroprevalence of *Helicobacter pylori* infections in Thailand. J Infect Dis 1990; 161:1237-41.
7. Holcombe C, Omotara BA, Eldridge J, Jones DM. *H. pylori*, the most common bacterial infection in Africa: a random serological study. Am J Gastroenterol 1992;87:28-30.
8. Goggin N, Rowland M, Imrie C, Walsh D, Clyne M, Drumm B. Effect of *Helicobacter pylori* eradication on the natural history of duodenal ulcer disease. Arch Dis Child 1998;79:502-5.
9. Drumm B, Koletzko S, Oderda G. *Helicobacter pylori* infection in children: a consensus statement. European Paediatric Task Force on *Helicobacter pylori*. J Pediatr Gastroenterol Nutr 2000 30:207-13.
10. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127-31.
11. International Agency for Research on Cancer. Schistosomes, Liver Flukes and *Helicobacter pylori*. Monographs on the evaluation of carcinogenic risks to humans, vol 61. Lyon: IARC, 1994:177-240.
12. Sherman P, Czinn S, Drumm B, et al. *Helicobacter pylori* infection in children and adolescents: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2002; 35 Suppl 2:S128-33.
13. Imrie C, Rowland M, Bourke B, Drumm B. Is *Helicobacter pylori* infection in childhood a risk factor for gastric cancer? Pediatrics 2001;107:373-80.
14. Hunt R, Thomson AB. Canadian *Helicobacter pylori* consensus conference. Canadian Association of Gastroenterology. Can J Gastroenterol 1998;12:31-41.
15. Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection. J Gastroenterol Hepatol 1998;13:1-12
16. Schmid CH, Whiting G, Cory D, Ross SD, Chalmers TC. Omeprazole plus antibiotics in the eradication of *Helicobacter pylori* infection: a meta-regression analysis of randomized, controlled trials. Am J Ther 1999;6:25-36.
17. Laheij RJ, Rossum LG, Jansen JB, Straatman H, Verbeek AL. Evaluation of treatment regimens to cure *Helicobacter pylori*

infection – a meta-analysis. Aliment Pharmacol Ther 1999;13: 857-64.
18. Oderda G, Rapa A, Bona G. A systematic review of *Helicobacter pylori* eradication treatment schedules in children. Aliment Pharmacol Ther 2000;14 Suppl 3:59-66.
19. Oderda G. Management of *Helicobacter pylori* infection in children. Gut 1998;43 Suppl 1:S10-3.
20. Yeung CK, Fu KH, Yuen KY, et al. *Helicobacter pylori* and associated duodenal ulcer. Arch Dis Child 1990;65:1212-6.
21. Drumm B, Sherman P, Chiasson D, Karmali M, Cutz E. Treatment of *Campylobacter pylori*-associated antral gastritis in children with bismuth subsalicylate and ampicillin. J Pediatr 1988;113:908-12.
22. Oderda G, Vaira D, Ainley C, et al. Eighteen month follow up of *Helicobacter pylori* positive children treated with amoxycillin and tinidazole. Gut 1992;33:1328-30.
23. Israel DM, Hassall E. Treatment and long-term follow-up of *Helicobacter pylori*-associated duodenal ulcer disease in children. J Pediatr 1993;123:53-8.
24. 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.
25. Walsh D, Goggin N, Rowland M, Durnin M, Moriarty S, Drumm B. One week treatment for *Helicobacter pylori* infection. Arch Dis Child 1997;76:352-5.
26. Dohil R, Israel DM, Hassall E. Effective 2-wk therapy for *Helicobacter pylori* disease in children. Am J Gastroenterol 1997; 92:244-7.
27. Kato S, Ritsuno H, Ohnuma K, Iinuma K, Sugiyama T, Asaka M. Safety and efficacy of one-week triple therapy for eradicating *Helicobacter pylori* in children. Helicobacter 1998;3:278-82.
28. Shashidar H, Peters J, Rabah R, et al. Lansoprazole in the treatment of H. pylori infection in children. J Pediatr Gastroenterol Nutr 1998;26:565.
29. Kalach N, Raymond J, Benhamou PH, Bergeret M, Dupont C. Short-term treatment with amoxycillin, clarithromycin and lansoprazole during *Helicobacter pylori* infection in children. Clin Microbiol Infect 1999;5:235-236.
30. Gottrand F, Kalach N, Spyckerelle C, et al. Omeprazole combined with amoxicillin and clarithromycin in the eradication of *Helicobacter pylori* in children with gastritis: A prospective randomized double-blind trial. J Pediatr 2001;139:664-8.
31. Rowland M, Lambert I, Gormally S, et al. Carbon 13-labeled urea breath test for the diagnosis of *Helicobacter pylori* infection in children. J Pediatr 1997;131:815-20.
32. Gisbert JP, Gonzalez L, Calvet X, Roque M, Gabriel R, Pajares JM. *Helicobacter pylori* eradication: proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics for 1 week-a meta-analysis of efficacy. Aliment Pharmacol Ther 2000;14:1141-50.
33. Houben MH, van de Beek D, Hensen EF, Craen AJ, Rauws EA, Tytgat GN. A systematic review of *Helicobacter pylori* eradication therapy – the impact of antimicrobial resistance on eradication rates. Aliment Pharmacol Ther 1999;13:1047-55.
34. Sung JJ, Chan FK, Wu JC, et al. One-week ranitidine bismuth citrate in combinations with metronidazole, amoxycillin and clarithromycin in the treatment of *Helicobacter pylori* infection: the RBC-MACH study. Aliment Pharmacol Ther 1999;13:1079-84.