An update on anti-*Helicobacter pylori* treatment in children

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Previous consensus statements have recommended one- to two-week proton pump inhibitor (PPI)-based triple therapies with clarithromycin and either amoxicillin or metronidazole as first-line treatments for children with *Helicobacter pylori* infection. The objective of the present review was to summarize data from pediatric studies that have examined treatment efficacy, safety, drug resistance and reinfection rates related to anti-*H pylori* therapies. Data from a recent meta-analysis of pediatric studies were used along with the authors' existing databases and searches of individual studies. Regimens that were identified as greater than 80% efficacious in children included a two-week therapy with a nitroimidazole and amoxicillin in Europe; a two-week regimen of bismuth, amoxicillin and metronidazole in developed countries (except Spain); a one- to two-week regimen of a PPI, clarithromycin and amoxicillin in Northern Europe, Asia and the Middle East; and a two-week regimen of a PPI, clarithromycin and metronidazole in Canada. Although recommended as a first-line treatment in adults, two-week treatment with a PPI, clarithromycin and amoxicillin eradicated only 68% of *H pylori* infections in North American children. Treatment efficacy was reduced in the presence of metronidazole and/or clarithromycin resistance. Further studies of anti-*H pylori* treatments in children in North America and developing countries are warranted.

Key Words: *Children;* Helicobacter pylori; *Review; Treatment efficacy; Update*

Mise à jour d'un traitement contre l'*Helicobacter pylori* chez les enfants

Dans les documents consensuels passés, on recommande une trithérapie aux inhibiteurs de la pompe à protons (IPP) associée à de la clarithromycine et à de l'amoxicilline ou à du métronidazole comme traitement de première intention pour les enfants atteints d'une infection à *Helicobacter pylori*. La présente analyse vise à résumer les données tirées d'études pédiatriques qui portaient sur l'efficacité et l'innocuité des traitements, la résistance aux médicaments et les taux de réinfection par rapport aux traitements contre l'*H pylori*. Les données tirées d'une récente méta-analyse d'études pédiatriques ont été utilisées en plus des bases de données existantes de l'auteur et de recherches dans des études individuelles. Les posologies efficaces à plus de 80 % chez les enfants sont un traitement de deux semaines à au nitroimidazole et à l'amoxicilline en Europe, un traitement de deux semaines au bismuth, à l'amoxicilline et au métronidazole dans les pays en voie de développement (sauf l'Espagne), un traitement de une ou deux semaines à l'IPP, à la clarithromycine et à l'amoxicilline en Europe du Nord, en Asie et au Moyen-Orient et un traitement de deux semaines à l'IPP, à la clarithromycine et au métronidazole au Canada. Bien qu'il soit recommandé comme traitement de première intention chez les adultes, un traitement de deux semaines à l'IPP, à la clarithromycine et à l'amoxicilline n'a éradiqué que 68 % des infections à *H pylori* chez les enfants nord-américains. L'efficacité du traitement diminuait en présence d'une résistance au métronidazole ou à la clarithromycine. D'autres études des traitements contre l'*H pylori* s'imposent chez les enfants de l'Amérique du Nord et des pays en voie de développement.

Helicobacter pylori infection acquired during childhood causes clinical disease in only a small proportion of infected individuals (1). Nevertheless, *H pylori* infection is a leading cause of peptic ulcer disease, and its eradication results in a long-term cure for patients (1-4). In 1999 and 2000, the Canadian Helicobacter Study Group (5) and the North American Society for Pediatric Gastroenterology and Nutrition (6) recommended proton pump inhibitor (PPI)-based triple therapies with clarithromycin (C) and either amoxicillin (PPI-CA) or metronidazole (PPI-CM) for one to two weeks as first-line treatment of *H pylori* infection in children. The North American Society for Pediatric Gastroenterology and Nutrition also recommended PPI-based triple therapy with amoxicillin and metronidazole (6). These previous guidelines were based on level I evidence from studies in adult populations and adult recommendations because there were insufficient pediatric clinical trials (7,8). The following review provides an updated summary of evidence from pediatric and adult studies regarding the efficacy, safety, drug resistance and reinfection rates of anti-*H pylori* therapies.

METHODS

To summarize the efficacy of anti-*H pylori* treatment and adverse events in children, evidence was used from the authors' recent meta-analysis of pediatric studies (unpublished data). Additionally, data were used from the authors' existing databases and Medline searches using the key words '*Helicobacter pylori*' or '*Campylobacter pylori*', and 'therapy' or 'treatment', 'reinfection', 'drug resistance', and 'rescue' or 'second-line therapy'.

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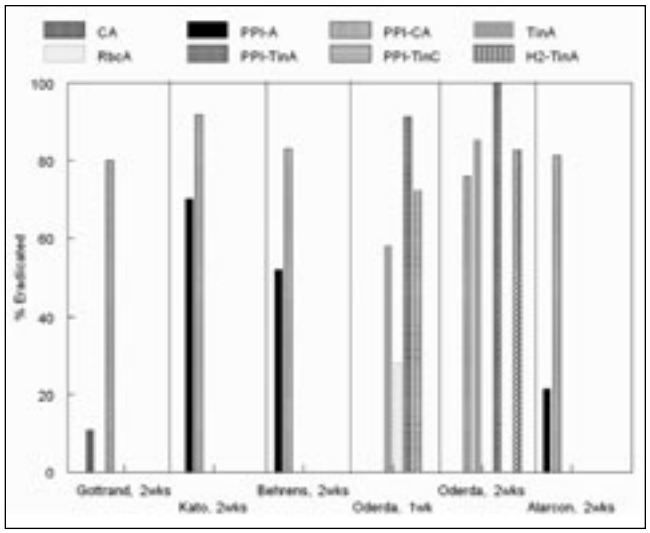

Figure 1) *Efficacy of head-to-head dual versus triple therapies given for the same duration. CA Clarithromycin and amoxicillin; H_2-TinA H_2-receptor antagonist, tinidazole and amoxicillin; PPI-A Proton pump inhibitor and amoxicillin; PPI-CA PPI, clarithromycin and amoxicillin; PPI-TinA PPI, tinidazole and amoxicillin; PPI-TinC PPI, tinidazole and clarithromycin; RbcA Ranitidine, bismuth citrate and amoxicillin; TinA Tinidazole and amoxicillin; wk Week*

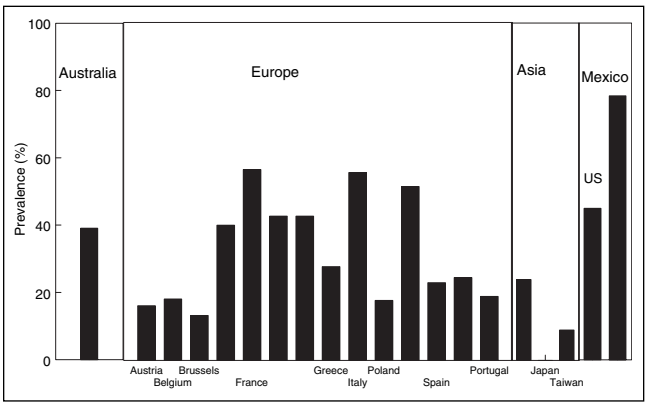

Figure 2) *Prevalence of primary metronidazole resistance in children. US United States*

RESULTS

Efficacy

The meta-analysis included 99 treatment arms and 67 studies from 25 countries across four continents (unpublished data). It provided data up to May 2004 on 23 treatment regimens used to eradicate *H pylori* in 3175 children. The vast majority of studies were nonrandomized with fewer than 50 subjects.

Treatment efficacy varied according to the number and type of drugs used in the regimen, treatment duration, geographical location and the methods used to assess eradication after treatment. Only 5% or less of the infections were eradicated using a placebo, H_2-receptor antagonist, sucralfate or omeprazole alone in five treatment arms (9-13). Dual therapy with amoxicillin and a nitroimidazole (tinidazole or metronidazole) (AN) was more efficacious in children than in adults (14). Overall, the mean eradication rate for this dual therapy was 83.9% (365 eradicated of 435 treated) in nine treatment arms when given from 10 days to six weeks (95% CI 80.2% to 87.2%); however, this dual therapy's efficacy was greatly reduced in Kuwait (15) and when given for only one week (10). Other dual therapies eradicated less than 80% of infections in most studies (unpublished data).

Triple therapies were more efficacious compared with dual therapies given for the same duration (Figure 1) (10,16-19). Tinidazole and amoxicillin dual therapy (TinA), which performed well when given for two weeks, tended to perform better when a PPI was added (PPI-TinA) (eradication 85% versus 100%; P=0.17) (10). However, eradication of *H pylori* with PPI-TinA was significantly better than with TinA when the treatment duration was one week (P=0.004) (10). PPI-CA, the most commonly tested regimen, cured 58% to 100% of *H pylori* infections in 29 treatment arms with 1014 children. More than 80% of *H pylori* infections in trials from Asia, the Middle East and European countries outside of Italy and Spain were eradicated using PPI-CA, irrespective of treatment duration. However, in the United States, only 68% of infections were eradicated using two-week PPI-CA treatments (20). Two-week therapy with a bismuth compound, amoxicillin and metronidazole (BAM), given in developed countries outside of Spain, eradicated *H pylori* in more than 80% of children. A PPI, macrolide and a nitroimidazole regimen (PPI-MacN) typically eradicated less than 80% of *H pylori* infections, but in one small nonrandomized study in Canada, 93.3% erradication was achieved with two-week therapy (21). Only three quadruple-treatment regimens were tested, each for one week in a small number of children. Treatment with a nitroimidazole, amoxicillin and furazolidone, and either ranitidine or omeprazole resulted in eradication of 70% (seven of 10) or 80% (four of five) of infections in Brazilian children, respectively (22). Furazolidone is an inexpensive antibiotic, commonly used in South America, but not available in North America. One-week treatment with metronidazole, clarithromycin, amoxicillin and omeprazole eradicated 94% (31 of 33) of *H pylori* infections in children in Hong Kong (23).

Adverse events

Only mild adverse events have been observed in *H pylori* treatment trials in children, but the manner in which adverse events were recorded and the occurrence of adverse events varied greatly between studies (unpublished data). Adverse events were observed in 0% to 34% of subjects given a dual therapy over one to six weeks of treatment, and in 0% to 80% of subjects given a triple therapy for one to three weeks (unpublished data). In head-to-head studies, triple therapies did not result in more adverse events compared with dual therapies. In one study (16), there were more adverse events with dual therapy using clarithromycin and amoxicillin compared with PPI-CA (34% versus 14%; P<0.0001). Although there has been some concern over the use of bismuth salts in children and its association with encephalopathy (3), bismuth levels were found to be well below toxic levels in children (24,25).

Drug resistance

Resistance of *H pylori* to commonly used antibiotics is a recognized problem (26,27). Marked geographical variation for primary drug resistance to *H pylori* in children was observed (Figures 2 and 3). Primary resistance to metronidazole ranged from 13% to 57% in Europe (20,25-43), 39% in Australia (44),

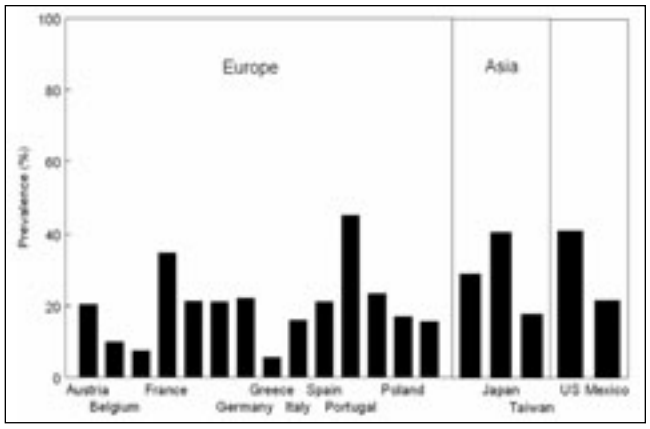

Figure 3) *Prevalence of primary clarithromycin resistance in children. US United States*

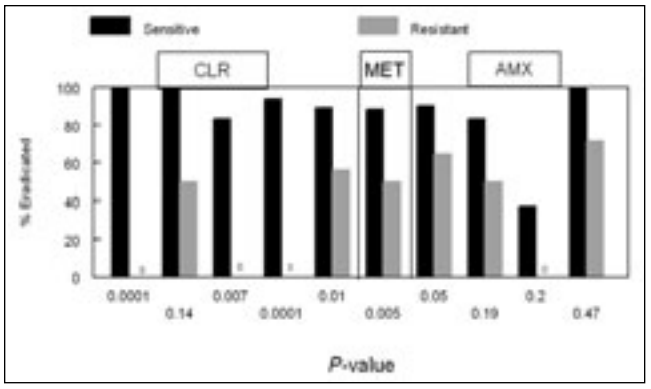

Figure 4) *Proportion of* Helicobacter pylori *eradication in clarithromycin (CLR)-, metronidazole (MET)- and amoxicillin (AMX)-sensitive and resistant strains in head-to-head studies*

0% to 24% in Japan (45,46), 9% in Taiwan (47) and 45% in the United States (48). The highest reported prevalence of primary metronidazole resistance (78.4%) was in Mexico (49). Prevalence of secondary metronidazole resistance was 4% in Australia, 30% in Belgium and 52% in France (35,42,44). The prevalence of primary clarithromycin resistance in children was lower than metronidazole resistance in Europe, where it ranged from 6% to 45% (33-43,50-55); in the United States, the prevalence of clarithromycin resistance was similar to that of metronidazole resistance (48). However, in Japan, the occurrence of clarithromycin resistance (29% to 41%) exceeded that of metronidazole resistance (46), and secondary clarithromycin resistance from France and Japan was reported to be as high as 52% and 78%, respectively (35,46). Combined resistance to metronidazole and clarithromycin ranged from 4% to 17% (34-38,40-42,44,46,48,49,53). Only three studies of children from Italy (37), the United States (48) and Mexico (49) reported primary resistance to amoxicillin; resistance in these populations was 3%, 5% and 16%, respectively (37,48,49).

Resistance of *H pylori* to a nitroimidazole, clarithromycin and other drugs plays a major role in treatment failure in adults (14). *H pylori* eradication in adults decreased by 0.5% for every 1% increase in the prevalence of metronidazole-resistant strains (14). While data were sparse for pediatric studies, treatment regimens in head-to-head studies were consistently more efficacious when the strain of *H pylori* was sensitive to the drugs in the regimen (Figure 4). In five studies (29,30,46,51,52) that reported treatment efficacy by clarithromycin resistance, 83% to 100% of clarithromycin-sensitive *H pylori* infections, versus 0% to 56% resistant infections, were cured after treatment with PPI-CA. In Spain, 88% of the metronidazole-sensitive strains were eradicated with BAM, compared with only 50% of the metronidazole-resistant strains (31).

Reinfection

When reported, some reinfection was observed in children, especially in the first six to 12 months after treatment. Reinfection occurred in 0% to 7% of children per month after eradication (4,9,12,56-59). Lower reinfection proportions were reported when the follow-up times were longer; for example, Oderda et al (60), Huang et al (12) and Kato et al (61) reported reinfection in 0.13% to 1% per month after 18 to 28 months of follow-up. Other studies (62) have observed reinfection to be associated with treatment efficacy, family size, age, socioeconomic status, exposure to subsequent endoscopies and geographical location. Because treatment efficacy is a predictor of reinfection, it seems likely that a proportion of cases are due to recrudescence rather than true reinfection.

Rescue therapies

Only two studies were identified that reported eradication proportions with second-line treatment. After the initial treatment failure using amoxicillin and cimetidine or cimetidine alone, or bismuth and metronidazole in combination, only 12.5% and 41.2% of *H pylori* infections were eradicated with rescue therapies containing a PPI with clarithromycin and a nitroimidazole for one week (63), or amoxicillin alone for two weeks (9), respectively.

DISCUSSION

The ideal therapy to eradicate *H pylori* should be safe and effective in both the short and long term for populations requiring treatment. Studies of *H pylori* eradication in children (6) were smaller and generally methodologically weak compared with the better designed randomized controlled trials in adults. The treatment regimens that were more than 80% efficacious in children included two-week dual therapy with AN in Europe; two-week BAM treatment in developed countries; one- to two-week PPI-CA treatment in Asia, Northern Europe and the Middle East; and two-week PPI-MacN treatment in Canada. PPI-AN, although used in only five treatment arms in France and Italy, eradicated 74% to 100% of infections; further testing may show this therapy to be effective in some populations of children.

Previous consensus statements for North American children have recommended one to two weeks of treatment with PPI-CA or PPI-CM (5,6), which reflect recommendations for adults (7,8). Although one- to two-week treatment with PPI-CA eradicated 84% of *H pylori* infections in trials in Northern Europe, Asia and the Middle East, and appears to be safe and readily available in most populations of children, it eradicated less than 75% of infections in children resistant to clarithromycin, and in populations in Latin America and the United States (20,29,30,46,64,65), where both metronidazole and clarithromycin resistance rates in children are high (48,49). Trials using PPI-CA in Canadian children have not been reported, but in one nonrandomized trial, the efficacy of PPI-MacN was 93% in Canada (21). In many populations outside of Canada, however, the efficacy of PPI-MacN was less than 80%. Furthermore, regimens containing metronidazole

may be less desirable for children because it is not available in liquid form and has an unpleasant taste (5). Many regimens have yet to be tested in developing countries and neither AN nor PPI-AN has been evaluated in North American children. However, the Canadian Helicobacter Study Group has endorsed this PPI-based triple therapy as an alternative therapy in adults (8).

There are some newer regimens that appear very promising in the treatment of *H pylori* in adults, which may also be effective in children. Quinolone triple therapies, when used in combination with a PPI and either amoxicillin, tinidazole or clarithromycin, have intention-to-treat eradication rates of approximately 90% in adults (66-68); however, the safety of quinolones in pediatrics has not been established. Another regimen, a one-week quadruple regimen with a PPI, amoxicillin, clarithromycin and metronidazole, eradicated 94% of *H pylori* infections in children (23). In adults, this regimen had an efficacy of approximately 90% when given for only five days (69-72). This would be a suitable regimen for children because shorter duration may help to improve compliance.

Although only minor adverse events have been reported with anti-*H pylori* therapies in children, tetracycline may damage the dental enamel, and this drug should not be used in children younger than 12 years of age (73,74). Thus, although the quadruple regimen of PPI, bismuth, metronidazole and tetracycline (PPI-BMT) is highly effective in adults, and has been recommended for both first-line and salvage therapy (8), it is recommended only for children older than 12 years of age. Acetylsalicylic acid and nonacetylsalicylic acid salicylates, such as bismuth subsalicylate, are associated with Reye's syndrome in children with febrile illness and should be used with caution (only if the child does not have a febrile illness [75]). The two studies that measured bismuth levels with *H pylori* therapy in children showed that levels were well below the neurotoxic range (24,25).

Because there were almost no data for treatment of *H pylori* eradication failures in pediatrics, recommendations stem largely from adult data. The present recommendation for rescue therapy is to administer a second course of alternate PPI triple therapy (PPI-CM if PPI-CA was used first or vice versa) or a quadruple therapy of PPI-BMT (8). While the PPI-BMT therapy is the most robust in adults, the use of tetracycline can be problematic as already discussed. Rifabutin- and levofloxacin-based therapies appear effective in adults, but rifabutin is expensive and there are limited safety data for either drug in children (76-78). Thus, at this time, these regimens would need further study in children before recommendations for their general use can be made.

Metronidazole and clarithromycin resistance are common in developing countries, Canada and the United States, and no therapy has yet been identified as safe and consistently effective to eradicate *H pylori* infection in children in these populations. Therefore, in addition to the need to identify safe and effective anti-*H pylori* rescue therapies in children throughout the world, there is also a need to identify safe and effective primary eradication therapies for *H pylori*-infected children in North America and developing countries, especially in populations where the prevalence of metronidazole and/or clarithromycin resistance is high.

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