A systematic review of Helicobacter pylori eradication treatment schedules in children

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Authors' objectives
To determine the overall efficacy of different drug schedules for the treatment of Helicobacter pylori (H. pylori) infection in children.

Searching
MEDLINE and Current Contents were searched from January 1987 to the end of October 1999. In addition, all relevant abstracts submitted to the three most important meetings on this field between 1997 and 1999, were examined. Only English or French language papers were considered.

Study selection

Study designs of evaluations included in the review
All study designs were eligible for inclusion provided they reported the following details: the number and children and their age; the type, total daily dose and duration of treatment; and eradication results.

Specific interventions included in the review
The review did not specify inclusion or exclusion criteria regarding the type of drug therapies to be included in the review. A wide range of drug treatments were included in the review, i.e. single, dual and triple therapies.

The single drug therapies were: cimetidine, omeprazole, amoxycillin and bismuth.

The dual therapies were: cimetidine plus amoxycillin; omeprazole plus amoxycillin; RBC (ranitidine-bismuth-subcitrate) plus amoxycillin; amoxycillin plus tinidazole; amoxycillin plus metronidazole; amoxycillin plus clarithromycin; bismuth plus ampicillin; bismuth plus amoxicillin; bismuth plus metronidazole; and bismuth plus tinidazole.

The triple therapies were: bismuth, amoxycillin and metronidazole; bismuth, amoxycillin and tinidazole; bismuth, metronidazole and clarithromycin; lansoprazole, amoxycillin and clarithromycin; omeprazole, amoxycillin and clarithromycin; omeprazole, amoxycillin and clarithromycin; omeprazole, amoxycillin and metronidazole; lansoprazole, amoxycillin and metronidazole; lansoprazole, spiramycin and metronidazole; omeprazole, metronidazole and clarithromycin; ranitidine, amoxycillin and metronidazole; ranitidine, amoxycillin and tinidazole; and amoxycillin, metronidazole and furazolidone.

In addition, two quadruple therapies were also considered: ranitidine, amoxycillin, metronidazole and furazolidone; and omeprazole, amoxycillin, metronidazole and furazolidone. For the purposes of the review, the authors ignored possible differences between bismuth compounds, between proton-pump inhibitors (omeprazole and lansoprazole), and between nitroimidazoles (metronidazole and tinidazole), in order to avoid groups with too few participants.

Participants included in the review
Children with H. pylori infection were included. No details of the participants were presented in the review.

Outcomes assessed in the review
Eradication rates were assessed, either per protocol or according to intention to treat principles. Eradication was assessed by biopsy or by urea breath test, at least 4 weeks after the end of the treatment.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following categories of data were extracted: reference details, the number of children treated, drug regimen and duration, tests performed, and eradication rates. Eradication rates and 95% confidence intervals (CIs) were calculated using the normal method, or the exact method when appropriate.

Methods of synthesis
How were the studies combined?
Studies using the same or very similar drug regimens were pooled in order to avoid groups with too few participants. The eradication rates and 95% CIs were calculated using the normal method, or the exact method when appropriate. A two-tailed chi-squared test was used to compare eradication rates between groups of treatment according to the combination of drugs used, and within each treatment according to the duration of treatment. The odds ratio (OR) and 95% CIs were calculated. Studies reported as full manuscripts or letters were not pooled with those reported as conference proceedings.

How were differences between studies investigated?
Only studies of the same or very similar drug regimens were pooled. No formal test of statistical heterogeneity was performed.

Results of the review
Thirty full articles and letters involving a total of 870 children were identified: 79 children were treated with monotherapy, 345 with dual therapy, and 446 with triple therapy. In addition, there were 17 abstracts (all published after 1997) involving 1,579 children: 352 received dual therapy, 1,212 received triple therapy, and 15 received quadruple therapy.

The results from the full manuscripts or letters are presented in this abstract.

Monotherapy resulted in poor eradication rates of around 30%.

Dual therapy that included only one antibiotic resulted in a pooled eradication rate of around 40%.

Dual therapy with two antibiotics gave pooled eradication rates of 73 to 76%: amoxycillin plus nitroimidazole (n=111), 76% (95% CI: 68, 84); bismuth plus amoxycillin (n=82), 74% (95% CI: 64, 83); and bismuth plus nitroimidazole (n=55), 73% (95% CI: 59, 84). There was no difference between these treatments. Triple therapy did not produce any statistically significantly better rates of eradication; the differences between some treatments may not have achieved significance on account of the small sample sizes. The calculated pooled rates were for:

- Bismuth with amoxycillin and nitroimidazole (n=127), 74% (95% CI: 64, 83);
- Lansoprazole with amoxycillin and metronidazole (n=57), 79% (95% CI: 66, 88);
- Proton-pump inhibitor with amoxycillin and clarithromycin (n=125), 83% (95% CI: 79, 90);
- Omeprazole with metronidazole and clarithromycin (n=47), 89% (95% CI: 77, 96);
- Bismuth with metronidazole and clarithromycin (n=22), 95.5% (95% CI: 77, 100).

Similar findings were obtained from the studies reported as abstracts only. The RBC plus amoxycillin combination (n=39) gave the poorest results with an eradication rate of 25% (95% CI: 13, 40). The most widely studied combination was bismuth with amoxycillin and nitroimidazole (n=632), for which the pooled eradication rate was...
82% (95% CI: 80, 85).

The effect of treatment duration was investigated where sufficient data were available. Amoxycillin plus nitroimidazole was significantly less effective when administered for 1 week, than when administered for 2, 4 or 6 weeks: eradication rate of 74% compared with 84% (OR 2.19, 95% CI: 1.07, 4.5, p=0.03). Similarly, bismuth with amoxycillin and nitroimidazole was less effective when administered for 1 week, than when administered for 2 or 4 weeks: eradication rate of 74% compared with 84% (OR 1.86, 95% CI: 1.14, 3.05, p=0.03). Proton-pump inhibitor-based triple therapies were equally effective when given for 1 or 2 weeks.

**Authors' conclusions**
The results need to be confirmed by randomised controlled trials, and no definite statement can be drawn at present. Some of the results appeared consistent; in particular, dual therapies with two antibiotics, or bismuth plus one antibiotic, seemed to be as effective as triple therapies if given for 2 weeks. Bismuth-based triple therapies were also more effective if given for 2 weeks, whereas proton-pump inhibitor-based triple therapies had a similar efficacy irrespective of the treatment duration. It therefore seems unnecessary to administer the expensive proton-pump inhibitor-based triple therapies for longer than one week.

**CRD commentary**
This review addressed a specific question with adequate inclusion and exclusion criteria. The literature search was fairly comprehensive although a greater number of databases could have been searched. The failure to include abstracts before 1997 and the language restrictions imposed may have resulted in some publication bias. It was not stated how many reviewers selected the studies and extracted the data, so it is possible there was some reviewer bias. All types of studies were eligible for inclusion in the review. No information was provided on the design of the included studies, and there was no validity or quality assessment. It appears that all the included studies were uncontrolled and unblinded, and consequently of very poor quality. The study details presented were limited; in particular, the children's ages were not reported.

The pooling of the studies appeared appropriate; only studies of the same drug combinations were pooled. The effect of treatment duration on the eradication rates may have been masked by the pooled results, although this was explored for some drug combinations. The authors' conclusions were generally supported by the results presented in the review. However, those concerning treatment duration were too pronounced given the weakness of the evidence upon which they were based.

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.