## Helicobacter pylori eradication treatment in children

### QUESTION

¿Should children with H.pylori infection be treated with eradication therapy compared to no treatment?

### CONTEXT

Helicobacter pylori (H. Pylori) is a gram-negative flagellated spiral bacterium found in the stomach. Infection with H pylori is predominantly acquired in childhood. The organism is associated with lifelong chronic gastritis and may cause other gastro-duodenal disorders. It is believed to be causally related to the development of duodenal and gastric ulceration, B cell gastric lymphoma, and distal gastric cancer. About 15% of people infected with H. pylori will develop a peptic ulcer, and 1% of people will develop gastric cancer during their lifetime. The causal relationship between H. Pylori and gastroduodenal disease is well established in children.

### INTERVENTION

**Helicobacter pylori eradication:**
- Proton pump inhibitor + clarithromycin + amoxicillin reached a range in the proportion of eradication from 66 to 93.3%. *Very low quality evidence*
- Proton pump inhibitor + amoxicillin + nitroimidazole reached a mean proportion of eradication of 74.7%. *Low quality evidence*
- Proton pump inhibitor + amacrolide + nitroimidazole reached a range in the proportion of eradication from 64.3% to 93.3% *Very low quality evidence*
- Bismuth + amoxicillin + nitroimidazole reached a range in the proportion of eradication from 22.2 to 90.1%. *Very low quality evidence*

* The eradication proportion is employed to estimate treatment efficacy assuming the eradication rate for placebos nears 0%.
**Summary of the Evidence**

### Benefits

A systematic review that assessed the H.Pylori eradication treatment efficacy in children was found (search date: 2005) \[1\]. It included 80 studies that used single, double, triple or quadruple treatment regimens in children less than 18 years of age (26 treatment regimens, 4436 children). Only 23 of these trials were randomized controlled trials, while the rest were cohort studies and case-series. Only four studies compared eradication treatment with treatments which did not contain medications aimed at the elimination of H. Pylori: they used as placebos H2-receptor antagonist and iron. The eradication rate with placebos was near to 0%, and the authors assumed that for placebos the eradication proportion approached to zero, and that the eradication proportion could be employed to estimate treatment efficacy. Different regimens were assessed in monotherapy, dual therapy and triple therapy without calculating a common effect estimator. The eradication rates reached with monotherapy, dual therapy and triple therapy were not compared with each other. There was high variability in type of antibiotic, dosage and treatment time.

The eradication rate reached with monotherapy ranged from 6% to 27%. The eradication rate reached with dual therapy ranged from 28.2% to 83.6%.

As in adults the recommended therapy to eradicate H.pylori is a triple therapy, this file will focus in that regimens. Four different regimens were evaluated. 1) PPI-CA: proton pump inhibitor + clarithromycin + amoxicillin; 2) PPI-AN: proton pump inhibitor + amoxicillin + nitroimidazole; 3) PPI-MacN: proton pump inhibitor, a macrolide (clarithromycin or spiramycin) and nitroimidazole; 4) BAM: Bismuth, amoxicillin and nitroimidazole.

1) PPI-CA (16 studies, 1771 children) reached a range in the proportion of eradication from 64 to 90.4%. This scheme was less effective in developing countries (65%) than in Europe (80%) and when adverse events where present. Duration of treatment (either 1 or 2 weeks) did not affect treatment efficacy.

2) PPI-AN (6 studies, 368 children) reached a mean proportion of eradication of 74.7% (95% CI 72.8 to 76.7).

3) PPI-NacN (10 studies, 230 children) reached a range in the proportion of eradication from 64.3% to 93.3%

4) BAM (8 studies) reached a range in the proportion of eradication from 22.2 to 90.1%.

### Risks

The occurrence of adverse events ranged from 0% to 34% with 1- to 2-week dual treatment regimens in five treatment arms. With triple therapies (25 treatment arms) during 1 to 3 weeks, adverse events ranged from 0 to 80%.

None of the included studies reported the occurrence of severe adverse events or the withdrawal of treatment due to adverse events.

### Applicability

The efficacy of therapies used to eradicate H.Pylori in children varied widely across treatment arms. This wide variation can be explained, in part, by geographic location, duration of treatment and specific drugs. As in adults, anti H.Pylori therapies have been insufficiently tested in populations that carry the greatest burden of this infection worldwide. Inadequate evidence currently exists to provide specific treatment recommendations for H.Pylori-infected children in developing countries.

### Comments

Of the 80 studies included, only 60% were peer-reviewed, only 17% used a randomized-controlled design and only 5% were placebo-controlled. The majority of the studies were case-series, done in unique centres and had very small sample sizes. The principal outcome was the eradication rate, which can be considerate as a surrogate variable of clinical variables that were not measured. In addition, the different regimens were not compared to each other. The authors assumed an eradication rate for placebos near 0%, and compared the different eradication rates reached by the different regimens. Therefore, all the evidence comes from indirect comparisons, which lowers the quality of evidence. In conclusion the evidence is uncertain to know what is the most effective regimen to eradicate H.Pylori infection. Well-designed, multi-centre and with enough sample trials in children are currently lacking and are needed, as many treatment options have not yet been tested in children.
An economic evaluation that assessed the costs of 7 different eradication regimens was found [2].

1) LAC: lansoprazole 30 mg twice daily, amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 7 days.
2) OCM: omeprazole 20 mg twice daily, clarithromycin 250 mg twice daily and metronidazole 500 mg twice daily for 14 days.
3) OAM: omeprazole 40 mg every day, amoxicillin 500 mg three times daily and metronidazole 500 mg three times daily for 14 days.
4) MARB: metronidazole 250 mg three times daily, amoxicillin 500 mg four times daily, ranitidine 300 mg at bedtime and bismuth 300 mg four times daily for 14 days.
5) OAC: omeprazole 20 mg twice daily, amoxicillin 1 mg twice daily and clarithromycin 500 mg twice daily for 14 days.
6) OCA: omeprazole 40 mg twice daily, clarithromycin 500 mg twice daily and amoxicillin 1 mg twice daily for 14 days.
7) OAB: omeprazole 20 mg twice daily, amoxicillin 500 mg three times daily and bismuth 300 mg four times daily for 14 days.

The study was done in adult people with peptic ulcer disease or chronic gastritis in Turkey. Cost data refers to 2001. The authors concluded that the highest eradication rates were observed with MARB and OCA and that OCM, OAM and OAB had unsatisfactory eradication rates, so they were excluded from the analysis.

The cost per successful eradication was $195.8 for LAC, $146.5 for MARB, $202.9 for OAC and $180.8 for OCA. The authors concluded that MARB regimen was the most cost-effective treatment alternative.

<table>
<thead>
<tr>
<th>Numer of studies (N)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality*</th>
<th>Consistency</th>
<th>Direct evidence*</th>
<th>Precision</th>
<th>GRADE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 (1771 children)</td>
<td>Helicobacter pylori eradication</td>
<td>Proton pump inhibitor+ clarithromycin+ amoxicillin</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>Very low</td>
<td></td>
<td>Different type of studies mixed. There is not a common effect estimator calculated.</td>
</tr>
<tr>
<td>6 (368 children)</td>
<td>Proton pump inhibitor+ Amoxicillin+ nitroimidazole</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
<td>Different type of studies mixed. Heterogeneity from studies not peer reviewed.</td>
<td></td>
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</tr>
<tr>
<td>10 (230 children)</td>
<td>Proton pump inhibitor+ macrolide + nitroimidazole</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>Very low</td>
<td>Different type of studies mixed. There is not a common effect estimator calculated.</td>
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<tr>
<td></td>
<td>Bismuth+ Amoxicillin+ nitroimidazole</td>
<td>4</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>Very low</td>
<td>Different type of studies mixed. Heterogeneity from studies conducted in Spain and Mexico.</td>
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</tr>
</tbody>
</table>

Type of evidence: 4 = RCT; 2 = Observational; 1 = non analytic / expert opinion. * Any of the studies did subgroup analysis for elderly patients.