

## Dual versus triple therapy of *Helicobacter pylori* infection: results of a multicentre trial

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### Abstract

**Objective**—To compare dual therapy (omeprazole and amoxicillin) with triple therapy (omeprazole, amoxicillin, and clarithromycin) in the treatment of *Helicobacter pylori* infection. The efficacy of 1 mg/kg/day omeprazole was randomly compared with 2 mg/kg/day.

**Study design**—252 patients (median age, 11.0 years; range, 3–18) presenting with chronic abdominal pain underwent endoscopy and a <sup>13</sup>C-urea breath test. Gastric biopsy specimens were taken for histological examination and for the rapid urease test. Patients were treated for two weeks: group A (n = 63) received amoxicillin (50 mg/kg; maximum, 2 g/day), group B (n = 73) received amoxicillin and clarithromycin (20 mg/kg; maximum, 1 g/day). Both groups were randomly treated with either 1 or 2 mg/kg omeprazole (maximum, 80 mg/day). Diagnostic procedures were repeated four weeks after the end of treatment.

**Results**—11 patients were excluded; 136 patients were *H pylori* positive (56%), 105 of whom were re-examined after treatment. *Helicobacter pylori* was eradicated in 52% of group A and 83% of group B. The dose of omeprazole had no influence on the eradication rate. Specificity and sensitivity of the rapid urease test were 94% and 93%, respectively. Specificity and sensitivity of the <sup>13</sup>C-urea breath test were 93% and 95%, respectively.

**Conclusions**—Dual therapy can no longer be recommended. Triple therapy is more effective than dual therapy in the eradication of *H pylori* infection. The lower dose of 1 mg/kg omeprazole was as effective as 2 mg/kg.

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**Keywords:** *Helicobacter pylori*; dual therapy; triple therapy; omeprazole; <sup>13</sup>C-urea breath test

*Helicobacter pylori* infection is the most important cause of duodenal and gastric ulcers and chronic gastritis in adults. Initially, treatment of this infection consisted of a proton pump inhibitor (mainly omeprazole) in combination with an antimicrobial agent (mainly amoxicillin, so called dual therapy).<sup>1,2</sup> By adding a second antimicrobial agent (mainly clarithromycin or metronidazole, triple therapy) the eradication rate can be increased to 79–96%.<sup>2-6</sup>

Since the first reports of *H pylori* infection in childhood in 1986 and 1987,<sup>7-9</sup> several studies

have confirmed the importance of *H pylori* infection in childhood.<sup>10</sup>

There have been few studies in paediatric patients, all with small numbers of cases. In addition, most were based on bismuth derivatives or combined treatment with amoxicillin or tinidazole.<sup>11-17</sup> Omeprazole was used in one study in a triple therapy design, but no dose finding data were presented.<sup>18</sup>

The aim of our prospective, multicentre trial was to compare dual and triple therapy regimens and to evaluate the effect of two different doses of omeprazole.

### Patients and methods

Between June 1994 and April 1997, 252 patients were examined prospectively in six centres (mean age, 10.9 years; median age, 11.0; range, 3–18).

Inclusion criteria were upper abdominal pain (242 patients) and nausea and/or vomiting (10 patients) for at least four weeks and an age of less than 18 years.

Exclusion criteria were: (1) any antimicrobial or acid inhibiting treatment in the previous month; (2) any known adverse reactions to the drugs to be administered; (3) a leucocyte count of < 3500/μl and a thrombocyte count of < 100 000/μl; (4) missing consent.

A standardised history of the patient's symptoms was taken. We classified the intensity of abdominal pain into mild, moderate, and severe and the duration of symptoms was recorded.

All patients underwent oesophagogastroduodenoscopy. We took two biopsies each from antrum and corpus for histological examination and rapid urease test (CLO-test, Angass-test; Medice, Iserlohn, Germany). The histological assessment was performed by one examiner (MS), who was unaware of the endoscopic findings and the result of the <sup>13</sup>C-urea breath test (<sup>13</sup>C-UBT), using haematoxylin-eosin and Warthin–Starry staining and according to the classification of Sydney. A patient was considered to be infected with *H pylori* if the histology was positive.

All patients were investigated by the <sup>13</sup>C-UBT. The test was analysed in one centre (MB) according to a recently described protocol.<sup>19</sup> Baseline breath samples were taken before the child consumed a continental breakfast. Thereafter, the patient received 75 mg <sup>13</sup>C-urea (99% <sup>13</sup>C; Promochem, Wesel, Germany). Breath samples were collected at 30 and 60 minutes after tracer ingestion. A <sup>13</sup>C-UBT with  $\delta > 5\%$  was considered to be pathological.

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The *H pylori* positive patients were treated either with amoxicillin (50 mg/kg/day; maximum, 2 g/day, group A), or amoxicillin and clarithromycin (20 mg/kg/day; maximum, 1 g/day, group B). All patients received randomly either 1 or 2 mg omeprazole/kg/day, with a maximum of 80 mg/day. The randomisation was done by the Institut für Datenanalyse und Versuchsplanung, Munich, Germany. All drugs were divided in two doses. Patients were treated for two weeks.

Four to six weeks after completion of treatment follow up investigations including history, endoscopy, histology, CLO-test, and <sup>13</sup>C-UBT were repeated, as described above.

The study was approved by the local ethics committees and carried out according to the declaration of Helsinki. In every case, written informed consent was obtained from the parents. No patient had taken part in another study in the previous six months.

Statistical analysis was done by simple  $\chi^2$  test or, in case of multiple application, by its  $\alpha$ -modification as described by Bonferoni.

### Results

Out of 252 patients, 136 were *H pylori* positive (56%); 63 of these patients received dual therapy and 73 triple therapy. One hundred and five patients were *H pylori* negative. Eleven patients were excluded retrospectively because they did not meet the inclusion criteria.

The median age of the *H pylori* positive patients was 11.6 years (range, 3.8–18.0); the median age of the *H pylori* negative patients was 9.7 years (range, 3.0–18.0). There was no significant difference between groups A and B. The sex distribution was similar in both groups.

The intensity and duration of the symptoms were not significantly different in groups A and B at the beginning of the trial. In 78% of the patients in whom eradication was successful the symptoms resolved completely, whereas this was the case in only 50% of the patients in whom eradication had failed ( $p < 0.01$ ).

Regardless of *H pylori* status, gastritis mainly localised in the antrum was found in 92% of all patients. Fourteen duodenal ulcers and two gastric ulcers were found in the *H pylori* positive patients, as opposed to only two duodenal ulcers and one gastric ulcer in the *H pylori* negative patients. Lymphofollicular hyperplasia was found significantly more often in *H pylori* positive patients (78% *v* 17%;  $p < 0.01$ ).

One hundred and five of the 136 *H pylori* positive patients were re-examined after completion of treatment (table 1). With dual

Table 2 Specificity and sensitivity of the rapid urease test (CLO-test) and the <sup>13</sup>C-urea breath test (<sup>13</sup>C-UBT)

	<i>H pylori</i> positive	<i>H pylori</i> negative
Histology positive for <i>H pylori</i>	136/241	105/241
CLO-test positive	126/136	6/105
<sup>13</sup> C-UBT positive	129/136	7/105

therapy, the infection was eradicated in 27 of 52 patients, with triple therapy it was eradicated in 44 of 53 patients ( $p < 0.01$ ; odds ratio, 4.53; 95% confidence limits, 1.84 to 11.13). The dose of omeprazole did not influence these results. Of the 27 patients treated successfully with dual therapy, 14 patients received 1 mg omeprazole/kg/day and 13 received 2 mg omeprazole/kg/day. Twenty of the 44 patients treated successfully with triple therapy received 1 mg omeprazole/kg/day and 24 received 2 mg omeprazole/kg/day (not significant). Similar results were obtained in the patients in whom *H pylori* was not eradicated: in group A, 14 of 25 patients received 1 mg omeprazole/kg/day and 11 received 2 mg omeprazole/kg/day. In group B, five of nine patients were treated with 1 mg omeprazole/kg/day and four with 2 mg omeprazole/kg/day. All ulcers healed and these patients became asymptomatic. No side effects or interruption of treatment were observed.

Twenty one patients did not reappear for a second examination after treatment.

With the histological examination as gold standard, the specificity and sensitivity of the CLO-test were 94% and 93% (table 2). Pretreatment values for the <sup>13</sup>C-UBT were 94% and 95%, post-treatment values were 92% and 94%; in summary, 93% and 95% respectively (table 2).

### Discussion

Since the discovery that *H pylori* infection is the most common cause of inflammation or ulceration of the stomach and duodenum, many treatment studies have been performed in adults.<sup>2-20</sup> Initially, treatment primarily consisted of a combination of an antimicrobial agent with a bismuth salt (dual therapy). In the early 1990s, bismuth was replaced by a proton pump inhibitor for a better compliance and tolerance.<sup>1</sup> Recently, studies on triple therapy with two different antimicrobial agents have reported that this form of treatment can further improve the eradication rate.<sup>4-6</sup> Published observations in paediatric patients mostly consist of small numbers of cases.<sup>11-17</sup> In addition, they are often based on bismuth derivatives, which have a higher number of side effects.<sup>21</sup> To the best of our knowledge, there is only one report on triple therapy in children. In this study, a triple therapy regimen based on omeprazole, metronidazole, and clarithromycin was used to treat 15 patients with *H pylori* infection and eradication was successful in 14 of these children.<sup>18</sup>

For the first time in children, our study compares dual and triple therapy regimens based on a proton pump inhibitor (omeprazole). An eradication rate of 83% was found with the triple therapy regimen. This is in line with other

Table 1 Eradication rate of *Helicobacter pylori* after dual or triple therapy

	Dual therapy	Triple therapy
Total number of patients	63	73
Patients after treatment	52	53
Eradication rate	27 (52%)*	44 (83%)*
Dependence on the dose of omeprazole (patients without eradication)		
1 mg/kg/day	14/27 (14/25)	20/44 (5/9)
2 mg/kg/day	13/27 (11/25)	24/44 (4/9)

\* $p < 0.01$ .

reports.<sup>4-6 18</sup> In contrast, dual therapy had an eradication rate of only 52%. Therefore, the dual therapy regimen can no longer be recommended.<sup>3 16</sup>

Whereas omeprazole is well established for treatment of *H pylori* infections in adults, there is still uncertainty about the dose for paediatric patients. Relatively higher doses compared with adults are needed for treating tetraplegic children with reflux oesophagitis.<sup>22</sup>

The results of our study showed that a higher dose did not improve the eradication rate. It is possible that doses lower than 1 mg/kg might be sufficient and further studies are needed to evaluate this question.

In general, histology is regarded as the gold standard in the diagnosis of *H pylori* infection. This procedure requires invasive endoscopy but has the advantage that samples can also be taken for the rapid urease test and resistance testing if necessary.

As has been shown previously,<sup>23-25</sup> the non-invasive <sup>13</sup>C-UBT is highly specific and sensitive. This test is more convenient for the patient and less expensive. Because there were no significant differences in the sensitivity and specificity in the pretreatment and post-treatment values for the <sup>13</sup>C-UBT, it can be considered as the first diagnostic approach for follow up investigations. Although not investigated in the our study, it is recommended that in patients with a negative <sup>13</sup>C-UBT, oesophago-gastroduodenoscopy should be performed to identify other causes of the symptoms. If a pathological <sup>13</sup>C-UBT is obtained during follow up, it must certainly be followed by histology and identification of the bacteria involved by culture methods.

Further studies with lower doses of omeprazole and possibly shorter durations of treatment will help to optimise the above treatment regimen.

#### CONCLUSION

In summary, triple therapy with omeprazole, amoxicillin, and clarithromycin is effective in the eradication of *H pylori* infection in children, whereas dual therapy is less effective. We have shown that a dose of 1 mg omeprazole/kg/day is sufficient. As far as diagnosis is concerned, apart from histology, the CLO test and <sup>13</sup>C-UBT showed a high sensitivity and specificity.

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