

One-Week Triple Therapy With Omeprazole, Clarithromycin, and Nitroimidazole for *Helicobacter pylori* Infection in Children and Adolescents

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ABSTRACT. *Background.* Resolution of *Helicobacter pylori* infection is important in the management of peptic ulcer disease and reduces peptic ulcer recurrence in both adults and children. Various anti-*H pylori* treatment regimens have been proposed, reflecting the incomplete clinical success of each. A combination of omeprazole, clarithromycin, and tinidazole, given for 1 week, has been shown to be highly tolerable and effective, achieving a success rate of >90% in the adult population.

Objective. The aim of this study was to evaluate this short-term regimen in pediatric and adolescent populations.

Methods. The study group consisted of 35 children referred for evaluation of dyspeptic symptoms. They all underwent upper gastrointestinal endoscopy, in which *H pylori* infection was confirmed by rapid urease test and/or histologic staining. They were given omeprazole (20 mg twice daily), clarithromycin (250 mg twice daily), and tinidazole or metronidazole (500 mg twice daily) for 1 week. The patients were divided into two groups: those who received the first course of anti-*H pylori* therapy during this study (group 1) and those who had previously received standard metronidazole and bismuth combination therapies that failed to eradicate *H pylori* (group 2). Therapeutic efficacy was assessed by a ¹³C-urea breath test performed 4 weeks after completion of treatment.

Results. The 35 study patients had a mean age of 15.9 years (range, 10 to 19) and included 19 males and 16 females, of whom 22 were born in Israel and 13 were immigrants from the former USSR. There were 27 patients (77.1%) in group 1 and 8 patients (22.9%) in group 2. Endoscopic findings were nodular gastritis (14), gastritis (11), gastric ulcer (1), duodenal ulcer (5), and duodenitis (4). *H pylori* resolution was significantly higher in group 1 patients (24/27, 88.9%) than in group 2 patients (1/8, 12.5%). There was no difference between patients with nodular gastritis and those with nonnodular gastritis, and between Israeli-born patients and patients born in the former USSR. Compliance in both groups was equally good, and no major side effects were recorded.

Conclusions. One-week omeprazole/clarithromycin/tinidazole triple therapy is highly tolerable and effective for treating *H pylori* in the pediatric age group, but previous treatment failure diminishes the likelihood of suc-

cess with this regimen. *Pediatrics* 1998;102(1). URL: <http://www.pediatrics.org/cgi/content/full/102/1/e14>; *Helicobacter pylori*, triple therapy, children, adolescents, omeprazole, clarithromycin.

ABBREVIATIONS. OCT, omeprazole/clarithromycin/tinidazole; UBT, urea breath test.

Peptic ulcer is a relatively rare disease in childhood. Although its association with *Helicobacter pylori* is not as well documented as it is for adults,¹⁻⁵ successful resolution of *H pylori* infection has been found to reduce the recurrence rate of primary duodenal ulcers in children.⁶⁻⁸ Some authors have found a beneficial therapeutic effect of targeting *H pylori* in infected children presenting with recurrent abdominal pain.⁹ Triple therapy with bismuth combined with two antibiotics for 14 days was found to be an effective therapeutic regimen for *H pylori*.¹⁰ There are, however, several drawbacks, including failure of total eradication (often associated with metronidazole resistance) and poor compliance because of side effects, the need for frequent dosing, and the relatively long duration of treatment.¹¹ These factors may play an important role in the success rate of the treatment of infected children and adolescents.⁷ Recently, it has been demonstrated that the addition of highly effective antisecretory agents to certain antibiotics increases success rates. The combination of omeprazole with two antibiotics, usually a nitroimidazole and amoxicillin, has been widely confirmed as a consistently effective means of eradicating *H pylori* among adults, achieving eradication rates of ~90%.¹² A short-term, low-dose therapy combining omeprazole, nitroimidazole, and clarithromycin (the latter being a new and more acid-stable macrolide antibiotic that is concentrated in the gastric mucosa) was found to be highly effective with fewer side effects in the treatment of *H pylori* infection in adults.^{13,14} A similar regimen given to a small group of pediatric patients for 2 weeks was found to be highly tolerable and effective.¹⁵ There are no data, however, on the efficacy and tolerability of this regimen for short durations in the pediatric age group. The aim of this study was to evaluate the efficacy of a 1-week, low-dose therapy combining omeprazole, nitroimidazole, and clarithromycin in *H pylori*-infected children and adolescents.

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PATIENTS AND METHODS

The study included 35 young patients who were referred to our pediatric gastrointestinal unit for evaluation of upper gastrointestinal symptoms and were found to have endoscopically verified duodenal ulcer, gastric ulcer, or chronic nodular or nonnodular gastritis. During endoscopy, prepyloric antral specimens were taken for rapid urease testing, using a commercially available urease test kit (CUTest, Temler-Pharma, Marburg, Germany) and/or for histologic assessment using Giemsa staining. All patients were treated for 7 days with omeprazole (20 mg twice daily), clarithromycin (250 mg twice daily), and tinidazole or metronidazole (500 mg twice daily) (OCT). The patients were divided into two groups: those who received their first course of anti-*H pylori* therapy during this study (group 1) and those who had previously received standard metronidazole and bismuth combination therapies that failed to resolve the *H pylori* (group 2). To evaluate *H pylori* resolution, all patients underwent a ¹³C-urea breath test (UBT) 4 weeks after completing the treatment. After a baseline breath sample was collected, they drank 100 mL of juice containing 75 mg of ¹³C-urea (Medical Instruments Corporation, Solothurn, Switzerland) and then sat quietly without additional food or drink. A single-point breath sample was taken after 30 minutes. The isotope ratio of ¹³CO₂ to ¹²CO₂ in the expired air was measured using a mass spectrometer and an automated Breath ¹³C Analyser (Europa Scientific, Ltd, UK) and was expressed as delta over baseline of ¹³CO₂ (per mL). Any delta over baseline values of CO₂ > 5/mL were considered positive for *H pylori* infection.

Statistics

χ^2 analysis and Fisher's exact test were used to compare therapeutic success rates among the groups, and 95% exact binomial confidence intervals for these rates were calculated.

RESULTS

Thirty-five patients (19 males and 16 females; mean age, 15.9 years; range, 10 to 19 years) were studied. The clinical and demographic characteristics and the therapeutic outcomes are summarized in the Table 1. There were 27 patients (77.1%) who received their first course of anti-*H pylori* treatment in this study (group 1) and 8 patients (22.9%) who had previously received standard bismuth-based nitroimidazole-containing triple therapy that failed to resolve the infection (group 2). There was no difference in the mean age of the patients between these groups. Complete resolution was achieved in 24 (88.9%) of 27 patients in group 1, whereas only 1 (12.5%) of 8 patients in group 2 was free of *H pylori* ($P < .05$). There were no significant differences in the success rates between patients with nodular antral gastritis and those with nonnodular gastritis or duodenitis (10/11, 90.9% in both groups) or between Israeli-born patients and those born in the former Soviet Union (14/15, 93.3% and 10/12, 83.3%, respectively; $P =$ not significant). Patient compliance, which was assessed by using a direct questionnaire

at the end of the study, was excellent and identical in both groups. Few minor side effects were reported, including nausea (5 patients, 14.3%), abdominal pain or discomfort (4 patients, 11.4%), fatigue (3 patients, 8.6%), and headache (1 patient, 2.9%). No major adverse effects requiring discontinuation of the study were recorded in any of the study patients.

DISCUSSION

A treatment protocol aimed at resolving *H pylori* is now accepted as the standard approach for patients with *H pylori*-associated peptic ulcer disease.¹⁶ The finding that recurrence rates of duodenal ulcers are as high as 80% after 1 year for patients in whom *H pylori* is not totally eliminated, compared with rates of 0% to 27% in those treated successfully, has been confirmed in both adults and children.^{3,17}

H pylori infection presents a unique therapeutic challenge. The requirements for optimal therapy include high degrees of effectiveness and safety coupled with low costs and low incidences of side effects. Although *H pylori* is sensitive to a wide variety of antibiotics in vitro, these antibiotics are generally ineffective in vivo. The finding that therapy with a single antimicrobial agent was relatively ineffective has led to the study of various combinations of antibiotics with bismuth salts or antisecretory agents. Triple therapy with nitroimidazole plus a bismuth compound and tetracycline or amoxicillin was found to be highly effective, with resolution rates of 75% to 85%.¹⁰ However, it is associated with poor compliance because of high rates of side effects, the need for frequent dosing, and relatively long treatment duration. These limiting factors are more far-reaching in the treatment of children. The importance of compliance in the successful treatment of *H pylori* was demonstrated in both pediatric and adult patient groups.^{7,11} To find more tolerable and convenient regimens, proton pump inhibitors in combination with antibiotics have been tried in several forms. Dual therapy with omeprazole and amoxicillin for 14 days resulted in poor and unsatisfactory outcomes for patients of all ages.¹⁸ The low-dose, 1-week triple therapy with OCT, first described by Bazzoli et al,¹³ is believed to provide an answer for most of the problems noted above. This regimen was found to be highly effective in several studies in adults, with success rates of 90% to 95%. The simplicity of dosing, the reduced treatment duration, and the low incidence of side effects all promote patient compliance. Dohil and colleagues¹⁵ showed recently that a similar

TABLE 1. Eradication Rate of *Helicobacter pylori* in Both Patient Groups With OCT Triple Therapy

	Group 1 (%) [CI]	Group 2 (%) [CI]
Overall	24/27 (88.9)* [86.6–91.5]	1/8 (12.5)* [4.2–20.8]
Diagnosis		
Nodular gastritis	10/11 (90.9)** [82.3–99.5]	1/3 (33.3)** [5.8–60.5]
Gastritis + duodenitis	10/11 (90.9) ^a [82.3–99.5]	0/4 (0) ^a
Duodenal + gastric ulcers	4/5 (80) ^a [62–98]	0/1 (0) ^a
Place of birth		
Israel	14/15 (93.3) ^a [86.7–99.9]	1/7 (14.3)
USSR	10/12 (83.3) ^a [72.3–94.3]	0/1 (0)

* $P < .001$; ** $P < .05$.

^a Not significant.

combination, but using metronidazole instead of tinidazole, for 2 weeks in a pediatric patient group is highly tolerable and effective and led to a success rate of 93%. Their study group consisted of 11 patients, and the treatment was given for 2 weeks. The present study demonstrates that 1-week OCT triple therapy is highly effective in children and adolescents if it is given as the initial treatment for *H pylori*. We had reported earlier that the success rate was significantly lower with this regimen in adult patients in whom attempts to resolve *H pylori* previously with standard bismuth and metronidazole-containing triple therapy had failed.¹⁸ The explanation for this is not clear. Acquired metronidazole resistance does not seem to be responsible, because a similar observation was seen in a combination therapy that did not contain nitroimidazole.¹⁹ Other factors such as smoking habits and previous H₂ antagonist administration have been found to influence the outcome with OCT,²⁰ and morphologic and functional changes of *H pylori* induced by previous exposure to antibiotics have been reported and might be the reason for the failure of OCT as a second-line regimen.²¹

For the primary evaluation of dyspepsia, we performed endoscopy because much more information than just the presence of *H pylori* infection is obtained. However, to monitor *H pylori* eradication after antimicrobial therapy, we used, as others, the ¹³C-UBT. This noninvasive method has found great acceptance in clinical practice and has been shown to be as accurate in the diagnosis of *H pylori* infection as histologic staining in adults as well as in the pediatric population, with sensitivity and specificity rates of at least 95% and 92%, respectively.^{22,23}

The UBT value represents the urease activity and may reflect the bacterial density inside the stomach. We have demonstrated previously that high bacterial density is associated with lower eradication rates.²⁴ However, this has been found only with treatment with the standard bismuth-containing triple therapy, but not with the OCT triple therapy discussed here.¹⁸

A significant proportion of our patients were recent immigrants from the former USSR. This correlates with our clinical impression of high prevalence of peptic ulcer disease in this population group. The explanation might be the poor socioeconomic conditions in these countries, because such variables have been found to be associated with an increase in *H pylori* infection.²⁵ We did not find any difference in outcome in *H pylori* by OCT triple therapy between this group and the Israeli-born group.

Another specific patient group consisted of individuals presenting with nodular gastritis. Antral nodularity was reported to be unique to children with *H pylori* infection²⁶; however, it is not uncommon in young adults. Sbeih and coworkers²⁷ found a very low success rate (38%) in their study on treatment with standard triple therapy (bismuth subcitrate, tetracycline, and metronidazole for 2 weeks) in a young adult patient group with nodular gastritis. This also was our clinical impression in children with nodular gastritis treated with the same antibacterial regimen. In contrast, using the

OCT triple therapy described in the present study, a high rate (91%) of *H pylori* eradication was achieved in this specific group.

CONCLUSION

We found that 1-week OCT triple therapy regimen is highly effective for resolving *H pylori* in children and adolescents. As with adult patients, the efficacy was significantly lower when the medications were given as a second-line treatment after failure of standard triple therapy. This regimen achieved high success rates in children born in a developed country (the former USSR) and in children with nodular as well as nonnodular gastritis. Because of its high efficacy, safety, and tolerability, we recommend that this regimen be given as the first-line treatment for *H pylori* eradication in children.

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