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Clarithromycin Resistance and Eradication of *Helicobacter pylori* in Children

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Outcome of *Helicobacter pylori* infection was analyzed in 61 children treated with a triple therapy including clarithromycin. Bacterial eradication was obtained in all children with clarithromycin-susceptible strains but not in children with clarithromycin-resistant ones ($P = 0.0001$). *H. pylori* antimicrobial susceptibility is mandatory before choosing a treatment, and clarithromycin should be avoided in case of resistance.

The role of *Helicobacter pylori* in the colonization of the stomach in adults and children with chronic gastritis, peptic ulcer, and possibly gastric carcinoma is now documented (11). Eradication of the bacteria is efficient for prevention of peptic ulcer relapses both in adults (1) and in children (4).

A recent consensus statement on *H. pylori* infection in children (4) indicates that upper gastrointestinal endoscopy with biopsies is the preferred method of investigation for children with upper digestive symptoms suggestive of organic disease. This statement did not deal with the optimal treatment for *H. pylori* infection in childhood. In adults, the recommended treatment combines an antacid with two antibacterial agents (one antibiotic plus a bismuth salt or two antibiotics). In France, where the bismuth salts are not authorized, treatment consists in the association of a proton pump inhibitor (PPI) together with amoxicillin and clarithromycin or metronidazole. Metronidazole resistance being high in children, 43% in France (9), the first choice is clarithromycin (7). The consensus statement (4) proposes a follow-up strategy for those who remain infected after a first-cure treatment, i.e., a second endoscopy with culture and antimicrobial susceptibility testing and the corresponding treatment adaptation. In contrast, no proposal is made recommending primary culture and antimicrobial susceptibility before first-line treatment.

The purpose of our study was to assess the effect of clarithromycin resistance on bacterial eradication of *H. pylori* in children and to evaluate the usefulness of testing *H. pylori* antimicrobial susceptibility in first gastric biopsy culture before choosing the appropriate treatment in children.

A prospective study was carried out from January 1997 to July 1999 in 61 *H. pylori*-positive children (37 girls and 24 boys) aged 11.9 ± 3.9 years (range, 3.75 to 18 years). Infection was proved by upper gastrointestinal endoscopy with gastric antral biopsies in the course of diagnostic evaluation of clinical gastritis, manifested by recurrent abdominal pain for at least 3 months, nausea, and vomiting. None of these children suffered from ulcer. Informed consent was obtained from parents. Children who had already suffered *H. pylori* gastric infection, institutionalized encephalopathic children, and those who had received antibiotics, acid-suppressing medications, or nonsteroidal anti-inflammatory drugs during the 3 months preceding evaluation were excluded from analysis.

Children received during 1 week a PPI, omeprazole (1 mg/kg/day) ($n = 38$), or lansoprazole (1 mg/kg/day) ($n = 23$), together with amoxicillin (50 mg/kg twice a day [bid]) and clarithromycin (7.5 mg/kg bid).

Three antral biopsy specimens were taken and analyzed for histology and culture as previously described (12). MICs of amoxicillin and clarithromycin were obtained with E tests on Mueller Hinton agar (Oxoid, Dardilly, France) supplemented with 10% horse blood. Suspensions adjusted to a turbidity approximating that of a McFarland no. 3 were used. Plates were incubated for 3 days at 37°C under microaerophilic conditions (10% CO_2). Strains were considered amoxicillin- and clarithromycin-resistant with MICs above 0.5 and 1 mg/liter, respectively (10). Both positive biopsy culture and histologic examination showing a chronic active gastritis were required for enrollment in the study. Six weeks after the end of treatment, bacterial eradication was defined by a negative [^{13}C]urea breath test. For patients with a positive breath test, additional perendoscopic biopsies were obtained and cultured in order to adapt a second-line antimicrobial treatment.

Differences between groups concerning bacterial eradication rate, using the Stat-View system, were assessed with the chi-square test of homogeneity for categorical variables (χ^2 test), with P values of <0.05 considered significant.

Clarithromycin-resistant *H. pylori* strains before treatment were detected in 11 of 61 children (18%), all strains being sensitive to amoxicillin. Clarithromycin MICs ranged from 0.01 to 256 mg/liter, with a MIC for 50% of strains (MIC_{50}) of 0.01 mg/liter and a MIC_{90} of 246 mg/liter. Among strains resistant to clarithromycin, 8 had a MIC of ≥256 mg/liter (MIC range, 8 to 256 mg/liter, MIC_{50} and MIC_{90} were 256 mg/liter). Amoxicillin MICs ranged from 0.01 to 0.09 mg/liter, with a MIC_{50} of 0.016 mg/liter and a MIC_{90} of 0.02 mg/liter. The mean age of children with a clarithromycin-susceptible strain was 139.8 ±

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43.2 months, versus 125.6 ± 52.2 months for the clarithromycin-resistant strains (not significant [NS]).

H. pylori eradication was obtained in 50 children (83.3%), more precisely, in all children infected with clarithromycin-sensitive strains versus none of those with clarithromycin-resistant ones ($P = 0.0001$).

Our study highlights the usefulness of *H. pylori* antimicrobial susceptibility testing in first gastric biopsy culture and the lack of efficacy of clarithromycin in case of resistance to this drug. Few data are available concerning the efficacy of *H. pylori* treatment in childhood. We have recently shown that a 1-week triple therapy allows a good eradication rate, 94.7% (Kalach et al., letter, Clin. Microbiol. Infect. **5:**235–236), even though a longer duration of treatment might prove preferable (Oderda et al., abstr., Gut **45:**[Suppl. 111]**:**A94, 1999). In children, several factors may interfere, among them the primary resistance rate of *H. pylori* strains against clarithromycin (Jesch et al., abstr., Gut **45**[Suppl. 111]**:**A93, 1999) or metronidazole (12), the potential resistance acquired to these antibiotics during treatment (Dezsöfi et al., abstr., Gut **45**[Suppl. 111]**:**A94, 1999), the compliance level to treatment (Gottrand et al., abstr., Gastroenterol. Clin. Biol. **24:**A43, 2000), and the intrafamilial dissemination of the infection (Kalach et al., abstr., J. Pediatr. Gastroenterol. Nutr. **28:**356, 1999).

Identification of the pathogenic role of *H. pylori* was soon followed by the demonstration of developing antibiotic resistance, first reported in 1996 for macrolides (14) and now for amoxicillin (2).

In adults, resistance before treatment of *H. pylori* to clarithromycin is amounting to 0 to 10% in European and American countries averaging 1% in the Netherlands, 3.5% in Spain, 5% in Ireland, 6% in the United States, and 10% in France (Glupczynski et al., Gut **45**[Suppl. 111]**:**A105, 1999). In contrast to our data, another study (Jesch et al., abstr.) indicates more clarithromycin-resistant strains in children <10 years old (16 to 19%) than in the older age group (9%). The high level of clarithromycin-resistant *H. pylori* strains in children compared to adults suggests the importance of macrolide use in this age group, especially in Europe. The impact of clarithromycin resistance on treatment success for regimens containing this drug has been reported in adults: *H. pylori* eradication rates ranged from 83 to 98% in patients infected with clarithromycin-susceptible strains, whereas clarithromycin resistance reduced effectiveness by an average of 55% (3), reaching 0% (5). For Toracchio (13), clarithromycin resistance is 100% predictive of treatment failure. The differences between these rates of eradication can be explained by the different breakpoints used and by different mutations involved in the mechanism of resistance: this leads to different levels of resistance and may explain heterogeneity found in the literature between clarithromycin resistance and infection outcome (5). In our study, the high level of resistance can probably explain the high failure rate in cases of resistance. High levels of resistance cannot be dealt with by increasing the dose or duration of therapy, as previously reported by Graham et al. (6).

Treatment failures should prompt endoscopy, culture, and susceptibility testing. Retreatment should exclude antibiotics with acquired resistance. A switch to metronidazole can be recommended in a case of susceptibility. Many studies have highlighted the difficulties of retreatment, and it can be stated that the best available first-line treatment regimen is still the best "rescue treatment" (8).

We conclude that *H. pylori* antimicrobial susceptibility testing of first gastric biopsy culture is useful before choosing the first tritherapy in infected children and that clarithromycin should not be used in case of primary resistance. We also suggest, if our results are validated by other large-scale studies, that children infected with clarithromycin-sensitive *H. pylori* strains may not require [^{13}C]urea breath test control following treatment.

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