

LETTER TO THE EDITOR

Low Antibiotic Resistance of *Helicobacter pylori* in The Netherlands

To the Editor,

Consensus guidelines on treatment of *Helicobacter pylori* (*H. pylori*) in adults as well as in children recommend in areas with prevalence of clarithromycin resistance <15–20%, 7–10 days triple therapy with amoxicillin, clarithromycin or metronidazole and a proton-pump inhibitor (PPI), and alternative eradication regimens if the resistance rate is higher [1,2]. With this regimen, eradication rates vary from 60 to 90%. However, the success rate of standard triple therapy for *H. pylori* eradication is decreasing worldwide due to increasing antimicrobial resistance of *H. pylori* to clarithromycin and/or metronidazole, probably because of the increasing use of clarithromycin for respiratory infections (especially in children) and the use of metronidazole for parasitic infections. Alternative regimens containing tetracyclines or bismuth are not allowed in children in many countries. Currently, sequential therapy is a topic of research in adults as well as in children to improve the eradication rate.

Dutch guidelines recommend test-and-treat, which is safe and as effective as direct endoscopy, in the absence of alarm symptoms in persons <45 years of age [3]. However, data on resistance of *H. pylori* isolated from adults are only available until 2003, [4] and resistance in children has never been investigated.

In order to estimate whether the test-and-treat approach is justified in the Netherlands, we analyzed the prevalence of resistance to clarithromycin and metronidazole in *H. pylori* -positive cultures from biopsies from the gastric antrum and/or corpus of adults and children (<18 years of age) from January 2000 to December 2009. For most adult patients, it was unknown whether or not they had undergone noninvasive testing before and whether or not they had been treated before. None of the children had been treated for *H. pylori* before the first endoscopy. Cultures of biopsies for *H. pylori* were carried out, and *H. pylori* positivity was determined with a Gram stain and a positive oxidase, catalase, and urease test. Strains were considered clarithromycin sensitive if MIC ≤ 0.25, metronidazole sensitive if MIC ≤ 8 mg/L, intermediate if MIC > 8 and MIC ≤ 16 mg/L, and resistant if MIC > 16 mg/L, according to the Eucast-criteria (www.eucast.org).

Demographic data and results of resistance to antibiotics are summarized in Table 1. From 1152 patients, 1214 cultures were positive for *H. pylori*. Susceptibility of clarithromycin and metronidazole could be determined in 1088 (90%) and 1095 (90%) cultures, respectively. All clarithromycin-resistant strains in children were detected in the period after 2004, while metronidazole-resistant strains were divided equally over the whole period. During the study period, the resistance to clarithromycin increased from <5 to 8.5–9.4% in adults and resistance to metronidazole increased from 7–33 to 20.7–22.9%.

In second occasion biopsies, *H. pylori* from 4 of 41 cultures from adults became resistant to clarithromycin and 4 to metronidazole. In third occasion biopsies, 1 and 2 strains from adults became resistant to clarithromycin and metronidazole, respectively.

Table 1 Demographic data and results

Parameters	Adults (N = 1080)	Children (N = 72)
Males (N)	510	42
Mean age, year (range)	55.8 (18.7–90.3)	11.5 (2.9–17.8)
Number of <i>Helicobacter pylori</i> isolates (N)	1137	77
Resistance to Cla (%) ^a		
R	8.5	6.5
S	81.2	83.1
NT ^b	10.4	10.4
Resistance to Cla, % of tested strains	9.4	7.2
Resistance to MNZ (%) ^a		
R	20.7	10.4
I	0.4	3.9
S	69.2	74.0
NT ^b	9.7	11.7
Resistance to MNZ, % of tested strains	22.9	11.7
Double resistance to Cla and MNZ (%)	2.8	0

R, resistant; S, sensitive; I, intermediate; NT, not tested due to viability problems of the strains; Cla, Clarithromycin; MNZ, Metronidazole.

^aPercentage of isolates.

The resistance rate to clarithromycin is low compared with other European countries, where the prevalence in adults has been reported from 17–26% up to 68% in case of secondary resistance. The most likely explanation is the restrictive policy for antibiotic prescriptions by Dutch physicians [5]. The prescription of clarithromycin has stabilized since 2003 (www.swab/nethmap.nl) in contrast to the prescription pattern in other European countries. In adults, *H. pylori* resistance to metronidazole has increased, [4] but it is still lower than reported from other European countries (27–61%). Double resistance to clarithromycin and metronidazole occurred in 2.8% of the strains and remained stable over time.

This study is the first to report data on the antimicrobial resistance of *H. pylori* in children living in the Netherlands and shows much lower resistance rates of *H. pylori* strains than those reported in other parts of Europe (24 and 25% to clarithromycin and metronidazole, respectively [6]). In the European study, 41% of the children with resistant strains were offspring of non-European mothers, in contrast to 11% of the children with resistant strains from non-Dutch mothers.

The low resistance rates to clarithromycin and metronidazole are remarkable, in view of the implementation of the stool antigen test in 2000 and subsequent gradual introduction of the test-and-treat regimen, without previous determination of *H. pylori* susceptibility. With such approach, one would have expected higher secondary resistance rates, as the endoscopic samples were probably more often from patients who failed first line therapy.

In summary, the low antibiotic resistance rate of *H. pylori* strains in Dutch adults and in children supports the recommendation to routinely perform a test-and-treat regimen in the Netherlands. Also in the coming years, surveillance of regional *H. pylori* resistance is needed to timely modify treatment regimens. It is hoped that future development of noninvasive susceptibility tests for clarithromycin in stool samples will facilitate this procedure.

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