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Adapted first-line treatment of *Helicobacter pylori* infection in Algerian children

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Abstract

Background *Helicobacter pylori* (*H. pylori*) infection is acquired in early life and continues to have a high prevalence, especially in developing countries. Growing antibiotic-resistant strains necessitate adapted treatments. This study aimed to compare the efficacy, side effects, and influence of resistance of *H. pylori* strains between two different treatments.

Methods This prospective, randomized blind study enrolled 112 symptomatic children infected with *H. pylori* (66 girls, mean age 11.1 years). Treatments, allocated randomly irrespective of the susceptibility of the strains, were either the standard omeprazole–amoxicillin–clarithromycin combination for 7 days (OAC7; group A) or omeprazole–amoxicillin with a higher dose of metronidazole (40 instead of 20 mg/kg/d) for 10 days (OAM10; group B).

Results Before treatment, the resistance rates of *H. pylori* strains to metronidazole or clarithromycin were 37% and 13%, respectively, with 7% resistant to both antibiotics and neither to amoxicillin. Eradication rates obtained with OAM10 (80% by intention-to-treat [ITT] and 88% by per protocol [PP] analysis) were higher than with OAC7 (68% in ITT and 71% PP) and the differences (12% in ITT and 17% PP) were statistically significant (P=0.03). Successful treatments with OAM10 were obtained in metronidazole resistant strains and were more effective in children aged >10 years (P=0.02 by ITT and P=0.04 by PP). Only light or moderate side effects, mainly digestive, were observed.

Conclusion Because of its therapeutic efficacy, good tolerance and lower cost the OAM10 can be considered as an appropriate first-line therapeutic scheme in Algeria.

Keywords *Helicobacter pylori*, children, first-line eradication treatment, antibiotic resistance

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Introduction

Helicobacter pylori (*H. pylori*) infection plays an important epidemiological role as one of the most prevalent chronic infections, with more than 50% of the world's population being infected. A prevalence of over 80% has been found in developing countries [1], whereas in industrial nations, a much lower and declining prevalence is usually reported [2]. These differences are thought to be due to several environmental factors, such as different infectious mechanisms, better hygienic and social conditions and, as an additional factor, the excessive use of antibiotics in the treatment of several bacterial infections [3-7], with the worrying negative consequence of an increased resistance of *H. pylori* strains [8,9]. The infection occurs mainly during childhood [10,11] and persists throughout life [12,13].

H. pylori infection is an important cause of ulcerations of the stomach and duodenum, not only in adults [14] but also in

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children [15]. It can also cause, mainly in adulthood, atrophy of the gastric mucosa and intestinal metaplasia responsible for gastric malignancies and mucosa-associated lymphoid tissue (MALT) lymphoma [16].

In Algeria an infection rate of 82% was found in 2006 in 275 symptomatic children with a mean age of 8.4 years [17], whereas in 2008 a study by Guechi and the Algerian *Helicobacter* Research Laboratory confirmed the early acquisition of *H. pylori* infection in Algerian schoolchildren with a seroprevalence of 38%, increasing with age to 57% [18]. The ESPGHAN-NASPGHAN evidence-based guidelines [19] and their 2016 update [20] insist that local conditions must be taken into account in order to achieve successful results from eradication treatments.

The primary goal of the present study, performed before the publication of the ESPGHAN-NASPGHAN guidelines, was to evaluate, in *H. pylori*-infected symptomatic children, the efficacy and tolerance of two first-line eradication treatments and to investigate factors influencing the efficacy of the treatments, mainly the resistance of *H. pylori* strains. Because some specific conditions are still lacking in our country, a secondary goal was to assess the efficacy, sensitivity and specificity of noninvasive diagnostic tools compared to invasive methods.

Patients and methods

In order to test the efficacy of different treatment regimens, a prospective randomized study was carried out from May 2006 to March 2010. The study population included 160 consecutive symptomatic children aged 5-16 years who underwent an upper gastrointestinal (GI) endoscopy for several indications, including chronic abdominal pain, chronic dyspepsia (vomiting, nausea, excessive belching, halitosis), history of upper GI bleeding, unexplained iron deficiency and growth retardation. Exclusion criteria were diabetes, severe chronic kidney, heart or liver disease, treatment with nonsteroidal anti-inflammatory drugs, previous treatment for *H. pylori* infection, and known GI diseases such as gastroesophageal reflux, active GI bleeding, celiac disease and inflammatory bowel diseases. *H. pylori* infection was based on several diagnostic tests, using gastric biopsies processed with a rapid urease test (RUT), the Pronto-Dry® (Medical Instruments Corporation, Lyon, France), and histology and culture with antimicrobial susceptibility testing for the determination of the sensitivity of *H. pylori* strains. Noninvasive diagnostic tests, including the rapid *H. pylori* monoclonal stool antigen test (HpStAR) (DakoCytomation Ltd., Liverpool, United Kingdom) and the non-radioactive ^{13}C urea breath test (^{13}C UBT), were also used. The diagnosis of *H. pylori* infection was based on the positivity of the culture and/or histology confirmed by the ^{13}C UBT. Only the patients who fulfilled these criteria were included.

The treatment protocol was explained to the parents and the children and their informed consent was obtained before enrolment. Randomization of treatment was done using the sorting method of closed envelopes where the treatment was attributed randomly in clusters of 4. Infection by *H. pylori* strains was found in 112/160 (70%) children, 66 girls and 45 boys aged 5.2 to 15.9 years (mean age 11.1 years). After randomization, patients were allocated to one of the two treatment schemes. Children in group A received for 7 days the classical treatment of the combination of omeprazole'amoxicill in'clarithromycin (OAC7), adjusted for the child's bodyweight: in children heavier than 30 kg (usually 10 years old) it consisted of omeprazole 2×20 mg/d, amoxicillin 50 mg/kg/d b.i.d. with a maximum of 2 g/d and clarithromycin 15 mg/kg/d b.i.d. The dose of omeprazole was reduced to 2×10 mg/d in children below 30 kg bodyweight. Children in group B received for 10 days the alternative treatment (OAM10) of omeprazole 2×20 mg/d with amoxicillin 50 mg/kg/d b.i.d. with a maximum of 2g/d and metronidazole 40 mg/kg/d b.i.d. with a maximum of 1.5 g/d in children above 30 kg and 1g/d in children below 30 kg bodyweight. The dose of omeprazole was reduced to 2×10 mg/d in the same way as in the OAC7. Side effects could be reported at any time to the prescribing physician and withdrawal from the study was granted. Patients were seen at the end of the treatment period to collect data on side effects and evaluate their compliance by recounting the tablets. The *H. pylori* status was assessed 8-12 weeks after the termination of the treatment by a second upper GI endoscopy with biopsies processed for RUT, histology and culture, a ^{13}C UBT and an HpStAR. Eradication of the *H. pylori* infection was attested by the negativity of all or 4/5 diagnostic tests, exempting the culture because of its high specificity. In case of treatment failure, attested by the positivity of all tests or at least positivity of the culture or histology + RUT, a rescue treatment was proposed.

Statistical analysis

The statistical analysis was performed using STATISTICA for Windows (Epi. Info, Atlanta USA) version 6.04. To test the statistically significant differences of two nominally distributed factors the χ^2 test (chi-square test) or Fisher test was used, whereas the Student's *t*-test was used for comparing mean values. The differences were considered significant for values of $P \leq 0.05$. Results expressed as "per protocol" (PP) are based on data obtained in patients who fulfilled all the items of the protocol, whereas results expressed as "intention to treat" (ITT) are based on data obtained from all the enrolled patients even if they did not complete all the items. The eradication rate was calculated with a confidence interval (CI) of 95%.

Results

Seven of the 112 recruited subjects were lost to follow up (5 in the OAM10 group and 2 in the OAC7 group) so that eventually data from 105 children were analyzed. The most common endoscopic finding (Table 1) in *H. pylori*-infected children was antral nodularity (76, 68%), whereas duodenal ulcer or erosions were observed in 5 children (4.5%).

Treatment compliance was evaluated according to the quantity of medication taken and considered as "good" in 98/105 (93%) patients, who took 100% of the medication, and as "average"

in the 2/105 patients who took only 75%. None of them was considered as "poor" (taking less than 75% of the medication).

Successful eradication of the infection was attained in 83 children, with an overall eradication rate of 74% by ITT and 79% by PP. Higher eradication rates were obtained with OAM10 than with OAC7, since treatment was successful in 44/55 (80%) by ITT and 44/50 (88%) by PP in the OAM10 group, and in 39/57 (68%) by ITT and 39/55 (71%) by PP in the OAC7 group. These differences were statistically significant for the PP (P<0.03) but not for the ITT values (Table 2).

There were important differences according to the resistance or sensitivity of the *H. pylori* strains: respectively 51% and 65% by ITT and PP for antibiotic-resistant *H. pylori* strains compared to 75% and 91% by ITT and PP for antibiotic-sensitive strains (P<0.03 and P<0.01, respectively) (Table 3).

The eradication rates in relation to clarithromycin or metronidazole resistance were analyzed in 31 *H. pylori* strains in the OAM10 group and in 28 strains in the OAC7 group. In the OAM10 group the eradication rate was similar whether the *H. pylori* strains were metronidazole-resistant or not (90% vs. 91%, P=0.67) whereas a difference, although non-significant, was observed for clarithromycin sensitivity or resistance (93% vs. 67%, P=0.27) (Table 4). In the OAC7 group, eradication rates were lower for metronidazole-resistant *H. pylori* strains than for sensitive *H. pylori* strains, although the difference was not statistically significant (50% vs. 78%, P=0.30). In contrast, eradication rates differed dramatically between clarithromycin-resistant and clarithromycin-sensitive *H. pylori* strains (83% vs. 0%, P<0.01) (Table 5).

Other factors studied concerned age and sex. A higher eradication rate was observed in children older than 10 years by both ITT (81% vs. 62%, P<0.02) and PP (85% vs. 68%, P<0.04) analysis. Better results, but without statistical significance, were observed in boys than in girls by ITT (80% vs. 70%, P=0.20) and PP (86% vs. 74%, P=0.14), although the antibiotic resistance of *H. pylori* strains did not differ significantly between boys and girls (P=0.85). The compliance was overall good, being average in only 5/105 patients, but this did not statistically influence the results (75% vs. 33% by ITT, P=0.16, and 80% vs. 50% by PP, P=0.37).

Because noninvasive diagnostic tests are not available in many developing regions of the world, the secondary goal of this study was to compare the different noninvasive diagnostic tests with the invasive RUT, histology and culture performed in all patients (Table 6).

Side effects were evaluated in all 112 children recruited, including the 105 who completed the program and the 7 who did not undergo the second upper GI endoscopy. Mild to moderate, mainly GI symptoms were reported in 44 patients, (80.4% by ITT and 79.5% by PP). In the OAM10 group, side effects were reported in 13 children (24%) and consisted of abdominal cramps or diarrhea in 12 patients and skin rash in one. In the OAC7 group, side effects were reported in 33 children (58%), including digestive symptoms in 25 children (75%) and a bitter or metallic taste, probably due to clarithromycin, in 8 (25%).

The cost of the treatment courses, calculated according to the number and cost of the tablets ingested, amounted to €42 for OAC7 and €39 for OAM10 but could probably be reduced by using generic drugs.

Table 1 Endoscopic findings

Endoscopic aspect	N	%
Normal	09	8
Nodularity	76	68
Enlarged gastric folds	01	0.9
Erosive duodenitis	03	2.7
Duodenal ulcer	02	1.8

Table 2 Eradication rates according to different therapeutic schemes

Scheme	PP			ITT		
	n	%	P	n	%	P
OAC 7	39/55	71		39/57	68	
OAM 10	44/50	88	0.031*	44/55	80	0.161 NS
Total	83/105	79		83/112	74	

*According to χ^2 test; P was considered significant when <0.05

NS, not significant; OAC, omeprazole–amoxicillin–clarithromycin; OAM, omeprazole–amoxicillin–metronidazole; PP, per protocol; ITT, intention to treat

Discussion

There are few randomized controlled trials of *H. pylori* eradication in children and none in Algeria. During the nineties, eradication rates of 90% were reported, but the

Table 3 Eradication rate with different therapeutic regimens depending on *Helicobacter pylori* antimicrobial susceptibility testing (n=28)

Susceptibility	Eradication with OAM10 n (%)	Eradication with OAC7 n (%)	Total	P
Metronidazole-susceptible strains	17 (89.5)	14 (77.8)	31	0.034*
Metronidazole-resistant strains	11 (91.5)	5 (50)	16	
Clarithromycin-susceptible strains	26 (93)	19 (83)	45	0.001*
Clarithromycin-resistant strains	2 (66.5)	0 (0)	2	

*According to Fischer's exact test; P was considered significant when <0.05

OAC, omeprazole–amoxicillin–clarithromycin; OAM, omeprazole–amoxicillin–metronidazole

Table 4 Eradication rate with OAM10 and *Helicobacter pylori* strains according to susceptibility testing (n=31)

OAM10	Metronidazole-susceptible strains n (%)	Metronidazole-resistant strains n (%)	Total	P*
Eradication	17 (89.5)	11 (91.5)	28	0.672 NS
Failed	2 (10.5)	1 (8.5)	3	
Total	19 (100)	12 (100)	31	
OAM10	Clarithromycin-susceptible strains n (%)	Clarithromycin-resistant strains n (%)	Total	
Eradication	26 (93)	2 (66.5)	28	0.271 NS
Failed	2 (7)	1 (33.5)	3	
Total	28 (100)	3 (100)	31	

*According to Fischer's exact test; P was considered significant when <0.05

NS, not significant; OAM, omeprazole–amoxicillin–metronidazole

Table 5 Eradication rate with OAC7 and *Helicobacter pylori* strains according to susceptibility testing (n=28)

OAC7	Metronidazole susceptible-strains n (%)	Metronidazole resistant-strains n (%)	Total	P*
Eradication	14 (77.8)	5 (50)	19	0.3 NS
Failed	4 (22.2)	5 (50)	9	
Total	18 (100)	10 (100)	28	
OAC7	Clarithromycin susceptible-strains n (%)	Clarithromycin resistant-strains n (%)	Total	
Eradication	19 (83)	0 (0)	19	0.001
Failed	4 (17)	5 (100)	9	
Total	23 (100)	5 (100)	28	

*According to Fischer's exact test; P was considered significant when <0.05

NS, not significant; OAC, omeprazole–amoxicillin–clarithromycin

Table 6 Comparative assessment of the different diagnostic tools

Tests	n	Efficacy %	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
UBT	112	97	97.3	95.6	98.2 (93.0-99.7)	93.5 (81.1-98.3)
RUT	112	97	95.5	100	100 (95.7-100)	90.6 (78.6-96.5)
Histology	109	96	99.1	89.4	95.6 (89.6-98.4)	97.7 (86.2-99.9)
Stool Ag	110	96	93.6	100	100 (95.5-100)	87.3 (74.9-94.3)
Serology	103	82	85.4	74.4	88.9 (80.6-94.1)	68.1 (52.7-80.5)
Culture	110	77	67.3	100	100 (93.9-100)	57.1 (45.9-67.7)

UBT, urea breath test; RUT, rapid urease test

efficacy of these first-line treatments, which combine a proton pump inhibitor with two antibiotics, has notably decreased to 70-74% [21], mainly as a result of primary antibiotic resistance of *H. pylori* strains [22,23] or the lack of therapeutic adherence [24,25]. The most widely used therapeutic scheme in the western world, based on the combination of the proton pump inhibitor omeprazole with 2 antibiotics, amoxicillin and clarithromycin, for 7 days, reaches only a rather disappointing eradication rate of 71% by PP and 68% by ITT analysis [26].

In a previous study [27], based on a combination of omeprazole with amoxicillin and a higher dose than usual of metronidazole, we obtained eradication rates of 78% with the 7-day course and 86% with the 10-day course, considerably higher than those achieved with the classical normal dose of metronidazole. However, the series of patients was too small to allow the 8% difference between the longer and the shorter courses to reach statistical significance.

In the present study, better results were obtained with our double dose of metronidazole during a longer course of 10 days, compared to the classical OAC7 (P<0.03 by PP). Higher eradication rates were obtained using the double dose of metronidazole in OAM for 10 days in the present study, in comparison with other schemes using OAM 7 days [24,28,29], the regular 20 mg/kg dose of OAM over 14 days [30], and our previous OAM 7-day study with a high dose of metronidazole (Table 7). Two factors, a higher metronidazole dose (40 mg/kg instead of 20 mg/kg), but also prolongation of the treatment from 7 days to 10 days, seem to have favorably influenced

Table 7 Eradication rates with different doses and durations of OAM treatments

Author	Year	OAM/days	Eradication rates
Faber [27] N=57			
Israel	2005	7	73.4
Oderda [23] N=388			
Italy	2007	7	66
Nguyen [28] N=117			
Vietnam	2008	7	62.1
Moubri [26] N=23			
Algeria	2008	7*	78
Chen [29] N=35			
China	2004	14	77
Present study N=50			
Algeria	2010	10*	88 PP N= 50 80 ITT N= 55

*High-dose metronidazole (40mg/kg/d)

OAM, omeprazole–amoxicillin–metronidazole; PP, per protocol; ITT, intention to treat

the outcome to reach almost the acceptable recommended eradication rate of 90% [19]. The most recent recommendations specify that the shorter 7-day treatment scheme should be abandoned in favor of the longer 14-day regimen [20]. However, apart from its higher cost, it may be difficult, in many day-to-day clinical contexts, to obtain good adherence to a 2-week-long duration of treatment.

Drug dosage, treatment duration and patients' adherence to therapy are factors that influence the outcome of treatment, but even more important is the growing resistance of *H. pylori* strains [22-23], especially to clarithromycin and nitroimidazoles, depending on the regional consumption of these drugs [9]. Over 50% resistance to metronidazole has been reported in developing countries [31]. Although resistance to metronidazole is rather stable, an increasing number of *H. pylori* strains are resistant to both macrolides and nitroimidazoles.

This double resistance still remains low in children, but raises major concern and accounts for the treatment failures of most therapeutic schemes [32]. Resistance to other antibiotics such as quinolones is also increasing [33], whereas resistance to amoxicillin is exceptionally rare and was not seen in our study. In regions where the resistance to clarithromycin is higher than 15-20%, the Maastricht V consensus [34] and recent pediatric guidelines recommend using this antibiotic for the treatment of *H. pylori* infections only after testing the resistance of the *H. pylori* strains [19,20]. Adaptation of the treatment according to the resistance of *H. pylori* strains allows treatment failures to be reduced. Treatment strategies need to be tailored according to the national, regional or even local antibiotic resistance of *H. pylori* strains. The data available in Algeria [27] show a high prevalence of metronidazole-resistant *H. pylori* strains in the general population, although, as reported elsewhere, it has been decreasing in the pediatric population [35]. In contrast, our personal data show a steady increase in clarithromycin resistance from 5% in 2002 to 13% in 2010, probably due to an increasing use of this antibiotic for other infections [33]. In our study, the results achieved with the OAM10 scheme with a high dose of metronidazole were superior to results reported in the literature [24,26].

The sensitivity of *H. pylori* strains strongly influences the efficacy of the antibiotic treatments in the developed [24] as well as in the developing [36] world. Because of the high prevalence of resistant *H. pylori* strains in children, first-line treatment should be started only after a strain's resistance to antibiotics has been tested using the classical antimicrobial susceptibility testing method or molecular polymerase chain reaction, when these techniques are available [19]. Since such techniques are either unavailable or too expensive in Algeria, and considering our results, the OAM10 scheme can be considered as an interesting first line treatment in children.

Compared to rates reported in the literature with OAM7 and OAM14, the eradication rates obtained with the high-dose metronidazole OAM 10-day triple therapy in the present study were 21% and 16% higher, respectively [24], while compared to OAC7 in the present study, gains of 17% by PP and 12% by ITT were observed. These better results are probably attributable to a moderate, acceptable extension of the treatment duration, but mainly to the higher dosage of metronidazole.

In the HOMER study in adults, Bardhan *et al* showed that a higher dose of metronidazole resulted in better global eradication rates, including in metronidazole-resistant strains of *H. pylori* [37]. A similar effect was observed in the present study, where the higher dose was associated with a rise in eradication rate from 71% to 88% (P=0.03), not so far from the recommended 90%. Poor therapeutic adherence is an important factor in treatment failure [25]. Parents and children should be instructed about the importance of respecting the timing and dose of medication and alerted about possible side effects that, wrongly interpreted, could induce poor compliance or even premature cessation of the treatment.

In the present study, performed before the publication of the first ESPGHAN-NASPGHAN consensus guidelines, better treatment efficacy was observed in children older than 10 years. Familial density and promiscuity in younger children, with more frequent reinfections, may account for the significant differences (0.04 by PP, 0.02 by ITT). Side effects were reported significantly (P=0.0004) more frequently in the OAC7 group (58%) than in the OAM 10 group (24%), although no treatment had to be stopped. The OAM10 triple therapy appeared to be better tolerated, despite the high dose of metronidazole and the longer duration of the treatment.

In conclusion, in Algeria, the triple therapy combining omeprazole, amoxicillin and a double dose of metronidazole for 10 days can be recommended as first-line treatment in *H. pylori*-infected children, since it shows better efficacy than the standard 7-day treatment with the association of OAC, its better tolerance and relatively cheaper cost. Because bismuth salts are still and wrongly unavailable in our country, re-treatment of eradication failures requires either a 14-day scheme, according to carefully tailored antimicrobial susceptibility testing, or sequential therapy.

Summary Box

What is already known:

- *Helicobacter pylori* (*H. pylori*) infection is acquired in early life and has a high prevalence in developing regions
- There is growing antibiotic resistance to *H. pylori* strains
- Eradication treatments can yield unsatisfactory results

What the new findings are:

- There is a high prevalence of resistance to clarithromycin and metronidazole in Algeria
- The poor results with the classical first-line treatment were confirmed
- Good results were obtained using a high dose of metronidazole, including in resistant *H. pylori* strains, with relatively few side effects

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