

RAPID COMMUNICATION

## Furazolidone-based triple therapy for *H pylori* gastritis in children

Elisabete Kawakami, Rodrigo Strehl Machado, Silvio Kazuo Ogata, Marini Langner, Erika Fukushima, Anna Paula Carelli, Vania Cláudia Guimarães Bonucci, Francly Reis Silva Patrício

Elisabete Kawakami, Rodrigo Strehl Machado, Silvio Kazuo Ogata, Marini Langner, Erika Fukushima, Anna Paula Carelli, Vania Cláudia Guimarães Bonucci, Peptic Diseases Outpatient Clinic, Pediatric Gastroenterology Division, Department of Pediatric, Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, SP, Brazil

Francly Reis Silva Patrício, Department of Pathology, Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, SP, Brazil

Correspondence to: Rodrigo Strehl Machado, 441 Pedro de Toledo Street, Sao Paulo 04041-039,

Brazil. rodrigo@gastroped.epm.br

Telephone: +55-11-55794351 Fax: +55-11-55795834

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rate seems to be higher in patients with duodenal ulcer.

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### Abstract

**AIM:** To evaluate the furazolidone-based triple therapy in children with symptomatic *H pylori* gastritis.

**METHODS:** A prospective and consecutive open trial was carried out. The study included 38 patients with upper digestive symptoms sufficiently severe to warrant endoscopic investigation. *H pylori* status was defined based both on histology and on positive <sup>13</sup>C-urea breath test. Drug regimen was a seven-day course of omeprazole, clarithromycin and furazolidone (100 mg, 200 mg if over 30 kg) twice daily. Eradication of *H pylori* was assessed two months after treatment by histology and <sup>13</sup>C-urea breath test. Further clinical evaluation was performed 7 d, 2 and 6 mo after the treatment.

**RESULTS:** Thirty-eight patients (24 females, 14 males) were included. Their age ranged from 4 to 17.8 (mean 10.9 ± 3.7) years. On intent-to-treat analysis ( $n = 38$ ), the eradication rate of *H pylori* was 73.7% (95% CI, 65.2%-82%) whereas in per-protocol analysis ( $n = 33$ ) it was 84.8% (95% CI, 78.5%-91%). All the patients with duodenal ulcer ( $n = 7$ ) were successfully treated (100% vs 56.2% with antral nodularity). Side effects were reported in 26 patients (68.4%), mainly vomiting (14/26) and abdominal pain ( $n = 13$ ). Successfully treated dyspeptic patients showed improvement in 78.9% of *H pylori*-negative patients after six months and in 50% of *H pylori*-positive patients after six months of treatment.

**CONCLUSION:** Triple therapy with furazolidone achieves moderate efficacy in *H pylori* treatment. The eradication

### INTRODUCTION

Available treatment regimens for gastritis due to *H pylori* show a lower success rate in children than in adult patients in the same geographic region. Several factors influence *H pylori* eradication rate, such as compliance with treatment, mutations generating resistances, sanctuaries (sites where there is no contact between the bacterium and antimicrobial drugs), deficiency in immunity of the host, low gastric pH, large infecting load, dormant forms and reinfection<sup>[1]</sup>. *H pylori* treatment in children has specific difficulties and the success rate of the current options is worse than that in adults. It is speculated that in children there is less compliance with treatment and the prevalence of resistant strains is higher due to the greater exposure to antibiotics because of common childhood diseases. In addition, patients without peptic ulcer seem to present a lower success rate<sup>[2]</sup>.

The ideal treatment regimen for *H pylori* eradication should present a higher than 80% cure index on intention-to-treat analysis. Antimicrobial resistance is a major concern and in the past decade there was the emergence of clarithromycin-resistant strains, reaching 34.7% of isolates in some, mainly developed countries<sup>[3-5]</sup>. Resistance occurs due to punctual mutations in the 23S rRNA<sup>[5]</sup>. Nevertheless, in developing countries, resistance to metronidazole is highly prevalent, possibly due to overuse of this antimicrobial drug in gynecology and parasite treatment; thus this drug is not a viable alternative<sup>[6]</sup>. Although amoxicillin resistance is regarded a rare phenomenon, recently there are an increasing number of

reports on resistant strains<sup>[7]</sup>.

Furazolidone emerges as an alternative for therapeutic regimens in developing countries due to its low cost and prevalence of resistant strains. This antimicrobial is a monoamine oxidase inhibitor usually utilized in the treatment of giardiasis. There are studies demonstrating its efficacy and safety in several developing countries<sup>[8-12]</sup>. The drug has been used in *H pylori* treatment regimens since 1990, initially tested in China with a reasonable success rate and constitutes an alternative in situations where there is high resistance prevalence to nitroimidazoles. In our country a triple regimen with furazolidone, clarithromycin and omeprazole can attain a 90% cure in adult patients on intention-to-treat analysis<sup>[13]</sup> while with furazolidone, levofloxacin and rabeprazole can reach 83% eradication as a third-line regimen<sup>[14]</sup>. Consensus statements providing guidelines for the management of *H pylori* infection in children have made recommendations for therapy based on data derived from adult trials but have not provided suggestions on therapeutic options<sup>[15,16]</sup>. The present study was to evaluate the triple regimen with omeprazole, clarithromycin and furazolidone for 7 d in children with *H pylori* gastritis, being the first study in children.

## MATERIALS AND METHODS

### Subjects

To warrant *H pylori* eradication, patients meeting the following criteria were included: (1) duodenal ulcer or erosive duodenitis ( $n = 7$ ); (2) ulcer-like functional dyspepsia, according to the Rome II criteria, sufficiently severe to justify upper gastrointestinal endoscopy and without major mucosal abnormalities ( $n = 29$ )<sup>[17]</sup>; (3) upper gastrointestinal bleeding ( $n = 1$ ); (4) iron-deficiency anemia refractory to standard treatment ( $n = 1$ ). Patients with former unsuccessful treatment for *H pylori* or with other organic diseases that could explain the symptoms were excluded. The study was approved by the Ethics Committee of the "Universidade Federal de São Paulo/Escola Paulista de Medicina". On inclusion of the patients in the study, the responsible person(s) received written information about the patients and signed a free and informed consent.

### Diagnosis of infection

Endoscopic examination was performed by our team, under deep sedation or general anesthesia supervised by an anesthetist. Four biopsy specimens were collected from the gastric antrum at approximately 2 cm from the pylorus, two for rapid urease test and two for histological analysis. The latter two were fixed in 100 mL/L formol, placed on filter paper and stained with hematoxylin-eosin and modified Giemsa. The findings were described according to modified Sydney criteria<sup>[18]</sup>. The histological diagnosis of the infection was established by an experienced pathologist, based on the typical appearance of the bacterium along the mucus layer covering the gastric mucous membrane. Rapid urease test was performed with a non-commercial solution (100 mg/mL aqueous urea solution with 10 mg/mL phenol red) as previously described<sup>[19]</sup>. The patient

Table 1 Endoscopic findings

Endoscopic findings	n	%
Nodular gastritis	16	42.1
Normal	13	34.2
Duodenal ulcer or erosive bulbitis	4	10.5
Erosive duodenitis and nodular gastritis	1	2.6
Erosive gastritis	1	2.6
Nodular gastritis and esophagitis	1	2.6
Duodenal ulcer and esophagitis	1	2.6
Erosive duodenitis, esophagitis and nodular gastritis	1	2.6

was considered infected when both tests were positive and non-infected when both were negative.

### *H pylori* treatment

The triple regimen was administered twice daily for seven days: 100 mg furazolidone or 200 mg furazolidone (> 30 kg), 250 mg clarithromycin or 500 mg clarithromycin (> 30 kg), 10 mg omeprazole or 20 mg omeprazole (> 30 kg). Antibiotics were prescribed after meals whereas omeprazole was administered before the first meal. Patients and their responsible persons were advised to maintain the treatment even with minor adverse effects. On the last day of the treatment, a complete physical examination was performed to evaluate the clinical conditions of patients. During this examination the patients were asked about adverse effects, and compliance was controlled by return of empty medication blisters. Compliance with treatment was defined by over 75% intake of the prescribed doses.

### *H pylori* eradication

A renewed clinical and endoscopic evaluation was performed two months after the treatment, with collection of antrum and corpus biopsies for histology and rapid urease test. Patients whose responsible persons did not give consent to another endoscopy were evaluated using the <sup>13</sup>C-urea breath test. This test was performed as previously described<sup>[20]</sup>. The cutoff value of breath test was delta over baseline 4‰. The patients were submitted to a new clinical evaluation two and six months after treatment and asked about the progress of symptoms and the frequency and intensity of epigastric pain in those with dyspepsia.

### Statistical analysis

Continuous variables were expressed by calculation of the mean and standard deviation. The eradication rates were expressed by calculation of the proportion with an 85% confidence interval (95% CI). Treatment groups were compared using Pearson's chi-square test with Fisher's exact test when necessary. Factors associated with treatment success were evaluated by estimation of the odds ratio with 95% confidence interval.  $P < 0.05$  was considered statistically significant.

## RESULTS

Thirty-eight patients were included (24 females) with their

Table 2 Adverse effects reported by 26 of the 38 patients

Adverse effect	n	%
Vomiting	14	36.8
Abdominal pain	13	34.2
Metallic taste	6	15.8
Diarrhea	5	13.2
Nausea	5	13.2
Dizziness	2	5.3
Headache	2	5.3
Asthenia	1	2.6
Skin rash	1	2.6

age ranging from 4 to 17.8 (mean  $10.9 \pm 3.7$ ) years. Results of the endoscopic examinations are shown in Table 1. The histological analysis showed active chronic gastritis in all patients. Intensity of the neutrophil infiltrate was low in 9 patients (23.7%), moderate in 19 (50%) and intense in 10 (26.3%). Intensity of bacterial density on histology was low in 11 patients (28.9%), moderate in 19 (50%) and intense in 8 (21.1%).

Slight side effects were reported in 26 patients (68.4%), disappearing with the interruption of the treatment (Table 2). Compliance with the protocol occurred in 33/38 patients (86.6%), intake of medications was not correct in 4 patients and control of treatment was very late in one. The eradication rate of infection was 84.8% in 28/33 patients treated according to the protocol (95% CI: 78.5%-91%), and 73.7% by intent-to-treat analysis in 28/38 patients (95% CI: 65.4%-82%). Influence of demographic, clinical and histologic data on the success of treatment is shown in Table 3. The infection was eradicated in all the 7 patients with erosive duodenitis or duodenal ulcer, while only 9/16 (56.2%) patients with nodular antrum gastritis as a single alteration were successfully treated ( $P = 0.08$ ).

Evaluation of *H. pylori* eradication was performed through histology and  $^{13}\text{C}$ -urea breath test in 26 patients who were successfully treated and breath test in 2 patients who were successfully treated. *H. pylori* eradication evaluation was not performed in 4 patients whose medication intake was less than 25% of that prescribed. Results of endoscopy were normal in 21 (65.6%), nodular antrum gastritis in 9 (28.1%) and erosive gastritis in 1 (6.5%). Cure of infection was achieved in two patients with erosive gastritis. After the treatment, among the 26 cured patients, 9 (34.6%) had normal histology, 7 (26.9%) inactive chronic gastritis, 9 (34.6%) low neutrophil infiltrate and 1 (3.8%) moderate neutrophil infiltrate. Among the 6 patients remaining infected, a second endoscopy revealed low neutrophil infiltrate in 4 (67%) and moderate neutrophil infiltrate in 2 (33%), decreased neutrophil infiltrate in 3 (50%). Gastritis activity did not worsen in any of the patients.

### Clinical progress

Success treatment of *H. pylori* infection in patients with functional dyspepsia is shown in Figure 1. After two months of treatment, 63% of the eradicated dyspeptic patients and 60% of the non-eradicated patients reported

Table 3 Influence of clinical and histological variables on therapeutic success

	Eradication rate (%)	Odds ratio <sup>1</sup>	95% CI	P
Demographic data				
Female gender	66.7	0.33	0.03-2.18	0.27
Age $\leq 10$ yr	66.7	0.56	0.1-3.11	0.47
Indication for treatment				
Ulcer-like functional dyspepsia	65.5	0.00	0.0-1.23	0.08
Initial endoscopy				
Normal examination	76.9	1.30	0.23-9.44	1
Nodular gastritis <sup>2</sup>	56.2	0.24	0.03-1.39	0.08
Duodenal ulcer or erosive bulbitis	100	undefined	undefined	0.16
Histology				
Intense activity	70.0	0.70	0.13-5.97	1
Moderate activity	78.9	1.73	0.32-10.17	0.46
Light activity	66.7	0.67	0.10-5.28	0.68
Intense density	75.0	1.09	0.15-13.19	1
Moderate density	73.7	1.00	0.18-5.45	1
Light density	72.7	0.93	0.16-7.01	1
Adverse effects				
Yes	76.9	1.67	0.27-9.37	0.69

<sup>1</sup> for therapeutic success; <sup>2</sup> without duodenal ulcer or erosive duodenitis.

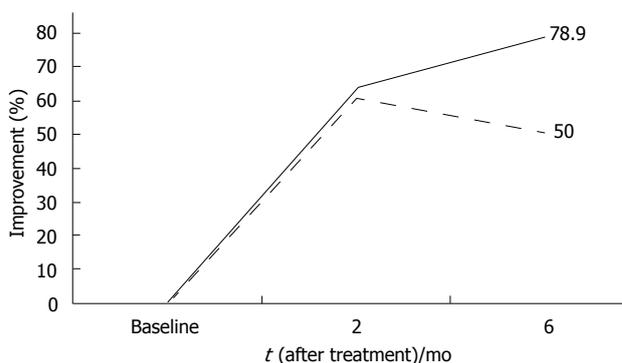


Figure 1 Patients with non-ulcer dyspepsia reporting symptom improvement after treatment according to *H. pylori* infection eradication in 2- and 6-mo follow-up. Continuous line: successfully eradicated patients; Dashed line: not eradicated patients.  $P$  (2 mo) = 1,  $P$  (6 mo) = 0.2.

improvement of symptoms ( $P = 1$ ), while at 6-mo follow-up 78.9% successfully treated patients and 50% of the non-eradicated patients reported improvement of symptoms ( $P = 0.2$ ). The hematological parameters of the patients with refractory iron deficiency anemia returned to normal after treatment and all patients with duodenal ulcer or erosive duodenitis were asymptomatic.

## DISCUSSION

The attained success rate (73.3% by intent-to-treat analysis) was higher than that observed by a former study with amoxicillin, clarithromycin and omeprazole for 7 d (50%, 95% CI: 19%-81%) in our service, but similar to that for 10 d (73%, 95% CI: 51%-95%)<sup>[21]</sup>. There is no other study

comparing triple therapy for 7 d with a longer treatment period. Other studies with clarithromycin, amoxicillin and proton pump inhibitor reported that the eradication rate of *H pylori* is 54%-77.8% in children<sup>[6,22,23]</sup>. At present, the first-line regimen recommended by Brazilian consensus for the treatment of adults is the triple treatment with clarithromycin, amoxicillin (or furazolidone) and proton pump inhibitor for 7-14 d<sup>[24]</sup>. A seven-day treatment period was chosen in our study because it is as effective as a ten-day period. The efficiency of a longer treatment period (14 d) is only 9% higher with a significant cost increase<sup>[25]</sup>. In Brazil there are 16% clarithromycin-resistant and 55% metronidazole-resistant strains, thus requiring alternative regimens for classical compositions<sup>[25,26]</sup>. Recently a sequential therapy has been described, consisting of two treatment regimens for five consecutive days. In these studies, amoxicillin and proton pump inhibitor (PPI) are used for five days followed by PPI, clarithromycin and tinidazole for another five days<sup>[27]</sup>. In children the regimen is more efficient than the traditional treatment with amoxicillin, metronidazole and PPI for 10 d (97.3%, 95% CI: 86.2%-99.5% *vs* 75.5%, 95% CI: 59.8%-86.7%), and has no more side effects (global rate 12%)<sup>[28]</sup>. A sequential regimen exposes the patients to three different drug classes as a first line treatment, which may make the choice of a second-line treatment difficult in eventual therapeutic failures.

There are no clinical or laboratory factors associated with a better result of the treatment (Table 3). The eradication rate of *H pylori* observed in our study in patients with duodenal ulcer is similar to that observed by Dani and coworkers<sup>[13]</sup> in adults with ulcer disease, but the difference in the eradication rate of *H pylori* in patients with functional non-ulcer dyspepsia did not reach statistical significance, perhaps due to the small number of patients with ulcer included in our study ( $P = 0.08$ ). A recent study has shown a lower eradication rate of *H pylori* in patients with non-ulcer dyspepsia<sup>[2]</sup>. Justifying factors include clarithromycin susceptibility to strains in patients with dyspepsia, less strain virulence (CagA negative) and differences in compliance with treatment. The lowest eradication index of *H pylori* observed in children may be due to the low prevalence of duodenal ulcer<sup>[29]</sup>. On the other hand, patients with antral nodularity present a lower eradication rate of *H pylori* (56.2%), but lymphoid follicles are found to be associated with treatment failure in adult patients<sup>[30]</sup>. Antral nodularity may be related to a higher inflammation intensity and more aggressive strains. However, it seems more difficult to eradicate infection with a CagA negative strain<sup>[31]</sup>. The high incidence of side effects (67.6%), although slight and self-limited, constitutes an inconvenience for the studied regimen. The reported side effects are slight and do not compromise the success treatment (Table 3). The reported symptoms may be attributed to clarithromycin or to furazolidone. Furazolidone is a nitrofurantoin compound which has been used in the treatment of giardiasis since the 1950s. The drug has minimal adverse effects, mostly nausea, vomiting and diarrhea. Other side effects include brown discoloration of urine and hemolysis in glucose-6-phosphate dehydrogenase deficient patients and infants

younger than 1-year old<sup>[32]</sup>. Treatment regimens with furazolidone usually present a higher incidence of side effects than traditional alternatives<sup>[9]</sup>. Lower furazolidone doses neither affect the success treatment rate, nor decrease the frequency of adverse effects<sup>[11]</sup>.

The omeprazole dose used may be considered small in view of recent evidence that some patients need higher doses<sup>[33]</sup>. The importance of antisecretory drugs in the eradication regimen is their direct effect on the bacterium and the better antibiotic activity at high pH<sup>[1]</sup>. Cytochrome P2C19 is responsible for hepatic metabolism of some proton pump inhibitors, such as omeprazole, and the CYP2C19 genotype, an isoform, is associated with more rapid metabolism, constituting another risk factor for unsuccessful eradication treatment of *H pylori*<sup>[34]</sup>. However, there are no studies describing the prevalent genotypes. Finally, some of our patients used generic omeprazole. The efficacy of *H pylori* eradication regimen with generic medication is lower than that with proprietary drugs in adult patients in Russia<sup>[35]</sup>. Omeprazole bioavailability depends on its presentation

Most of our patients presented non-ulcer dyspepsia, a situation in which treatment of *H pylori* infection is still controversial. The treatment seems to be beneficial to some adult patients and it is estimated that 1 in 18 patients improves after the treatment<sup>[36]</sup>. There are still important limitations in therapeutic trials for dyspepsia in children. There are no criteria for the selection of patients and no validated diagnostic and functional dyspepsia severity scores in children, which makes the generalization of results difficult. Over 50% of physicians in USA treat *H pylori* in children with dyspeptic symptoms without endoscopy<sup>[37]</sup>. In spite of the higher symptom improvement proportion among the successfully treated patients (78.9% *vs* 50%), the study could not draw a conclusion about the clinical validity of the treatment because of the small number of studied patients (Figure 1). Other studies have reported a similar response rate in children with recurrent chronic abdominal pain<sup>[6,38]</sup>. Long-term symptom resolution in patients with severe symptoms requiring endoscopy shows differences in epigastric pain resolution between *H pylori*-negative (3/26) and positive (7/10) patients ( $P = 0.001$ ) after one to two years<sup>[38]</sup>. Early clinical evaluation may underestimate the beneficial effects of the treatment and longer follow-up periods may show effective *H pylori* eradication and symptom resolution.

The tested regimen may be superior to the regimen with clarithromycin, amoxicillin and omeprazole, and can be used in the treatment of infection in patients with duodenal ulcer. Its success rate is lower in non-ulcer dyspepsia. Treatment regimens with a longer time should be tested in children.

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