

Successful eradication rate of *Helicobacter pylori* with empirical antibiotic treatment in pediatric patients from a Tertiary Hospital

Porcentaje de éxito de erradicación de *Helicobacter pylori* con tratamiento antibiótico empírico en pacientes pediátricos de un Hospital Terciario

Sofía Darritchon Lama^a, Diego Díaz García^a, Marcela Toledo Cumplido^b, Yalda Lucero Álvarez^{c,d}

^aPrograma de Especialización en Pediatría, Facultad de Medicina, Universidad de Chile. Santiago, Chile.

^bHospital de Niños Roberto del Río. Santiago, Chile.

^cDepartamento de Pediatría y Cirugía Infantil Norte, Hospital Roberto del Río y Programa de Microbiología y Micología, ICBM, Facultad de Medicina, Universidad de Chile. Santiago, Chile.

^dUnidad de Gastroenterología Pediátrica, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo.

Received: April 6, 2023; Approved: September 27, 2023

What do we know about the subject matter of this study?

Helicobacter pylori infection is common, usually acquired in childhood, and has potential complications, including gastric cancer, which can be prevented with effective treatment. The usual treatment is empirical antibiotics, which often fail.

What does this study contribute to what is already known?

This is the first study describing eradication rate of *H. pylori* under real healthcare conditions in children in South America with first-line empirical treatment. Low adherence to the follow-up protocol was evidenced and in those with eradication confirmation test, the success rate was only 38%, which highlights the urgency of promoting more effective treatment and follow-up strategies.

Abstract

Helicobacter pylori infection is a common condition that, in the long term, is associated with the development of peptic ulcer disease and eventually gastric cancer, which could be prevented with timely treatment. Optimally, eradication success should be greater than 90%, but the recommended empirical treatments do not achieve these rates in real-life conditions. **Objective:** To determine the success rate of first-line empirical eradication treatment against *H. pylori* in pediatric patients treated in a tertiary hospital. **Patients and Method:** Retrospective descriptive study in patients with *H. pylori* infection detected in gastric biopsies and who had received first-line antibiotic treatment during the period 2017-2021. A negative result of an antigen test in stools or new biopsies after ≥ 1 month after

Keywords:

Helicobacter pylori;
Child;
Anti-Infective Agents;
Ulcer Disease;
Gastric Cancer

Correspondence:
Yalda Lucero Alvarez
ylucero@uchile.cl

Edited by:
Macarena Gajardo Zurita

completing treatment was considered a successful eradication. **Results:** 82 patients with *H. pylori* infection were identified, of which 53 received eradication treatment. Of these, 26 (49%) were controlled with eradication tests after treatment with a success rate of only 38% (10/26). **Conclusions:** The eradication rate with the empirical regimens used was lower than expected which highlights the challenge of seeking more effective treatment strategies, including the study of antimicrobial susceptibility. Patient adherence to the follow-up protocol was also low, which should be reinforced in the future to ensure more appropriate clinical management.

Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative bacillus, which can colonize and survive in the highly acidic environment of the gastric mucosa¹. This microorganism represents the most frequent chronic bacterial infection in humans, affecting about 50% of the world population and up to 90% in developing countries^{2,3}. In Chile, there is an estimated prevalence of 18-30% in school children, which can increase to 70% in adults⁴⁻⁸. Although most infected individuals are asymptomatic, about 10% develop peptic ulcer disease and 0.1% may develop gastric cancer in adulthood⁹ which could be prevented with effective eradication treatment. In addition, infection by this agent has been associated with the appearance of immune thrombocytopenic purpura and unexplained anemia. Hence the relevance of an effective and timely eradication from childhood¹⁰.

In adult patients, there is evidence supporting the usefulness of *H. pylori* eradication treatment at any clinical stage, regardless of the presence of symptoms and/or digestive lesions⁸. However, in pediatrics, treatment is only recommended for patients with proven peptic ulcer disease, immune thrombocytopenic purpura, or a family history of gastric cancer¹⁰ since in pediatric patients we try to avoid the deleterious effects of unnecessary antibiotic use in the context of an infection that is predominantly asymptomatic. However, when therapy is justified, it should be effective, precisely to achieve the beneficial effects of eliminating the infection in a more susceptible patient, avoiding having to use second- or third-line therapies with even broader spectrums.

According to the joint consensus of the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition published in 2017, first-line treatment should include a 14-day combination of some proton pump inhibitor associated with amoxicillin and clarithromycin or metronidazole, depending on the regional frequency of resistance to clarithromycin¹¹. There are few reports on the frequency of resistance to clarithromycin and metronidazole in Chilean children, making the choice of antibiotic regimen difficult.

The desirable eradication rate for these empirical schemes would be at least 90%⁹, however, in practice, these ranges are not reached, among other reasons due to the growing resistance to antibiotics and lack of adherence to the scheme. Serrano et al. described in a study on antimicrobial resistance in children a 75% eradication success rate (18/24 patients); however, being in the context of a clinical study, these patients had been educated about the relevance of *H. pylori* and its treatment during the informed consent process and had telephone follow-up 2 weeks after starting treatment¹², which does not represent the usual healthcare reality in our sphere. To our knowledge, there are no previous reports in our country on the success rate of eradication schemes against *H. pylori* in the context of the reality of care in children, which would allow us to propose more rational strategies for education, treatment, and follow-up. The objective of this study was to determine the success rate of first-line empirical eradication treatment against *H. pylori* in a tertiary pediatric healthcare center.

Patients and Method

Study design

Retrospective descriptive study based on the review of records of pediatric patients at the *Hospital Roberto del Río* who had had *H. pylori* detected in gastric biopsies collected by endoscopy and who had received first-line empirical treatment for eradication of this agent between January 2017 and December 2021. This protocol was approved by the Research Ethics Committee of the North Metropolitan Health Service and authorized by the Hospital Management.

Identification of cases and recorded data

Initially, anatomic pathology records were reviewed to identify all patients who had undergone gastric biopsies collected by endoscopy. Of these, patients in whom *H. pylori* had been detected by histology were identified. The clinical records of these patients were reviewed to identify those in whom eradication treatment had been indicated. For the latter, demogra-

phic data, the treatment regimen received, and the result of the eradication confirmation test were recorded.

***H. pylori* detection tests used**

Detection in gastric biopsies was performed by commercial rapid urease test and/or visualization by a pathologist in histology with hematoxylin and eosin staining. Eradication follow-up was determined at least 1 month after the end of antibiotic treatment, by detection of antigen in stool by commercial ELISA kit at the Clinical Hospital of the University of Chile or by gastric biopsies collected in endoscopy by urease test and/or histology.

Operational definitions

***H. pylori* infection**

identification of *Helicobacter*-like bacilli in histological report of gastric biopsies, with or without concomitant positive rapid urease test.

Patient with indication for first-line treatment: patients whose indication for treatment had been recorded in her/his clinical record and/or who had a record in the system of the prescription issued by the corresponding scheme. Patients who had received previous treatment against the same agent were excluded.

Successful eradication

negative result of antigen in stool or gastric biopsy collected by endoscopy at least 1 month after the end of treatment.

Statistical analysis

Data were recorded in an Excel® spreadsheet. Descriptive statistics were performed with GraphPad Prism 7.0® software. Continuous variables were compared by t-Student test (age had normal distribution) and categorical variables by Chi-square or Fisher exact test according to the number of patients in each group. A p-value < 0.05 was considered significant.

Results

During the study period, 82 patients were identified with a diagnosis of *H. pylori* infection in gastric biopsies collected by endoscopy. Empirical eradication treatment against *H. pylori* was indicated in 53 patients (65%), of whom 26 (49%) continued to be followed up and underwent tests to confirm eradication; the remaining 27 did not return for follow-up. Of the 26 patients who continued follow-up, eradication confirmation was performed in 19 patients by detection of antigen in stool and in 7 through gastric biopsies collected by EGD; in both cases at least 1 month after the end of treatment (Figure 1).

Of the 26 patients with complete follow-up, only 10 achieved successful eradication (38%) (Figure 1). It is noteworthy that the proportion of success was higher in patients in whom eradication was observed by urease test, although this difference did not reach statistical significance ($p = 0.13$; Figure 1).

Table 1 shows the demographic and clinical characteristics of the patients, comparing according to compliance with follow-up and successful eradication. It is noteworthy that in the group of patients who had successful eradication, there was a significantly higher proportion of females compared with the group that failed treatment and those who did not complete follow-up. No statistically significant differences were found in terms of age, reason for endoscopy, main endoscopic finding, or level of histological gastritis.

Several different regimens were used (Table 2), most of which included amoxicillin. The 2 patients who did not receive amoxicillin were allergic to this antimicrobial. The second most commonly used antibiotic was clarithromycin, followed by metronidazole. No statistically significant differences were found in the success rate of the different regimens.

Table 3 shows the distribution of cases according to the year in which treatment was indicated. It is noteworthy that in 2020, at the beginning of the COVID-19 pandemic, there was only 1 case, and this did not complete follow-up. There was no statistically significant difference in the percentage of follow-up or eradication success throughout the period.

Discussion

To our knowledge, this is the first study describing the proportion of *H. pylori* eradication with empirical treatment in South American children under real care conditions. Of note is not only the low proportion of patients who adhered to the follow-up protocol and underwent tests to confirm eradication (49% of those treated) but also the low proportion of success with first-line empirical regimens (38% of those who underwent tests to confirm eradication). This could be due, among other factors, to adherence to treatment, metabolism of the drugs used, and antimicrobial resistance of the strains involved.

Regarding the first point, due to the retrospective design of this study, it was not possible to record information on adherence or tolerance to the eradication schemes, which is a limitation. The low eradication rate found in this series of patients contrasts with that reported by Serrano et al. in a prospective descriptive study of pediatric patients in Santiago, in which they found 71% adherence to the follow-up protocol and 75% eradication success in those who underwent

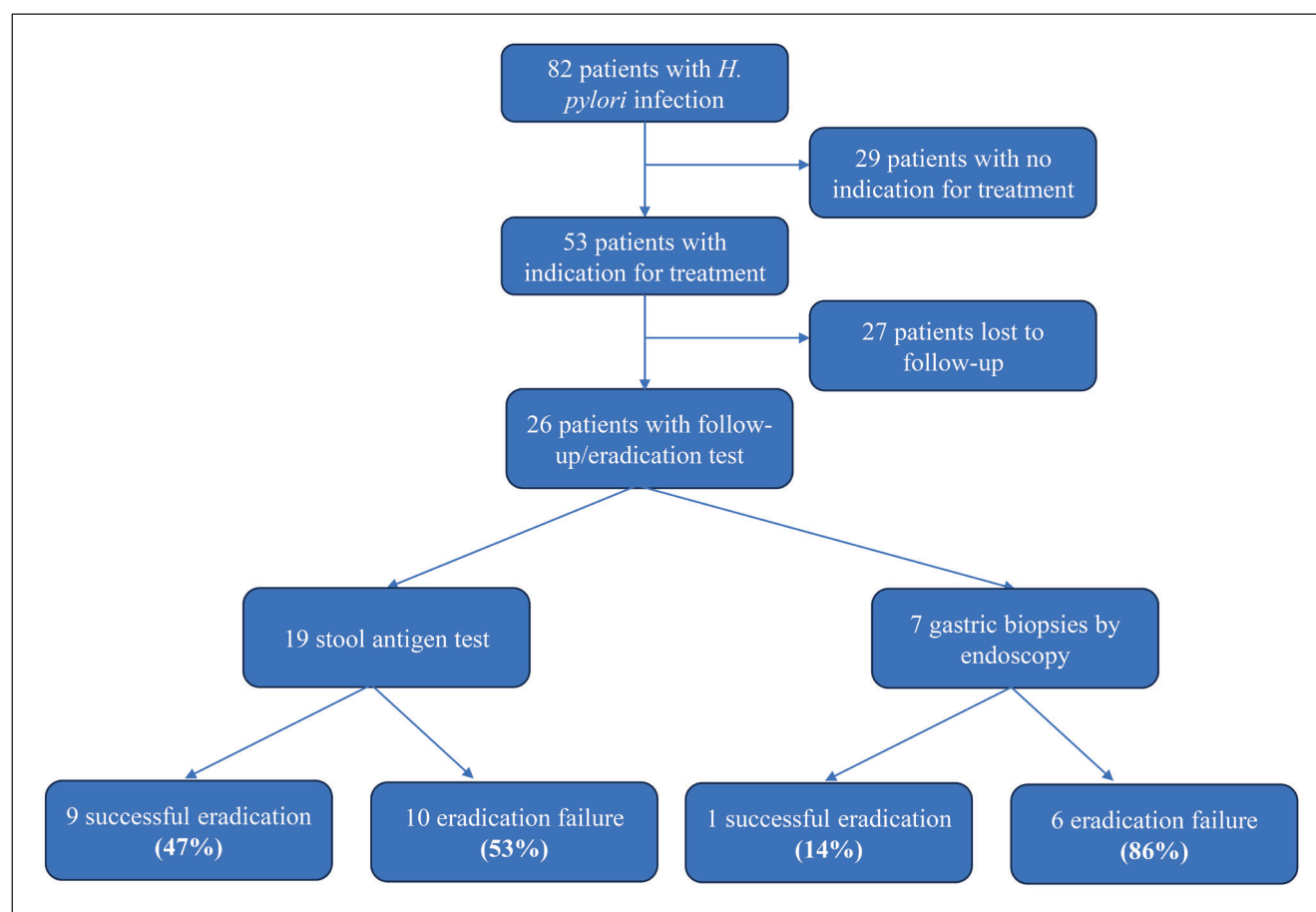


Figure 1. Flowchart of recruited patients according to indication of treatment, follow-up and eradication success.

Table 1. Demographic and clinical characteristics of treated patients, based on follow-up and eradication success

		Treated overall, n (%)	Treated with no follow-up, n (%)	Treated with follow-up, n (%)		p
				Treated successful eradication	Treated eradication failure	
N° of patients, n (%)		53	27	10	16	
Female, n (%)		23 (43)	9 (33)	9 (90)	5 (31)	0.0043* 0.0053**
Mean age ± DS		11.8 ± 3.2	12.3 ± 3.3	12.6 ± 2.2	10.5 ± 3.2	NS
Reason for undergoing endoscopy	Abdominal pain	41 (77)	19 (70)	10 (100)	11 (69)	NS
	Digestive bleeding	8 (15)	6 (22)	0	3 (19)	
	Other	4 (8)	2 (7)	0	2 (12.5)	
Main endoscopic finding	Nodular gastropathy	34 (64)	17 (63)	6 (60)	11 (69)	NS
	Erosive gastropathy	11 (21)	7 (26)	3 (30)	1 (6)	
	Gastric or duodenal ulcer	8 (15)	3 (11)	1 (10)	4 (25)	
Severity of histological gastritis	Mild	32 (60)	18 (67)	3 (30)	11 (69)	NS
	Moderate	18 (34)	7 (26)	6 (60)	5 (31)	
	Severe	3 (6)	2 (7)	1 (10)	0	

*Chi-square for comparing the success treatment group versus treated individuals without follow-up. **Chi-square for comparing the successful treatment versus eradication failure group

Table 2. Comparison of eradication success rates among the treatment regimens used*

	Treated with follow-up	Treated succesful eradication	Treated eradication failure	p
N° of patients, n (%)	26	10 (38)	16 (62)	
Treatment				NS **
O+A+C 10d	5	2 (40)	3 (60)	
O+A+C 14d	11	4 (40)	7 (60)	
O+A+M 10d	2	1 (50)	1 (50)	
O+A+M 14d	6	3 (50)	3 (50)	
O+C+M 10d	1	0	1 (100)	
O+C+M 14d	1	0	1 (100)	

O: omeprazole; A: Amoxicillin; C: clarithromycin; M: methronidazol; d: days. *Medication doses adhere to the recommendations outlined in the ESPGHAN/NASPGHAN 2017 guidelines (ref 11). **Chi square for trend.

Table 3. Distribution of cases according to the year of treatment

	Treated subjects, overall	Treated with no follow-up, n (%)	Tratados con seguimiento, n (%)	Tratados con erradicación exitosa, n (%)*	Tratados con fracaso de erradicación, n (%)*
N° of patients	n (%)	27 (51)	26 (49)	10 (38)	16 (62)
Year of treatment	n (%)				
2017	n (%)	4 (50)	4 (50)	1 (25)	3 (75)
2018	18	9 (50)	9 (50)	2 (22)	7 (88)
2019	15	8 (53)	7 (47)	4 (57)	3 (43)
2020	1	1 (100)	0	0	0
2021	11	5 (45)	6 (55)	3 (50)	3 (50)

*percentage calculated relative to the total number of patients who underwent eradication testing during follow-up. Analyzed using Chi-square for trend.

eradication confirmation tests. In contrast to our study, in which the data recorded in the patients' clinical records were analyzed retrospectively and under real-life condition, in the study by Serrano et al. the treatment and follow-up were protocolized, the patients and their guardians were informed about *H. pylori* and its treatment during the informed consent process, and were contacted by telephone 2 weeks after starting treatment to verify adherence, which probably contributed to increasing the proportion of complete treatments and patients with eradication tests performed.

In a previous study of our group carried out with schoolchildren from Colina, we found a 96% eradication rate (30/31 patients treated with a sequential scheme of omeprazole + amoxicillin for 7 days, followed by omeprazole + clarithromycin + metronidazole for 7 more days). All patients completed treatment (with only a few missed doses) and follow-up with eradication testing¹³. Unlike the current study, these results were in the context of a clinical trial conducted with patients who had been part of a follow-up cohort for

8-10 years. These were families and patients who were highly educated about the implications of *H. pylori* and the relevance of appropriate treatment. In addition, a telephone follow-up was performed 7 days after treatment and a face-to-face follow-up at the end of the therapy. These results as a whole support the idea that adherence to the treatment regimen is relevant to its success^{14,15}. In this sense, the process of educating the patient and her/his guardians regarding the relevance of treatment and complete follow-up at the time of indicating therapy could be relevant in the proportion of adherence and finally the success of eradication.

It is noteworthy that in the group with successful eradication, there was a significantly higher proportion of females compared with the group that failed to eradicate and the group that did not complete follow-up. This contrasts with those described by Weiner et al. in the context of a clinical trial, in which they found a higher eradication success rate in males (75%) compared with females (63%)¹⁶. However, other authors have found no effect of sex on the success of the therapy (14,15). With a prospective design, the relationship

between sex and eradication success could be elucidated in the future.

The schemes used were adjusted to the recommendations of international guidelines¹¹, which support the use of proton pump inhibitor associated with amoxicillin but allow some flexibility in the choice of the second antibiotic, between clarithromycin or metronidazole, which is subject to the patient's previous history of antibiotic exposure, drug allergy, and *H. pylori* resistance in the region. The latter data is scarce in our setting, which makes decision-making difficult.

Serrano et al. described a frequency of resistance to clarithromycin of 21% in pediatric patients in Santiago¹². International guidelines do not recommend using schemes that include this antibiotic when the resistance rate in the region is higher than 15%, so it would not be advisable in our sphere. However, researchers from the Biobío Region described a resistance rate to metronidazole of 37.5% in a group of patients that included some patients under 18 years of age¹⁷, so this antibiotic does not give certainty of success either. In our series, the success rate was less than 50% and quite similar between 10- and 14-day regimens, regardless of whether they included clarithromycin or metronidazole. Anecdotally, the 2 patients allergic to amoxicillin, who received schemes without this antimicrobial, failed in eradication¹⁴⁻¹⁶.

Another point to highlight was the low adherence to the follow-up protocol. The contingencies experienced by our society from the end of 2019 to 2021, undoubtedly could have influenced adherence to follow-up, however, we can see that this already had low compliance in previous years. *H. pylori* eradication treatment is a pathology that has been within the Explicit Health Guarantees (GES) Program since 2013 and within the health benefits basket, tests to confirm eradication are included. For this reason, patients should be informed in greater detail about the implications of this infection, the relevance of eradication, and the benefits that are guaranteed to ensure adequate treatment and eradication confirmation. However, in practice, more than half of the patients did not continue in follow-up. This could be attributed at least in part to the communication gap that can be generated between health personnel and patients due to the use of technical language and/or lack of time to explain in detail, but it could also be due to the lack of time of

patients/families who, once the symptoms have resolved, do not see the need to attend the health check-up to confirm the resolution of the episode. These results support the need to seek more effective education strategies to achieve patient adherence to both therapy and follow-up.

Although the retrospective design of this study is a limitation, we believe that it highlights a relevant problem that is likely to be extrapolated to other pediatric healthcare centers and that we must address with better strategies to ensure adherence to treatment and follow-up in order to confirm the eradication of this agent that has potentially serious implications in the long term. It would be advisable to carry out a prospective study in the future that includes a larger number of patients to confirm these findings and to consider the factors of adherence to treatment in the analysis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Fondecyt Regular Project 1190456.

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