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Evolution of antibiotic resistance pattern of *Helicobacter pylori* in Spanish children: A 10-year multicenter study

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Abstract

Objectives: To delineate the evolution of antibiotic resistance over the past decade in Spanish children diagnosed with *Helicobacter pylori* (*H. pylori*) infection.

Methods: An observational, retrospective, multicenter study was conducted in Madrid, Spain. This study included children diagnosed with *H. pylori* infection via endoscopy with positive culture and antimicrobial susceptibility testing between 2011 and 2020.

Results: A total of 1205 patients (56.7% female) were included in the study. Of these, 18.7% had previously undergone unsuccessful treatment. The resistance to the antibiotics tested was as follows: clarithromycin, 42.9% ($n = 504$, [95% confidence interval, CI: 40.1%–45.8%]); metronidazole, 24% ($n = 280$, [95% CI: 21.5%–26.5%]); rifampicin, 14.8% ($n = 120$, [95% CI: 12.4%–17.4%]); levofloxacin, 5.2% ($n = 58$, [95% CI: 3.9%–6.6%]); amoxicillin, 2.6% ($n = 30$, [95% CI: 1.7%–3.6%]); and tetracycline, 0.9% ($n = 10$, [95% CI: 0.4%–1.6%]). The double resistance rate was 12.2% ($n = 143$, [95% CI: 10.4%–14.2%]). During the study period, antibiotic resistance remained relatively stable, with a notable decrease in metronidazole (incidence rate ratio [IRR]: 0.941, [95% CI: 0.898–0.985], $p = 0.01$) and double resistance (IRR: 0.933, [95% CI: 0.875–0.995], $p = 0.03$) values. The overall eradication rate was 76.6%

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(*n* = 752, [95% CI: 73.8–79.2%]), which was significantly higher in patients without prior treatment. The temporal progression of eradication rates showed a substantial increase, with an average annual increase of 2.9% (IRR: 1.029, [95% CI: 1.015–1.043], $p < 0.001$).

Conclusions: The prevalence of antibiotic resistance in our setting (Madrid, Spain) was remarkably high and remained stable throughout the study period, except for a notable decline in metronidazole and double resistance.

KEYWORDS

clarithromycin, eradication therapy, metronidazole

1 | INTRODUCTION

In 2015, the global prevalence of *Helicobacter pylori* (*H. pylori*) infection was estimated to be approximately 4.4 billion. *H. pylori* infection is a significant contributing factor in the development of various digestive diseases.[1] Recommendations for diagnosing and treating *H. pylori* in children and adolescents differ from those for adults.[2] Some studies have shown that there are no specific symptoms in non-ulcer dyspeptic *H. pylori*-infected children compared to uninfected children.[3] Furthermore, eradication of *H. pylori* in the absence of peptic ulcer has not been shown to improve symptoms in children.[4] The primary objective in children with gastrointestinal symptoms should be to ascertain potential underlying causes rather than focusing solely on the presence of *H. pylori* infection.[5,6]

The emergence of antibiotic resistance represents a significant challenge to the efficacy of current treatment regimens. The prevalence of antibiotic resistance varies according to geographical region, age, previous eradication therapies, and antibiotic consumption in the general population.[7–10] Given the dynamic nature of antibiotic resistance and the considerable geographical variability, updated studies on resistance prevalence should be conducted to determine the optimal therapeutic options when the indicated treatment cannot be guided by antimicrobial susceptibility testing.

This study aimed to examine the evolution of antibiotic resistance patterns in children diagnosed with *H. pylori* infection over the past decade. Furthermore, we sought to explore the risk factors associated with the emergence of resistance as well as the presence of peptic ulcer disease. Additionally, the study assessed the eradication rates in patients who received treatment and examined their evolution throughout the study period.

What is Known

- Antibiotic resistance of *Helicobacter pylori* (*H. pylori*) represents the primary factor influencing the efficacy of current therapeutic regimens.
- Given the dynamic and geographically variable nature of antibiotic resistance, it is crucial to conduct updated studies to identify the most appropriate therapeutic strategies when antimicrobial susceptibility testing is unavailable.

What is New

- The prevalence of antibiotic resistance in Spain has remained consistently high over the past decade, with a notable decline in the incidence of metronidazole resistance and double resistance but no change in clarithromycin resistance.
- The therapeutic changes set out in the "Joint European Society for Pediatric Gastroenterology, Hepatology and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Management of *Helicobacter pylori* in Children and Adolescents (Update 2016)" have resulted in enhanced eradication rates.

2 | METHODS

2.1 | Ethics statement

The study was approved by the local ethics committee for research (Hospital Universitario Puerta de Hierro, February 23, 2021) and by the ethics committees of all participating centers (study number 21/56). The processing of all personal patient data was conducted in accordance with the provisions of Regulation (EU) 2016/679 of the European Parliament and Council of April 27, 2016 (General Data Protection Regulation).

2.2 | Study design and participants

We conducted an observational, retrospective, multicenter study across 10 hospitals in Madrid, Spain. The study included patients (aged 5–17 years) with *H. pylori* infection, diagnosed by endoscopy, with positive

gastric culture and antimicrobial susceptibility test results between January 2011 and December 2020.

2.3 | Antimicrobial susceptibility testing

Biopsy specimens of the gastric antrum and body obtained via endoscopy were used for *H. pylori* isolation. The resulting samples were subsequently cultured together on a selective medium designed for *H. pylori* growth. Antibiotic susceptibility testing was performed using the *E*-test method, with resistance defined according to the European Committee on Antimicrobial Susceptibility Testing guidelines.[11] The susceptibility of *H. pylori* to a range of antibiotics, including amoxicillin, clarithromycin, metronidazole, tetracycline, levofloxacin, and rifampicin, was evaluated.

2.4 | Treatment and eradication

Patients who received treatment were guided by antimicrobial susceptibility testing and followed the recommendations of the joint guidelines of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) that were in force at the time of treatment.[12,13] The efficacy of treatment in eradicating *H. pylori* was assessed using the ^{13}C-urea breath test or monoclonal stool antigen test 6–8 weeks following the completion of treatment.

2.5 | Data collection

The data set comprised demographic, clinical, and endoscopic data, as well as resistance and eradication rate patterns. The presence of a resistant *H. pylori* strain in patients with no prior eradication therapy and pre-culture treatment failure indicated primary and secondary resistance, respectively. Double resistance was defined as the presence of *H. pylori* strains that were resistant to both clarithromycin and metronidazole.

2.6 | Data analysis

A thorough and comprehensive descriptive analysis was conducted. The primary result was the frequency of resistance, with a 95% confidence interval (CI) calculated using the Wilson method. The linear trend of resistance over time was estimated using generalized linear models with Poisson or negative binomial distributions, accounting for overdispersion. Trend analysis by age, sex, and origin subgroup was conducted by including a time interaction term in the model. The presence of a statistically significant interaction effect indicates disparate linear trends across distinct subgroups.

An exploratory univariate analysis was performed to examine potential risk factors associated with resistance and peptic ulcer disease. Modified Poisson regression models, both univariate and multivariate, were then employed to estimate the unadjusted and adjusted relative risks, respectively. Data analysis was conducted using IBM SPSS version 20 (IBM Corp.) and STATA version 17 (StataCorp LLC).

3 | RESULTS

3.1 | Study population

A total of 1205 patients (56.7% female) from 10 centers in Madrid, Spain, were included in the study (Table S1). The mean age was 11.2 years (±2.8 SD). Most participants (89%) were Spanish, 4.5% South Americans, 2.8% Eastern Europeans, 2.4% North Africans, and 1.2% Asians.

3.2 | Medical history and symptoms

The most common symptoms prompting diagnostic endoscopy were epigastric pain (42.4%), abdominal pain in other locations (31.0%), reflux or pyrosis (5.3%), nausea or vomiting (5.2%), and refractory iron deficiency anemia (1.6%). Fortuitous diagnosis was made in 14.5% of cases during endoscopy conducted for a different indication. The most commonly associated digestive diseases were eosinophilic esophagitis (9.0%), gastroesophageal reflux (7.3%), celiac disease (6.4%), and inflammatory bowel disease (0.8%) (Table 1).

3.3 | Endoscopic findings

Overall, 7.3% ($n = 87$, [95% CI: 5.8%–8.8%]) of the patients were diagnosed with peptic ulcer disease, defined as the presence of gastric or duodenal erosions or ulcers, via endoscopy. The risk of peptic ulcer disease was significantly higher in older patients (12–17 years) than in younger ones (5–11 years) (relative risk [RR]: 1.52, [95% CI: 1.01–2.30], $p = 0.04$). Similarly, non-Spanish individuals exhibited a significantly higher risk of peptic ulcer disease than those born in Spain (RR: 2.12, [95% CI: 1.34–3.36], $p = 0.001$) (Table S2).

TABLE 1 Clinical and demographic characteristics of study patients.

Clinical and demographic characteristics	Total number of patients ($n = 1205$)		Prior treatment ($n = 1183$)				
			Yes ($n = 221$)		No ($n = 962$)		
	n/N	%	*n/N*	%	*n/N*	%	*p* value*
Sex (female)	683/1,205	56.7	128/221	57.9	537/962	55.8	0.599
Age (years), mean ± SD	11.2 ± 2.84	-	11.4 ± 2.83	-	11.2 ± 2.85	-	0.404
Country of birth							0.330
Spain	1000/1124	89.0	194/216	89.8	788/886	88.9	
South America	51/1124	4.5	10/216	4.6	39/886	4.1	
Eastern Europe	32/1124	2.8	5/216	2.3	25/886	2.8	
Africa	27/1124	2.4	2/216	0.9	25/886	2.8	
Asia	13/1124	1.2	5/216	2.3	8/886	0.9	
Other	1/1124	0.1	0/216	0	1/886	0.1	
Main symptom							**<0.001**
Epigastric pain	504/1189	42.4	105/221	47.5	397/962	41.3	
Abdominal pain	369/1189	31.0	87/221	39.4	278/962	28.9	
Reflux or pyrosis	63/1189	5.3	6/221	2.7	56/962	5.8	
Vomiting or nausea	62/1189	5.2	7/221	3.2	55/962	5.7	
Iron deficiency anemia	19/1189	1.6	3/221	1.4	16/962	1.7	
Endoscopic incidental finding	173/1189	14.5	13/221	5.9	160/962	16.6	
Associated diseases							0.058
Eosinophilic esophagitis	109/1211	9.0	10/222	4.5	99/961	10.3	
Gastro-esophageal reflux	88/1211	7.3	16/222	7.2	72/961	7.5	
Celiac disease	78/1211	6.4	11/222	5.0	67/961	7.0	
Inflammatory bowel disease	10/1211	0.8	2/222	0.9	8/961	0.8	
Other	63/1211	5.2	13/222	5.9	47/961	4.9	
Peptic ulcer disease	87/1192	7.3	16/222	7.2	71/959	7.4	0.942
Eradication	752/982	76.6	124/196	63.3	628/786	79.9	**<0.001**

Note: Bold *p* values indicate significant differences ($p < 0.05$).

Abbreviations: n, number of patients; SD, standard deviation; %, percentage of patients.

**p* Values were obtained using the chi-square test or Fisher's exact test for qualitative variables and the Student's *t* test for quantitative variables.

3.4 | *H. pylori* antibiotic resistance and risk factors

A total of 221 out of 1183 patients (18.7%) had previously received unsuccessful treatment for *H. pylori* infection. During the study period, 61% ($n = 721$, [95% CI: 58.2%–63.8%]) of patients exhibited resistance to any antibiotic: clarithromycin 42.9%, ($n = 504$, [95% CI: 40.1%–45.8%]); metronidazole, 24% ($n = 280$, [95% CI: 21.5%–26.5%]); rifampicin, 14.8% ($n = 120$, [95% CI: 12.4%–17.4%]); levofloxacin, 5.2% ($n = 58$, [95% CI: 3.9%–6.6%]); amoxicillin, 2.6% ($n = 30$, [95% CI: 1.7%–3.6%]); tetracycline, 0.9% ($n = 10$, [95% CI: 0.4%–1.6%]) and double resistance, 12.2% ($n = 143$, [95% CI: 10.4%–14.2%]). The full pattern of primary and secondary resistances is shown in Table 2.

Regarding the factors that increase the likelihood of resistance development, patients who had previously undergone unsuccessful eradication treatment exhibited markedly elevated levels of resistance to clarithromycin (RR: 1.50, [95% CI: 1.32–1.71], $p < 0.001$), metronidazole (RR: 2.55, [95% CI: 2.09–3.10], $p < 0.001$), and double resistance (RR: 4.29, [95% CI: 3.17–5.80], $p < 0.001$) compared to those who had no prior treatment. Spanish patients exhibited significantly

TABLE 2 Antimicrobial resistance patterns: primary resistance (patients with no prior treatment) and secondary resistance (patients with prior unsuccessful treatment).

Antibiotics	Primary resistance			Secondary resistance			*p* value*
	n/N	%	95% CI	*n/N*	%	95% CI	
Resistance to any antibiotic	535/940	56.9	53.7–60.1	166/219	75.8	69.5–81.2	**<0.001**
Amoxicillin	18/933	1.9	1.1–3.0	12/214	5.6	3.1–9.8	**0.002**
Clarithromycin	357/934	38.2	35.1–41.4	133/218	61.0	54.1–67.4	**<0.001**
Metronidazole	165/929	17.8	15.4–20.4	102/217	47.0	40.2–53.9	**<0.001**
Tetracycline	5/926	0.5	0.2–1.3	5/213	2.3	0.8–5.6	**0.024**
Levofloxacin	47/908	5.2	3.8–6.8	11/204	5.4	2.9–9.7	0.9
Rifampicin	100/663	15.1	12.4–18.0	17/138	12.3	7.5–19.2	0.403
Double resistance	65/932	7.0	5.4–8.8	71/217	32.7	26.5–39.4	**<0.001**

Note: Bold *p* values indicate significant differences ($p < 0.05$).

Abbreviations: CI, confidence interval; Double resistance, resistance to clarithromycin and metronidazole; n, sample size; N, total number of patients; %, percentage of patients.

*p values obtained by chi-squared test or Fisher's exact test.

elevated resistance to clarithromycin (RR: 2.59, [95% CI: 1.82–3.68], $p < 0.001$) and double resistance (RR: 2.24, [95% CI: 1.12–4.45], $p = 0.022$), whereas non-Spanish patients demonstrated heightened resistance to metronidazole (RR: 1.45, [95% CI: 1.11–1.90], $p = 0.006$) (Table 3).

3.5 | Time trend of *H. pylori* antibiotic resistance

Concerning the evolution of antibiotic resistance over the study period (2011–2020), resistance levels remained largely stable, with a significant decrease in metronidazole resistance, showing an average reduction of 5.9% per year (incidence rate ratio [IRR]: 0.941, [95% CI: 0.898–0.985], $p = 0.01$), as well as in double resistance, with an average reduction of 6.7% per year (IRR: 0.933, [95% CI: 0.875–0.995], $p = 0.03$) (Figure 1; Tables S3 and S4).

3.6 | Treatment and eradication rate

A total of 86.4% (1018/1178) of the patients received treatment. Treatment was administered in accordance with the findings of the antimicrobial susceptibility study and aligned with the prevailing guidelines provided by ESPGHAN and NASPGHAN at the time. The overall eradication rate in patients who received treatment and had eradication control ($n = 982$) was 76.6% ($n = 752$, [95% CI: 73.8%–79.2%]), being significantly higher in patients who had not received prior treatment, with an eradication rate of 79.9% ($n = 628$, [95% CI: 76.9%–82.6%]) versus 63.3% ($n = 124$, [95% CI: 56.1%–70.0%]) in previously treated patients ($p < 0.001$) (Table 1). The eradication rates according to the various therapeutic regimens employed, as well as the resistance patterns to clarithromycin and metronidazole, are detailed in Table S5.

The temporal progression of eradication rates exhibited substantial enhancement, manifesting as a mean annual augmentation of 2.9% (IRR 1.029 [95% CI: 1.015–1.043] $p < 0.001$) (Figure S1). The data were grouped according to the publication date of the 2016 ESPGHAN-NASPGHAN guidelines. A significant improvement in the eradication rates was observed following the publication of the guideline, with an eradication rate of 74.0% ($n = 381$, [95% CI: 69.9%–77.7%]) from 2011 to 2016, compared to 85.5% ($n = 370$, [95% CI: 81.7%–88.6%]) from 2017 to 2020 ($p < 0.001$).

4 | DISCUSSION

In our setting, antibiotic resistance was markedly elevated, with primary resistance to clarithromycin and metronidazole at 38.2% and 17.8%, respectively, and a notable increase to 61% and 47%, respectively, in patients with prior unsuccessful eradication treatment. The results revealed resistance rates that are highly comparable to those previously documented in our country in studies with a smaller sample size.[14–16] The European Pediatric Registry of *H. pylori* Infection (EuroPedHp Registry) has yielded significantly lower overall rates of primary clarithromycin resistance (20%–25%). However, when the resistance pattern was analyzed according to the patient's origin, those from Southern Europe showed higher rates (32.5%–36.7%), consistent with those of our study. This origin has been previously identified as a risk factor for clarithromycin resistance.[17–19] These data reflect the

TABLE 3 Risk factors for clarithromycin, metronidazole, and double resistance assessed by calculating relative risk using univariate and multivariate analyses.

				Univariate analysis			Multivariate analysis		
		n/N	%	RR[a]	*p* value	95% CI	RR[a]	*p* value	95% CI
Clarithromycin									
Sex	Female	288/668	43.1						
	Male	216/506	42.7	0.99	0.884	0.87–1.13	1.02	0.733	0.90–1.16
Age (years)	5–11	260/625	41.6						
	12–17	243/548	44.3	1.07	0.343	0.93–1.22	1.11	0.121	0.97–1.26
Country of birth	Outside Spain	27/145	18.6						
	Spain	471/974	48.4	2.60	**<0.001**	1.84–3.67	2.59	**<0.001**	1.82–3.68
Previous treatment	No	357/934	38.2						
	Yes	133/218	61.0	1.60	**<0.001**	1.40–1.82	1.50	**<0.001**	1.32–1.71
Metronidazole									
Sex	Female	172/667	25.8						
	Male	108/501	21.6	0.84	0.096	0.68–1.03	0.87	0.179	0.70–1.07
Age (years)	5–11	158/622	25.4						
	12–17	121/545	22.2	0.87	0.202	0.71–1.08	0.89	0.247	0.72–1.09
Country of birth	Spain	229/971	23.6						
	Outside Spain	46/144	31.9	1.35	**0.024**	1.04–1.76	1.45	**0.006**	1.11–1.90
Previous treatment	No	165/929	17.8						
	Yes	102/217	47.0	2.65	**<0.001**	2.17–3.23	2.55	**<0.001**	2.09–3.12
Double resistance									
Sex	Female	90/667	13.5						
	Male	53/504	10.5	0.78	0.126	0.57–1.07	0.85	0.317	0.62–1.17
Age (years)	5–11	75/624	12.0						
	12–17	67/546	12.3	1.02	0.895	0.75–1.39	1.12	0.470	0.83–1.51
Country of birth	Outside Spain	8/145	5.5						
	Spain	134/972	13.8	2.50	**0.009**	1.25–4.99	2.24	**0.022**	1.12–4.45
Previous treatment	No	65/932	7.0						
	Yes	71/217	32.7	4.69	**<0.001**	3.47–6.35	4.29	**<0.001**	3.17–5.80

Abbreviations: 95% CI, 95% confidence interval; Double resistance, resistance to clarithromycin and metronidazole; RR, relative risk.

Note: Bold *p* values indicate significant differences ($p < 0.05$).

[a]RR estimated using modified Poisson regression and univariate and multivariate models.

considerable variability in antibiotic resistance patterns observed in the European pediatric population, which is influenced by several factors, including geographical area, age, and previous antibiotic use.[20–23] Our study demonstrated that unsuccessful prior treatment was the primary risk factor for resistance development. In addition, we observed that clarithromycin and double resistance were significantly more prevalent in patients of Spanish origin, whereas metronidazole resistance was more prevalent in patients of non-Spanish origin.

Regarding the evolution of resistance over the 10-year study period, we observed that clarithromycin resistance remained stable at high levels, whereas metronidazole and double resistance exhibited a notable decline. The results obtained are in line with those published by the EuroPedHp Registry, which, in its first publication covering patients enrolled from 1999 to 2002, described primary resistance to metronidazole of 23%, 21% in the period 2013–2016, and 18% in the most recently published data covering the period 2017–2020.[17–19] In another study conducted in the

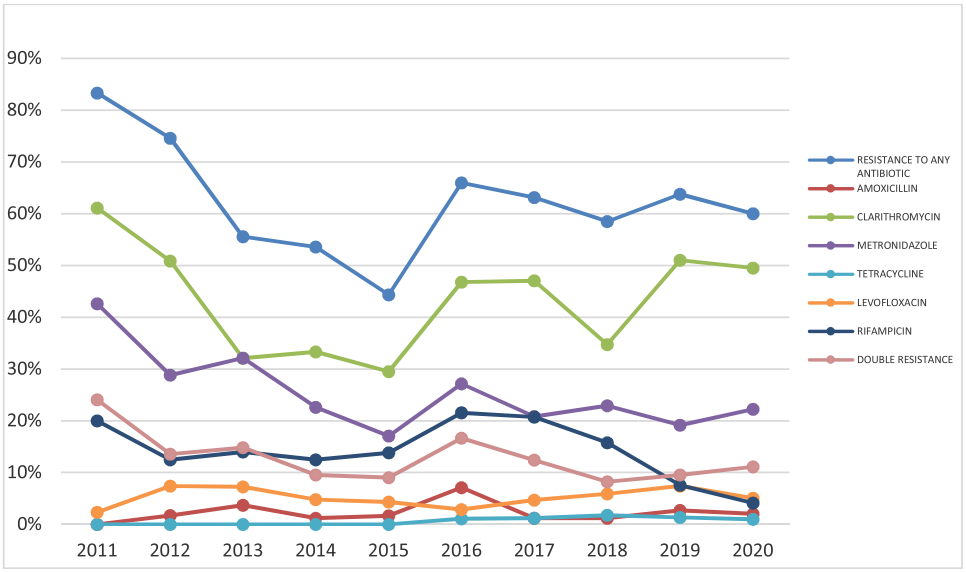

FIGURE 1 Temporal evolution of *Helicobacter pylori* antibiotic resistance among the pediatric population (aged 5–17 years) in Madrid (Spain) between 2011 and 2020.

French pediatric population over 11 years, a decrease in primary metronidazole resistance was observed, with resistances of 43% in the first period (1994–1998) compared to 32% in the second part of the study (1999–2005).[20] However, this trend was not observed in all studies conducted in the European pediatric population, as a study published in Germany between 2002 and 2015 showed an increase in metronidazole resistance when comparing the first study period (21%) with the second (34%).[22] With regard to double resistance, data from the EuroPedHp Registry have also demonstrated a substantial decrease in recent years, from 8.6% in the period 2013–2016 to 3.8% in the period 2017–2020.[18,19] In relation to the progression of resistance in adults, our findings align with those disseminated by the European Registry on *H. pylori* Management (Hp-EuReg), which also documented a significant decline in primary resistance to metronidazole when comparing the period 2013–2016 (33%) with the subsequent period 2017–2020 (24.5%), as well as a reduction in primary double resistance from 14% in the period 2013–2016 to 11% in the period 2017–2020, although in this case, the reduction was not significant.[24]

Furthermore, considerable variation in resistance was observed according to age. In the inaugural publication of the European pediatric registry, it was observed that younger children (i.e., those <6 years) exhibited significantly elevated clarithromycin resistance compared to older children (i.e., those >11 years).[17] Subsequent pediatric studies, as in our own, have not identified any significant differences in resistance patterns according to age. This is likely due to the fact that most recent studies have not included younger patients (<5 years). There was a significant divergence in the resistance pattern when comparing the pediatric and adult series. In Spain, several studies conducted on adult subjects have demonstrated significantly lower levels of primary resistance to clarithromycin (14%–22%) compared to those observed in the pediatric population. Conversely, a higher prevalence of primary resistance to metronidazole has been documented, with percentages ranging from 27% to 45%, compared to the pediatric population.[25–28] The higher rate of primary clarithromycin resistance in children compared to adults indicates that resistance is acquired in vivo during childhood. The alarming incidence of clarithromycin resistance in previously untreated pediatric patients may be associated with the increasing use of macrolide, which is commonly employed not only in empirical therapy of *H. pylori* but also in other infections prevalent in this age group, primarily respiratory infections.[9,10]

The pandemic of severe acute respiratory syndrome coronavirus 2 has precipitated a marked shift in the pattern and severity of childhood respiratory infections.[29] In November 2023, the World Health Organization issued a warning regarding an increase in respiratory diseases in children in Northern China.[30] Subsequently, this increase has been associated with a higher incidence and severity of *Mycoplasma pneumoniae* (*M. pneumoniae*) infections in children in both Asian and several European countries.[31] The impact this frequency and severity of *M. pneumoniae* infections may have on pediatric macrolide consumption and, secondarily, on *H. pylori* resistance needs to be assessed.

The eradication rates were markedly higher in patients with no prior treatment. However, despite being

targeted by sensitivity studies, eradication rates remained below the desired level (>90% eradication). This may have been influenced by other factors that could not be evaluated, such as treatment adherence. Non-adherence to treatment, defined as the ingestion of <90% of prescribed doses, is a significant contributor to therapy failure despite the use of targeted treatments.[32]

In 2016, the ESPGHAN-NASPGHAN clinical practice guidelines for the management of *H. pylori* infection in childhood and adolescence were updated. The guidelines introduced substantial alterations to the recommended treatment approach, including increasing the treatment duration to 14 days and using high doses of proton pump inhibitors, particularly in young children.[12] A comparison of eradication rates according to the date of publication of the new guidelines revealed a statistically significant improvement in eradication rates in the period following guideline publication. This improvement reflects the positive impact of the new proposed therapeutic recommendations on eradication rates.

This study has several important limitations. In particular, its retrospective nature means that some treatment-related data, such as adherence, dosage, and side effects, were not collected. Additionally, we lack data on heteroresistance, and the results on resistance patterns are specific to a particular population, meaning they cannot be generalized. Nevertheless, the extensive sample size, lengthy study period, and paucity of pediatric studies of this magnitude render these findings highly valuable, as they facilitate a comprehensive understanding of the resistance pattern and its temporal evolution. Consequently, they enable the formulation of the most suitable therapeutic strategy when culture or antibiotic sensitivity studies are unavailable.

5 | CONCLUSION

The prevalence of antibiotic resistance in our setting was exceedingly high and remained stable over the 10-year study period, with the exception of a notable decline in metronidazole and double resistance. Previous unsuccessful treatments are the primary risk factors for the emergence of antibiotic resistance. Despite the implementation of targeted treatments, eradication rates remain below the desired target (eradication >90%). However, following the publication of the 2016 ESPGHAN-NASPGHAN guidelines, a significant improvement in eradication rates was observed. This reflects the favorable impact of the new treatment recommendations proposed in the guidelines. Future research should focus on multicenter, longitudinal studies to assess *H. pylori* resistance patterns across varied populations and geographic regions, ensuring generalizable findings.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology*. 2017;153(2):420-429. doi:10.1053/j.gastro.2017.04.022
2. Homan M, Jones NL, Bontems P, et al. Updated joint ESPGHAN/NASPGHAN guidelines for management of *Helicobacter pylori* infection in children and adolescents (2023). *J Pediatr Gastroenterol Nutr*. 2024;79(3):758-785. doi:10.1002/jpn3.12314
3. Kalach N, Mention K, Guimber D, Michaud L, Spyckerelle C, Gottrand F. Helicobacter pylori infection is not associated with specific symptoms in nonulcer-dyspeptic children. *Pediatrics*. 2005;115(1):17-21. doi:10.1542/peds.2004-0131
4. Ashorn M, Rägö T, Kokkonen J, Ruuska T, Rautelin H, Karikoski R. Symptomatic response to *Helicobacter pylori* eradication in children with recurrent abdominal pain: double blind randomized placebo-controlled trial. *J Clin Gastroenterol*. 2004;38(8):646-650. doi:10.1097/01.mcg.0000135366.58536.b3
5. Spee LAA, Madderom MB, Pijpers M, van Leeuwen Y, Berger MY. Association between *Helicobacter pylori* and gastrointestinal symptoms in children. *Pediatrics*. 2010;125(3):e651-e669. doi:10.1542/peds.2010-0941
6. Buonavolontà R, Miele E, Russo D, Vecchione R, Staiano A. *Helicobacter pylori* chronic gastritis in children: to eradicate or not to eradicate? *J Pediatr*. 2011;159(1):50-56. doi:10.1016/j.jpeds.2011.01.033
7. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. *Gastroenterology*. 2018;155(5):1372-1382.e17. doi:10.1053/j.gastro.2018.07.007
8. Perez Aldana L, Kato M, Nakagawa S, et al. The relationship between consumption of antimicrobial agents and the prevalence of primary *Helicobacter pylori* resistance. *Helicobacter*. 2002;7(5):306-309. doi:10.1046/j.1523-5378.2002.00096.x
9. Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut*. 2013;62(1):34-42. doi:10.1136/gutjnl-2012-302254
10. Megraud F, Bruyndonckx R, Coenen S, et al. *Helicobacter pylori* resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. *Gut*. 2021;70(10):1815-1822. doi:10.1136/gutjnl-2021-324032
11. The European Committee on Antimicrobial Susceptibility Testing, Version 14. Breakpoint Tables for Interpretation of MICs and Zone Diameters. 2024. http://www.eucast.org
12. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents (update 2016). *J Pediatr Gastroenterol Nutr*. 2017;64(6):991-1003. doi:10.1097/MPG.0000000000001594

13. Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children. *J Pediatr Gastroenterol Nutr*. 2011; 53(2):230-243. doi:10.1097/MPG.0b013e3182227e90
14. Agudo S, Alarcón T, Cibrelus L, et al. High percentage of clarithromycin and metronidazole resistance in *Helicobacter pylori* clinical isolates obtained from Spanish children. *Rev Esp Quimioter*. 2009; 22(2):88-92.
15. Montes M, Villalon FN, Eizaguirre FJ, et al. *Helicobacter pylori* infection in children. Antimicrobial resistance and treatment response. *Helicobacter*. 2015;20(3):169-175. doi:10.1111/hel.12187
16. Botija G, García Rodríguez C, Recio Linares A, Campelo Gutiérrez C, Pérez-Fernández E, Barrio Merino A. Resistencias antibióticas y tasas de erradicación en infección por *Helicobacter pylori*. *Anales de Pediatría*. 2021;95(6): 431-437. doi:10.1016/j.anpede.2020.10.010
17. Koletzko S, Richy F, Bontems P, et al. Prospective multicentre study on antibiotic resistance of *Helicobacter pylori* strains obtained from children living in Europe. *Gut*. 2006;55(12): 1711-1716. doi:10.1136/gut.2006.091272
18. Kori M, Le Thi TG, Werkstetter K, et al. *Helicobacter pylori* infection in pediatric patients living in Europe: results of the EuroPedHP Registry 2013 to 2016. *J Pediatr Gastroenterol Nutr*. 2020;71(4):476-483. doi:10.1097/MPG.0000000000002816
19. Le Thi TG, Werkstetter K, Kotilea K, et al. Management of *Helicobacter pylori* infection in paediatric patients in Europe: results from the EuroPedHp Registry. *Infection*. 2023;51(4): 921-934. doi:10.1007/s15010-022-01948-y
20. Kalach N, Serhal L, Asmar E, et al. *Helicobacter pylori* primary resistant strains over 11 years in French children. *Diagn Microbiol Infect Dis*. 2007;59(2):217-222. doi:10.1016/j.diagmicrobio.2007.05.003
21. Oleastro M, Cabral J, Ramalho PM, et al. Primary antibiotic resistance of *Helicobacter pylori* strains isolated from Portuguese children: a prospective multicentre study over a 10 year period. *J Antimicrob Chemother*. 2011;66(10):2308-2311. doi:10.1093/jac/dkr293
22. Regnath T, Raecke O, Enninger A, Ignatius R. Increasing metronidazole and rifampicin resistance of *Helicobacter pylori* isolates obtained from children and adolescents between 2002 and 2015 in Southwest Germany. *Helicobacter*. 2017; 22(1):e12327.doi:10.1111/hel.12327
23. Silva GM, Silva HM, Nascimento J, Gonçalves JP, Pereira F, Lima R. Helicobacter pylori antimicrobial resistance in a pediatric population. *Helicobacter*. 2018;23(5):e12528. doi:10.1111/hel.12528
24. Bujanda L, Nyssen OP, Vaira D, et al. Antibiotic resistance prevalence and trends in patients infected with *Helicobacter pylori* in the period 2013-2020: results of the European Registry on *H. pylori* Management (Hp-EuReg). *Antibiotics*. 2021; 10(9):1058. doi:10.3390/antibiotics10091058
25. Agudo S, Pérez-Pérez G, Alarcón T, López-Brea M. High prevalence of clarithromycin-resistant *Helicobacter pylori* strains and risk factors associated with resistance in Madrid, Spain. *J Clin Microbiol*. 2010;48(10):3703-3707. doi:10.1128/JCM.00144-10
26. Cuadrado-Lavin A, Salcines-Caviedes JR, Carrascosa MF, et al. Antimicrobial susceptibility of *Helicobacter pylori* to six antibiotics currently used in Spain. *J Antimicrob Chemother*. 2012;67(1):170-173. doi:10.1093/jac/dkr410
27. Macías-García F, Llovo-Taboada J, Díaz-López M, Bastón-Rey I, Domínguez-Muñoz JE. High primary antibiotic resistance of *Helicobacter pylori* strains isolated from dyspeptic patients: A prevalence cross-sectional study in Spain. *Helicobacter*. 2017; 22(6):e12440. doi:10.1111/hel.12440
28. Morilla AM, Álvarez-Argüelles ME, Duque JM, Armesto E, Villar H, Melón S. Primary antimicrobial resistance rates and prevalence of *Helicobacter pylori* infection in the north of Spain. A 13-year retrospective study. *Gastroenterol Hepatol*. 2019; 42(8):476-485. doi:10.1016/j.gastrohep.2019.05.002
29. Gao Y, Feng X, Yuan T, Li M, Wei M, Li S. Post-pandemic trends: epidemiological and etiological insights into acute respiratory infections in southern China. *Diagn Microbiol Infect Dis*. 2024; 109(3):116293. doi:10.1016/j.diagmicrobio.2024.116293
30. World Health Organization. Disease Outbreak News: Upsurge of Respiratory Illnesses Among Children in Northern China. 2023. https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON494
31. Méndez-Echevarría A, Calle-Miguel L, Miralbés S, et al. Increased severity of *Mycoplasma pneumoniae* infections in Spanish children. *Pediatr Infect Dis J*. 2024;43:1113-1119. doi:10.1097/INF.0000000000004461
32. Kotilea K, Mekhael J, Salame A, et al. Eradication rate of *Helicobacter pylori* infection is directly influenced by adherence to therapy in children. *Helicobacter*. 2017;22(4):e12383. doi:10.1111/hel.12383

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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