

Can Sequential Therapy Overcome Antimicrobial Resistance in Children with *Helicobacter pylori* Infection ?



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Abstract

Introduction: Eradication rates of many therapeutic regimens for *Helicobacter pylori* (*H. pylori*) infection are not yet satisfactorily, mainly due to bacterial resistance to antibiotics, and to a limited availability of antibiotics in children.

Materials and Methods: Fifty-three children with *H. pylori* infection were prospectively enrolled, characterized by clinic, endoscopic findings and antibiotic resistance and treated with sequential therapy (ST cohort); this cohort was compared with an historic cohort of 106 children treated with standard triple therapy (TT cohort). The eradication rate of the two treatments was obtained, based on antibiotic resistance towards amoxicillin (AMO), metronidazole (MET), and clarithromycin (CLA).

Results: In the ST cohort: 27 patients (51%) resulted susceptible towards antibiotics; the eradication rate was of 88.7% (47/53 patients) overall, and of 84.6% (22/26 patients) among patients with resistance. In the TT cohort: 53 (50%) resulted susceptible towards antibiotics; the eradication rate was of 87.7% (93/106 patients) overall, and of 79.2% (42/53 patients) among patients with resistance. The two cohorts had a similar overall eradication rate (p value 0.23), while the eradication rate in patients with resistance was significantly higher for the ST cohort (p value 0.04).

Conclusion: Sequential regimen could be a valid option to eradicate *H. pylori* infection, especially in case of antimicrobial resistance.

Abbreviations: AMO: amoxicillin; CLA: clarithromycin; MET: metronidazole; PPI: Proton Pump Inhibitor; SPSS: Statistical Package for Social Science triple; TT: therapy; ST: sequential therapy; PPI: Proton Pump Inhibitor

Introduction

Although its progressive decline over the years, the prevalence of *Helicobacter pylori* (*H. pylori*) is still high in most countries. Epidemiological studies report that in North European and North American populations, about one-third of adults are infected, whereas in south and east Europe, South America, and Asia, the prevalence of *H. pylori* is often higher than 50% [1]. Nevertheless, the prevalence in paediatric age ranges from 11% to 66.5% in Western Europe [1]. *H. pylori* infection is typically acquired during childhood and persists throughout life in absence of specific treatments. The epidemiological interest related to *H. pylori* is due

to its major role in the pathogenesis of several gastrointestinal diseases, from chronic gastritis to gastric adenocarcinoma [2]. Gastric malignancies are mainly observed in adulthood, whereas few cases of lymphomas are also described in children [3,4].

However, the eradication of *H. pylori* is advised despite the age of the patient because it represents an appropriate primary chemoprevention of gastric cancer, especially among younger people, as well as of the development of atrophic gastritis and intestinal metaplasia [5], which are well known precursors of malignancy [5]. Since the discovery of *H. pylori*, many therapeutic

regimens have been proposed and used in both adults and children to obtain a good eradication rate of the bacterium. However, in children the currently available antibiotics are limited. Basically, amoxicillin (AMO), clarithromycin (CLA), metronidazole (MET), and bismuth-salts in different combinations are the more frequently used [6], although bismuth salts are no longer available in some countries like Italy.

Other effective medications, such as fluoroquinolones and tetracycline, which are currently used in adults to eradicate *H. pylori*, cannot be administered in pediatric ages due to the risk of, respectively, arthropathy and damage to the immature cartilage [7], and permanent tooth discoloration [8-10]. Moreover, the current guidelines for pediatric age do not recommend a single therapeutic regimen, but indicate multiple combinations as a first-line therapy: 10-days triple therapy with a Proton Pump Inhibitor (PPI) + AMO + imidazole, or PPI + AMO + CLA, or bismuth salts + AMO + imidazole, or sequential therapy with PPI + AMO for the first 5 days followed by PPI + CLA + imidazole for the next 5 days [6]. In case of *H. pylori* infection, the goal of treatment should be an at least 90% eradication rate in a per-protocol analysis at the first attempt [6].

However, the most used triple therapy has been shown to achieve most of the time an eradication rate lower than 80% [2]. This reduced efficacy is due to several factors, above all to the bacterial resistance to antibiotics, especially to CLA. Several studies documented high levels of CLA resistance (CLA-R) and MET resistance (MET-R) in pediatric and adult populations [11-13] all over the world. Particularly in the last years, the CLA-R rate has increased (in Italy is around 25% in both adults and children) [14-16], whereas MET-R rate has been decreasing [14]. As the high antimicrobial resistance rate is mainly to CLA, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition/ North American Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN/NASPGHAN) guidelines recommend investigating either the personal or the local antimicrobial susceptibility patterns before treating *H. pylori*-infected children in order to achieve the best eradication rate.

As the availability of antibiotics in children is limited, the CLA-R and MET-R should be overcome in the eradication of *H. pylori* infection. The reduction of antibiotic resistance would result not only in an improvement of the eradication rate, but would also limit the spread of resistant *H. pylori* strains through the population [6]. In this perspective, the resistance rates of the area where the patient lives or comes from should be taken into account while choosing the initial therapeutic regimen for eradication. Therefore, CLA-based triple therapy can only be recommended as first-line therapy if susceptibility testing in the individual patient revealed a CLA-susceptible strain or if the CLA-R rate known for that area is low. In absence of these conditions, CLA-based triple therapy is not recommended as first-line therapy [6].

Alternatively, a sequential therapy has been proposed [6]. Several trials demonstrated that the eradication rate following this 10-day sequential regimen is significantly higher than either the 7- or 10-day standard triple therapy [17-20]. Although the exact mechanism has not yet been understood, studies suggest that the initial use of

AMO reduces the bacterial load and provides protection against CLA-R [21]. Moreover, some studies demonstrated that sequential therapy could overcome CLA-R and MET-R [22]. A meta-analysis by Tong et al. showed that sequential therapy eradicated *H. pylori* infection in 70.7% vs. 33.8% of patients with CLA-R and in 96% vs. 67.6% of those with MET-R compared to standard triple therapy [23]. Of note, most of the studies included in the meta-analysis were conducted in adults, while only a few tested the sequential therapy in pediatrics. The present study aims to evaluate the effectiveness of sequential therapy in overcoming CLA and MET resistances and consequently in improving eradication rates in children with *H. pylori* infection in Italy, where we can mainly use three different antibiotics: AMO, CLA and MET in different combination.

Materials and Methods

Children with *H. pylori* infection consecutively admitted to the Department of Pediatric Gastroenterology of the University Hospital of Parma, Italy, were eligible for recruitment. *H. pylori* infection was confirmed by using at least two tests among the following: detection of fecal antigen (with monoclonal antibodies), rapid urease test, urea breath test, histological detection and culture from gastric biopsies [24]. Only patients with confirmed diagnosis of *H. pylori* infection were eligible for the inclusion. Patients were screened for eligibility during the clinic visits.

Exclusion criteria were: refusal to sign the informed consent, previous *H. pylori* treatments and therapies with either proton pump inhibitors or antibiotics in the 4 weeks before esophagogastroduodenoscopy [6]. Eligible patients and their family were given information describing the study, and subsequently, written consent to participate was gathered. The study protocol was approved by the local ethics Committee and was conducted in accordance with the Declaration of Helsinki (1964). The eligible patients underwent esophagogastroduodenoscopy with biopsies according to evidence-based guidelines for *H. pylori* infection in children [6]. The biopsy specimens for histology were fixed in formalin, embedded in paraffin, sectioned, and stained with haematoxylin-eosin. Histological examination was made following the Sydney Criteria (at least two biopsies from the gastric antrum and two biopsies from the corpus) [2].

The microbiological culture was made on two biopsies (one from the antrum and one from the corpus) [2,6,25]. The biopsy specimens for the bacterial culture were immediately placed in an appropriate transport medium (Portagerm-Pylori, bioMérieux, France) and then homogenised and cultured on both selective (Pylori agar, bioMérieux) and nonselective (10% horse blood agar, Kima, Italy) media. After seven days of incubation at 37°C under microaerophilic conditions, typical oxidase and catalase positive colonies were identified by API Campy strips (bioMérieux) and subsequently tested for antibiotic sensitivity to AMO, CLA, and MET. Data about demographics, country of origin, clinical status, endoscopic findings and antimicrobial resistance were prospectively collected. In case of failure of the bacterial culture and antimicrobial susceptibility testing, patients were excluded from the study.

All the included patients received a 10-day sequential therapy, consisting in: esomeprazole (0.8-1.3mg/kg/die) + AMO (50-60mg/kg/die b.i.d.) for the first 5 days followed by esomeprazole (0.8-1.3mg/kg/die) + CLA (15-20 mg/kg/die) and tinidazole (20-30mg/kg/die b.i.d.) for the next 5 days, regardless of their antimicrobial susceptibility testing. The correct intake of antibiotics was checked by regular phone calls to the patients' parents during and at the end of the sequential therapy. The eradication was verified by Urea Breath Test after two months from the end of the antibiotic administration. Familial screening was also advised for all the patients, to limit the risk of reinfection[6].

The antibiotic resistance was additionally classified based on the country of origin of the patients to verify if the prevalence differed among countries. The cohort of the enrolled patients receiving the sequential therapy was compared with a historic cohort of 106 paediatric patients with *H. pylori* infection, who were treated with standard triple therapy [26]. Statistical analyses were

performed with SPSS (Statistical Package for Social Science, IBM SPSS Statistics, version 23 for Macintosh; IBM, Armonk, NY). Data are presented as mean (standard deviation) or number and (%). Groups were compared by using chi-square test, Fisher's exact test, or Mann-Whitney U test.

Results and Discussion

Between July 2013 and July 2015, 61 children admitted at the Department of Pediatrics Gastroenterology with suspected *H. pylori* infection were evaluated for the enrollment in the present study. Finally, 53 children (mean age: 10.13 years, standard deviation: 3.67) met the inclusion criteria and were included in the study analyses. Demographics, clinical, and endoscopic findings are displayed in Table 1. Clinically, the most frequent presentation of *H. pylori* gastritis was epigastric pain and/or abdominal pain in 32 patients (60.4%), while the most frequent endoscopic appearance was a nodular aspect of the mucosa in 41 patients (77.4%).

Table 1: Demographic and clinical characteristics of the ST and TT groups.

Variables	ST Group (n=53)	TT Group (n=106)	P Value
Sex [n (%)]:			
-Males	32 (60.4)	66 (62.3)	0.88
-Females	21 (39.3)	40 (37.7)	
Age, years [median (range)]	10.3 (3-18)	11 (2-18)	0.65
Symptoms [n (%)]:			
-Epigastric/abdominal pain	32 (60.4)	63 (59.5)	0.12
-Pyrosis/dyspepsia	6 (11.3)	21 (19.8)	
-Vomit	8 (15)	13 (12.2)	
Endoscopic findings [n (%)]:	8 (15.1)		0.24
-Macroscopically normal	4 (7.5)	24 (22.6)	
-Hemorrhagic aspect	41 (77.4)	4 (3.3)	
-Nodular aspect		78 (73.5)	
Antibiotic resistance [n (%)]	26 (49)	53 (50)	1
Eradication rate [n (%)]			
-Overall	47 (88.7)	93 (87.7)	0.23
-In patients with resistance	22 (84.6)	42 (79.2)	0.04

ST stands for sequential therapy; TT for triple therapy.

Regarding the antimicrobial susceptibility testing, 27 patients (51%) showed susceptibility towards all antibiotics, 13 (24.5%) had isolate MET-R, 12 (22.6%) had isolate CLA-R, and 1 (1.9%) had MET-R and CLA-R simultaneously. None of the patients showed AMO-R. Overall, the eradication rate following the sequential therapy was 88.7% (95% Confidence Interval (CI) = 0.79-0.96), corresponding to 47/53 patients. Among the 27 full-susceptible patients, a 95% eradication rate was observed. Among the children with MET-R or CLA-R, the majority showed *H. pylori* eradication following treatment (92.8%, 95%CI = 0.79-1.06 for MET-R; 75%, 95% CI = 0.51-0.99 for CLA-R), including the children with double

resistance, i.e., MET-R and CLA-R (Table 2). Moreover, two out of three children with CLA-R are brothers and their parents had *H. pylori* infection too.

Table 2: Eradication rate in the ST group.

Variables	Overall study population [n(%)]		Eradication rate [%]
CLA-R	12	(22.6%)	75
MET-R	13	(24.5%)	92.8
CLA-R+MET-R	1	(1.9%)	100

Full-susceptible	27 (51%)	95
Total	53 (100)	88.7

ST stands for sequential therapy

The study sample was compared with a historic cohort of 106 children (mean age: 11 years, standard deviation: 2.53) with *H. pylori* infection (Table 1). Even in this cohort, epigastric and/or abdominal pain were referred by the majority of the patients (59.5%; 63patients); endoscopically, a nodular gastritis was present in 78patients (73.5%), while in 24 patients (22.6%) the mucosa was macroscopically normal. All patients were treated with triple therapy (TT). Half of them showed an antimicrobial resistance. With TT, 93 patients were eradicated achieving an overall eradication rate of 87.7% (95% Confidence Interval (CI) =0.79-0.96). Among the patients with antibiotic resistance, a 79.2% eradication rate was achieved with TT.

Compared to sequential therapy (ST), the overall eradication rate was not different between the groups; however, a significant difference was observed when comparing the eradication rate between ST and TT treatments in the subgroup of pediatric patients showing antibiotic resistance (p=0.04). The present study suggests the use of sequential therapy as the first choice for

H. pylori infection eradication in children, due to its satisfactory eradication rate (88.7%), even in presence of antibiotic resistance (84.6%). Especially in patients with antibiotic resistance, the eradication rate of *H. pylori* appears to be superior by administering a 10-day sequential therapy than a triple therapy. The importance of achieving an elevated eradication rate at a first attempt is not only associated to the elimination of a risk factor for potentially evolutionary lesions, but also to the limitation of the development and spread of new antibiotic resistances through the population [1,6].

The current guidelines for the treatment of *H. pylori* infection do not advise a single treatment neither in adult nor in pediatric age, but suggest a spectrum of preferential therapies [6,24]. The absence of a unique strategy is due to different causes. First, the sensibility of *H. pylori* is limited to a few molecules [2,6,24]. Secondly, the availability of antibiotics varies among countries, being for example the bismuth salts not available in Italy. Moreover, some classes of antibiotics are contraindicated in pediatric age [7,8,10]. Finally, the available data in the literature are not completely concordant, being the eradication rate of the various regimens comparable in some studies [27,28], and different in others [29-31]. The majority of the recent studies conducted in pediatrics compared standard triple therapy with sequential therapy (Table 3).

Table 3: Comparative studies of sequential therapy vs. triple therapy in pediatric age.

Author	N°	Mean age (range)	Eradication rate by Sequential therapy (10 days)		Eradication rate by Triple therapy (7 days)		Eradication rate by Triple therapy (10 days)	
Huang et al	360	8.8 (3-16)	81.4%	89.7%	61.9%(it)	70.8%(pp)	67.7% (itt)	77.8% (pp)
2013			(itt)	(pp)				
Ali Habib et al 2013	18	(12-15)	57.1%		na		55.6%	
Iwanczak et al 2016	69	(5-17)	91.3%		na		78.2%	
Kutluk et al	148	12.2 (3-18)	50%	56%		na	52.7% (itt)	55.7% (pp)
2014			(itt)	(pp)				
Laving et al 2013	71	8.9 (2- 16)	84.6%		na		48.8%	

Itt: intention-to-treat analysis

Pp: per-protocol analysis

Na: not available

The reported eradication rate following 10-day sequential therapy ranges from 50% to 91.3%, whereas the eradication rate following 10-day triple therapy ranges from 48.8% to 78.2%. Thus, the majority of the studies, as well as meta-analyses, support the superiority of the sequential therapy over the triple therapy in the eradication of *H. pylori* infection in patients with or without antibiotic resistances [23,32,33]. However, when looking further into the literature concerning the use of sequential therapy in patients with antibiotic resistance, results are controversial [34]. A recent paediatric European multicentric study [35], observed the eradication of *H. pylori* by sequential therapy in less than 80% of patients with antibiotic resistances; thus, the authors did not

recommend the use of this therapeutic regimen in presence of antibiotic resistance.

The comparison of the eradication rate based on the presence of antibiotic resistance appears to be of primary importance not only in response to the epidemiology of different strains of *H. pylori* with the relative antimicrobial resistance, but also to evaluate which therapeutic regimen is preferable in the different countries. The present study demonstrated that the standard triple therapy and sequential therapy have a similar eradication rate (87.7% and 88.7% respectively) considering the whole sample of patients, but the sequential therapy achieves a significantly higher efficacy in the

eradication of resistant strains (84.6% vs 79.2%). The superiority of the sequential therapy in the eradication of *H. pylori* resistant strains supports its choice even in absence of a well-known resistance.

As both the clinic and the endoscopic appearance may be non-specific, this infection can be discovered incidentally during esophagogastroduodenoscopy for reflux symptoms, for example. In the present study the majority of patients of both cohorts presented with epigastric and/or abdominal pain (60.4% and 59.5%). On the contrary, the endoscopic appearance was most frequently characteristic, presenting with a nodular gastritis in 77.4% and 73.5% of cases, although the aspect of the mucosa cannot be considered diagnostic but only suspect. Moreover, in 15.1% and 22.6% of the patients, the esophagogastroduodenoscopy was completely normal, and the diagnosis of *H. pylori* gastritis could be confirmed only by specific tests, including histology and culture.

In absence of a specific suspect, the microbiological culture and the consequent susceptibility tests might not be made for all patients who undergo upper endoscopy. In the case of unknown antibiotic resistance, it is possible to assume to be in presence of a resistant strain, and consequently the therapeutic regimen with the highest eradication rate against resistant strains should be preferred, i.e. sequential therapy. Although the sequential therapy has been used for many years, the exact mechanism of action remains unknown. AMO can eradicate *H. pylori* in about 50% of infected patients and reduces the bacterial load in the remaining cases, improving the response to the subsequent short course of triple therapy. Indeed, AMO destroys the bacterial cell wall, increasing the intracellular diffusion of the macrolide, and improving the treatment outcome. AMO in the initial dual therapy phase is thought to prevent the selection of secondary CLA-R and thus increasing the efficacy of CLA in the second phase of treatment [22]. Furthermore, the higher efficacy may also be due to the addition of a new drug, tinidazole, to the standard regimen.

Tinidazole is similar to MET but has a longer duration of action. While evaluating the efficacy of an eradication regimen, the risk of reinfection, for instance due to the presence of an infected family member, should always be considered. Of note, in the present study, two patients among those with CLA-R who were not eradicated had their parents infected by *H. pylori* too. The failure of the eradication in patients like these could be due to a reinfection by the parents and not to a lack of efficacy of the sequential therapy. This hypothesis should be verified in larger studies, but it would further increase the percentage of success of sequential therapy in patients with CLA-R and consequently the overall eradication rate. The present study has some limitations, including the small sample size and the comparison with an historic cohort as control group. The choice of using only the sequential therapy for the patients prospectively enrolled was guided by the already available literature that, although limited, supports its higher efficacy compared to the standard double or triple therapy [28,29].

In future studies, it would be of interest to understand if a large-scale application of the sequential regimen in pediatric age could effectively change the epidemiology of *H. pylori* infection, by

lowering the overall prevalence thanks to the efficacy in overcoming antimicrobial resistance. Consequently, also the epidemiology of resistant strains may change, following to the limited diffusion of resistances. Moreover, in order to broaden the spectrum of available antibiotics in children with *H. pylori* infection, further studies should evaluate the efficacy of antibiotics as bismuth salts, furazolidone and fluoroquinolones [36,37], as well as of other non-pharmacological substances, like probiotics and vitamins, which has been already studied in *H. pylori* infection [34] and could be helpful to improve the eradication rate.

Conclusion

In conclusion, the present study confirms that the sequential therapy can overcome the antibiotic resistance in children with *H. pylori* infection, with an acceptable eradication rate (88.7%). Antibiotic-resistant strains of *H. pylori* remain a challenge for a successful eradication and a tailored therapy may be required.

Data availability all the data collected during the conduction of the study is described in the paper. There is no additional data available. Conflicts of interest the authors of this manuscript have no conflicts of interest to disclose. Funding statement the present study did not receive any funding. The research was performed as part of the employment of the authors, in the context of their institutions.

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