



Assessment of the Effectiveness of Eradication Therapy and its Predictors in Children with *Helicobacter Pylori* Infection



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Abstract

Helicobacter pylori (HP) is the most common bacterial infection in humans. However, recently, the effectiveness of HP treatment has fallen. The aim of this work is to evaluate the effectiveness of eradication therapy in children infected with HP and to identify the factors that may influence treatment effectiveness. A retrospective, single-centre study of 94 children, with chronic gastritis and duodenitis associated with HP infection during the period 01.01.2014 to 31.12.2016 was performed. The mean age was 11.2±4.9 years (range 2 to 18 years). Of these, 81% received 10- or 14-day triple therapy and 19% 10-day sequential therapy. Success was indicated by a correct result on the urea breath test. The influence of selected demographic and clinical parameters was analyzed, and an esophagogastroduodenoscopic and histopathological evaluation. Eradication of HP infection was achieved in 77 children (82%), 66 of whom (86.8%) were treated by the triple therapy regimen and 11 (61.1%) with sequential therapy (p=0.01). Remission was confirmed in 48 of 77 children (62.3%) treated effectively, and nine of 17 (52.9%) treated ineffectively (p=0.02). A statistically significant predictor of successful HP eradication was moderate microscopic gastritis and the use of omeprazole. Ineffective therapy was predicted by high-grade microscopic gastritis and the use of pantoprazole. The therapies currently used to treat HP infection in Poland are unsatisfactory. New treatment regimens are needed which take into account the antibiotic susceptibility of bacteria. Patient-related factors appear to be of little value in predicting treatment efficacy.

Keywords: *Helicobacter pylori*; Eradication in children; Urea breath test; Treatment effectiveness

Introduction

Helicobacter pylori (HP) is a helical Gram-negative bacterium that was first discovered in 1982 by two Nobel prize winners: Robin Warren and Barry Marshall [1]. The bacterium is helical in shape and has several flagella, allowing it to penetrate under the mucus layer covering the gastric and duodenal epithelial cells [1]. HP multiplies only in a microaerophilic environment and has strong adaptability, demonstrating resistance to acid environments [1,2]. Infection with HP is considered chronic [3]. HP is believed to be the most common bacterial infection among humans, being present in approximately 50% of the global population [4-7]. A meta-analysis by Zamani et al. found 32.6% of children to have HP infection globally [8]. Similarly, to the adult population, the highest rate of HP infection is recorded in developing countries, i.e. up to 60%, and the lowest in highly-developed countries, i.e. below 10% [9]. In Europe, the highest rate of infection was observed in Bulgaria (61.7%), and the lowest in the Netherlands (1.2%) [10]. In Poland,

studies performed in 2002-2003 found the prevalence of HP in the pediatric population to be 32% [11] with a clear downward trend observed in the following years [12].

Although it remains unclear how HP is spread, it is assumed that humans constitute the only natural reservoir [3]. HP infection appears to occur between humans, most often in early childhood, probably due to intra-family transmission i.e. the pathogen spreading among family members living together [3,10]. The pathogen is most often transmitted through the alimentary-oral, oral-oral or faecal-oral routes, and as such, the risk of infection is facilitated by contaminated food and water [3,9,10]. In children, the risk of infection is influenced by low socioeconomic status, improper hygiene, high density accommodation, comorbidities, parental education level, sex, age and geographical area, and individual predisposition [3,7,9]. Although it is believed that 85% of those infected with HP remain asymptomatic for many

years [9,13]. HP infection is associated with a range of symptoms, the most common being nausea, occasional vomiting, early postprandial satiety, diarrhoea, recurrent abdominal pain, iron deficiency anaemia, gastrointestinal bleeding, vitamin B12 deficiency, allergic skin lesions (urticaria) and weight loss [9,10,13,14]. Long-term infection with HP may also lead to chronic gastritis and / or duodenitis, peptic ulcer disease or even gastric cancer or MALT lymphoma [14,15].

The available diagnostic methods include invasive methods, such as gastroscopy with biopsy, bacterial culture, genetic testing of HP and rapid urease test performed with the use of biopsies, as well as non-invasive methods, such as respiratory test with C13-labeled urea, presence of HP antigen in faeces and serological testing [14]. The recommended standard for diagnosing HP infection in children should be a histopathological examination (confirmation of the presence of HP in a mucosal biopsy) together with at least one positive result of another test performed in biopsy specimens or a positive culture [14]. The aim of treating HP infection is to eradicate the pathogen, and various eradication therapy protocols have been devised. These protocols are divided into empirical and individualized approaches [16]. The former can be further divided into sequential, triple or quadruple therapy, and takes into account the current antibiotic resistance of the strain from a given area [14,16]. Of these, sequential therapy appears to offer no advantage over triple therapy for the treatment of HP infection in children [7]. Therefore, doctors should follow the ESPGHAN and NASPGHAN guidelines when selecting treatment for HP infection, especially in children; an individualized approach should be taken for both diagnosis and treatment, after detailed discussion of the potential risks and benefits of treatment with the patient or her parents [14,17]. Following completion, the effectiveness of the therapy should be evaluated at least four weeks after completion using a reliable and non-invasive test [14].

The aim of this study is to determine the effectiveness of eradication therapy in children infected with HP and to identify the factors that may determine its outcome.

Materials and Methods

A retrospective, single-centre study was performed based on the medical records of all patients with HP infection hospitalized in the Department of Paediatrics, Allergology and Gastroenterology, Collegium Medicum (CM), and under the care of the Clinical Gastroenterological Outpatient Clinic in the period from 01.01.2014 to 31.12.2016. The study group comprised 94 children with chronic gastritis or duodenitis associated with HP infection. Of these, 56 were female (59.6%) and 38 male (40.4%). The age of the participants ranged from 2-18 years (mean age 11.2±4.9 years). Of the group, 44 (47%) patients had comorbidities: three with gastroesophageal reflux disease (7%), one with celiac disease (2%), three with inflammatory bowel disease (7%), two with neurological disorders (5%), ten with allergies (23%), two with thyroid disease (5%) and 23 with other conditions

(52%). In all patients, HP infection was diagnosed on the basis of a positive histopathological examination of gastric biopsies and a positive rapid urease test. The indication for endoscopic examination of the upper gastrointestinal tract was gastrological symptoms, mainly chronic abdominal pain that did not meet the criteria for functional disorders (87 patients: 92.6%). The endoscopy results indicate that 91 (97%) patients had chronic gastritis, three of whom (3%) were severe, and 23 (25%) with duodenitis, including eight (35%) with erosive duodenitis. Based on the histopathological examination of gastric biopsies, seven (8%) patients were diagnosed with mild gastritis, 50 (53%) with moderate gastritis and 37 (39%) with severe gastritis according to the Sydney classification.

During eradication therapy, 76 (81%) patients were treated with triple therapy (amoxicillin, metronidazole, proton pump inhibitor, PPI) for 10 - 14 days, and 18 (19%) with sequential therapy. In sequential therapy, amoxicillin with PPIs was used for the first five days, and clarithromycin with metronidazole and PPIs for the next five. The doses of drugs used in eradication therapy were consistent with those recommended by ESPGHAN / NASPGHAN [17]. In 33 (35.1%) patients, the eradication therapy protocol included a probiotic (*Saccharomyces boulardii* or *Lactobacillus*). The effectiveness of HP eradication was determined on the basis of a detailed medical history and a urea respiratory test performed in the period from four to eight weeks after the end of therapy. Medical history was used to establish clinical remission (complete relief of symptoms) or absence (presence of any clinical symptoms). The characteristics of the participants are presented in Table 1.

Endoscopic examination, together with macroscopic evaluation, was performed in the Pediatric Endoscopy Laboratory by a pediatric gastroenterologist with more than 10 years of experience, using GIF-160, GIF Q165 and GIFH180J endoscopes (Olympus, Europa). Four biopsies were collected for histopathological examination, including two from the gastric body and two from the antral part; these were assessed at the Chair and Department of Clinical Pathomorphology, CM, according to the Sydney classification, using standard hematoxylin and eosin staining. An additional two biopsies of the gastric mucosa were collected for evaluation by rapid urease test (Lencomm Trade); the result was assessed by an endoscopist, who performed the test 5-60 minutes after applying the biopsy to the test plate. The urea respiratory test was performed using C13-labeled urea and FANci 2 equipment (Olympus) according to the manufacturer's recommendations. A value of ≤ 4 per ml was assumed as a successful result, indicating eradication of HP bacteria. In order to assess the prognostic factors of effective eradication, the occurrence of selected demographic parameters was analysed (sex; age; body weight assessment according to BMI i.e. underweight, normal, overweight, obese; social circle i.e. kindergarten or school; place of residence, i.e. city or village), as well as certain clinical factors (chronic abdominal pain, nausea, vomiting, chronic

flatulence, fetor ex ore, empty belching, heartburn, weight loss, the presence of comorbidities). In addition, the results of endoscopic evaluation of the stomach and duodenum were included: the presence of chronic gastritis, including severe gastritis, and erosive inflammation of the duodenal mucosa. Finally, problems

associated with the gastric mucosa (chronic low, medium and high degree inflammation) and the type of drugs used in eradication therapy were included in the analysis. The group of patients who achieved HP eradication were compared with those who did not.

Table 1: The characteristics of the study group.

Parameter	Study Group n=94 (100%)
Age in years, n (%) ≤ 12 y.o. > 12 y.o. mean ± SD min - max	60 (63.8) 34 (36.2) 11.2 ± 4.9 2-18
Sex, n (%) boys girls	38 (40.4) 56 (59.6)
Body weight assessment according to BMI, n (%) obese (>97c) overweight (90-97c) normal (3-90c) underweight (<3c)	2 (2) 18 (19.2) 59 (62.8) 15 (16)
Place of residence, n (%) city village	66 (70.2) 28 (29.8)
Attending human communities (creche, kindergarten, school), n (%)	90 (95.8)
Type of complaints reported before treatment, n (%) chronic abdominal pain nausea vomiting heartburn fetor ex ore empty belching chronic flatulence weight loss	87 (92.6) 21 (22.3) 20 (21.3) 13 (13.8) 9 (9.6) 9 (9.6) 7 (7.5) 3 (3.2)
The presence of comorbidities, n (%)	44 (47)
The macroscopic image of endoscopic lesions before treatment, n (%) chronic gastritis chronic duodenitis	91 (97) 23 (25)
The result of a histopathological examination of biopsies taken from the stomach during the endoscopy before treatment, n (%) chronic low-grade gastritis chronic medium grade gastritis chronic high grade gastritis	7 (8) 50 (53) 37 (39)
The used treatment, n (%) triple therapy sequential therapy	76 (81) 18 (19)

The frequency of occurrence of categorical variables and their basic risk factors were analysed using the Chi2 test. The distributions of the continuous variables were checked for normality using the Shapiro-Wilk test: the groups were then compared using the Student's t-test if the distribution was normal, or the Mann-Whitney non-parametric test if it was not. Qualitative variables were described as number (N) and percentage (%) of cases, and continuous variables as either median and range (Me,

Min - Max) or mean and standard deviation (M, SD). The obtained results were then verified by univariate and multivariate logistic regression; these procedures tested the statistical significance of individual risk factors and calculated their odds ratios (ORs) with 95% confidence intervals. Statistical hypotheses were verified at a significance level of $p < 0.05$. The calculations were performed using the STATISTICA version 13 statistical package (StatSoft). 1.

Results

Table 2: Analysis of the effectiveness of eradication treatment depending on the selected demographic and clinical parameters, endoscopic evaluation of the stomach and duodenum and histopathological evaluation of the gastric mucosa, as well as the type of therapy used.

Parameter	The Result of the Urea Respiratory Test after Treatment		p	OR	95% CI
	Correct n=77 (82%)	Incorrect n=17 (18%)			
Sex, n (%)					
Boys	32 (42)	6 (35)	0.63	1.3	0.44 - 3.89
Girls	45 (58)	11 (65)	0.63	0.77	0.26 - 2.29
Age in years, n (%)					
≤ 12 y.o.	29 (38)	5 (29)	0.35	1.45	0.46 - 4.55
>12 y.o.	48 (62)	12 (71)	0.35	0.69	0.22 - 2.16
Body weight assessment according to BMI, n (%)					
Underweight	11 (14)	4 (24)	0.35	0.54	0.15 - 1.97
Normal	48 (62)	10 (59)	0.31	1.77	0.59 - 5.32
Overweight	16 (21)	3 (18)	0.77	1.22	0.31 - 4.78
Obese	2 (3)	0 (0)	0.92	0.85	0.30 - 2.96
Attending human communities (creche, kindergarten, school), n (%)	75 (97)	15 (88)	0.3	5	0.50-38.33
Place of residence, n (%)					
City	54 (70)	12 (71)	0.97	1.02	0.32-3.23
Village	23 (30)	5 (29)	0.97	0.98	0.31-3.10
Type of complaints reported before treatment, n (%)					
Chronic abdominal pain	70 (91)	17 (100)	0.2	0.27	0.01 - 4.93
Nausea	17 (22)	4 (24)	0.79	0.92	0.26 - 3.19
Vomiting	11 (14)	9 (53)	0.53	0.15	0.05 - 0.47
Chronic flatulence	5 (7)	2 (12)	0.45	0.52	0.09 - 2.94
Heartburn	12 (16)	1 (6)	0.29	2.95	0.36 - 24.41
Fetor ex ore	8 (10)	1 (6)	0.57	1.85	0.22 - 15.91
Empty belching	6 (8)	3 (18)	0.4	0.39	0.09 - 1.77
Weight loss	3 (4)	0 (0)	0.82	1.64	0.08 - 33.31
The presence of comorbidities, n (%)	37 (48)	7 (41)	0.67	1.32	0.46 - 3.83

The endoscopic image of lesions before treatment, n (%)					
Chronic gastritis	72 (94)	16 (94)	0.93	0.9	0.09 - 8.24
High grade gastritis	2 (3)	1 (6)	0.49	0.46	0.04 - 5.36
Chronic duodenitis	13 (17)	2 (12)	0.6	1.8	0.37 - 8.89
Erosive duodenitis	6 (8)	2 (12)	0.6	0.63	0.12 - 3.45
The result of a histopathological examination of biopsies taken from the stomach during the endoscopy before treatment, n (%)					
Chronic low-grade gastritis	5 (7)	2 (12)	0.92	0.52	0.09 - 2.94
Chronic medium grade gastritis	45 (58)	5 (29)	0.03*	3.37	1.08 - 10.53
Chronic high-grade gastritis	27 (35)	10 (59)	0.02*	0.38	0.13 - 1.10
The used treatment, n (%)					
Triple therapy	66 (86.8)	10 (13.2)	0.01*	4.2	1.31 - 13.37
Sequential therapy	11 (61.1)	7 (38.9)	0.01*	0.24	0.07 - 0.76
The used PPI, n (%)					
Omeprazole	47 (61)	6 (35)	0.05#	2.87	0.96 - 8.59
Pantoprazole	30 (39)	11 (65)	0.05#	0.35	0.12 - 1.04
Use of a probiotic, n (%)	25 (32)	8 (47)	0.38	0.54	0.19 - 0.57

*p<0.05, #p=0.05

In total, 77 children (82%) demonstrated eradication of HP infection, as indicated by normal urea breath test results: 66 (86.8%) treated with the triple therapy and in 11 (61.1%) with sequential therapy. The use of triple therapy significantly increased the chance of successful eradication, i.e. by more than fourfold (p = 0.01; OR 4.2; 95% CI 1.31 - 13.37). Clinical remission was confirmed in 48 of 77 children (62.3%) whose HP infection had been eradicated, and in nine of 17 children (52.9%) who had not, i.e. those who still demonstrated an abnormal UBT result after treatment. The chance of achieving clinical remission was found to significantly depend on the effectiveness of eradication (p = 0.02). None of the analysed demographic parameters, nor any of the symptoms occurring before treatment, nor the coexistence of other diseases influenced to failure of HP eradication therapy. A detailed analysis of the relationship between effective eradication and selected demographic and clinical parameters is presented in Table 2.

However, the histopathological analysis of the gastric mucosa indicated that moderate gastritis was a statistically significant predictor of successful HP eradication (p = 0.03; OR 3.37; 95% CI 1.08-10.53), while high-grade lesions increase the risk of treatment failure (p = 0.02; OR 0.38; 95% CI 0.13-1.10). None of the endoscopic diagnoses significantly influenced the effectiveness of eradication. The influence of selected aspects of the endoscopic evaluation of the stomach and duodenum on eradication efficiency, as well as the effect of histological characteristics indicated by gastric mucosa biopsies, is presented in Table 2.

Regarding the type of proton pump inhibitor used in eradication therapy, children who received omeprazole were almost three times more likely to eliminate HP (p = 0.05; OR 2.87; 95% CI 0.96 - 8.59), while treatment with pantoprazole reduced the effectiveness of therapy by 65% (p = 0.05; OR 0.35; 95% CI 0.12 - 1.04). The relationship between the type of drug used in treatment and the effectiveness of eradication is presented in Table 2.

Discussion

The effectiveness of the antibacterial treatment of HP infection has significantly decreased in recent years, mainly due to the increasing resistance of bacteria to antibiotics [18]. Although scientific associations and working groups recommend taking bacterial cultures to determine their antibiotic sensitivity [17,19], this is rarely done in Poland due to the price of the test and the specific requirements of HP culture, which restricts its use to only half of cases. Therefore, it is necessary to identify effective empirical therapies, and factors that can predict the effectiveness of therapy. The study examines the effectiveness of eradication treatment in 94 children with chronic gastritis and / or duodenitis associated with HP infection, and evaluates the role played by selected demographic, clinical, endoscopic and therapy-related factors in determining the treatment outcome. Of the patients in the present study, treated in the period 2014-2016, 18% demonstrated total failure; all were treated using empirical therapies viz. triple therapy without clarithromycin and sequential therapy; this approach is recommended by the

Polish Society of Gastroenterology for the treatment of diseases caused by *Helicobacter pylori* (HP) [20]. Similar percentages have been observed in other European countries [18] with the mean prevalence of HP resistance against specific antibiotics being 18% against clarithromycin, 32% against metronidazole and 1% against both [21]. This failure to achieve the accepted efficacy (> 85%) has resulted in the change of treatment recommendations for both adult [19] and pediatric populations [17].

In the present study, as predicted, 10- to 14-day triple therapy without clarithromycin yielded significantly higher effectiveness than 10-day sequential therapy. One of the most important factors influencing the effectiveness of eradication, apart from the selection of antibiotics, is the duration of treatment. Meta-analyses of studies in pediatric [22] and adult populations [23] indicate that while 10-day sequential therapy is indeed more effective than seven-day triple therapy, but significantly less effective than 10-day triple therapy. Therefore, the updated guidelines from pediatric gastroenterological societies warn against the use of sequential therapy in children with HP strains of unknown antibiotic sensitivity [17].

In the present study, almost 40% of children did not demonstrate complete resolution of clinical symptoms that caused the initiation of invasive endoscopic diagnosis, despite successful eradication of infection. In addition, these children were significantly more likely to experience clinical remission than those receiving ineffective therapy. This could suggest that the causes of their most common ailments (i.e. chronic abdominal pain) may derive from factors outside of HP infection, which was asymptomatic in these patients; however, some patients may benefit from eradication therapy. This hypothesis is confirmed by the results of a literature review comparing the incidence of HP infection in healthy children (33%) and symptomatic children (39%) [24]. It also indicates that the identification of pediatric patients requiring gastroenterological diagnostics is complicated by the presence of subjective clinical symptoms and an unreliable history from the patient.

However, to effectively identify paediatric patients who may benefit from antimicrobial therapy, it is necessary to first determine the bacterial and host-related factors that influence the effectiveness of treatment. Therefore, the present study also evaluates selected demographic, clinical, endoscopic and therapy-related factors to determine their effect on treatment. None of the analysed demographic parameters or clinical symptoms were associated with higher treatment effectiveness. Neither place of residence [25], sex [26,27] or patient age [28] was found to influence the effectiveness of eradication, despite them being previously reported to influence the treatment effectiveness of infected adults. In the present study, children younger than 12 years were more likely to experience full eradication than older children, although this difference was not statistically significant. Although the present study did not analyse the degree of compliance with

therapeutic recommendations or its impact on the effectiveness of treatment, it can be presumed that the recommendations were better implemented in the group of younger children, because treatment was supervised by caregivers. Strict adherence to therapeutic recommendations has been found to increase the chance of successful eradication in adult patients by many times [29].

The literature does not include any data regarding the impact of the endoscopic picture of the stomach or the histopathological image of gastric biopsies on the effectiveness of eradication in children. However, one study of a small group of infected adult patients found that the presence of microscopic inflammatory changes and the absence of lymphatic lumps in gastric biopsies increased the chance of successful eradication [30]. The fact that children with moderate inflammatory lesions demonstrated greater treatment effectiveness in the present study is probably of little clinical significance, as the severity of the lesions differs depended on the site of collection, and no such relationship was observed for the macroscopic lesions. Regarding proton pump inhibitor type, the use of omeprazole was associated with more frequent eradication, and pantoprazole less frequent, but these relationships were of borderline statistical significance. Literature indicates that the dose of the PPI, adjusted not only to the body weight but also to the age of the child, is more important than the type of inhibitor used, as younger children require higher doses per body weight than older children. Due to the fact that a high percentage of people in the Caucasian population are rapid metabolizers, due to them possessing a genetic polymorphism of CYP2C19, treatment strategies in this group should favour the use of esomeprazole and rabeprazole, as these are less susceptible to degradation [17].

Conclusion

Although eradication treatment was effective in more than 75% of studied children with HP infection, it was not always associated with clinical improvement. Patient-related factors were of low value in predicting treatment efficacy. The therapies currently used to treat HP infection in Poland are unsatisfactory, and they should be superseded by new treatment regimens which take into account the antibiotic susceptibility of bacteria.

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