

REVIEWS

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Treatment of *Helicobacter pylori* Infection in the Aspect of Increasing Antibiotic Resistance

Leczenie zakażenia *Helicobacter pylori* w świetle narastającej oporności na antybiotyki

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article; G – other

Abstract

In the present work, the problem of *Helicobacter pylori* infection in the world and its increasing antibiotic resistance are analyzed. The authors discuss the efficacy of treatment, noting that the clarithromycin – and metronidazole-resistance of *H. pylori* is the main cause of this treatment failure. Because of this phenomenon, a quadruple therapy is being introduced and clarithromycin is being replaced by new antibiotics. The authors also present various schemes of triple and quadruple therapy as well as sequential therapy. Attention is directed to the fact that, in order to obtain better results of the eradication, the treatment should be prolonged from 7 to 10 or even 14 days, and that the doses of the drugs should be increased (*Adv Clin Exp Med* 2012, 21, 5, 671–680).

Key words: *Helicobacter pylori*, resistance, treatment, sequential therapy.

Streszczenie

W pracy przedstawiono problem zakażenia *Helicobacter pylori* na świecie oraz narastającą oporność *H. pylori* na antybiotyki stosowane w leczeniu zakażenia. Autorzy omawiają skuteczność leczenia zakażenia, zwracając uwagę, że przyczyną niepowodzenia eradykacji jest oporność *H. pylori* na stosowaną w leczeniu klarytromycynę i metronidazol. Z tego powodu wprowadza się terapię czteroskładnikową, zastępuje się klarytromycynę nowymi antybiotykami. Wprowadza się do leczenia sole bizmutu. Autorzy przedstawiają różne schematy terapii trójskładnikowej i czteroskładnikowej oraz leczenie sekwencyjne. W celu osiągnięcia lepszych wyników eradykacji wydłuża się czas leczenia z 7 do 10 lub 14 dni, a także zwiększa dawki stosowanych leków (*Adv Clin Exp Med* 2012, 21, 5, 671–680).

Słowa kluczowe: *Helicobacter pylori*, oporność, leczenie, terapia sekwencyjna.

Helicobacter pylori (*H. pylori*) infection is one of the most common infections worldwide. The frequency of *H. pylori* infection is variable and depends on age, ethnicity, gender, geography and socioeconomic status. Most of the infected people are living in developing countries in Africa, South America and Asia. The lowest rate of infection is observed in Australia, Canada and the USA. A high rate of small children among infected patients in developing countries draws attention. In Bangladesh, the rate of infected children younger than two years has reached 50–60%, in Ethiopia among children aged two to four years, the infection rate is

48%, and in Egypt 50% of three-year-old children are infected. The infection rate in these countries exceeds 90% in adults [1]. Table 1 presents the frequency of *H. pylori* infection in children and adults in selected countries. In Europe, the highest rate of infection is observed in Poland, Albania and Estonia and the lowest in Sweden and Switzerland. The highest number of infected children is noted in Bulgaria (Table 2) [1, 2].

Helicobacter pylori colonizes gastric mucosa. The possibility of *H. pylori* survival in the gastric acidic environment is possible due to urease production, an enzyme giving protection against the

acidic environment by hydrolysis of the urea to carbon dioxide and ammonia that neutralizes acid. The discovery by Marshall and Warren in 1983 of *Helicobacter pylori* bacteria in the human stomach with chronic gastritis and peptic ulcerative disease has changed the viewpoint on the ethio-pathogenesis of upper gastric diseases and their management [3]. *H. pylori* infection evokes the inflammation of gastric mucosa. The inflammatory process is of a chronic and progressive character and may, after many years, lead to the atrophy of mucosa, ulcerative disease of the stomach and/or duodenum, metaplasia, dysplasia, gastric cancer, and gastric MALT lymphoma (mucosa-associated lymphoid tissue). The development of the above-mentioned diseases depends on the genotype of

H. pylori and bacterial virulence connected with this genotype [4, 5]. Numerous studies have confirmed that the composition of s1m1 alleles in the VacA gene is typical for most virulent strains. The CagA gene codes the immunogenic protein with potent inflammatory properties. The induction of the inflammatory process, the development of peptic ulcerative disease, neoplastic transformation and the natural course of infection strongly depend on the genome of the *H. pylori* strain. It has been demonstrated that the *H. pylori* genotype cagA(-), vacA(-) has a low pathogenicity and does not lead to neoplastic diseases [6-8].

Table 1. Prevalence of *Helicobacter pylori* infection in the world (acc. 1)

Tabela 1. Częstość występowania zakażenia *Helicobacter pylori* na świecie (wg 1)

Country (Kraj)	Age (years) and prevalence (Wiek – lata i częstość występowania)			
	children	prevalence %	adults	prevalence %
Ethiopia	2-4	48	adults	> 95
Nigeria	5-9	82	adults	70-90
Egypt	3	50	adults	90
Mexico	5-9	43	adults	70-90
Canada	5-18	7.1	50-80	23.1
USA and Canada			adults	30
Brazil	6-8	30	adults	82
	10-19	78		
Chile	3-9	36	adults	70-90
Bangladesh	0-2	50-60		
	8-9	82	adults	> 90
India	0-4	22		
	10-19	87	adults	88
Japan			20-70	55.4
South Korea	16	56		
Taiwan	9-12	11	>25	45.1
Australia	1		59	15.4
Turkey	6-17	64%	adults	80

Table 2. Prevalence of *Helicobacter pylori* infection in Europe (acc. 1, 2)

Tabela 2. Częstość występowania zakażenia *Helicobacter pylori* w Europie (wg 1, 2)

Country (Kraj)	Age (years) and prevalence (Wiek – lata i częstość występowania)			
	children	prevalence %	adults	prevalence %
Albania			16-64	70.7
Bulgaria	1-17	61.7		
Czech Republic			5-100	42.1
Estonia			25-50	69
Germany			50-74	48.8
Iceland			25-50	36
Netherlands	2-4	1.2		
Poland	0-18	32.01	19-89	84.19
Sweden			25-50	11
Switzerland			18-85	11.9

Table 3. Antibiotic resistance of *Helicobacter pylori* in the world (acc. 1, 10–15)
Tabela 3. Oporność *Helicobacter pylori* na antybiotyki na świecie (wg 1, 10–15)

Antibiotic (Antybiotyk)	Country (Kraj)										
	China Song et al. [10] – 2011 %	Taiwan Wu et al. [11] – 2010 %	India acc. [1] – 2005 %	Mahachaj et al. [12] Thailand – 2011 %	Egypt acc. [1] – 2004 %	Brazil acc. [1] – 2002 %	Korea Moon et al. [15] – 2011 %	Children. in European Centers – 2011 [13] %	Children. Sixteen European Centers – 2006 [14] %	Children. Greece – 2011 [16] %	
Amoxicillin	4.9	0.6	0	5.6	2		10.8	0	0		
Clarithromycin	37.8	6.6	0	3	4	9	8.8	15	24	45.3	
Azithromycin											
Tetracycline	2.3	0.6	7	1.9			0	0	0		
Metronidazole	69.7	33.5	85	47.1	100	53	45.1	15	23	28.1	
Levofloxacin	36.4	10.2			2		32.4			0.2	
Moxifloxacin	38.2										
Ciprofloxacin				5.3							
Gentamycin	2.5										
Rifampicin	6.6										
Furazolidone			0								
Clarithromycin and metronidazole								4	5.3		

Treatment of *Helicobacter pylori* Infection

The discovery of *Helicobacter pylori* caused a breakthrough in the treatment of the diseases of the stomach and duodenum. These diseases can be treated or prevented by eradication of the *H. pylori* infection which can be regarded as a causative factor. An acceptable efficacy of *H. pylori* eradication of more than 80% can be achieved using treatment with three or four drugs concomitantly. Among these drugs are substances decreasing gastric secretion, most often a proton pump inhibitor PPI, antibiotics: amoxicillin, clarithromycin, tetracycline, chemotherapeutics: metronidazole or tinidazole, levofloxacin, moxifloxacin, furazolidone and bismuth salts. The efficacy of various treatment schemata depends on the *H. pylori* sensitivity to the antibiotics and chemotherapeutics used, the selection of the drugs in the schema, the duration of treatment and patient adherence to a recommended treatment regimen.

Helicobacter pylori Antibiotic Resistance

In the last decade, unsatisfactory results of *H. pylori* eradication with proton pump inhibitors, amoxicillin and clarithromycin have been observed. In 2008, Graham and Shiotani presented the results of treatment of 9000 patients with *Helicobacter pylori* infection. The authors of that study have demonstrated that the rate of eradication with the above described regimen was unsatisfactory. In the USA, Europe, Japan, Korea and China it was below 80%. In contrast, the eradication rate obtained in Hong Kong and Singapore was above 80% [9]. The principal cause of *H. pylori* treatment failure is a high clarithromycin resistance [10–14]. Table 3 summarizes *H. pylori* resistances to drugs used in various countries of the world. A high *H. pylori* resistance to clarithromycin (37.8%), azithromycin (49.8%), metronidazole (69.7%), levofloxacin (36.5%) and moxifloxacin (38.2%) exists in China [10]. In Taiwan there is a high resistance to metronidazole (85%), similar to in Egypt (100%), Brazil (53%) and Thailand (47.1%) [1, 11]. Studies conducted by Moon et al. have demonstrated frequent *H. pylori* resistance to drugs used in eradication in South Korea which differs from that in Europe [15]. Studies on *H. pylori* resistance conducted in South Korea have demonstrated *H. pylori* resistance to amoxicillin – 10.8%, clarithromycin – 8.8%, metronidazole – 45.1%, levofloxacin – 32.4% and 0% to tetracycline [15]. In multicenter studies conducted

in China by Song et al., a high resistance was demonstrated not only to clarithromycin (37.8%), metronidazole (69.7%), levofloxacin (36.4%), azithromycin (49.8%) and moxifloxacin (38.2%), but also to amoxicillin (4.9%), tetracycline (2.3%), gentamycin (2.5%) and rifampicin (6.6%). In children living in Greece, high resistance to clarithromycin (45.3%) and metronidazole (28.1%) has been observed. According to Mégraud, *H. pylori* resistance in particular European countries and in other parts of the world is different and depends on the use of antibiotics in the treatment of other diseases in various regions [17].

In European countries, *H. pylori* clarithromycin resistance amounts to 5–28%, and metronidazole resistance to 20–40%. In Europe, *H. pylori* resistance to amoxicillin and tetracycline, which is present at a low rate in China and Thailand, is not noted. Koletzko et al. analyzed *H. pylori* resistance in children in 14 countries in Europe and observed clarithromycin resistance reaching up to 24%, but was different in various countries [14]. In Poland, the studies conducted by Dzierżanowska-Fangrat et al. in 2005 have demonstrated the resistance to clarithromycin to be 28% in children and 15% in adults. Resistance to metronidazole was high and equal to 40% and 42% in children and adults, respectively. Double resistance to clarithromycin and metronidazole was observed in 20% of patients. Resistance to amoxicillin, ciprofloxacin and tetracycline has not been observed [18]. Gościński et al. demonstrated an increasing *H. pylori* resistance in children in Lower Silesia [19, 20]. In the years 1997–2000 primary *H. pylori* resistance to clarithromycin was 5.7% and to metronidazole 30.4%. Resistance checked four to six weeks after completion of treatment was 15.7% to clarithromycin and 51% to metronidazole. A study conducted in the years 2007–2008 has demonstrated an increase in the primary resistance to clarithromycin to 24% and to metronidazole to 32%. Moreover, an increase in the resistance of *H. pylori* after the first unsuccessful treatment with metronidazole and clarithromycin has been observed. Similar results of studies on primary and secondary *H. pylori* resistance were obtained by Koletzko et al. [14]. These authors have demonstrated an increase in secondary resistance to clarithromycin from 23 to 35% and to metronidazole from 20 to 42%. Secondary resistance to both drugs also increased, from 5.3 to 15.3% [14]. The latest studies on primary *H. pylori* resistance in Poland using the E-test method in the years 2009–2011 in adults aged 19–89 years with functional dyspepsia have demonstrated a resistance to clarithromycin to be 24%, to metronidazole – 68% and to levofloxacin – 8%. Resistance to more than one antibiotic was 26%

and the resistance to clarithromycin and metronidazole together – 20%. No resistance to rifampicin, tetracycline and amoxicillin has been observed [21]. Epidemiological studies on *H. pylori* infection in Poland have proved significant regional differences in *H. pylori* resistance to clarithromycin and metronidazole. Resistance to clarithromycin in children ranged from 9 to 29% and in adults from 3 to 27% and resistance to metronidazole in children from 16 to 43% and in adults from 27 to 52% [2]. *H. pylori* resistance in children in Poland is presented in Table 4.

The issue of *H. pylori* resistance to the drugs used is important for obtaining efficient eradication. Fischbach and Evans, by analyzing the influence of *H. pylori* resistance on the efficacy of eradication, demonstrated that in triple therapy, clarithromycin resistance diminished this efficacy of eradication by 66% and metronidazole resistance by 14%. In quadruple therapy consisting of a proton pump inhibitor, amoxicillin, clarithromycin and metronidazole, the influence of *H. pylori* resistance to clarithromycin and to metronidazole was smaller [22]. Moon et al. demonstrated a significant influence of clarithromycin resistance on the diminishing of the *H. pylori* eradication index [15]. The authors demonstrated that the success of *H. pylori* infection therapy consisting of a proton pump inhibitor, amoxicillin and clarithromycin as well as of sequential therapy with metronidazole

for ten days depended mainly on *H. pylori* sensitivity to clarithromycin [15].

Sequential Therapy

In recent years, reports demonstrating the superiority of sequential administration of drugs in *H. pylori* infection therapy have been published. In sequential therapy, the manner of drug administration has been changed. During the 10-day therapy, a proton pump inhibitor and amoxicillin is given for the first five days and is followed by a proton pump inhibitor, clarithromycin and metronidazole for the subsequent five days. The results of treatment following this schema are diverse. Graham and Shiotari analyzed the results of 16 studies of sequential therapy conducted for 10 days in 1805 patients and nine studies on parallel administering of the same drugs (PPI, amoxicillin, clarithromycin and metronidazole for 3–7 days) in 715 patients [9]. The intention to treat index was similar and was 93.4% vs. 91.7%. Recent studies emphasize that the efficacy of sequential therapy depends on *H. pylori* resistance to clarithromycin and metronidazole as well as on the compliance of patients. Schwarzer et al. evaluated the efficacy of sequential therapy in 160 children from nine European countries with an average age of 12.3 years [13]. The therapy encompassed: esomeprazole – 1 mg/kg/day and amoxicillin 50 mg/kg/day for five days and for the next five

Table 4. Antibiotic resistance of *Helicobacter pylori* in Poland (acc. 2, 18–21)

Tabela 4. Oporność *Helicobacter pylori* na antybiotyki w Polsce (wg. 2, 18–21)

	Dzierżanowska-Fangart et al. [18] Warsaw 2005		Gościński et al. [19–21] Lower Silesia		Łaszewicz [2] Poland 2004	
	children	adults	children (2007–2008)	adults (2011)	children	adults
Amoxicillin	0	0	0	0	0	0
Clarithromycin	29%	15%	24%	24%	20% (9–26%)	15% (3–27%)
Tetracycline	0	0	0	0	0	0
Metronidazole	40%	42% F/M 58.5% vs 37%	32%	68%	27% (16–43%)	42% (27–52%)
Levofloxacin				8%		
Moxifloxacin						
Gentamycin						
Rifampicin				0		
Clarithromycin and metronidazole	20%			20%	10% (0–16%)	8% (3–11%)

F – female (kobiety), M – male (mężczyźni).

Table 5. Comparison of diagnostic tests for *Helicobacter pylori* infection (acc. 1)**Tabela 5.** Porównanie testów diagnostycznych w rozpoznawaniu zakażenia *Helicobacter pylori* (wg 1)

Test (Test)	Sensitivity (Czułość)	Specificity (Swoistość)	Positive predictive value (Dodatnia wartość predykcyjna)	Comments (Komentarz)
Rapid urease test (Szybki test ureazowy)	> 98%	99%	99%	rapid and cheap
Histology (Histologia)	> 95%	>95%		detection improved by use of special stains
Culture (Hodowla)				highly specific
PCR				sensitive and specific
ELISA serology	85–92%	79–83%	64%	does not identify active infection
13 or 14 C urea* breath test (Ureazowy test oddechowy)	85%	96%	88%	recommended for diagnosis
Stool antigen (Antygen w kale)	95%	94%	84%	inexpensive and noninvasive
Finger-stick serology test (Testy serologiczne krwi)				very poor

PCR – polymerase chain reaction.

PCR – polimerazowa reakcja łańcuchowa.

ELISA – enzymatyczny test immunoabsorbcyjny.

ELISA – enzyme-linked immunosorbent assay.

* Recommended for diagnosis of Hp before treatment and for confirming eradication.

* Zalecany do diagnostyki przed leczeniem i do potwierdzenia eradykacji.

days: esomeprazole, clarithromycin (25 mg/kg/day) and metronidazole (25 mg/kg/day) in two divided doses. In all children, the diagnosis of the *H. pylori* infection was based on a culture. *H. pylori* resistance to the antibiotics was also examined. Primary clarithromycin resistance was 15%, metronidazole resistance was also 15% and resistance to both antibiotics was 4%. The index of *H. pylori* eradication was 82% (131/160) and was significantly higher if the *H. pylori* strains were sensitive to clarithromycin and metronidazole and amounted, in this case, to 91%. In the case when clarithromycin resistance was present, this index was only 70%, in the case of metronidazole resistance – 67% and in resistance to both antibiotics – 29%.

Wu et al., in a randomized study, compared the efficacy of sequential and parallel treatment (concomitant therapy with four drugs) of *H. pylori* infection for 10 days [11]. The concomitant therapy consisted of omeprazole 40 mg, amoxicillin 1000 mg, clarithromycin 500 mg and metronidazole 500 mg given twice a day for 10 days or 10-days sequential therapy (esomeprazole 40 mg, amoxicillin 1000 mg twice a day for five days and esomeprazole 40 mg, clarithromycin 500 mg and metronidazole twice a day to complete the 10 day therapy). An intention to treat analysis has demonstrated simi-

lar eradication rates for sequential (92.3%; 95% CI:87.5–97.1%) and concomitant therapy (93.0%, 95% CI:88.3%–97.7%). Resistance to clarithromycin, compliance and adverse events reduced the level of eradication. Univariate analysis showed that compliance and resistance to clarithromycin were independent determinants of eradication. According to the authors, concomitant therapy is more suitable for areas with dual resistance to antibiotics [11]. The results of these studies are in concordance with guidelines of pediatric scientific societies (ESPGHAN and NASPGHAN) [23]. In a population with high resistance to clarithromycin, exceeding 20% in first line therapy, this antibiotic usage should be reduced or *H. pylori* resistance should be determined and antibiotics should be used according to it [23].

Indication for Eradication Treatment of *Helicobacter pylori* Infection in Children and Adults

The indication for diagnosis and treatment of *H. pylori* infection are proposed by experts of scien-

Table 6. Treatment options of *Helicobacter pylori* infection (acc. 1, 24)**Tabela 6.** Leczenie zakażenia *Helicobacter pylori* infection (wg 1, 24)

Therapy (Leczenie)	Treatment options (Schematy leczenia)	Notes (Uwagi)
First-line therapies (resistance to clarithromycin is not known) (Pierwsza linia leczenia)	PPI + Amx + Met PPI + Cl + Met PPI + Amx + Cl	twice daily for 7, 10 or 14 days (1)
Triple-therapy treatment regimens: PPI + 2 antibiotics: Amx and Cl, or Met and Cl	sequential therapy: 10 day therapy with PPI + Amx for 5 days and PPI + Cl + Met for 5 days	eradication rates 70–85% (increasing resistance to clarithromycin)
In case of a clarithromycin resistance rate of more than 20%: Quadruple therapy: PPI + Bismuth + 2 antibiotics: Amx + Cl or Met + Tet	quadruple therapy: PPI b.i.d. + Amx + Met + Tet ** all. q.i.d. PPI+ Bismuth + Amx + Met PPI + Bismuth + Tetr + Met	for 7, 10 or 14 days
Second-line therapies (after failure of clarithromycin-containing regimen) (Druga linia leczenia)***	PPI + Bismuth + Tet + Met PPI + Amx + Lev PPI + Fur + Tet + Bismuth PPI + Fur + Lev	for 10–14 days for 10 days for 10 days for 10 days
Third-line therapies (Trzecia linia leczenia) Sensitivity determination of <i>H. pylori</i> to Amx, Cl, Met, Lev, Tetr	treatment according to sensitivity of <i>H. pylori</i> to antibiotics	

b.i.d. bis in die (twice a day), q.i.d. quater in die (four times a day).

PPI – proton-pump inhibitor*; Amx – amoxicillin; Cl – clarithromycin; Met – metronidazole; Tet – tetracycline; Lev – levofloxacin; Fur – furazolidone.

* Conventional dosage: Omeprazole 20 mg, Lansoprazole 30 mg, Pantoprazole 40 mg, Esomeprazole 40 mg.

* Dawkowanie: Omeprazole 20 mg, Lansoprazole 30 mg, Pantoprazole 40 mg, Esomeprazole 40 mg.

** Tetracyclin should not be used in children under 9 years of age.

** Tetracykliny nie należy stosować u dzieci poniżej 9 lat.

*** In children, the determination of sensitivity of *H. pylori* to claritromycine is recommended [23].

*** U dzieci zaleca się badanie wrażliwości *H. pylori* na klarytromycynę.

Table 7. Dosage of the medicine used in children**Tabela 7.** Dawkowanie leków stosowanych u dzieci

Omeprazole	1 mg/kg of body weight per 24h, maximum 20 mg/24h twice daily
Amoxicillin	50 mg/kg of body weight per 24h, maximum 1000 mg/24h b.i.d.
Clarithromycin	15 mg/kg of body weight per 24h, maximum 500 mg/24h twice daily
Metronidazole or tinidazole	20 mg/kg of body weight per 24h, maximum 500 mg/24h twice daily
Bismuth salts	8 mg/kg of body weight per 24h, 2 or 4 times per 24h, maximum 2 or 4 × 120 mg four times daily, (maximum 480 mg/24h)
Tetracycline*	25–50 mg/kg of body weight/24hour, maximum 250 mg four times daily

* May be used after the 9th year of life.

* Może być stosowany po 9. roku życia.

tific societies all over the world [23–26]. According to the accepted consensus, diagnostic procedures toward *H. pylori* infection in children should be undertaken if symptoms suggest the presence of organic disease and are an indication for esogastroduodenoscopy with sampling of the gastric mucosa.

The Working Group of the Polish Society of Gastroenterology prepared the guidelines for in-

dications for eradication therapy [24]. Indications for the treatment of *Helicobacter pylori* infection in children are: active or previous gastric and duodenal ulcer, chronic gastritis independent of the stage, long term NSAID (not-steroidal anti-inflammatory drug) use, immunosuppressive treatment, anemia due to iron deficiency for unknown reasons and idiopathic thrombocytopenia.

Table 8. Dosage of the medicine used in adults**Tabela 8.** Dawkowanie leków u dorosłych

Medicine (Lek)	Dosage (Dawkowanie)
Omeprazole	20 mg/twice a day
Lanzoprazole	30 mg/twice a day
Pantoprazole	40 mg/twice a day
Rabeprazole	20 mg/twice a day
Esomeprazole	40 mg/twice a day
Amoxicillin	1000 mg/twice daily
Clarithromycin	500 mg/twice daily
Tetracycline	250 mg/four times daily
Metronidazole or tinidazole	500 mg/twice daily
Levofloxacin*	500 mg/twice daily
Moxifloxacin**	400 mg/twice daily
Bismuth salts	120 mg/four time daily
Furazolidone	100 mg/four time daily

* tuberculostatic.

* przeciwpłatkowy.

** should not be used until the 18th year of life.

** nie należy stosować do 18. roku życia.

Indications for the eradication treatment of *H. pylori* infection in adults are: active, previous or postoperative duodenal and/or gastric ulcer, gastritis (exacerbated by aphtae), atrophic gastritis, metaplasia, dysplasia, gastric resection due to premature cancer, gastric cancer in the family, adenomatous and hyperplastic polyps (after removing them), MALT (mucosa associated lymphoid tissue) lymphoma, Menetrier's disease, functional dyspepsia, long term NSAID treatment and at the patients request (after consulting a doctor). The utility of the suggested diagnostic tests is presented in Table 5.

Options for the Treatment of *H. pylori* Infection

In literature from all over the world, the efficacy of eradications with various schemes of treatment is described. In the case of an unknown sensitivity of *H. pylori* to clarithromycin, treatment with a proton pump inhibitor and two antibiotics: amoxicillin and metronidazole or clarithromycin and metronidazole or amoxicillin and clarithromycin, as well as sequential therapy for 10 days is advised. The duration of a triple therapy should be 7, 10 or 14 days. If in a certain region the resistance to clarithromycin is higher than 20%, or even, according to Romano et al., higher than 15%, the scheme of treatment should be modified. Quadruple therapy should be introduced, clarithromycin should be replaced with bismuth salts or tetracycline or levofloxacin and the duration of therapy should be prolonged to 10 or even 14 days [1, 23–30]. After a failure of that treatment, the sensitivity of *H. pylori* to antibiotics should be determined and *H. pylori* infection should be treated according to the results of this determination. The proposed schemes of treatment are presented in Table 6. It should be noted that tetracyclines should not be given to children younger than nine years and that levofloxacin is tuberculostatic and is not accessible in Poland. Tables 7 and 8 present the dosage of drugs in children and adults. Schwarzer et al., in a case of 62 children with double resistance (to clarithromycin and metronidazole), used a 14-day therapy with increased doses of a proton pump inhibitor, amoxicillin and metronidazole. They have obtained an eradication rate of 73% (per protocol, mild to moderate adverse events were reported by 21 children). Among the most frequent adverse events were nausea, diarrhea and vomiting (Table 9) [31].

Table 9. Treatment of *H. pylori* infection with double resistance in 62 children [31]**Tabela 9.** Dawkowanie leków w leczeniu zakażenia *H. pylori* z podwójną opornością u 62 dzieci (wg 31)

Medicine (Nazwa leku)	Dosage/24h, 14 days (Dawkowanie/dobę, przez 14 dni)		
	15–25 kg	25–35 kg	> 35 kg
Esomeprazole	2 × 20 mg (1.6–2.6 mg/kg)	30 × 20 mg (1.6–2.0 mg/kg)	2 × 30 mg (?–1.7 mg/kg)
Amoxicillin	2 × 750 mg (60–100 mg/kg)	2 × 1000 mg (57–80 mg/kg)	2 × 1500 mg (?–85 mg/kg)
Metronidazole	2 × 250 mg (20–33 mg/kg)	500 × 250 mg (21–30 mg/kg)	2 × 500 mg (?–28 mg/kg)

Eradication rate: 73%.

Wskaźnik eradykacji 73%.

Adverse events: nausea (10.8%), diarrhea (8.9%), vomiting (7.1%), abdominalgia (5.4%), headache (3.6%).

Objawy niepożądane: nudności (10,8%), biegunka (*8,9%), wymioty (7,1%), ból brzucha (5,4%), ból głowy (3,6%).

Increasing *H. pylori* resistance to clarithromycin and metronidazole forces the introduction of new drugs and treatment schemes. Triple therapy composed of a proton pump inhibitor, amoxicillin and clarithromycin is being replaced by quadruple therapy. Clarithromycin is being replaced

by newer antibiotics and bismuth salts are being introduced. The length of treatment is being prolonged from 7 to 10 or 14 days. The principal goal of these changes is the achievement of the most effective eradication of *Helicobacter pylori*.

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