

# Effectiveness of *Helicobacter pylori* eradication established on the basis of examination of antibiotic resistance of the bacteria

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## Abstract

**Introduction:** The treatment of *Helicobacter pylori* (HP) tends to be empirical despite a high number of failures (over 20%). The efficacy of eradication therapies is declining, reaching in some countries 60%, which correlates inversely with the growing drug resistance of the bacteria.

**Aim:** Given the frequent inefficacy of the hitherto proposed treatment schemes for HP infection, an attempt was made to assess the efficacy of a therapy based on the antibiotic resistance of the cultured bacteria, and to analyse factors with possible contribution to the inefficacy of HP eradication treatment.

**Material and methods:** The study covered patients from one region of Central Poland in the years 2005–2015. The total material for bacteriological assessment was collected from 154 patients who had previously been subject to HP eradication treatment at least two times, including 80 women and 74 men, reporting subsequently to the Clinic.

**Results:** The efficacy of the antibiogram-based treatment was merely 65.62%. A low, but slightly higher than expected, resistance to amoxicillin (3.48%) and tetracycline (2.27%), as well as to clarithromycin (27.27%) and metronidazole (70.69%), was established.

**Conclusions:** In Polish patients resistance to clarithromycin and metronidazole of HP is high and becoming increasingly resistant; however, we found low bacterial resistance to tetracycline.

## Introduction

*Helicobacter pylori* (HP) infection belongs to the infections most common in the human population. According to World Health Organization (WHO) estimates, HP infection affects approximately 70% of inhabitants of developing countries and approximately 30% of developed countries – ranging from 15% to over 95% in countries where the infection affects the majority of the population [1]. The incidence of the infection in Poland, in people over 60 years old, is as high as 90% [2, 3]. The treatment is provided by numerous medical specialties. The efficacy of eradication is assessed as ranging broadly from 65% to 94% of cases; Szadkowski *et al.* [4] reported 65%, Gispert *et al.* [5] reported 90.5%, and Muszyński *et al.* reported 94% [6].

A meta-analysis of 32 studies (4727 patients) found the mean cure from the infection with the help of a triple therapy to be achieved in 80% of patients [7].

The treatment of HP infection tends to be empirical despite a high number of failures (over 20%) [8, 9]. The efficacy of eradication therapies is declining, reaching in some countries 60%, which correlates inversely with the growing drug resistance of the bacteria [10]. This resulted in the Maastricht recommendations, which suggest the performance, in high HP clarithromycin resistance regions, of an antibiogram prior to the commencement of the treatment [11]. In Poland, resistance to clarithromycin reaches 29% while to metronidazole it is 40% [12]. In patients in whom cure was not obtained during the first- or second-line therapy, secondary resistance to the recommended antibiotics may develop with selection of resistant strains [13]. It is thus logical

to institute another treatment, provided it is absolutely necessary, after the examination of the antibiotic resistance of the bacteria.

Given the frequent inefficacy of the hitherto proposed schemes of treatment of HP infection, an attempt was made to assess the efficacy of a therapy based on the antibiotic resistance of cultured bacteria. The study covered patients from one region of Poland (Płock and Mazowieckie Voivodeship) in the years 2005–2015.

## Aim

Evaluation of the efficacy of the eradication of HP infection, conducted in an out-patient course, in patients with a history of at least two inefficacious eradication treatments. Analysis of factors of possible contribution to the inefficacy of the HP eradication treatment based on the drug-susceptibility of the bacteria.

## Material and methods

The study covered patients treated by the CM Medica Gastroenterology Outpatient Clinic in Płock (Orlen Medica until June 2014) in the period from January 2005 to December 2015.

The total material for bacteriological assessment was collected from 154 patients: 80 women and 74 men, reporting subsequently to the Clinic, who had previously been subject to HP eradication treatment at least two times. All the patients studied were referred for a check-up endoscopic examination of the upper segment of the digestive tract due to dyspepsia. A culture positive for HP infection was obtained in 59 patients (in three of them (5%) the urease test was negative). In one patient an antibiogram could not be performed due to abundant accompanying flora.

Finally, 58 patients were started on another eradication therapy (triple – antibiotic + metronidazole or two antibiotics in the case of confirmed resistance to metronidazole) in accordance with the HP susceptibility-to-antibiotics result. In addition, the therapy included a proton pump blocker in a standard dose of 2 × daily as well as a probiotic. Initially, a 7-day therapy was instituted, and in the following years a 10-day or sequential therapy. The treatment of HP was consistent with the Maastricht guidelines and Polish Society of Gastroenterology recommendations then in force [14, 15].

No side effects were observed that would require discontinuation of the pharmacological treatment. The efficacy of the HP treatment was assessed after 6–8 weeks from the termination of the treatment, with the use of the certified urease test Gold Hpdry by Lencomm (the reading was performed after 1 h, as recommended by the manufacturer, in patients undergoing a subsequent repeat gastroscopy or HP stool antigen test (SAT),

Helicobacter Antigen Test by Hydrex Diagnostix Ltd.). The stool test is recommended by American Gastroenterological Societies, American Gastroenterological Association (AGA) and American College Gastroenterology (ACG), as very accurate in terms of both recognition of HP infection and efficacy of eradication [16].

Bacteriological examination was performed in the Institute of Bacteriology of the Voivodeship Combined Hospital in Płock, in the anaerobic microorganism diagnostic laboratory. Biopsy specimens of gastric mucosa were placed on the *Protragrem pylori* transport substrate and then transferred (without selection) onto Columbia agar substrate and the same substrate with the addition of antibiotics. The identification was based on the determination of biochemical activity and a preparation from Gram-stained cultures. The drug-susceptibility of HP strains was assessed on Wilkins-Chalgren agar substrate in relation to the following antibiotics: amoxicillin, clarithromycin, tetracycline, rifampicin, levofloxacin, and metronidazole. The assessment of the drug susceptibility to individual antibiotics was extended in the following years of the applied treatment.

Evaluation was also made of the efficacy of eradication depending on age, sex, body mass index (BMI), and cigarette smoking, as well as the presence of a bile reflux to the stomach disclosed on gastroscopy. The presence of a bile reflux was defined as a very large quantity of liquid bile and dense bile in the gastric lake as well as visible bile precipitates on the gastric mucosa. For a period of at least 2 weeks prior to the performance of the tests, the patients did not take any proton pump inhibitors (PPIs) or antibiotics.

## Statistical analysis

The results of the examinations were subjected to a statistical analysis; a standard error was calculated from the binomial distribution and the statistical significance with the use of Student's *t*-test.

## Results

From among the 58 patients with a positive culture result, efficacious eradication control was achieved in 32 patients. In 11 patients the urease test was negative, while in 10 the stool test was negative. A positive urease test was reported in nine and a positive stool test in 2 patients.

The efficacy of the antibiogram-based treatment amounted to 65.62% (Table I).

Table II shows the development of resistance to individual antibiotics in the subsequent 5 years of observation.

The culture towards HP infection was positive in 59 patients, and the antibiogram was obtained for

**Table I.** Comparison of the efficacy of 7-day, 10-day, and sequential *Helicobacter pylori* eradication therapies in 32 controlled patients

Type of therapy	Number of patients	Efficacious therapy	Inefficacious therapy	Therapy efficacy (%)
7-day therapy	7	6	1	85.71
10-day therapy	16	8	8	50
Sequential therapy	9	7	2	77.78
Total eradication therapies used	32	21	11	65.62

58 patients. In one patient an antibiogram could not be performed due to abundant accompanying flora.

Table III presents the influence of age, sex, body mass, cigarette smoking, and the presence of bile reflux into the stomach on the efficacy of the treatment.

## Discussion

The hitherto applied therapeutic schemes of HP eradication are burdened with high inefficacy. As early as in 1997, Maastricht guidelines recommended that treatment efficacy of 80% be achieved, and according

to the Kyoto consensus of 2015 it is advisable that only treatment schemes giving a chance of efficacious HP eradication in at least 90% be applied [17]. The 2014 Guidelines of the Polish Gastroenterological Society indicated the advisability of the control of the efficacy of eradication of the *H. pylori*, which should be performed with the use of non-invasive tests after a lapse of 4–6 weeks from the end of the treatment [14].

The urease test is recommended as an examination of first choice in the diagnostics of HP infection, but it is not recommended as an examination evaluating the

**Table II.** Resistance of *Helicobacter pylori* to antibiotics in subsequent years

Type of antibiotic	Number of patients (2005–2010)		Number of patients (2011–2015)		Number of patients (2005–2015)		% of drug-resistant patients
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	
Amoxicillin	27	1	29	1	56	2	3.48
Clarithromycin	21	7	19	8	40	15	27.27
Metronidazole	7	21	10	20	17	41	70.69
Tetracycline	26	1	17	0	43	1	2.27
Rifampicin	2	0	13	0	15	0	0.00
Levofloxacin	1	0	10	0	11	0	0.00

**Table III.** Assessed factors with their possible contribution to the inefficacy of the *Helicobacter pylori* eradication

Factor/feature	Number of patients	Inefficacious eradication (number of patients)	Inefficacy of therapy (%)
Male	16	5	31.25
Female	16	6	37.50
Smoking	10	6	60.00*
Non-smoking	22	5	22.73
BMI > 24 kg/m <sup>2</sup>	15	5	33.33
BMI < 24 kg/m <sup>2</sup>	17	6	35.29
Bile reflux	11	4	36.36
No bile reflux	21	7	33.33

\*Statistically significant difference –  $p < 0.05$  (smoking SE – 15.5, non-smoking SE – 8.5).

efficacy of eradication, primarily due to the fact that it requires the performance of an endoscopy. What is recommended in the first place is the breath test, but the urease test or the stool test, applied in this study, are much more easily accessible in clinical practice and are devoid of false positive results [11].

The Maastricht V Consensus recommends, in patients with an at least twofold therapeutic failure and/or allergy to the antibiotic planned to be used, a repeat gastroscopy with biopsy with the purpose of performing a culture and assessment of HP susceptibility to antibiotics, whenever possible [18]. The value of the microbiological examination refers primarily to the determination of resistance to clarithromycin, levofloxacin, and metronidazole. Studies by Wenzhen *et al.* [19] as well as Sugimoto *et al.* [20] indicate that a therapy based on an antibiogram is more effective than a standard empirical therapy and, consequently, is more economical.

The results obtained in this study seem to indicate an unexpectedly low efficacy of HP eradication therapy based on an antibiogram, at just 65.62%.

Several earlier studies assessing the result of an antibiogram-based treatment also did not reveal its advantage over an empirical treatment in patients after the first unsuccessful therapeutic attempt [21]. Similarly, Miwa *et al.* [13] did not find differences in the percentage of successful eradications between groups treated on the basis of drug-susceptibility treatment and groups treated in a standard way.

This may be caused by a variety of factors. The latter may involve poor compliance, but the relatively small study group in this study was particularly motivated and monitored as regards their compliance with the rules of the treatment. Thus, other causes should be taken into account. It is known that a simultaneous infection with a few strains is possible, some in the antrum and others in the body of the stomach, strains of different susceptibility to antibiotics [22].

Other factors making eradication impossible include the presence of HP in the oral cavity – subgingival biofilm and dental plaque. Despite the infection having been cured in the stomach, approximately 60% of patients still have the same bacteria in the oral cavity, and it is these bacteria that may re-infest gastric mucosa [23].

Other factors that may influence the efficacy of the treatment may include multi-resistance of bacteria, infection with *cagA* [24] strains, low sensitivity of the culture, and cigarette smoking. An analysis of factors of potential contribution to the inefficacy of the treatment shows that sex, age, BMI, and the presence of a bile reflux into the stomach did not have an influence on the result of the applied eradication schemes.

The small size of the study group does not, however, allow us to determine non-ambiguous dependences. Nevertheless, a dependence was found for tobacco smoking, which decreased the efficacy of the eradication in a statistically significant way. This is consistent with the meta-analysis of 22 studies, which revealed that tobacco smoking increases the percentage of failed eradications by 8.4% [25]. One of the studies did not confirm the influence of tobacco smoking on the result of the HP infection treatment. The Polish study by Al-Medhagi *et al.* [26] did not confirm the influence of stimulants (tobacco smoking, coffee drinking, alcohol drinking) on the efficacy of eradication with the use of amoxicillin, metronidazole, or tinidazole and lansoprazole.

Persistent HP infection in some of the patients studied could not be a re-infection because the assessment was performed after a lapse of 6–8 weeks from the end of the treatment.

An eradication therapy based on drug-susceptibility is subject to numerous limitations. It requires endoscopy. It requires time. The culture is costly and the sensitivity is limited 80–90% [27]. And, first and foremost, this therapy is difficult to apply in practice.

The question is thus how to proceed in view of the low efficacy of the antibiogram-based eradication. The regional antibiotic resistance of HP should be monitored, quadruple therapies with bismuth in the first line mainly applied, the same treatment schemes never repeated, clarithromycin and also levofloxacin [28] avoided, and a 14-day treatment promoted as a new standard. Triple therapies with high doses of antibiotics have shown promising results but as yet without recommendations [29, 30].

Resistance to tetracycline and amoxicillin is rare – to tetracycline it is estimated at below 1%, to amoxicillin at 1–3% [29, 31].

Meanwhile, in this study a tendency towards a higher percentage resistance, reaching almost 1.3% for amoxicillin and almost 2.5% for tetracycline, was observed, and this was during the past 10 years of the duration of the study. This means that at present this percentage can be even higher and the resistance of HP to both these antibiotics, hitherto considered as very helpful and basic in the treatment of this infection, should be monitored.

Resistance to levofloxacin was examined only in a few cases, and drug resistance to it was not established. However, due to reports of high (over 30%) and fast-growing HP resistance to this chemotherapeutic agent, it should be avoided (the US Food and Drug Administration (FDA) approves safety labelling changes for fluoroquinolones) [32].

What can be considered after the failure of the first eradication treatment, if it is necessary to perform endoscopy, is the performance of a microbiological examination, in particular in regions where the chance of infection with antibiotic resistant strains is high [28].

On the other hand, if a therapy with bismuth and tetracycline, resistance to which is extremely low, is planned, resistance to metronidazole is of lesser importance [33]. Resistance to metronidazole is high but, according to experts, remains stable at 30–40% [11]. Meanwhile, in this study it exceeded 70%.

In turn, with doubled resistance to clarithromycin and metronidazole and the absence of a possibility to apply bismuth, what is left is a choice between levofloxacin, ribabutin, or therapy with high doses of amoxicillin ( $3 \times 1000$  mg/day).

It should be emphasised that the present Toronto guidelines do not recommend that probiotics be added to the HP eradication therapy to avoid side effects or to improve the efficacy of the treatment [31].

## Conclusions

The study of the drug-resistance of HP does not increase the efficacy of the eradication therapy established on the basis of an antibiogram. In Polish patients resistance to clarithromycin and metronidazole of HP is high and becoming increasingly resistant; however, we found low bacterial resistance to tetracycline. Tobacco smoking decreases the efficacy of eradication in a statistically significant way.

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## Conflict of interest

The authors declare no conflict of interest.

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