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RESISTANCE OF *HELICOBACTER PYLORI* TO ANTIBACTERIAL MEDICATIONS AS A RISK FACTOR OF INFECTION DEVELOPMENT

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The authors have analyzed research works, both by domestic and foreign researchers that dwell on frequency of H.pylori being resistant to antibacterial medications, the reasons for its occurrence, methods applied to determine it and ways to overcome it. Over the last 15 years there has been a growth in frequency of detecting H.pylori that was resistant to basic antibiotics used to eradicate the pathogen. The authors have established geographical diversity in resistance related to antibiotics intake by population. Bacteriological technique is the most valid for determining H.pylori sensitivity; however, it is rather difficult to apply it due to complicated procedures for the microorganism cultivation. Therefore, molecular-genetic techniques are widely used. H.pylori resistance to Clarithromycin has great practical significance as this antibiotic is able not only to produce antibacterial effects but also to destroy biofilms. Helicobacter that was resistant to Clarithromycin was the least frequently detected in northern European countries (1–3 %); it was the most frequently detected in Southern Europe, Asia, and South America (30–40 %). Research performed in several Russian regions revealed significant variations in frequency of detecting H.pylori resistant to Clarithromycin (5–40 %) and a growth in dynamics of this detection (from 5 to 15 %). Frequency of detecting helicobacter resistance to another widely used medication, Metronidazole, is also different in different geographic regions; it amounts to 17 % in Europe, 24 % in Russia, and 92 % in Africa. H.pylori still has low resistance to Amoxicillin and another reserve medication, Rifabutin.

The article also dwells on probable ways to overcome non-sensitivity of the pathogen to antibiotics and the necessity to develop procedures for treating H.pylori infection based on the results of examining the pathogen sensitivity with standardized techniques performed in different regions. Efficient H.pylori eradication reduces inflammation in the gastric mucosa, prevents ulcer formation and atrophy and reducers risks of stomach cancer.

***Key words**: Helicobacter pylori, eradication, resistance to antibiotics, Clarithromycin, Metronidazole, Amoxicillin, Levofloxacin, Tetracycline.*

Over the last decades *Helicobacter pylori* has been one of the most widely examined reasons for destructive gastric pathology [1, 2]. Treating patients infected with *H. pylori* with relevant eradication therapy is viewed as an efficient way to prevent stomach and duodenum ulcer and certain malignant neoplasms in the stomach [3, 4]. Therapy aimed

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at eradicating the pathogen usually includes the following antibacterial medications: Amoxicillin, Metronidazole, Clarithromycin, Tetracycline, Rifabutin, and Levofloxacin; their efficiency depends on a microorganism's sensitivity to them [5]. Eradication therapy has become less efficient in many countries all over the world due to a growth in number of *H. pylori* strains that are resistant to antibiotics; it is a most significant factor that determines infection persistence in patients with gastroduodenal pathology with variable morphological and clinical pictures of the disease. Bismuth preparations and proton pump inhibitors are basic medications applied to treat the infection as they create conditions that are favorable for effects produced by antibiotics [6, 7]. It is especially important to examine *H. pylori* resistance to Clarithromycin and Metronidazole as these two medications are most frequently used to eliminate the microorganism. *H. pylori* resistance to other antibiotics that are also used quite often, namely Amoxicillin and Tetracycline, remains quite weak [8, 9]. Clarithromycin produces direct anti-bacterial effects and is able to destroy matrices of biofilms that include the microorganism, promote its resistance to therapy with antibiotics, and protect the pathogen from a macro-organism's immune response. A growing prevalence of strains that are resistant to Clarithromycin is the leading cause for eradication therapy becoming less efficient [10, 11]. According to the 4th and 5th Maastricht agreements, it is possible to apply Clarithromycin to treat helicobacter infection only provided that the microorganism's resistance to this antibiotic is lower than 15–20 %. In all cases when resistance exceeds this level, it is not recommended to apply standard three-component first-line eradication therapy (Amoxicillin, Clarithromycin, and proton pump inhibitor) [12, 13].

Our research goal was to analyze literature sources published both in Russia and abroad that focused on *H. pylori* resistance to antibacterial preparations applied for eradication; to estimate significance of this resistance for antibacterial therapy efficiency; and to determine probable ways how to overcome *H. pylori* resistance in clinical practice.

Data and methods. We analyzed research works published by both domestic and foreign experts over the last 15 years. Literature sources were searched for in domestic (eLibrary, CyberLeninka.ru) and international (PubMed, CochraneLibrary) databases in Russian and English. A free access to the full text of a work was our priority.

Results and discussion. *H. pylori* has two types of resistance to antibiotics, natural (genetic) and acquired one [14]. Antibacterial preparations that *H. pylori* is naturally resistant to are applied in creating transport and selective media; they are Vancomycin, sulfonamides, nalidix acid, Trimethoprim, and Polymyxin [9, 15]. Acquired *H. pylori* resistance to antibiotics can be primary and secondary [9]. Primary *H. pylori* resistance to antibacterial preparations is viewed as an adaptive response by the microorganism to adverse environmental conditions occurring due to antibacterial preparations intake aimed at treating certain communicable diseases excluding helicobacter infection. Secondary *H. pylori* resistance to antibacterial preparations occurs after unsuccessful eradication therapy. Acquired resistance to antibiotics mostly occurs due to uncontrolled application of antibiotics and inadequate anti-helicobacter therapy [16, 17].

Helicobacter also tends to have phenotypic (reversible, non-genetic) resistance to antibiotics that occurs when a patient is treated with anti-helicobacter therapy and some bacteria are metabolically inactive (they are in cocci state). This resistance to antibiotics becomes apparent via eradication therapy being inefficient but true persistent resistance to antibacterial preparations

doesn't develop and it allows their successful application as a repeated course via prolonging treatment with anti-helicobacter therapy [18].

Up-to-date and standardized procedures are usually applied to determine *H. pylori* resistance to antibiotics; they are serial cultivations (in agar or broth, micro-cultivations); diffusion ones (disc diffusion test and E-test); variable molecular techniques. A serial cultivation involves inhibiting *H. pylori* on nutritional agar that contains an antibiotic in specific concentrations [19, 20]. Serial cultivations and E-test (determining minimal inhibiting concentration (MIC) with gradient bands) are used to estimate a minimal quantity of an antibiotic that is necessary to inhibit an infectious agent. Some researchers also applied molecular techniques, namely various polymerase chain reaction (PCR) modifications [1, 21].

According to systemic reviews published by foreign researchers prevalence of *H. pylori* strains that are resistant to antibacterial medications has been growing all over the world over the last decades. Studies performed worldwide from 2006 to 2009 allowed revealing the following parameters of the microorganism's resistance: 17.2 % to Clarithromycin; 26.7 %, Metronidazole; 11.2 %, Amoxicillin; 5.9 %, Tetracycline; 16.2 %, Levofloxacin; 1.4 %, Rifabutin; 9.6 % poly-resistance [22]. Variability of these parameters depended on geographical locations and frequency of medications intake by a population [23].

A large multi-center observational study was performed in 2008–2009 in Europe. As per its results high *H. pylori* resistance to several antibiotics was revealed; thus, it was 34.9 % to Metronidazole; a bit lower to Clarithromycin (17.5 %) and Levofloxacin (14.1 %); at the same time resistance to Tetracycline and Amoxicillin amounted to approximately 1 % [11].

An issue related to a possibility to efficiently apply Clarithromycin is of vital importance for practical healthcare. In 2004 a research group supervised by F. Megraud analyzed 20 research works published in Europe that focused on efficiency of conventional triple therapy applied to treat 2,751 patients. In case *H. pylori* strains were sensitive to Clarithromycin, eradication was successful in 88 % cases; but when the strains were resistance to the medication, it was successful in 18 % cases only [24].

Recently a mechanism of acquired *H. pylori* resistance to macrolides has been described. It involves nucleotides replacements in sections where antibiotics are bound with a big sub-unit of bacterial ribosome (structural changes in V domain of 23S-ribosomal RNA under effects produced by erythromycin-resistance methylase enzyme in 2142 and 2143 positions) [25]. This nucleotides replacement leads to weaker antibiotics binding with their target and occurrence of a microorganism's resistance to Clarithromycin. There can be point mutations that cause loss of sensitivity to this medication in previously sensitive strains [26]. And here cross-resistance to all macrolides occurs.

In case there are strains with A2142G replacement MIC for helicobacter increases up to 32–256 mg/L; accordingly, efficiency of three-component eradications goes down to 57.1 %. In case there is mutation in A2143G MIC increases up to 4–128 mg/L, and pathogen eradication efficiency goes down to 30.7 % [27]. Accordingly, research on phenotypic and/or genotypic *H. pylori* resistance is extremely important for predicting anti-helicobacter therapy efficiency and selecting preparations for eradication.

Apart from above mentioned chromosome mutations, activity of efflux pumps belonging to RND-family is also extremely important for occurrence of the microorganism's resistance to Clarithromycin [27, 28]. Efflux pumps are protein complexes that allow a bacterium to rapidly remove alien substances, including medications, from

a cell thus preventing any possibility for an antibiotic binding with a microorganism's ribosome.

Frequency of primary *H. pylori* resistance to Clarithromycin is different in different countries [29]. There was a study performed in Chile; it revealed a growth in frequency of detected *H. pylori* strains that were not sensitive to Clarithromycin over a 10-year period. The study involved serial cultivations and polymerase chain reaction that allowed revealing mutation in V domain of 23 pRNA: A2142C and C2147G. Over 2005–2007 in that country registered *H. pylori* resistance to Clarithromycin amounted to approximately 20 %. From 2015 to 2017 this bacterium's resistance to Clarithromycin grew up to 29.2 % [30]. These results obtained in Chile indicate that triple eradication first-line therapy is hardly efficient in the country.

Similar *H. pylori* resistance to Clarithromycin was registered in several Italian regions where it amounted to 21–24.1 % [31]. Researchers detected both single mutations in *H. pylori* strains and double ones, A2143G and C2195T. Similar results were obtained by Korean scientists. Having examined patients with helicobacter infection who had not been previously treated with eradication therapy, they revealed *H. pylori* in clinical isolates with a combination of mutations A2143G and T2182C [32].

On the contrary, in Northern European countries *H. pylori* resistance to Clarithromycin was rather weak. Most frequent resistance to macrolides was detected in the Netherlands (11 %) and Finland (2 %) via diffusion procedures applied to determine sensitivity [33, 34]. These results are probably due to antibacterial preparations being consumed in low doses by people living in these countries.

A later analysis, performed in 2009–2012, also confirmed there were regional differences in *H. pylori* resistance to Clarithromycin. Thus, in the Northern Ireland resistance amounted to 3 %; the highest resistance was detected in Japan (38.8 %) and China (37.2 %) [35, 36]. In Uzbekistan detected *H. pylori* resistance to Clarithromycin didn't exceed acceptable 20 % as it amounted to 13.3 % [37]. These differences can result from an ambiguous approach to applying macrolide antibiotics in these countries as well as due to more frequent use of these antibiotics to treat patients with extragastric, communicable, and respiratory diseases in Japan and China.

There were large-scale multi-centered studies performed in 18 European countries in 1998–2018 on *H. pylori* strains obtained from 1,232 patients; they revealed that there was a 2-time increase in frequency of microorganisms resistant to the most popular antibiotics applied for eradication. It was true for Clarithromycin also as resistance to it grew from 9.9 % in 1998 to 21.6 % in 2018 [38]. The greatest quantity of resistant bacteria was detected in Southern Europe, in particular Southern Italy (39.9 %), Croatia (34.6 %), and Greece (30 %). This high resistance in these countries is most likely due to frequent intake of antibacterial medications to treat respiratory diseases and flu [39, 40].

Clinical recommendations issued by the Russian Gastroenterological Association contain results obtained via several studies on *H. pylori* resistance to Clarithromycin in different regions in Russia; according to them, resistance doesn't exceed 15 % [41].

According to the 4th and 5th Maastricht recommendations, resistance to Clarithromycin is a determining factor for poorer efficiency of eradication therapy applied to treat *H. pylori*-associated gastroduodenal pathology. We analyzed results obtained in studies performed in Russia and revealed a growth in the microorganism's resistance to Clarithromycin with its maximum levels reached in central megacities. In the middle 1990-ties in Moscow there were no detected *H. pylori* strains that were resistant to

Clarithromycin[1]. But already in 1999 *H. pylori* resistance to Clarithromycin amounted to 17.1 % among adult population in Moscow. In 2005 the parameter was a bit higher – 19.3 % and it went down to 14.5 % by 2012 [42].

When interpreting resistance parameters, it is necessary to take into account a procedure that was applied to determine sensitivity. *H. pylori* resistance to Clarithromycin amounted to 40 % among patients suffering from ulcer in Saint Petersburg and the figure was obtained via molecular procedures for determining sensitivity [43]. Probably, the figure combined both primary and secondary *H. pylori* resistance to Clarithromycin. Another study also performed in Saint Petersburg involved disk diffusion test and as a result obtained primary *H. pylori* resistance to Clarithromycin was lower and amounted to 7.7 % [19].

H. pylori resistance to Clarithromycin was also low in Smolensk region over a period from 2009 to 2017. Antimicrobial resistance of *H. pylori* isolates was estimated in the region via serial cultivations. Resistance amounted to 5.3 % in 2009–2010 and it grew insignificantly in a period from 2015 to 2017, to 6.3 % [44]. Similar results were obtained in cities located in Volga region. In 2012 in Nizhniy Novgorod region primary *H. pylori* resistance to Clarithromycin amounted to 7.3 % as per data obtained via PCR; it grew up to 15.1 % in 2016 [45]. In Kazan researchers applied PCR procedure combined with restriction analysis to reveal A2142G, A2143G, and T2717C mutations in 23S gene of *H. pylori* pRNA that could lead to the microorganism's resistance to Clarithromycin. As per data published in 2012, they detected 12.9 % resistant clinical isolates [46]. In Novosibirsk primary *H. pylori* resistance to Clarithromycin determined via PCR was also low and amounted to 6 % [47]. Results obtained via studies performed in Russian cities indicate that patients with *H. pylori*-associated gastroduodenal pathology can be empirically prescribed first-line eradication therapy if it hasn't been used previously. Unfortunately there have been no studies on *H. pylori* sensitivity to antibiotics in most regions in Russia.

Frequency of detecting *H. pylori* resistance to another widely used preparation, Metronidazole, also has some geographical differences. In those countries where Metronidazole is actively applied to treat parasitic and urogenital diseases resistant *H. pylori* strains are detected much more frequently. In African countries the bacterium resistance reached 92.4 %; it was two times lower in America where in amounted to 44.1 %; 37.1 % in Asia, and it was significantly lower in Europe being equal to 17.0 % [16, 48, 49]. A basic reason for resistance to Metronidazole is inability of this antibacterial medication to transform into its active form. It is most likely due to mutations in genes that code oxygen-insensitive nitroreductase and flavin reductase.

Studies performed in Russia over a 10-year period allowed revealing a considerable growth in resistance to Metronidazole, from 3.8 % in 2009–2010 to 23.8 % in 2015–2017 [44]. There are also data on absence of any significant *H. pylori* resistance to Metronidazole and on rare resistance to bothmedications, Clarithromycin and Metronidazole [41].

Recently, experts and practical specialists have been paying their attention to Fluoroquinolones [11]. *H. pylori* resistance to Fluoroquinolones results from changes in nucleotide sequences in gyr A gene. Wide

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use of such preparations to treat various somatic and communicable diseases made for an increase in resistant strains quantity. Thus, in Smolensk region *H. pylori* resistance to Levofloxacin increased from 8.3 % in 2009–2010 to 24.5 % in 2015–2017 [44]. Should resistance reach such levels, Levofloxacin can't be recommended to replace Clarithromycin.

Rifabutin is rarely used in eradication schemes, only in cases when the first and second line therapy hasn't been successful. *H. pylori* resistance to Rifabutin is quite low and amounts to 1.4 %, and a mechanism of resistance formation is related to point mutations in rpo B gene that codes β – subunit in bacterial RNA-polymerase [50].

An issue related to occurrence and growth in number of poly-resistant *H. pylori* strains is the most pressing. Greater prevalence of such *H. pylori* strains may well be a reason for eradication therapy not being efficient and it requires searching for more optimal therapeutic schemes applied to treat an infection caused by *H. pylori* [15, 36]. To overcome primary *H. pylori* resistance to antibiotics, it is advisable to apply antibacterial therapy combined with double doses of proton pump inhibitors; to prolong therapy up to two weeks; to add bismuth preparations; to include probiotics into therapeutic schemes in order to increase eradication efficiency, reduce risks of side-effects, and the infection relapse.

Conclusion. *H. pylori*-associated pathology is a communicable infection regardless of its symptoms or stage. *H. pylori* eradication should be prescribed to all infected people in order to eliminate inflammation in stomach mucosa, prevent further progression of the disease until it turns into ulcer and atrophy, and reduce stomach cancer risks. Resistance to antibacterial preparations considerably reduces efficiency of therapy schemes, especially those that include macrolides. The World Health Organization ranks *H. pylori* that is resistant to Clarithromycin among bacteria that are the most hazardous for human health. Recommendations on treating patients with helicobacter-associated diseases proposed by Russian and world consensuses are based on awareness about regional *H. pylori* resistance to antibacterial medications. Judging on data given by various researchers, it seems necessary to standardize procedures for examining *H. pylori* resistance to most common antibacterial medications in Russia. Use of results obtained via standardized studies will allow working out regional recommendations for practical healthcare on how to select the most optimal and personified therapy schemes aimed at treating this infection.

As issue related to *H. pylori* resistance to antibacterial medications requires searching for new eradication strategies in order to prevent ulcer and oncologic gastric pathology and, consequently, to achieve higher life quality for patients suffering from *H. pylori*-associated gastroduodenal pathology.

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