REVIEW

Treatment of Helicobacter Pylori – an Overview of Current Strategies of Diagnostic and Treatment

Ruxandra BABIUC[1,2], Raluca Anica IONESCU[1,2], Lucian NEGREANU[1,2]

Abstract

Helicobacter Pylori infection, responsible for ulcerous disease, atrophic gastritis,gastric cancer and MALT lymphoma (mucosa-associated lymphoid tissue) has a very high prevalence in the general population (approximately 50%). In Romania there are few data related to the prevalence of Helicobacter Pylori infection, as well as the resistance to antibiotic treatment, and the methods of patient surveillance are limited by costs and low accessibility. The aim of our paper is to recall the current possibilities of treatment and supervision of this category of patients, taking into account that the appropiate treatment and good monitoring of the patient can cure the complications of the disease and may prevent the occurrence of malignancies.

Keywords: Helicobacter Pylori, antibiotics, eradication.

Rezumat

Infecția cu Helicobacter Pylori, bacterie responsabilă de apariția bolii ulceroase, gastritei atrofice și a limfomului MALT (mucosa associated lymphoid tissue), are o prevalență foarte mare în populația generală (aproximativ 50%). În România există puține date legate de prevalența infecției precum și de rezistența la tratamentul antibiotic, iar metodele de supraveghere a pacienților sunt limitate de costuri și de o accesibilitate redusă. Scopul lucrării noastre este de a reaminti posibilitățile actuale de tratament și supraveghere ale acestei categorii de pacienți, ținând cont că diagnosticul, tratamentul prompt și corect, precum și monitorizarea corespunzătoare a pacientului pot vindeca complicațiile bolii, dar și preveni apariția neoplaziilor digestive.

Cuvinte cheie: Helicobacter Pylori, antibiotice, eradicare.

Helicobacter pylori (H. pylori) has a proven role in the pathogenesis of gastritis since its description in 1983 (R. Warren & B. Marshal) [1].

It is responsible for ulcerous disease, atrophic gastritis, gastric cancer and MALT lymphoma (mucosa-associated lymphoid tissue). Estimative prevalence of this infection is almost 50% and diagnosis, appropriate treatment, as well as good monitoring of patients are mandatory, being able to cure these complications, but also to prevent the occurrence of neoplastic diseases.

Epidemiological data related to H. pylori infection vary both globally and regionally. The highest prevalence rates are found in Africa (79.1%), Latin America (63.4%) and Asia (54.7%)[2].

In Romania, the epidemiological data is scarce and most of the collected information are from the Western areas of the country. While in 2003 the overall prevalence of H. pylori infection in the west of the country was 68.5%, newer studies point to a decrease in incidence in recent years to around 41% [3,4].

[1] Department of Gastroenterology, Emergency University Hospital, Bucharest, Romania
[2] „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author:
Lucian NEGREANU, Department of Gastroenterology, Emergency University Hospital, Bucharest, Romania.
E-mail: negreanu_99@yahoo.com

The evalution of patients with dyspepsia, the use of NSAIDs/aspirin/anticoagulants in patients with a history of gastroduodenal ulcer, evaluation of iron deficiency anemia, idiopathic thrombocytopenic purpura, vitamin B12 deficiency or gastric-MALT lymphoma require research of HP infection[5].

The management of H. Pylori infection depends on prevalence of the disease in certain geographical areas, the presence of certain „alarm symptoms" (weight loss, dysphagia, gastrointestinal bleeding, iron deficiency anemia), previous eradications treatments, as well as bacterial resistance to antibiotics in certain areas.

Most patients are asymptomatic due to the widespread of infection in general population. Thus, diagnostic and treatment of H. pylori infection are very important, as well as the proof of bacterial eradication, given the possible late complications of the disease, including the impact they have on the health system. For the patient, the most feared complication is gastric cancer, and studies conducted in Asia (an area with a high prevalence of both H. pylori infection and gastric cancer) and West Europe show a marked decrease in the risk of gastric adenocarcinoma in conditions of proper treatment of infection[6].

A suitable treatment of any bacterial infection should be guided by the results of an antibiogram. Unfortunately, the antibiogram is rarely used in case of infection with H. pylori, due to its low availability, high cost and long time to get a result. However, it remains useful and should be performed in situations of failure in eradication therapy, except the cases where quadruple bismuth-based therapy is expected [5]. When antibiotic resistance is suspected, an alternative is to perform molecular tests using PCR (polymerase chain reaction) to amplify bacterial DNA from biopsy, stool or saliva [7], but low accessibility and high cost limit its use on a wide scale. The option of empirical treatment remains frequent and must be oriented according to the presumed resistances in a certain geographical area.

The data on the resistance of H. pylori to antibiotics are also scarce in Romania. In 2020 a study of 90 subjects shows a resistance rate of approximately 20% to clarithromycin and 30% to fluoroquinolones. Similar results were obtained in France in 2019[8,9]. In China, an area with a high prevalence of H. pylori infection, a retrospective study analyzed the resistance to 4 antibiotics of a number of 1463 patients, adults and children, naive and experienced to previous treatments. The results showed a high primary resistance to metronidazole (78.4%), clarithromycin (19%) and levofloxacin (23.3%) among adults, and in those who received prior treatment the resistance was even higher, 99.2% for metronidazole and up to almost 60% for clarithromycin and levofloxacin. Children had a higher rate of primary resistance to clarithromycin compared to adults, possibly due to the higher use of macrolides in the treatment of interstitial pneumonia in this population[10].

Looking at these results, triple therapy based on the association of clarithromycin, amoxicillin, metronidazole with PPI remains the first line of treatment in areas with low clarithromycin resistance (<15%), according to the Maastricht V Consensus. However, triple therapy would probably not be the first choice in Romania due to the lack of overview of H. pylori antibiotic resistance with the preferred alternative of a quadruple therapy that includes or not bismuth, depending on its availability. However, in a study conducted in 2018 in Bucharest on a group of 78 patients with H. pylori infection who received treatment with PPI, clarithromycin and amoxicillin treatment efficacy in eradication was 70.5%. The results were superior for a 14 days regimen when compared to a shorter 7 days alternative (efficacy of 84.6% vs. 42.3%)[11].

Metronidazole sensibility is a key factor in the successful eradication of H. pylori using empirically quadruple therapy. Although this sensitivity is not routinely determined, metronidazole resistance could be overcome using high doses (1500 mg) for at least 10 days. The posology of amoxicillin is also important; administration of 3 grams/day or 50 mg / kgc / day ensures an eradication rate of approximately 90%[7,9,12,13].

Quadruple therapy based on the association of bismuth with metronidazole, tetracycline and double dose PPI, provides very good results in areas with high resistance to clarithromycin and metronidazole being the first therapeutic option in this setting. It is also indicated as the second line of treatment if clarithromycin resistance is <15 % [14,5]. The effectiveness of this regimen seem to be greater than that triple clarithromycin-based therapy[9].

Bismuth salts have an intrinsic bactericidal effect on H. pylori, allowing antibiotics to exert a better effect by destroying the bacterial wall. It also has a protective effect on the gastric mucosa facilitating ulcer healing by stimulating the secretion of prostaglandins and epidermal growth factor [15]. Administered in 4 doses per day it is better tolerated and has an increase in the topical bactericidal effect. Duration of the

bismuth-based therapy is an important aspect in the eradication of H. pylori, and current guidelines do not have precise indications. It is usually recommended to use a 10-14 days regimen[5]. In France, where the resistance rates to metronidazole are low, a 10-day course of treatment is considered optimal[12,13]. Pylera®, a drug that combines in each capsule 140 mg of bismuth subcitrate, 125 mg of tetracycline and 125 mg of metronidazole, is available on the market in France, Spain or Italy. The posology consists of 3 capsules 4 times a day for 10 days. The combination of three antibiotics in a single capsule leads to a better compliance and easier administration and therefore better adherence to treatment. Quadruple bismuth therapy is an alternative for penicillin allergy, an unfavorable situation in which an extremely effective antibiotic against H. pylori will have to be missing from the therapeutic arsenal. Although amoxicillin resistance is low, allergies can be common and it is very important to detect them or at least discuss with the patient about this possibility[9,10].

Levofloxacin, associated with PPI and amoxicillin, in a 10 day regimen, has been shown to be four times more effective than quadruple bismuth-based therapy in some studies. It also has a lower rate of side effects [16,17]. The Maastricht IV consensus recommends the use of levofloxacin in second-line therapy (level of evidence 1a, recommendation grade A) [18]. At present, given the increasing resistance to fluoroquinolones, it would be wiser to keep levofloxacin as a rescue therapy, or a solution for patients allergic to penicillins [5,8,9]. The empirical use of levoflxacin was 60% effective in a study that included 100 patients who failed two treatment lines, and the rate of minor side effects was estimated at 25%, the most common being metallic taste and nausea [17]. This emphasizes the importance of performing the antibiogram before resorting to a third line of treatment [5,9].

Rifabutin remains an alternative when other therapies fail. H. pylori resistance to rifabutin is almost non-existent, the analysis of 39 studies involving 9721 patients demonstrating a rifabutin resistance of 0.07%[19]. Results like these encourage us to reserve this antibiotic for extreme cases. In 2019, a study of 302 patients who were empirically treated with rifabutin 150 mg, amoxicillin 1 g and PPI twice a day for 14 days after previous therapies failed, demonstrated a 71.5% rate of eradication. Data were collected over a period of 10 years, and in the last part of the study period a decrease in treatment efficacy by approximately 15% was observed. However, the paper does not mention myelotoxicity as an adverse reaction [20]. In a recent study (2020) that included patients with clarithromycin and levofloxacin resistance similar results on the efficacy of rifabutin were described (79.5%), with few side effects, but one of the limitations of the study is the small number of subjects included [21].

The combination of bismuth and the transformation of triple therapy with rifabutin, amoxicillin and PPI into a quadruple therapy might be a promising option [19].

The effectiveness of the eradication treatment is closely related to the type of PPI, the dose, the frequency of administration, as well as the genetic differences in metabolism (involving the activity of cytochrome P450). Analysis of 35 studies showed that the use of esomeprazole and rabeprazole (next-generation PPI) was more effective than the use of omeprazole, pantoprazole or lansoprazole in H. pylori treatment (82.3% vs. 77.6%), without differences, however, between esomeprazole and rabeprazole (efficacy 78.7% vs. 76.7%). The Caucasian population is considered to have an increased ability to metabolize PPI in a large proportion (up to 81%), due to the production of the enzyme CYP2C19 in higher amounts [12,13,22]„type":„article-journal",„volume":"24"},„uris":[„http://www.mendeley.com/documents/?uuid=7fcd836b-b91d-4dd2-8f68-28a6c95a8f52"]},{„id":„ITEM-2",„itemData":{„DOI":„10.3748/wjg.v25.i34.5097",„ISBN":„0000000170383",„ISSN":„22192840",„PMID":„31558859",„abstract":„The survival and replication cycle of Helicobacter pylori (H. pylori. However, new-generation PPIs (esomeprazole, rabeprazole) do not depend on this enzyme in the metabolic process, which is why we could consider them the first choice in the treatment of H. pylori infection. Taking into account these data, as well as the general recommendations, high doses, twice daily, are preferred [5]. On the other hand, bismuth eradication therapy requires a lower gastric pH to be effective, consequently choosing omeprazole, for example, in this situation seems to be a favorable solution[9].

Vonoprazan is a drug that has aroused interest lately. Its very good efficacy has been demonstrated in East Asia, including clarithromycin-resistant bacterial strains (efficacy> 80%). The high ability to inhibit gastric acidity, including at night, the rapid onset of effect, increased tolerability, the safety of administration, and the fact that its metabolism does not depend on CYP2C19 polymorphisms, are properties that place

vonoprazan high in the PPIs hierarchy used in H.pylori eradication therapy [22]. Unfortunately, this drug is only available on the Japanese market, and additional studies are needed for its approval in other territories.

The role of probiotics has been also investigated proving beneficial as an adjunct to eradication therapy, and more recently, in the prophylaxis of infection. Decreased adhesion of the bacteria to the gastric mucosa (through a competitive mechanism), reduction of mucosal inflammation, production of compounds with inhibitory effect on H. pylori (lactate, peroxides, short-chain fatty acids) are some of the mechanisms of action of probiotics. It has been found that single administration of probiotics only reduces the severity of pre-existing H. pylori infection, so probiotics cannot be an alternative to the antibiotic medication. In addition, it attenuates the severity of the adverse effects of antibiotics used in eradication therapy[23,24].

Recently, various vaccines (EpiVax / H.pylori vaccines, Helicovax, Imevax, etc.) have been developed by small companies and academic institutes but more research is needed on their efficacy. Given the high prevalence of H. pylori infection globally, as well as the complications that this bacteria can cause, especially neoplastic ones, the motivation of large companies to develop and produce vaccines on a large scale should be up to par[25].

It is important to check the eradication of the infection using various tools. ^{13}C urea breath test (UBT) is one of the most reliable methods for monitoring the patient after anti-H. pylori treatment. With great specificity and sensitivity (97% and 98% respectively), UBT is the first line test to verify the eradication of H. pylori [5]. Some of the limitations of this test are the low accessibility and high costs, and this is the reason why, in our country, the fecal antigen test is frequently used. Simplicity, lack of invasiveness, as well as a specificity and sensitivity comparable to UBT are advantages of this method used both in the diagnosis and in the eradication of H. pylori infection[9].

Serological tests represent only a diagnostic method. The use of this test to verify the effectiveness of the eradication treatment is unjustified given that anti-HP antibodies persist in the serum for a long time, even after infection has been eradicated [9].

The role of upper digestive endoscopy (EDS) in H. pylori infection should also be emphasized. The follow-up of lesions associated with infection (atrophy, metaplasia, dysplasia, cancer, lymphoma), as well as taking biopsies for histopathological / immunohistochemical examination or performing the culture with antibiogram, respectively PCR test are the main advantages offered by this technique. The role of culture and antibiogram, as previously presented, remains an important step in patient management, and should not be omitted in the event of failure in two empirical eradication treatments [9].

Strategies to address H. pylori infection can also be applied in general practice offices. Communication of GPs with gastroenterologists has been beneficial in the proper treatment and monitoring of patients [26], and this could be a significant support for then during the COVID-19 pandemic.

However, the role of the gastroenterologist remains essential in the event of treatment failure or in the presence of precancerous lesions.

Compliance with ethics requirements:
The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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