Clinical aspects of *Helicobacter pylori* infection*

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Abstract: The *Helicobacter pylori* (Hp) infection is common. However, only 10–20% of infected individuals require antibacterial treatment. The main indications to such treatment are peptic ulcer disease, atrophic gastritis, dyspeptic symptoms, previous surgical procedure for gastric cancer, family history of gastric cancer and low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma. The treatment may also be undertaken at the patient's request. To detect the infection the urease test (when the patient has indications for gastroscopy), the urea breath test or serologic test are most commonly used. A standard treatment of Hp infection consists of a 7-day administration of one of the proton pump inhibitors and 2 out of 3 antibiotics such as amoxicillin, clarithromycin and metronidazole. After failure of the first-line treatment, the recommended second choice treatment is a quadruple treatment regimen consisting of bismuth salts, tetracycline, metronidazole and proton pump inhibitor. European guidelines (Maastricht III) allow the use of the quadruple treatment regimen already as the first choice treatment and therapy prolongation up to 14 days. Ineffectiveness of the second-line treatment is an indication for antimicrobial susceptibility testing. New antibiotics used for Hp eradication are levofloxacin and rifabutin. Eradication treatment should be obligatorily assessed with the use of the urease or breath test only in patients with peptic ulcer bleeding. The current guidelines do not envisage an active search for Hp infection in an asymptomatic population and treating people infected with this bacterium, for gastric cancer prevention.

Key words: antibacterial treatment, clarithromycin, eradication, gastric cancer, *Helicobacter pylori*, metronidazole, peptic ulcer

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Helicobacter pylori (Hp) is a Gram-negative, spiral microorganism possessing flagelli, dwelling on the surface of the epithelial cells underneath a layer of mucus covering the mucosal membrane of the prepyloric region of the stomach. The bacteria survival in the acidic environment of the stomach is aided by urease – an enzyme produced by them, which catalyzes urea degradation with alkaline ammonium ion formation.

The coexistence of Hp with human subjects has a long history. Genetic studies of bacterial species combined with studies on people's migration showed that the contemporary man was infected with Hp already 58,000 years ago, thus before leaving from his cradle in Eastern Africa [1]. 25 years ago Marshall and Warren have demonstrated the etiological role of Hp in gastritis and peptic ulcer, for which they were awarded a Nobel Prize in 2005. This crucial discovery gave birth to numerous studies on diagnosis and treatment of infections caused by these bacteria. The present review relies on the results of the more recent studies in this field.

Infection epidemiology

The Hp infection is common. Over 50% of the world's population is infected with this microorganism. The human is its reservoir. The factors predisposing to infection are shown in Table 1. The quality of these factors indicates the spreading of the infection from human being to human being. The transmission of Hp involve oral-oral and fecal-oral routes. The infection takes place usually in childhood, within one's own family (between parents and children or between siblings) [2].

Helicobacter pylori induced diseases

The Hp infection does not always mean the disease. In many ways the microorganism behaves as a commensal, and not a pathogen. This has been confirmed by the observation that the majority of the infected persons do not demonstrate any symptoms of the disease and only 10–20% develop diseases which are an indication for antibacterial treatment. The main disease caused by Hp is the gastric mucosal membrane inflammation. Final clinical implications of the infection depend upon the localization and extent of the inflammation. Until now there have been 3 different disease phenotypes related to the Hp infection

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Table 1. Factors conducive of spreading the *Helicobacter pylori* infection

Living in a developing country
Low socioeconomic status
Large number of family members in a household
Large families with little children
Poor sanitary conditions
Food and water contamination
Contact with stomach content (physicians and nurses)

such as mild gastritis phenotype, duodenal ulcer phenotype and gastric cancer phenotype. The most frequent is the first phenotype, the simple gastritis phenotype, which is not accompanied by significant alterations in gastric acid secretion and does not lead to serious complications. The duodenal ulcer phenotype occurs in 15% of infected people and is characterized by inflammatory lesions in the antral region of the stomach along with increased gastrin and hydrochloric acid secretion. Individuals with such a constellation of disorders have duodenal ulcers and/or ulcers of the antral region of the stomach. The most serious type of lesion is the gastric cancer phenotype with gastric corpus inflammation, mucosal membrane atrophy in this region of the stomach and decreased hydrochloric acid secretion. Such anatomical alterations and functional disorders develop in about 1% of the infected subjects and significantly increase the risk for gastric cancer. The cancer phenotype occurs most frequently in inhabitants of the Asian countries, in which gastric cancer is particularly common [3]. It is noteworthy that the ulcer and cancer phenotypes are mutually exclusive and Hp-induced duodenal ulcer patients never develop gastric cancer. This apparent paradox is explained by complex interactions between bacteria and the hosts of various genetic backgrounds [4].

Indications for treatment

In Poland the Hp infection affects 84% of adults and 32% of children and adolescents up to age 18 [5]. The diseases induced by this microorganism and requiring antibiotic treatment are presented in Table 2.

The results of low-grade mucosa associated lymphoid tissue (MALT) lymphomas treatment are very good. Authors from Korea have recently reported 85% complete remissions of this tumor with Hp eradication. Tumors located in the distal stomach were particularly sensible to antibacterial treatment. Lymphoma relapses were in 2, 8 and 9% of patients, respectively at 1, 2 and 3 years after Hp eradication [6].

Out of the diseases mentioned in the Table 2, the dyspepsia defined as chronic or recurrent pain or discomfort in the epigastrium should be commented on. This is a very common gastrointestinal complaint, in which a symptomatic improvement can be achieved with antibacterial treatment. This relates to uninvestigated and to functional dyspepsia that coexists with Hp infection [7].

Table 2. Indications for *Helicobacter pylori* infection treatment

Peptic ulcer disease – active, inactive, complicated
Gastric MALT lymphoma
Atrophic gastritis
History of gastric resection for gastric cancer
First degree relatives of gastric cancer patients
Uninvestigated or functional dyspepsia
Long-term proton pump inhibitor treatment
Scheduled longer NSAID treatment
Idiopathic thrombocytopenic purpura
Sideropenic anemia of unknown origin
The patient's request

MALT – mucosa-associated lymphoid tissue, NSAID – non-steroidal anti-inflammatory drugs

Other indications for eradication include long-term proton pump inhibitors (PPI) used in patients with gastroesophageal reflux disease, and scheduled long-term treatment with non-steroidal anti-inflammatory drugs. In these situations, the Hp diagnostic tests should be performed and antibacterial treatment should be initiated in infected individuals. These recommendations also refer to individuals with ischemic heart disease, who are to receive low-dose acetylsalicylic acid, and have a history of the previous ulcer hemorrhage. Both indications are mentioned in the European guidelines published in 2007 known as the Maastricht III Consensus Report [8]. Moreover, the European guidelines contain two new indications for antibacterial treatment, that is idiopathic thrombocytopenic purpura and sideropenic anemia related to chronic gastric mucosal membrane inflammation induced by Hp infection. Apart from Hp related diseases, an indication for treatment may be the patient's request, provided that the patient has been informed all possible advantages and complications of antibiotic therapy in detail.

Gastric cancer is a serious health problem worldwide, responsible for about 10% of cancer deaths in the general population [9]. In 2004, 5700 individuals died of this cancer in Poland [10]. There is an unquestionable relation of gastric cancer located outside the cardia with the Hp infection. It has been demonstrated in numerous epidemiological, clinical, pathological and experimental studies [11]. If these bacteria play an etiologic role, the question arises whether their eradication may prevent gastric cancer development? Earlier studies have demonstrated slower progression or even resolution, of gastric precancerous lesions, with Hp infection treatment [12,13]. A meta-analysis of studies in the years 2004–2006 did not however provide evidence of decreased cancer prevalence in individuals after eradication treatment [14]. The only randomized, controlled study, in which gastric cancer was

Table 3. Tests used to diagnose *Helicobacter pylori* infection

Serologic test for the presence of class IgG antibodies	Noninvasive, sensitivity >80%, specificity about 90%	Is not suitable for eradication confirmation
Breath tests with urea, ^{13}C or ^{14}C tagged	Noninvasive, simple, sensitivity and specificity 90–99%	Relatively expensive, small radiation dose in the ^{14}C test
Fecal *Helicobacter pylori* antigen testing	Noninvasive, simple, sensitivity and specificity similar to breath tests	Unavailable
Urease test (CLO-test)	The simplest method with gastroscopy	Invasive, may be falsely negative
Bacterial culture	Useful with treatment failure	Invasive method, expensive and time consuming

the endpoint, demonstrated that Hp eradication may reduce the occurrence of this cancer provided that the treatment is applied in young individuals without gastric precancerous lesions [15]. This study was conducted in China, in a province with a high gastric cancer prevalence. In summary, previous evidence showing that Hp eradication prevents gastric cancer in the corpus of the stomach and pylorus, is weak. In developed countries active testing of asymptomatic population for Hp and treating of infected individuals is not performed. For these reasons such a recommendation has not been included in the Maastricht III consensus report.

Diagnosis of Hp infection

Noninvasive and invasive tests used to diagnose Hp infection are shown in Table 3. The breath test is optimal to prove the current infection, or to assess treatment efficacy. A similar role could be played by the Hp fecal antigen test; however it is not yet available in Poland. The urease test is characterized by good sensitivity but requires the sample to be obtained with endoscopy. It is thus performed in individuals with clinical indications for gastroscopy. Serologic tests, easily accessible and sufficient in the case of peptic ulcer disease and its complications, are essential in patients recently on PPI or antibiotics as in such a situation other tests may be falsely negative. Culture, and particularly Hp antibiotic susceptibility assessment, is necessary with treatment failure. Moreover the Maastricht III recommendations consider the use of this method for the assessment of clarithromycin susceptibility in areas, where the percentage of species resistant to this drug is 15–20%. Recent studies demonstrate that Poland has joined such countries [16]. According to the current views the so called rapid tests performed at bedside and the Hp antibodies assessment in the saliva and urine are useless and should not be used [8].

Treatment of Hp infection

According to the current Maastricht III recommendations and the recent consensus of the Polish Society of Gastroenterology Task Force, the Hp first-line treatment relies on one of the PPI and two of the three antibiotics: amoxicillin (2×1 g), clarithromycin (2×500 mg) and metronidazole (2×500 mg) [8,17]. All these drugs are administered twice daily for 7 days. The type of PPI used in standard doses does not significantly influence the treatment outcome.

However, the percentage of eradication, being previously about 80%, has recently dropped to about 70%. According to Megraud [18], a world known expert on this issue, the main problem is the Hp resistance to clarithromycin. The use of this drug for resistant bacteria decreases the eradication percentage from 88 to 18%! Therefore the Maastricht III report allows clarithromycin administration only in regions, where primary resistance to this antibiotic does not exceed 15–20%. The percentage of clarihtromycin resistant strains in Poland is 15% in adults and 28% in children [16]. According to the most current recommendations this antibiotic should not be used in Hp eradication without an initial assessment of bacterial susceptibility. As this requirement does not seem possible to fulfill, amoxicillin and metronidazole are recommended for the first-line treatment with the exclusion of clarithromycin. Although the primary Hp resistance to metronidazole in Poland is greater than to clarithromycin (42% resistant strains in adults) [16], the metronidazole resistance phenomenon has a lesser influence on the final treatment outcome [19].

In the case of first therapy failure the usual second-line treatment is based on 4 drugs administered for 7–10 days: bismuth salts, PPI, tetracycline (4×500 mg) and metronidazole (3×500 mg). Instead of this regimen Italian authors suggest the use of ranitidine with bismuth citrate (2×400 mg), amoxicillin (2×1 g) and tinidazole (2×500 mg) for 14 days. Such management is to ensure 81% eradication [20]. Other reports confirm the effectiveness of Hp treatment prolongation from 7 to 10–14 days when for instance individuals with dyspepsia are prevalent; the chance for efficacious eradication during a 7-day treatment is lower in such patients than in peptic ulcer patients [21]. The use of a quadruple regimen first-line treatment and an extension of the antibiotic treatment up to 14 days has been allowed in the Maastricht III recommendations. As bismuth salts are not available in Poland a triple regimen with PPI, amoxicillin or tetracycline and metronidazole has been proposed.

It is not necessary in most patients to test whether treatment resulted in Hp eradication. A favorable opinion on the treat-

ment result is usually based on clinical improvement. Patients with a history of a past ulcer hemorrhage are an exception to this rule. In such patients an endoscopic examination and eradication assessment is necessary. In the event of giving up gastroscopy with the biopsy to perform the urease test, the best way of checking for the Hp presence after the treatment is the noninvasive breath test. As mentioned, serological tests are not suitable for this purpose.

New model of treatment

The new treatment method is a 10-day sequential treatment consisting of a PPI with amoxicilin (2 × 1 g) for 5 days, followed by a PPI, clarithromycin (2 × 500 mg) and tinidazole (2 × 500 mg) for the next 5 days [22]. With such a treatment regimen, the percentage of eradication may exceed 90%, regardless of the patients' age [23]. Sequential treatment is efficacious also in case of bacterial resistance to clarithromycin [24].

Among new drugs for Hp eradication there are levofloxacin and rifabutin [25]. Recent studies in Italy demonstrated a higher efficacy of levofloxacin administered together with claritromycin and esomeprazole in comparison with a 7-day standard treatment [26]. The second drug – rifabutin will be of lesser significance in Poland because of the growing tuberculosis prevalence and the risk of selecting mycobacteria resistant to this antibiotic.

Probiotics, recommended in the literature as drugs supporting the eradication and diminishing the antibiotic adverse effects [27,28], have not been included in the Polish Society of Gastroenterology and Maastricht III recommendations. It seems that a rational administration of antibiotics by physicians and strict adherence to the recommendations by patients could have the greatest influence on the improvement of eradication treatment in Poland.

The infection recurrence rarely follows a successful Hp eradication, especially in developed countries (1–3%). In developing countries this percentage exceeds 10% after the first and the same after the second year from eradication, which rather provides evidence for recurrent infection than for relapse of latent infection [29]. One of the factors increasing the Hp infection relapse risk is dental disease requiring treatment [30].

For Hp infection prophylaxis the simplest recommendations to inhibit the bacteria propagation must not be forgotten, such as washing hands and providing separate beds for children.

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