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Helicobacter pylori infection: from biology to clinical features

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ABSTRACT

The discovery of bacterium *Helicobacter pylori* and the association of its occurrence with gastritis and peptic ulcer disease, was one of the most significant events of the 20th century. Almost 40 years have passed since that event, but we are still far from fully understanding of the impact of *H. pylori* infection on the human body. It is confirmed, that the infection causes chronic gastritis, which increases the risk of diseases such as: duodenal and/or gastric ulcer, gastric cancer and gastric MALT lymphoma. Nevertheless, constantly appear new studies linking *H. pylori* with many other disorders, often not directly related to the digestive system. Cardiovascular, neurological, hematological, dermatological, metabolic and also gynecological diseases are in sphere of assumptions. The authors of the following work attempted to select key information available in the medical literature on the discovery of *H. pylori*, epidemiology and pathophysiology of infection, as well as diseases to which it predisposes and the latest methods of eradication.

Keywords: *Helicobacter pylori*, peptic ulcer disease, gastric cancer, MALT lymphoma

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1. INTRODUCTION

The discovery of bacterium *Helicobacter pylori* and the association of its occurrence with gastritis and peptic ulcer disease, was one of the most significant events of the 20th century. It initiated an avalanche of scientific research on appreciating how *H. pylori* causes tissue injury and related diseases. Furthermore, the discovery of *H. pylori* coincided with the introduction of antihistamines and proton pump inhibitors (PPI), which had a significant impact on improving the treatment results of patients with peptic ulcer disease. Almost 40 years have passed since that event, but we are still far from fully understanding of the impact of *H. pylori* infection on the human body. The certainty is that the relationship between this bacterium and the human immune system is very complex, which makes the eradication of the infection difficult.

The authors of the following work attempted to select key information available in the medical literature on the discovery of *H. pylori*, epidemiology and pathophysiology of infection, as well as diseases to which it predisposes and the latest methods of eradication.

2. HELICOBACTER PYLORI DISCOVERY

Helicobacter pylori is a gram-negative, spiral bacterium which has the ability to colonize the gastric mucosa (1). It was discovered in 1979 by the Australian pathologist -John Robin Warren. During the assessment of the previously taken gastric biopsy, he noticed small microorganisms located on the surface of the epithelium. The uniqueness of this discovery was based on the fact, that human stomach was thought to be sterile and no microorganism is able to survive in its unfavorable environment. To find a connection between the presence of bacteria and the clinical condition of patients, Warren teamed up with Barry James Marshall, who was an internal medicine trainee at the gastroenterology ward. In 1984 they published an article describing the new bacteria species and their suspected influence on causing active chronic gastritis and peptic ulcer disease (2). Furthermore, the isolated bacterium has been found to be sensitive to some of the commonly used antibiotics, including tinidazole and metronidazole. Warren proved the ability to fight the infection by himself, conducting a controversial experiment. In 1984 he swallowed the bacteria isolated from a patient with gastritis and then went through effective antibiotic therapy. Initially, the new microorganism was called *Campylobacter pyloridis*, but in 1989 it was renamed to *Helicobacter pylori* (3). What is more, in 2005 Warren and Marshall's discovery was awarded the Nobel Prize in Physiology or Medicine (4).

3. HELICOBACTER PYLORI EPIDEMIOLOGY

Analyses of genetic sequences of different *Helicobacter pylori* strains show, that the genetic diversity of this microorganism decreases with increasing distance from East Africa. This fact leads to the conclusion, that H. pylori bacterium has co-existed with humans for many thousands of years and has spread from Africa to the whole world (5).

The latest statistics from 2015 indicate that *H. pylori* infection is a huge social problem and affects around 4.4 billion people around the world. The percentage of people infected

within the population varies significantly, depending on the geographical location. The highest level is observed in developing countries, especially in Africa - where it reaches approximately 80%, and the lowest in North America - about 37% (6).

The transmission pathways of *H. pylori* infection are the subject of many studies. So far, this bacterium has been isolated from dental plaque, faeces and vomit. Therefore, the possible transmission routes of infection include: oral-oral, fecal-oral and gastro-oral (7). Interestingly, *H. pylori* may be also transmitted by animal vectors, e.g. houseflies. Consumption of contaminated water may lead to the infection as well (8).

Most of infection occur already in childhood and children in developing countries are particularly vulnerable. Many scientific sources confirm that the main risk factor for infection is low socioeconomic status. Other factors include: low educational status of parents, numerous siblings or eating a large amount of salty food (9)(10)(11).

Genetic factors predisposing to *H. pylori* infection are not fully characterised, although studies suggest that Hispanics and Afro-Americans are more susceptible to infection (12). Recently a decrease in the number of registered infections has been observed in highly developed countries (USA, Japan, China). However, it is still unknown, whether the downward trend will be maintained or stabilized over the years (6).

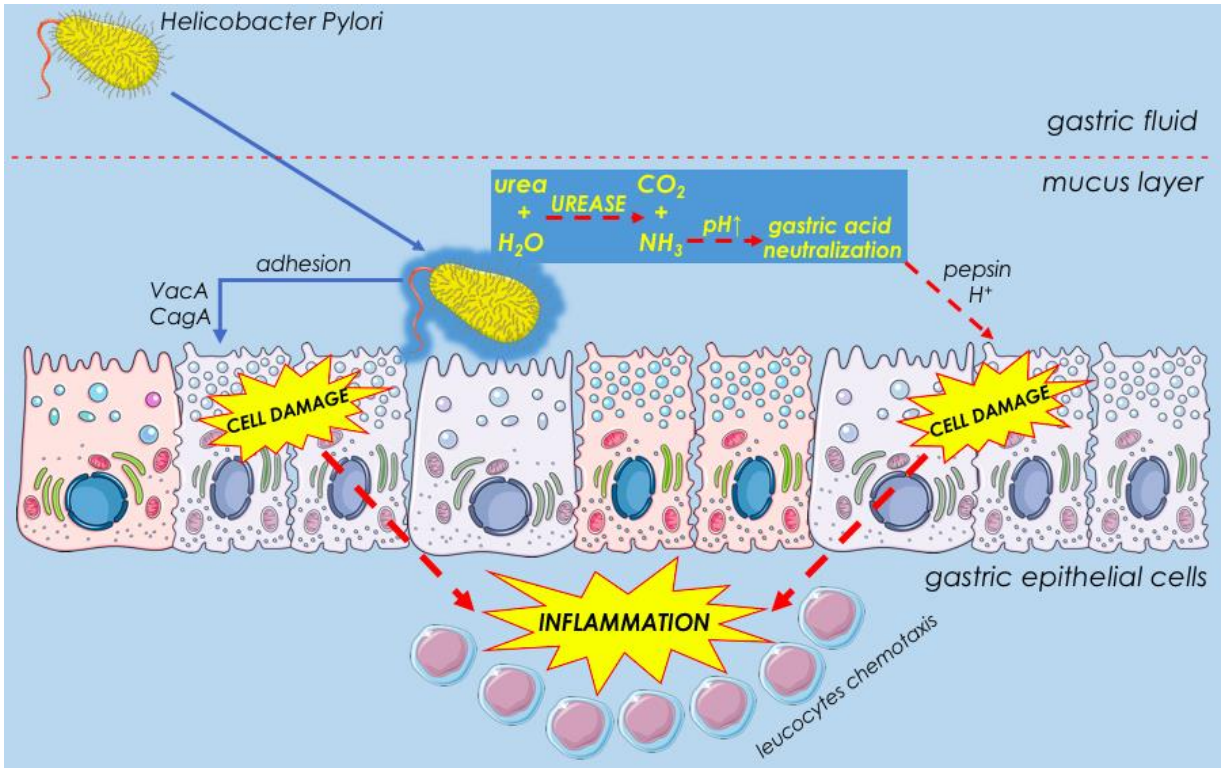
4. HELICOBACTER PYLORI PATHOPHYSIOLOGY

Helicobacter pylori is a bacterium with many unique mechanisms allowing the infection of the gastric mucosa. The colonization process is complicated and consists of several stages. The first of them is chemotaxis and bacterial adhesion to the gastric mucosa. The cell adhesion molecules (CAMs), mainly BabA and SabA, play a key role in the whole infection process. BabA combines with antigens presented on the normal mucosa of the stomach, while SabA with antigens that appear during inflammation. The presence of various forms of adhesins allows the bacteria an adaptation to the changing microenvironmental conditions and makes them resistant to the host's immune response. Due to this, *Helicobacter pylori* is able to induce chronic infections (13).

Adhesins are not the only proteins that participate in colonization of the gastric mucosa. In this process participate also *outter membrane proteins* (OMP), located in the *H. pylori* outer membrane. OMP include proteins that act as ion channels, proinflammatory proteins, micropores and proteins of still unknown function (14).

The aim of the next stages of colonization is neutralization of low pH in the stomach and overcome the mucosal barrier, so as to reach the epithelial cells and obtain the nutrients necessary for further living. Increasing the adverse pH is possible due to the presence of urease enzyme, which occurs inside the bacterium and on its cell surface. The urease action is based on the hydrolysis of urea to basic ammonia and carbon dioxide, which leads to an increase in gastric pH and protects bacteria against the acidic environment of the stomach (15).

After adhesion and neutralization of low pH, *H. pylori* overcomes the mucosal barrier, thanks to proteolytic enzymes and phospholipases. In the last phase of colonization, cytotoxic factors (including VacA toxins, CagA proteins) are released and epithelial cells are destroyed (Scheme 1) (16).



Scheme 1. The mechanism of *Helicobacter pylori* colonization.
Modified from: https://smart.servier.com website.

5. HELICOBACTER PYLORI RELATED DISEASES

Although most people infected with *H. pylori* are asymptomatic, the infection is not irrelevant to the body. Many researchers have proven that this infection may have serious health. The major conditions related to chronic *H. pylori* infection are: peptic ulcer disease (mostly duodenal), and less commonly - gastric cancer and MALT lymphoma. The risk of the above mentioned diseases is strictly dependent on the bacterial strain and the polymorphism of the host's immune system (17). Only 10% of infected individuals will develop peptic ulcer disease.

The acute phase of *H. pylori* infection is mostly asymptomatic, although some patients present symptoms of acute gastritis (dyspepsia, vomiting, diarrhea). The situation looks similar when the infection passes into a chronic form. There are asymptomatic cases, as well as symptomatic, with the dominance of dyspeptic symptoms. Interestingly, often no correlation is observed between the severity of clinical symptoms and the macroscopic or microscopic condition of the gastric mucosa. Depending on the location, chronic *H. pylori* infection occurs as an antral-predominant inflammation or as pan-gastritis. In the case of antral-predominant inflammation, the inflammatory process damage D-cells (producing somatostatin) and G-cells (producing gastrin), which leads to abnormal secretion of the above-mentioned hormones (decrease in the level of somatostatin and increased level of gastrin) (18)(19). The overproduced gastrin strongly stimulates the parietal cells of the stomach to produce hydrochloric acid.

The hyperacidity predisposes to gastric metaplasia within the duodenum and, consequently to the duodenal ulcer. The situation is significantly different in the case of *H. pylori* induced pan-gastritis. The inflammatory process includes the parietal cells, so that they do not respond to elevated gastrin levels. What is more, the lack of reaction to gastrin leads to constant stimulation of G-cells and their excessive proliferation. It significantly increases the risk of non-cardia gastric adenocarcinoma. Chronic inflammation in the stomach body leads to atrophy of the mucous membrane and predisposes to the occurrence of gastric ulcer. Accompanying pan-gastritis hypochlorhydria has a protective effect on the duodenal and esophageal mucous membrane, so the risk of duodenal ulcer and complications associated with GERD is lower than in the general population (20). Moreover, in terms of pan-gastritis, *H. pylori* acts as a carcinogen and leads to precancerous conditions such as chronic active gastritis and atrophic gastritis. Gastric cancer developing on the basis of infection occurs within the distal parts of the stomach - the body and pylorus (21).

The reason for the significant variation in the clinical picture among infected patients is not fully understood. Some studies suggest, this is related to the virulence of a *H. pylori* strains, as well as the host's immune response and environmental factors. *H. pylori* induced pan-gastritis and gastric cancer may be caused by the polymorphism within certain genes of immune system. The currently known polymorphisms are: IL-1β gene polymorphism (IL-1B-511T), IL-1 receptor antagonist (IL-1RN*2), TNF-α (TNF-A-308A) and IL-10 (IL-10) haplotype ATA). Recent reports alert, that the coexistence of four different polymorphisms may increase the risk of gastric cancer by up to 27 times (22). Moreover, infection with the *H. pylori* CagA+ strain appears to be associated with a greater risk of developing gastric cancer (23). Further research aimed at the possibility of early identification of patients with an increased risk of gastric cancer, may contribute to the diagnosis improvement, as well as to the reduction of mortality associated with this cancer.

In 1991, for the first time a connection between *H. pylori* infection and the occurrence of gastric MALT lymphoma appeared (24). Since then, many studies confirming that fact have been carried out (25)(26). Lymphomas are tumors of the lymphatic tissue, which arise within the lymph nodes or in extranodal location. The extranodal neoplasms are described by the abbreviation: MALT (*mucosa associated lymphoid tissue lymphoma*). Gastric MALT lymphoma is a clonal B-cell neoplasm arising from post-germinal center B-cells in the marginal zone of the lymphoid follicles. These types of lymphomas are rare and belong to slow growth tumors (27). Similarly to non-cardia gastric cancer, the risk of MALT lymphoma depends on the virulence of the bacteria and the immune response of the host – particularly, on genetic polymorphisms in the HLA system (28).

Considering the strong correlation between the occurrence of *H. pylori* infection and MALT lymphoma, since 1991 attempts have been made to treat this neoplasm with antibiotic therapy (24). The trials proved to be effective and to this day the eradication of *H. pylori* is the first line of treatment for gastric MALT lymphomas (29).

The association of *H. pylori* infection with gastritis and peptic ulcer disease was already suggested by Warren and Marschall in 1984 (2). The connection between an infection and increased risk of neoplastic growth in the stomach was discovered later. In 1994, the World Health Organization's International Agency for Research on Cancer (IARC) included *H. pylori* to Group 1 carcinogens - which directly affects the process of carcinogenesis (30). Currently, the discussion about the impact of infection on the human body is still open.

New studies linking *H. pylori* with many disorders, often not directly related to the digestive system, constantly appear (31).

5. 1. IRON AND VITAMIN B_{12} DEFICIENCY

Many studies confirm the contribution of *H. pylori* infection to reduced iron level, the supply of ferritin and consequently, genesis of iron-deficiency anemia. The exact mechanism of this phenomenon has not been yet known. It is still unclear whether the bacterium causes an increased loss or decreased absorption of iron (32). Moreover, the reduction of vitamin B_{12} caused by *H. pylori* infection has been proven. In the conducted studies, the MCV parameter improved and the vitamin B_{12} level increased within 2-6 months after eradication, even without the use of supplementation (33).

5. 2. IMMUNE THROMBOCYTOPENIC PURPURA

The increase in the blood platelets level after *H. pylori* eradication was noticed by Gasbarrini A. et al. in 1998 (34). Since then, the correlation was confirmed in other independent studies (35). Despite numerous attempts, the mechanism of this action has not been yet recognized. However, the possible molecular mimicry between platelet antigens and *H. pylori* antigens is taken into account (36).

5. 3. GROWTH DELAY

Determining the impact of *H. pylori* infection on the growth process in children is very difficult due to the interfering role of socio-economic factors and diet. However, some studies suggest that children infected with *H. pylori* may develop more slowly than their peers. The observation was confirmed by the study published in 2017, in which the refugee children were assessed in terms of weight, malnutrition severity and *H. pylori* infection. Infected children were found to be thinner than their peers. Considering the fact, that abnormal physical development may result in a disruption of mental progress, *H. pylori* infection work up seems to be the proper way among children with growth disorder (37).

5. 4. SKIN DISORDERS

Skin diseases possibly correlated with *H. pylori* infection are rosacea and chronic idiopathic urticaria. Surprising are results of the study, in which among 52 patients suffering from rosacea, eradication of *H. pylori* infection brought improvement in 51 of them (38). Very good results were also observed in chronic idiopathic urticaria. In 2013, Chiu et al. noticed remission in 63.3% of patients undergoing eradication in a prospective study (39).

5. 5. PARKINSON'S DISEASE

The correlation between *H. pylori* infection and idiopathic Parkinson's disease was suggested in 1996 by Altschuler et al. (40). Since then, the connection is still widely commented in the scientific literature. Many studies confirm the improvement in the clinical status of patients after eradication of *H. pylori* infection (41)(42). In addition, the improvement in the clinical response to L-DOPA was observed after *H. pylori* eradication (43). Unfortunately, the pathomechanism of this correlation is still unknown. The current hypotheses include the effect of inflammation and the action of cholesterol glucosides arising

from *H. pylori* infection, which act as neurotoxins, promoting the degeneration of the dopaminergic neurons affected in parkinsonism (44).

5. 6. THE CARDIOVASCULAR SYSTEM

The correlation between *H. pylori* infection and the increased risk of coronary heart disease development, is the subject of many studies. In 1994, Mendall et al. showed that the risk of coronary artery disease is more than twice higher in people infected with *H. pylori*, than in non-infected patients (45). The results were confirmed in subsequent studies, in which a higher level of antibodies against *H. pylori* was found in patients with ischemic heart disease (46). The participation of these bacteria in the atherogenesis is suggested in the results of the study, in which the material originating from atherosclerotic plaques was analyzed and *H. pylori* DNA was identified (47). Xu et al. found a molecular mimicry between *H. pylori* antigens and antigens of blood vessels. The level of the *anti-HSP 60/65 antibody* (*anti-heat shock protein 60/65 antibody*), which is a well-known risk factor for atherosclerosis, was found as increased in infected persons. Furthermore, after eradication of *H. pylori*, the decreased level of *anti-HSP 60/65* was revealed (48). Reports on the correlation between infection and ischemic heart disease are numerous, but some scientists negate the existence of such dependence (49).

5. 7. METABOLIC SYNDROME

Although the results of the studies conducted so far are ambiguous, it can be assumed, that *H. pylori* has a triggering impact for the occurrence of metabolic syndrome and insulin resistance. This may be related to the activation of proinflammatory cytokines and the production of active oxygen radicals (50). Stomach colonization by *H. pylori* affects the body's hormonal balance by disturbing the normal balance between leptin and ghrelin (51). The results of studies allow to conclude that *H. pylori* infection is not neutral for the metabolism of an infected person, however further research is necessary to determine the clinical significance of this correlation.

5. 8. OTHERS

Other diseases in which the correlation with *H. pylori* infection was observed include: migraine (52), hyperemesis gravidarum (53), infertility (54), bile duct diseases (55), SIBO - *small intestinal bacterial overgrowth* (56), COPD – *chronic obstructive pulmonary disease* (57). However, it should be emphasized that all above-mentioned reports require confirmation in subsequent studies.

6. HELICOBACTER PYLORI – DIAGNOSIS

The most common indication to start the diagnosis of *H. pylori* infection is dyspepsia. According to the latest recommendations, patients with this condition should follow the "*test-and-treat*" strategy, which is based on a non-invasive diagnostic test and treatment, if the result is positive. The recommended non-invasive test is an urea breath test (UBT). However, the assessment of *H. pylori* antigens in feces with the use of monoclonal antibodies may be also used. In the case of patients who have alarming symptoms or are older than 45 years, it is

recommended to perform an endoscopic examination with a biopsy and a quick urease test if there are no contraindications. Diagnostic tests are also the best method to confirm *H. pylori* eradication. It is worth remembering, that PPI should be discontinued at least 2 weeks before the test for *H. pylori* infection. Antibiotics and bismuth compounds should be discontinued ≥4 weeks before the test to obtain reliable test result [58].

7. TREATMENT

The Maastricht V/Florence Consensus Report is the latest and the most important document summarizing experts' recommendations regarding the diagnosis, treatment and prevention of *H. pylori* infection. It was created in 2015 during the Maastricht V/Florence Consensus Conference. 43 experts from 24 countries worked on a reliable summary of the latest reports related to *H. pylori* (58).

The main difference from the previous 2012 guidelines (59), is a recommendation that every patient diagnosed with *H. pylori* infection, regardless of the clinical symptoms presence, should receive treatment. In out-of-date guidelines, antibiotics were recommended only for those patients, who had clinical signs of infection. According to the current indications, the selection of an appropriate drugs set depends on the sensitivity and / or resistance of *H. pylori* strains found in a patient. What is more, when choosing a therapy, any previous macrolide antibiotics therapy should be taken into consideration, because previous therapies carry the risk of resistance to this group of medications. If the resistance is suspected, the therapy without macrolides should be recommended. The new guidelines support the conclusion, that it is necessary to apply multi-drug therapy for complete cure. The first line therapy in areas with low resistance to clarithromycin (<15%) and in patients who have not taken macrolides in the past, is *triple therapy* consisting of a proton pump inhibitor (PPI) and 2 of 3 antibiotics - clarithromycin, amoxicillin or nitroimidazole derivative (metronidazole / tinidazole).

The therapy should last 14 days. The *triple therapy* should not be initiated without prior determination of *H. pylori's* sensitivity to this antibiotics. For patients who are allergic to penicillin or have previously taken macrolide antibiotics, alternative therapy is a *quadruple therapy* containing: bismuth, PPI, tetracycline and metronidazole. In this configuration, the treatment lasts for 10-14 days. In many countries a significant increase of strains that are resistant to clarithromycin or to clarithromycin and metronidazole simultaneously has been noticed (60). In such cases, it is recommended to use *quadruple therapy* with bismuth or *non-bismuth quadruple therapy* (PPI, amoxicillin, clarithromycin and nitroimidazole derivative) for 10-14 days. In areas with high, double resistance to clarithromycin and metronidazole, the recommended first line treatment is *quadruple therapy* with bismuth.

The effectiveness of *non-bismuth quadruple therapy* can be increased by different drug delivery schedules. The existing therapy options are:

a) *concurrent* - PPI, amoxicillin, clarithromycin and nitroimidazole derivative, for 10-14 days;
b) *sequential* - for the first 5-7 days PPI and amoxicillin, for the next 5-7 days PPI, clarithromycin and a nitroimidazole derivative;
c) *hybrid* - for the first 7 days of PPI and amoxicillin, additional clarithromycin and nitroimidazole derivative over subsequent days.

In case of treatment failure, salvage therapy, avoiding previously taken antibiotics, should be considered. The new guidelines suggest also, that the use of PPI at high doses, twice a day, may increase the effectiveness of the *triple therapy*. In Europe and North America, where the percentage of people rapidly metabolising PPI is high, esomeprazole and rabeprazole may be preferred.

Eradication of *H. pylori* infection is challenging due to the increasing bacterial resistance to the used drugs, side effects of therapy and patients' non-compliance. During the 1990s, the eradication rate of the therapy reached 90%, but it dropped to 70% just few years later (61)(62). Over time, bacterial resistance seems to increase in many different countries. High rates of resistance are noted especially for clarithromycin and metronidazole. According to Vasilios et al. study, resistance to these drugs s accounted for 29,3% / 44,1% in America, 18,9% / 37,1% in Asia and 11,1% / 17% in Europe respectively (63). In some studies these rates are even higher. The study carried out in Vietnam in 2014, showed that 42.4% of bacterial strains were resistant to clarithromycin, 41.3% to levofloxacin and 76.1% to metronidazole. Fortunately, the bacterium seems to remain sensitive to amoxicillin (64). High resistance rates make the assessment of antibiotic sensitivity a very important element of therapy and correlate with its effectiveness.

Side effects of antibiotic therapy are widely known and include the following clinical conditions: vomiting, nausea, diarrhoea, indigestion, abdominal pain, loss of appetite, allergic reactions and adverse changes in intestinal microbiota. PPI side effects are less known and many patients are unaware of them. Recent reports suggest, that long-term PPI therapy might contribute to osteoporosis, *Clostridium difficile* infection, community-acquired pneumonia, iron and vitamin B_{12} deficiency, SIBO and dementia (65). The aforementioned side effects contribute to patients' non-compliance, which further hinders the eradication process.

8. FUTURE – VACCINATION

A breakthrough in the fight against *H. pylori* infection may be the development of an effective vaccine against this pathogen. The invention of vaccine is a huge challenge, due to very complex relationship between *H. pylori* and the host's immune system, as well as the diversity of *H. pylori* strains. Scientist suggest, that adhesion antigens, flagella proteins or an extract of whole bacterial cells may be a potential vaccine components.

Expectations are awakened by the work published in 2015 by Zeng et al. Researchers conducted a randomized, double-blind, placebo-controlled, Phase III study in China. The investigation involved 4464 children aged 6-15 years, who received 3 doses of an oral *H. pylori* vaccine. The scientists found a statistically significant efficacy of the used vaccine, although they mentioned, that further research is still needed to fully evaluate its effects and the possibility of widespread use (66).

9. CONCLUSIONS

Since the discovery of *H. pylori* bacterium in 1989, many studies were carried out to specify its impact on the human body. It is confirmed, that the infection causes chronic gastritis, which increases the risk of diseases such as: duodenal and/or gastric ulcer, gastric

cancer and gastric MALT lymphoma. In addition, studies suggest the impact of infection on many other diseases - often unrelated to the digestive system. Cardiovascular, neurological, hematological, dermatological, metabolic and also gynecological disorders are in sphere of assumptions. Current guidelines recommend eradication of infection in all persons, regardless of the presence of clinical symptoms. Multidrug regimens are used in the treatment, however the choice of the proper therapy depends on the patient's disease history and sensitivity of the specific *H. pylori* strain. Despite numerous studies, many aspects related to *H. pylori* infection still remain in the sphere of hypotheses, which should be confirmed in future reports.

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