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Review article ■

Helicobacter Pylori Infection and Upper Gastrointestinal Disease

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SUMMARY

***Helicobacter pylori* infection is one of the most common bacterial infections in humans, being present in over a half of the world population. *Helicobacter pylori* infection, by itself, does not necessarily produce the symptoms of gastrointestinal tract diseases, but certainly presents a risk for their development. The clinical outcome of *Helicobacter pylori* infection depends on the interaction of numerous factors: the virulence of a bacterial strain, genetic predisposition and premorbid host conditions, as well as the environmental factors. Accordingly, a diagnosis of *Helicobacter pylori* infection will be of clinical relevance only if it is necessary to establish the cause of a disease associated with this infection. Thus, a thorough knowledge of the diseases associated with *Helicobacter pylori* infection is a key factor in any relevant assessment of the need for eradication therapy.**

***Key words:* *Helicobacter pylori*, disease**

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INTRODUCTION

The presence of bacteria in the human stomach was noted a century before (1), but they have been regarded as contaminants for years. The studies indicating the importance of gastric bacteria started at the end of the 20th century, when Barry Marshall and Robin Warren isolated Gram negative bacilli in the stomach bioptates (2). It was believed that the bacteria belonged to the *Campylobacter* genus, but the results of subsequent studies indicated that it was a new genus, termed *Helicobacter pylori* (*H. pylori*) (3). The results of initial experimental research, in which the volunteers underwent autoinfection with the bacteria showed that *H. pylori* colonized the gastric mucosa, producing inflammation (4). These data incited numerous studies confirming the association of *H. pylori* infection with the upper gastrointestinal diseases such as chronic gastritis, peptic ulcer disease, MALT lymphoma, and gastric carcinoma. More than two decades after the isolation of *H. pylori*, Barry Marshall and Robin Warren were awarded the Nobel Prize in Physiology or Medicine for the discovery of *Helicobacter pylori* and its role in the etiology of gastritis and peptic ulcer disease.

H. pylori infection is one of the most common bacterial infections in humans, being present in over a half of the world population (5, 6). The infection usually occurs in early childhood, persisting throughout life in most of the infected. The acute phase of infection is associated with transient, non-specific symptoms of dyspepsia, that may commonly resolve unnoticed. In the infected, an inflammation occurs, humoral and cellular immune responses are evoked, resulting not in a cure but in a life-long infection (7, 8). However, in most of the infected the symptoms are absent, and only in 10-20% of the infected there is a risk of developing peptic ulcer disease, and in 1-2% for gastric carcinoma (9-11). The clinical outcome of *H. pylori* infection depends on the interaction of numerous factors: the virulence of a bacterial strain, genetic predisposition and premorbid host conditions, as well as the environmental factors.

H.pylori virulence factors

The most important factors of virulence of *H. pylori* are the *cag* pathogenicity island(*cagPAI*), vacuolating cytotoxin A (VacA), urease, outer membrane proteins. Based on the degree of pathogenicity, *H. pylori* isolates are divided into two types: type I strains of *H. pylori* contain a 40 kb segment on their chromosome, termed *cagPAI*, they produce functional VacA toxin, and the infection by the strains is associated with more severe disease forms; type II strains of *H. pylori* do not contain *cagPAI*, do not produce VacA toxin, and induce only a mild form of gastritis (12).

The *cagPAI* region contains the genes coding the synthesis of about 30 proteins. The cytotoxin-associated protein (CagA), the synthesis of which is regulated by the *cagA* gene from the region, is an immunogenic protein representing a serologic marker of the *cagPAI* presence. The genes of the region code the synthesis of type IV secretion system, which serves to inject the effectors into gastric epithelial cells, enabling CagA protein and portions of the bacterial cell wall to be translocated into the host cell. In gastric epithelial cells, CagA is phosphorylated, and an interaction with cellular kinases occurs, which induces morphologic changes and proliferation of epithelial cells (13, 14). The interaction of type IV secretion system with gastric epithelial cells induces the production of IL-8, a proinflammatory cytokine, which is related to the translocation of portions of the cell wall peptidoglycans (15). In individuals infected with CagA positive strains of *H. pylori*, a more intense inflammation occurs, with a higher risk of developing an upper gastrointestinal tract disease (16, 17).

Vacuolating cytotoxin A is an immunogenic protein that induces vacuole formation in epithelial cells. In strains with a functional *vacA* gene, there is a pronounced variability in biologic activity of the toxin. The differences in VacA toxin biologic activity are the consequence of *vacA* gene heterogeneity, especially in the signal (s) and middle (m) domains. *H. pylori* strains may have one of 2s and one of 2m types: s1 or s2, i.e. m1 or m2. *VacA* s1/m1 genotypes have a marked cytotoxic activity, while in s2/m2 genotypes cytotoxic activity is very low (18). Biologic activity of VacA toxin is a complex one: it causes the formation of pores in the cell membrane, increasing its permeability and escaping of nutritive substances and ions (19); it stimulates proinflammatory reaction (20); after its entry into the cell, it accumulates on the mitochondrial membrane and induces apoptosis (21); apoptosis of parietal cells leads to diminished secretion of gastric acid, which is a predisposing factor for the development of carcinoma (22); it induces vascuolation of the cell (23); it penetrates deeper into the tissue and inhibits activation and proliferation of T lymphocytes (24). *H. pylori* strains of the s1/m1 *vacA* genotype are associated with the development of peptic ulcer disease and gastric carcinoma (23), and although these strains are often *cagA* positive, clinical outcome of a *H. pylori* infection cannot be predicted based solely on these virulence factors (25).

A significant characteristic of *H. pylori* is the ability to colonize gastric mucosa in spite of low pH values, accomplishing this via the production of urease. Urease, by way of hydrolisis of urea to ammonia and carbon dioxide, protects the bacterial cell from the effects of gastric acid, thus enabling initial colonization. Moreover, ammonia is toxic on epithelial cells, leads to weaker intercellular bonds, facilitating thus diffusion of hydrogen ions and helping tissue erosion (26).

During an infection, most bacterial cells persist in the gastric mucus layer, while only a few adhere to the

epithelial cells. *H. pylori* adheres via the action of surface proteins. The BabA protein (blood group antigen binding adhesin) reacts with Lewis b (Le^b) antigens of the human cells. Some studies have indicated the association of adhesive activity of this protein with the development of more severe disease forms (27), though its role cannot be properly considered independently of other factors of virulence (28). SabA protein (sialic acid binding adhesin) reacts with Lewis x (Le^x) and Lewis a (Le^a) antigens expressed during the inflammation. A study by Yamaoka et al. has suggested the role of this protein in the pathogenesis of gastric diseases, proving the association of SabA production with the development of intestinal metaplasia, gastric atrophy, and gastric carcinoma (29). The expression of OipA surface protein (outer membrane inflammatory protein) is associated with elevated secretion of IL-8, development of ulcer disease, and gastric cancer (30).

Immune response

During *H. pylori* infection, both local and systemic, humoral and cellular immune responses occur, being ineffective in the elimination of this bacterium. Individuals infected with *H.pylori* produce serum anti- *H. pylori* antibodies IgM, IgA and IgG classes. Anti-*H.pylori* IgM antibodies can be detected in the acute phase of infection. Serum IgA and IgG antibodies indicate chronic infection. Anti-*H.pylori* IgA antibodies can be detected in about one third of infected subjects, while almost all produce IgG antibodies. Anti-*H.pylori* IgG antibodies persist during the infection and after successful eradication, the level of these decreases by 50% at 6 months compared with pretreatment level (31-33).

It is believed that *H. pylori* succeeds in maintaining the inflammation at a low level, enabling a decades-long persistence. However, inflammatory reaction is significant for the development of infection-associated diseases (30). In individuals with predominant Th-1 immune response there is a higher risk of developing of clinically evident disease. In contrast, in individuals with *H. pylori* infection, chronic gastritis, and absence of ulcer disease, T cells belong predominantly to the Th-0 phenotype. The differences in immune response are attributed to host genetic factors in synergy with environmental factors (34).

H.pylori associated diseases

H. pylori infection most commonly occurs in early childhood. An acute gastritis develops, with symptoms gradually disappearing and most commonly remain unnoticed. Untreated infections persist, evolving into chronic gastritis, with a correlation between the distribution of gastritis and premorbid conditions related to the level of gastric acid secretion. In individuals with intact gastric acid secretion, *H. pylori* predominantly colonizes the gastric antrum, while in the region of corpus there are few bacterial cells. Inflammation of the antral mucosa results in hyperacidity, resultant damage of duodenal mucosa, and increased risk of duodenal ulcer (35).

As the consequence of inflammation of gastric mucosa, the production of somatostatin is decreased. Since it downregulates the production of gastrin, hypergastrinemia occurs. In anthral gastritis, the parietal cells in the corpus are intact, so that increased gastrin levels lead to an increased secretion of gastric acid. Moreover, long-term increased gastrin level have an impact on the increase of mass of parietal cells. As the reaction to increased gastric acid secretion, gastric metaplasia occurs in the duodenal mucosa. Since *H. pylori* colonizes only the gastric mucosa, the site of gastric metaplasia is colonized in the duodenum and inflammation and ulceration occur (36). In individuals with reduced secretion of gastric acid, a gastritis develops, predominantly involving the corpus, with bacterial cells in close contact with the mucosa. Inflammation of the corpus stomach mucosa has a supressive effect on the function of parietal cells, leading to hypochlorhydria. The development of *H. pylori* corpus-predominant gastritis represents a predisposition to gastric ulcer, atrophic gastritis, intestinal metaplasia, and gastric cancer (35). The inflammatory reaction directly inhibits the secretory function of parietal cells and indirectly influences decreased histamin production. Hypochlorhydria occurs despite any gastrin stimulation. Reduced acid secretion further influences an increased gastrin level. Since the increased gastrin level cannot lead to an increased secretion of gastric acid, gastric cells proliferate, which together with inflammation result in the appearance of atrophic changes. However, hypochlorhydria has a protective effect against duodenal ulcer and development of esophageal reflux (36).

Chronic inflammation and precancerous changes, such as intestinal metaplasia and atrophic gastritis, constitute a risk for gastric cancer. As shown by various studies, precancerous changes occur more often in individuals with *H. pylori* infection, compared to non-infected controls (37). Moreover, multifocal nature of the process does not produce any specific symptoms. It has been estimated that *H. pylori* infection significantly increases the risk of gastric carcinoma, being thus classified as a class I carcinogen (38). *H. pylori* infection is associated with two types of gastric cancer: the intestinal and diffuse type. The intestinal type is a common type and occurs following precancerous lesions, such as atrophic gastritis, intestinal metaplasia and dysplasia (39). Virulence of the strain, as well as host-related factors, significantly influence the level of risk of gastric carcinoma. The risk is markedly higher in individuals infected by *cagA*-positive strains, as well as in those with genetic predisposition towards higher production of IL-1 during the infection (16).

The association of *H. pylori* infection with MALT lymphoma is corroborated by the information that in all patients with this malignancy, a *H. pylori* infection is present, although the percentage of *H. pylori*-positive

individuals in whom a MALT lymphoma occurs is very low (1%). In addition, after *H. pylori* eradication in patients with MALT lymphoma, the disease regression occurs, so that the detection of *H. pylori* infection and its eradication are the standard in the treatment of this tumor (35).

The association of non-ulcer or functional dyspepsia with *H. pylori* infection has not been completely elucidated yet. The symptoms of dyspepsia occur with similar frequency in those with and without a *H. pylori* infection. In addition, an eradication therapy commonly cannot eliminate the symptoms (40).

CONCLUSION

H. pylori infection, by itself, does not necessarily produce the symptoms of a gastrointestinal tract disease, but certainly presents a risk for their development. Accordingly, a diagnosis of *H. pylori* infection will be of clinical relevance only if it is necessary to establish the cause of a disease associated with this infection. Thus, a thorough knowledge of the diseases associated with *H. pylori* infection is a key factor in any relevant assessment of the need for eradication therapy.

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HELICOBACTER PYLORI INFEKCIJA I OBOLJENJA GORNJEG GASTROINTESTINALNOG TRAKTA

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Sažetak

Helicobacter pylori **infekcija je jedna od najčešćih bakterijskih infekcija kod ljudi i prisutna je kod preko polovine svetske populacije.** ***Helicobacter pylori*** **infekcija sama po sebi ne dovodi uvek do pojave simptoma oboljenja gastrointestinalnog trakta ali predstavlja rizik za njihov razvoj. Klinički ishod** ***Helicobacter pylori*** **infekcije zavisi od interakcije brojnih faktora: virulencije bakterijskog soja, genetske predispozicije i premorbidnog stanja domaćina, faktora životne sredine. Dijagnoza** ***Helicobacter pylori*** **infekcije imaće klinički značaj samo ukoliko je potrebno naći uzrok nekog od oboljenja povezanih sa ovom infekci-**

jom. Poznavanje oboljenja povezanih sa *Helicobacter* infekcijom predstavlja ključni faktor pri adekvatnoj proceni potrebe za primenom eradikacione terapije.

***Ključne reči: Helicobacter pylori*, oboljenje**