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In Patients with Gastroduodenal Peptic Ulcer Disease, an Analysis of the Immunological Properties of H.Pylori Infection

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Abstract: H. pylori causes chronic gastritis, which can develop into severe diseases of the gastroduodenal region, such as stomach ulcers, stomach cancer and lymphoma associated with the gastric mucosa. If left untreated, H. pylori is usually transmitted in childhood and persists for life. About half of the world's population is infected with this infection, but the prevalence varies depending on the region and sanitary standards. Due to its characteristics, H. pylori can colonize the epithelium of the stomach in an acidic environment. Pathophysiology of H. pylori infection depends on the complex mechanisms of bacterial virulence, their interaction with the host's immune system and environmental conditions. This leads to different phenotypes of gastritis, which can lead to various problems in the gastroduodenal region. The causal relationship between the development of gastric cancer and H. pylori infection provides grounds for preventive screening and treatment methods. Invasive, endoscopic and non-invasive methods, including exhaled air analysis, stool and serological tests, are used to diagnose H. pylori infection. The article discusses in detail the complex mechanisms of pathogenesis, including virulence factors and the interaction of the host organism. Traditional and modern molecular diagnostic methods are considered with an emphasis on their strengths and weaknesses. Changes in treatment methods are being carefully studied. This includes antibiotic treatments and new treatments. The article provides a valuable overview of current knowledge about H. pylori based on a critical analysis of recent studies. Also, this review examines recent studies that expand our knowledge of how H. pylori causes chronic inflammation, as well as signs that, from an immunological point of view, explain gastritis with H. pylori. This helps doctors and researchers develop effective treatments for infection and identifies new ways to address this global health problem.

Keywords: stomach cancer, gastric ulcer, duodenal ulcer, lymphoma, immunological point, immune system, complex interaction.

Introduction. The most common cause of chronic gastritis is *Helicobacter pylori (H. pylori*), which can also lead to serious diseases of the gastrointestinal tract, such as stomach cancer, peptic ulcer of the stomach and duodenum, and lymphoma associated with the gastric mucosa. Before its discovery, gastric ulcer was mainly associated with stress and nutritional factors, which changed our understanding of its etiology. This is a revolutionary discovery that brought Barry J. Marshall and Robin Warren received the Nobel Prize in Physiology or Medicine in 2005, which laid the foundation for a complete study of the role of *H. pylori* in various diseases of the gastrointestinal tract. Bacteria are very well adapted to the acidic and unpleasant environment of the stomach, which has led to a variety of body reactions and pathological consequences. [1,2,3,4,5]. Significant progress has been made in the study of *H. pylori*, as the scientific community continued to uncover the mystery of this pathogen. About half of the world's population is infected with *H. pylori* colonizes the gastric mucosa, which makes the infection one of the most common. It is known as a dangerous pathogen because of its ability to cause infection in the gastric mucosa, which persists throughout life. The complex interaction of bacterial virulence, host genetics and environmental factors leads to various phenotypes

of chronic gastritis. Depending on the severity of gastritis in certain parts of the stomach, these phenotypes are called antrally predominant gastritis, fundally predominant gastritis or pangastritis [6,7,8,9].

Infection caused by the *H. pylori* bacterium is still the main cause of stomach and duodenal diseases in humans, especially in countries with high incidence. Its acquisition usually occurs in childhood and can have long-term consequences [10,11]. In children and adults, *H. pylori* can cause chronic gastritis and ulcers of the stomach and duodenum. Sometimes it can lead to stomach cancer after several decades. *H. pylori* can cause lymphoma associated with the gastric mucosa, although this is quite rare, especially in children. It may also be associated with some extra-intestinal diseases, such as iron deficiency anemia, Schenlein-Henoch purpura, chronic idiopathic thrombocytopenic purpura and nutritional status. In addition, this bacterium affects not only the stomach. Its effect on autoimmune diseases, cardiovascular diseases and metabolic syndromes is also being studied. If we want to reduce the negative impact of *H. pylori* infection on public health, we must understand its pathogenesis, diagnose them correctly and treat them effectively. [12,13,14,15]. When innate immune cells detect infection or tissue damage, inflammation occurs. Although *H. pylori* affects the body's immune system, inflammation and an inadequate immune response still occur, leading to chronic active gastritis. Inflammation is an important and complex biological process that protects the body from infection or injury. This occurs in response to molecular patterns associated with the pathogen (PAMPs) *H. pylori* and molecular patterns associated with damage (DAMPs) of damaged epithelial cells. Pattern recognition receptors (PRRS) are membrane-bound or soluble cells of both immune and nonimmune cells. They respond to PAMPs and DAMPs by triggering downstream signaling cascades that include the production and secretion of pro- and anti-inflammatory cytokines, which leads to further modulation of the immune response [16,17,18]. Their use depends on the patient's medical history and the availability of drugs in the region. In the treatment of *H. pylori*, acid-suppressing drugs are used, often in combination with antibiotics and/or bismuth. The emergence of resistance to the main antibiotics used to kill *H. pylori* requires the reasonable use of antibiotics and testing of antibiotic sensitivity [19,20,21].

The main purpose of this brief review is to analyze its immunological characteristics in relation to *Helicobacter pylori*, which is considered the main cause of gastric and duodenal ulcer, as well as the possibility of developing serious complications such as cancer.

Epidemiology of *H. pylori* infection. Age, ethnicity, comorbidities, location, socioeconomic status, and hygiene conditions affect prevalence. According to a 2002 study, most cases of *H. pylori* infection occurred before the age of 10. The overall incidence rate was 1.4% per year, amounting to 2.1% at the age of 4-5 years, 1.5% at the age of 7-9 years and 0.3% at the age of 21-23 years [1,5,6,8]. Due to the improvement of socio-economic conditions and sanitary conditions, the prevalence of *H. pylori* in children is decreasing, but in 2014-2020, the prevalence of infection in children in the world remained at the level of 34%. The majority (90%) of *H. pylori* infections are acquired in childhood and persist throughout life, rather than being more common in old age. This explains why infections are more common in older people compared to children. In adults in developed countries, the rate of re-infection or relapse after successful eradication is low (less than 2%), but higher in children and adults in developing countries (5-10%). Some randomized studies have shown that *H. pylori* treatment at the family level and screening methods can reduce the recurrence rate more than treatment of a single patient. Further well-planned large-scale randomized trials are needed to confirm that *H. pylori* eradication and screening in families can reduce the spread of infection within families [25,26,27,28,29,30].

Immunity and inflammation. Activation of gastric epithelial cells triggers the immune response of the mucous membrane to *H. pylori.* These cells react to various bacterial substances, such as cytotoxin-associated gene A or the intermediate lipopolysaccharide heptose-1,7-bisphosphate. Intracellular protein 1, containing the nucleotide oligomerization domain, and the extracellular epidermal growth factor receptor are just some of the receptors that control the reaction of these cells [29,30,31,32,33]. Due to this non-specific response, various myeloid (e.g., dendritic cells and macrophages) and T cells

are attracted and activated. These cells enhance and support inflammation. In this review, we summarize the main achievements over the past year in the field of initiation, control and the role of adaptive and innate immune response to *H. pylori* infection. In addition, we briefly describe the efforts aimed at creating effective vaccination methods [18,24,2,3,33].

Virulence and pathogenic pathways of *H. pylori.* *H. pylori* is classified into three stages. It colonizes the gastric mucosa, triggers an immune response and then causes disease. When the bacterium enters the stomach, it moves towards the epithelial membrane, using the damaged parts of the stomach wall. Based on chemical signals from the environment surrounding the cell, it controls the movement of flagella using Tlp receptors, mainly TlpB. The main component of microbial invasion is urea, as well as reactive oxygen species, gastric acid, lactate and hydrochloric acid serve as signals for these receptors [21,22,23,24].

Table 1. *H. pylori* virulence factors: how they affect host cells and are involved in pathogenesis.

H.pylori	**Secretory enzymes**	**Mucinase, protease and lipase**	**Stomach mucosal ingury**
	Urease	**Neutralize acidity of the stomach**	**Injury of gastric mucosa using ammonia**
	Type IV secretion system	**Pilli-like structure**	**For injection of effectors**
	Effectors (CagA)	**Actin remodeling**	**Inhibition of apoptosis**
	Flagella	**Motility and chemotaxis to colonize under mucosa**	
	Lipopolysaccharides	**Induce gastritis**	**Adherence to the host cells**
	Outer proteins	**Adherence to the host cells**	
	Exotoxins	**Vacuolating toxin**	**Injury of gastric mucosa**

In addition, there are molecules that no one knows about that may be involved in this mechanism. *H. pylori* uses urease to protect itself from an acidic environment. With the help of urease, urea is converted into ammonia and other useful compounds. This increases the pH of the microenvironment, protecting bacteria from stomach acid. Due to this barrier, the mucous gel covering the walls of the stomach becomes less viscous. This allows the bacteria to move through the mucus into the gastric pits, where they will eventually settle (Table 1) [25,26,27,28].

The latest developments in the field of diagnosis and treatment. Over the past few years, significant advances have been made in the diagnosis and treatment of patients infected with *H. pylori*. Over the past few years, the development of nanoparticles has become one of the most exciting developments in the field of therapy and diagnostics. In the near future, nanoparticles may help replace expensive and invasive endoscopic procedures with more affordable and less invasive options. Thus, the use of a biosensor is one of the technologies, since it is able to transform certain biological elements that are on the surface of the transducer to create audio signals. This method is easier to use than other methods such as PCR testing or immunoassays, but it still gives accurate results and allows diagnosis [28,29,30,31]. In the process of performing this complex procedure, it is necessary to identify either antibodies to *H. pylori* or antigens to the bacterium. Piezoelectric materials sense changes in acoustics, sensor arrays sense changes in fluorescence or light absorption, and thermal sensors sense changes in temperature. The electromotive force or conductivity of the converting element changes when it adheres to the converting surface. Yadav et al. proposed a unique use of single-stranded genomic DNA patterns that are very precisely tuned to specific antigens, peptides or antibodies. This raised high hopes for their potential therapeutic use [13,14,15,16,17,21]. According to the latest meta-analysis of clinical trials, VPZ fought infection just as well, or even better, than proton pump inhibitors when

using different strategies and in areas with low and high resistance to clarithromycin. VPZ consumers also reported more positive impressions of using the drug. The structure of antimicrobial peptides allows them to damage the negative charge of the cell membrane, destroying the cell and disrupting its functions. Photodynamic therapy uses molecules produced by microbes that sense light. These molecules in turn produce cytotoxic reactive oxygen species that destroy bacteria. When bacteriophages specific to *H. pylori* are used, they suppress cells and destroy the pathogen [15,16,18,23,25,26,31].

Prospects for determining the immune response of *H. pylori*. The immune system is constantly faced with various threats, which it must evaluate in order to identify possible threats. The success of the immune response balances the costs and benefits for the host organism. *H. pylori* has created sophisticated methods of evading immune control, affecting the cost-benefit ratio. Improving our understanding of the involvement of this cell type in host-pathogen interactions in ongoing infections requires understanding the role of dendritic cells in immune recognition and management of adaptive immune responses [6,7,8,18,24]. Recent discoveries have shown how the interaction of *H. pylori* with the myeloid compartment affects the response to immunotherapy aimed at treating cancer in tissues unrelated to gastric cancer. The emergence of ex vivo organoid models, such as cultivation of epithelial cells, stroma and immune cells or "stomach-on-a-chip" methods, can complement existing in vitro and in vivo models to determine the effect of *H. pylori* on pathologies and possible treatments in humans [27,28,30,31,33].

Discussion. It was first discovered that *H. pylori*, a highly mobile gram-negative bent-shaped bacterium, is present in the gastrointestinal tract, at the end of the XIX century. In 2005, the Nobel Prize was awarded to scientists who demonstrated that *H. pylori* can cause gastritis [2]. Due to the low pH level of the stomach, it was considered a sterile organ in which bacteria could not reproduce, so it was assumed that bacteria entered the body through the mouth, and not through the stomach. But since *H. pylori* was discovered by Warren and Marshall in the early 1980s, it has been associated with several diseases of the digestive system that cause indigestion [4,7,8,9,11,15]. *H. pylori* bacteria live in glands under the surface of the mucous membrane and are usually associated with chronic active gastroenteritis. *H. pylori* infection and gastric cancer, peptic ulcer disease and lymphoma of the gastric mucosa are closely related. A study conducted by Shatila and Thomas showed that in 90% of cases, *H. pylori* infection can lead to mucosal lymphoma and stomach cancer. In addition, *H. pylori* infection is closely associated with gastric ulcer (up to 80% of cases) and duodenal ulcer (about 90% of cases). In addition, there is a direct correlation between *H. pylori* infection and duodenal ulcer (80% of cases), gastric ulcer (80% of cases) and cancer. WHO proposed the eradication of *H. pylori* in 2014 to reduce deaths from stomach cancer worldwide. Clarithromycin-resistant strains of *H. pylori* are one of the potential risks to public health and the environment [21,22,23,24,25,26,27].

How this pathogen affects the development of stomach diseases is still unclear and controversial. Not only does *H. pylori* cause passive inflammation inside the epithelium of the stomach and alter the signaling pathways, creating the basis for pathogenesis, but it also contributes to the development of antimicrobial resistance due to genetic changes and biofilm formation. In addition, it is important to note that the variability of *H. pylori* strains affects the virulence of the bacterium. The development of specific virulence genes facilitates the exchange of information between bacteria and the host organism [1,4,9,10,11,12]. A previous study conducted by Palamides et al. showed that different strains of *H. pylori* have different pathogenicity and are associated with different assumptions. To date, the removal of *H. pylori* has been somewhat successful, despite the complexity of the process. In order to develop effective methods to combat *H. pylori* infection, it is extremely important to determine the virulence and pathogenic pathways of *H. pylori.* These virulence mechanisms can be used to develop therapeutic strategies. Therefore, it is important to determine exactly how virulence factors affect *H. pylori* in order to create new vaccines and drugs susceptible to *H. pylori*. This article discusses the features and clinical manifestations of *H. pylori* infection. He also briefly describes traditional and modern detection methods that are effective in detecting and treating infections caused by this pathogen. In

addition, an overview of various approaches to vaccination and the pathogenicity of *H. pylori* is presented [11,12,21,23,24,25].

CD4+ T cells are important for many components of the immune response. The Th1 and Th17 subtypes of the inflammatory response contribute to protection against H. pylori through cytokine secretion and activation of effector cells. However, it also supports ongoing inflammation and damage, which can lead to the development of stomach cancer. Clinical studies conducted last year showed that Th1 and Th17 reactions occur in H. pylori infection. The researchers found that Swedish patients with H. infection pylori had higher levels of expression of genes encoding the prototype cytokine Th17 IL-17A and lymphokine Th1 IFN-γ in the body and antrum of the stomach compared with people without infection. Moreover, they confirmed by immunofluorescence that the number of IL-17A+ and IFN-γ+ cells is also higher in patients with infection [28,29,30,31,32,33].

Conclusions. Because it is a widespread and complex pathogen, H. pylori has always attracted attention. Side effects of H. pylori infection include cancer and stomach ulcers. Therefore, early detection, proper monitoring and the search for alternative treatments are necessary. We were able to identify diagnostic and therapeutic targets by knowing the pathogenesis of H. pylori infection. In particular, we can better monitor bacterial reinfection and spread, and better manage outbreaks.

This type of actor strikingly evades the control of the host's immunity and affects its immunity, which leads to an unstable balance between pro-inflammatory and anti-inflammatory signals, a violation of which can cause cancer and other dangerous diseases for the host. A hasty immune response balances costs and benefits for the host body. H. pylori has created sophisticated methods of evading immune control, affecting the cost-benefit ratio. Improving our understanding of the involvement of this cell type in host-pathogen interactions in ongoing infections requires understanding the role of DC in immune recognition and management of adaptive immune responses.

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