Helicobacter pylori: Commensal, symbiont or pathogen?

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Abstract

This review considers the data on *Helicobacter pylori* (*H. pylori*), which have been accumulated over 40 years since its description as an etiological factor in gastrointestinal diseases. The majority of modern publications are devoted to the study of the pathogenic properties of the microorganism in the development of chronic gastritis, peptic ulcer disease, and gastric cancer, as well as methods for its eradication. However, in recent years, there have been more and more studies which have suggested that *H. pylori* has a beneficial, or potentially positive, effect on the human body. The authors have attempted to objectively analyze the information accumulated in the literature on *H. pylori*. Some studies consider it as one of the recently identified human bacterial pathogens, and special attention is paid to the evidence suggesting that it is probably part of the composition of the human microbiome as a commensal (*commensal* from French to English is a table companion) or even a symbiont. The presented data discussing the presence or absence of the effect of *H. pylori* on human health suggest that there is an apparent ambiguity of the problem. The re-assessment of the data available on *H. pylori* infection is important in order to answer the question of whether it is necessary to create a program of mass *H. pylori* eradication or to apply a more personalized approach to treating patients with *H. pylori*-associated gastrointestinal diseases and to perform eradication therapy.

Key Words: *Helicobacter pylori*; Pathogen; Commensal; Microbiome; Peptic ulcer; Gastric cancer; Asthma; Inflammatory bowel diseases

Core Tip: This review provides data on *Helicobacter pylori* (*H. pylori*) as one of the recently identified human bacterial pathogens. On the one hand, its role as a human

pathogenic bacterium that is commonly found in patients with chronic gastritis, peptic ulcer disease, and gastric cancer is discussed. On the other hand, the high prevalence of *H. pylori* in the population and its asymptomatic coexistence with humans in most of the world's population indicates its persistence in the body as a representative of the microbiome and as a nonpathogenic microorganism. The presented data suggest that there is an apparent ambiguity of the problem and a need for an analytically developed, comprehensive approach to study the effect of *H. pylori* infection on human health and to perform eradication therapy.

INTRODUCTION

Over four decades, the problem of studying *Helicobacter pylori* (*H. pylori*) has occupied the minds of many scientists around the world. *H. pylori* is a bacterium that is commonly found in patients with chronic gastritis, peptic ulcer disease (PUD) and gastric cancer (GC), as well as among the healthy population. *H. pylori* was first reported in 1875, when Bottcher and Letulle observed it on the margins of peptic ulcers[1]. Despite the high prevalence of the microorganism demonstrated later, its discovery occurred only at the beginning of the 1980s[2]. It is obvious that since 1983 *H. pylori* has been colonizing more than half of the world population[3]. This event has produced a major multidisciplinary interest including gastroenterologists, microbiologists, and infectious disease specialists among others. The role of *H. pylori* as a true pathogen has been the center of major discussions for many years. *H. pylori* infection has been linked to gastric and duodenal ulcers (in 1%-10% of infected patients), gastric carcinoma (0.1%-3%), and gastric mucosa-associated lymphoid tissue (MALT) lymphoma (less than 0.01%)[4,5]. However, the vast majority of the infected population will never develop symptoms related to *H. pylori* infection.

H. pylori colonization of the human stomach occurs early in life and persists indefinitely unless treated[3]. At the same time, transmission of *H. pylori* is mainly in a family setting[6].

The decline in *H. pylori* prevalence with time was first reported in 1997[7], and later confirmed in two large population-based studies in the United States[8]. As a result of *H. pylori's* gradual decline, a series of negative consequences have been described[2]. There has been an alarming increase in asthma[9,10], as well as a potential increase in the susceptibility to diarrheal diseases[11]. However, a more serious consequence related to the decline of *H. pylori* is the escalation of esophageal diseases, such as gastroesophageal reflux disease (GERD), Barrett's esophagus, and adenocarcinoma of the esophagus[12,13]. We do not know if the decline in *H. pylori* infections is the cause of these emerging diseases or if it is just an indicator of the hygiene hypothesis[2]. Due to its low virulence and the fact that disease is observed mostly in elderly infected individuals, *H. pylori* could be considered a commensal organism and only an opportunistic pathogen.

GENERAL CHARACTERISTICS OF *H. PYLORI*

Basic facts

H. pylori is a gram-negative, S-shaped, or helical microaerophilic bacterium belonging to the genus *Helicobacteraceae*[14,15]. In 1979, R. Warren identified *Campylobacter pylori* and suggested that this microorganism was an etiological agent of gastritis. In 1982, B.J. Marshall isolated a culture of *H. pylori* and showed the relationship between its persistence and PUD development[16].

According to the modern concepts, the predominant habitat (life, growth, and reproduction) of *H. pylori* is the supraepithelial mucus layer in the region of the gastric pits and in the first parts of the duodenum[16]. *H. pylori* is generally not detected neither

in the subepithelial space of the stomach nor in the epithelium of gastric glands[13]. The motility of the microorganism through the mucus layer occurs due to the presence of several mobile flagella, which contributes to the migration of the bacterium to areas with suitable conditions for existence[17].

The most favorable conditions for bacterial life have been found to be the optimum temperature of 37°C, pH 4.0-6.0, microaerophilic conditions, the presence of water and nutrients[15]. *H. pylori* does not contain enzymes that metabolize carbohydrates. The metabolism of a bacterial cell is provided by the energy released during the utilization of amino acids obtained from the host[18]. The microorganism is characterized by its possible persistence in the human body as S-shaped, C(U)-shaped, and coccoid forms[2,15,16]. The similar mechanism of transition from one form to another is an adaptation to survival during adverse environmental conditions (temperature or pH shifts, long intervals between meals, and antibiotic therapy)[15].

Epidemiology and routes of transmission

The data currently available suggest that there is a high prevalence of *H. pylori* in the population. The detection rates of *H. pylori* vary from 35% to 90% in representatives of the population in different regions[15,19-22]. A large variation of the indicator depends on a number of factors, including the socio-economic state of the country, age, the method of detecting *H. pylori* and other factors[20]. Thus, in their article, Mentis *et al*[19] reported the detection of *H. pylori* in 71.6% of the population in Italy and in 84.2% of those surveyed in Poland. Luzza *et al*[20] reported that in Italy among 518 subjects who were evaluated by both the ^{13}C-urea breath test (UBT) and serology, 310 (59.8%) were UBT positive, 479 (92.4%) *vacA*-positive, and 369 (71.2%) *cagA*-positive. Similar indicators for Africa and Asia were distributed in the following order: Ethiopia (72.2%) and Rwanda (75.3%), China 83.4%, Japan (39.9%), and Taiwan (72.1%)[19]. Burucoa *et al*[21] established the largest proportion of *H. pylori*-positive patients in Africa (70.1%) [95% confidence interval (CI): 62.6%-77.6%], South America (69.4%) (95%CI: 63.9%-74.9%), and West Asia (66.6%) (95%CI: 56.1%-77.0%). The regions with least occurrence were Oceania (24.4%) (95%CI: 18.5%-30.4%), Western Europe (34.3%) (95%CI: 31.3%-37.2%), and North America (37.1%) (95%CI: 32.3%-41.9%). In Russia, the prevalence of *H. pylori* in children aged 5–10 and 11–14 years and in adults was 29%, 50%, and 70%-92%, respectively[13,23].

To date, the main route of transmission of *H. pylori* is not known. Infection most often occurs from person to person; in this case this generalized mechanism can be divided into vertical (that is, transmission of the pathogen within one family), and horizontal (contact with people outside the family or infection with environmental objects-environmental contamination)[19]. Possible transmission routes, such as fecal-oral, oral-oral, and gastro-oral, have been comprehensively studied in recent years[21,24,25]. *H. pylori* can be isolated from different body fluids. The pathogen was detected in the dental plaque, saliva, tonsil tissue, root canals, and on the oral mucosa (including on the surface of the tongue), using a polymerase chain reaction assay[21]. Particular attention is paid to the environmental contamination associated with the consumption of *H. pylori*-containing water and food[26].

The majority of authors consider the intrafamilial transmission of the pathogen to be the predominant and most significant route. This opinion is confirmed by factors, such as close interpersonal contacts in the family, the single socioeconomic status of family members, and genetic predisposition to *H. pylori* persistence[24,27].

PATHOGENIC PROPERTIES OF *H. PYLORI*

H. pylori virulence factors and its role in systemic diseases

To survive the unfavorable, hyperacid conditions of the stomach, *H. pylori* synthesizes a number of virulence factors that both improve conditions for vital activity in an acidic environment and have a damaging effect on the gastric mucosa.

In their work, Kao *et al*[28] noted that on entry into the host stomach, *H. pylori* uses urease activity to neutralize hydrochloric acid that is one of the protective factors and has a pronounced antimicrobial effect. Regulation of urease synthesis is encoded by a number of genes called the *urease gene cluster*. This set of genes includes catalytic units (*urea A/B*), an acid-gated urea channel (*ureI*), and accessory assembly proteins (*ure E-H*)[29].

Of interest is the fact that urease synthesis depends on the pH surrounding the bacterium: The ureI-channels are tightly closed at pH 7.0 and are completely open at pH 5.0[28,30]. That is, when the external conditions change, namely, when stomach

lumen acidity increases, *H. pylori* releases urease that hydrolyzes urea into CO_2 and ammonia (NH_3) that in turn binds to water and forms unstable ammonium hydroxide. This sequence of biochemical reactions leads to medium alkalization[28]. This mechanism of overcoming the acid barrier is extremely important for the survival of the bacterium along with a spiral shape, a smooth cell wall, and helicoidal movements. Schoep *et al*[31] demonstrated that urease-negative bacteria were unable to colonize the gastric mucosa of gnotobiotic piglets.

Another important virulence factor promoting the spread of the bacterium to the gastric epithelium is its motility due to the presence of 4-7 mobile sheathed flagella. The flagellum is a complex organ that is composed of several types of protein subunits and consists of the basal body, hook, and filament[32,33]. There are several types of flagella-driven motility: "Swimming motility", "spreading motility", and "swarming motility"[33]. Along with urease activity, flagellar motility has been shown to be an essential factor for colonization of the gastric mucosa[34]. There are also studies which demonstrate the utmost importance of flagella in the formation of microbial biofilms on the surface of the gastric mucosa[35,36].

Bacterial adhesion is the key stage of colonization, which determines a whole set of processes of gastric *H. pylori* persistence. The literature describes adhesion molecules (outer membrane proteins), such as blood-antigen-binding protein A, sialic acid-binding adhesin, neutrophil-activating protein, heat shock protein (Hsp) 60, adherence-associated proteins (AlpA and AlpB), *H. pylori* outer membrane protein, and LacDiNAc binding adhesin[28,37-40]. Among the key factors of colonization, virulence factors that have a direct damaging effect on the gastric mucosal epithelium can be separated out; these are cagA, γ-glutamine transferase, high-temperature requirement A, and vacuolating cytoxin A (vacA)[38,39].

CagA is a highly antigenic protein with a molecular weight of 120-145 kDa[41,42]. The locus of a gene responsible for the synthesis of cagA and a type IV secretion system (T4SS) is named *the cag pathogenicity island*[38]. CagA acts intracellularly through the epithelial cells *via* the T4SS: The latter forms a syringe-like pilus structure, through which the cagA molecule enters the host epithelial cell[40]. After translocation into the cell, cagA undergoes phosphorylation on the inner side of the cytoplasmic membrane of an epithelial cell and thus acquires biochemical activity[43]. It was found experimentally that cagA phosphorylation-competent mice developed cancers, such as gastrointestinal adenocarcinoma, myeloid leukemia, and B-cell lymphoma. Moreover, these pathogenic processes were not observed in phosphorylation-resistant forms[44]. The main pathogenetic effect of cagA is to enhance the mitotic activity of gastric epithelial cells, which contributes to malignancy if the microbe persists long-term[43,45].

VacA is a protein with a molecular weight of 88 kDa, which consists of two subunits (p33 and p55) and has multiple pathogenetic effects[43]. After protein internalization, large pores are formed in the cytoplasmic membrane of gastric epithelial cells, which makes the cells more susceptible to the effects of bacterial urease[46]. Beyond that point, the launch of a cascade of biochemical reactions promotes the accumulation of large vacuoles inside the cells, which leads to the functional inferiority of epithelial cells. Through the intracellular transporter system, vacA is able to enter the mitochondria, where it disrupts the integrity of the inner mitochondrial membrane. This induces a drop in the mitochondrial transmembrane potential ($\Delta\Psi m$) with the subsequent release of cytochrome C and the activation of the proapoptotic factor Bcl-2 associated X protein[47]. There are data showing that vacA is involved in avoiding a pronounced immune response to the entry of an infectious agent. This is achieved by both the reduction in the activation of T lymphocytes in the lamina propria and disruption of the autophagy process[48].

Immune response to H. pylori invasion

When entering the human body, *H. pylori* is constantly controlled by the immune system. The inflammatory response is well-known to be a marker for a developing immune response. In *H. pylori* persistence, the focus of inflammation primarily affects gastric epithelial cells; in this case the inflammatory reaction involves neutrophils, lymphocytes, macrophages, and dendritic cells (DCs), which migrate to the site of infection through the systemic circulation[49,50].

The contact of DCs with *H. pylori* antigenic determinants results in autocrine activation of the pool of immature CD4+ T cells, followed by their differentiation into T-helper (Th) 1 lymphocytes through interleukin (IL)-12 production[51]. There are Th1 lymphocytes that are the major inflammatory effector cells for *H. pylori* invasion[52]. In addition, proinflammatory cytokines, such as IL-1, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, are involved in the immune response[53].

The initial Th1 cell immune response is aimed at completely eradicating the

infectious agent. However, it has been shown experimentally that vacA is able to exert an immunosuppressive effect on the cells of the immune system, by inhibiting the production of IL-23 by DCs[54]. Furthermore, *H. pylori* HspB is capable of inhibiting the proliferation of mitogen-stimulated T cells, by enhancing the suppressive effects of regulatory T (Treg) cells in both innate and adaptive immune responses[55,56].

The interaction of *H. pylori* with Th2 lymphocytes is not obvious. Due to the activation of the Th1 cellular component of the immune system, the Th2 cellular pathway for differentiation of immature lymphocytes is not believed to play a considerable role in the immune response[52]. At the same time, it has been proven that the level of immunoglobulin G (IgG) is a reliable indicator of *H. pylori* persistence. In infected individuals, a Th2 response induces IgG1 production while a Th1 response contributes to a significant increase in the overall levels of IgG2 through IL-2 and IFN-γ production. IgG2 titers are higher than IgG1 titers in *H. pylori*-infected patients, particularly in those with ulcer disease[57].

Thus, the persistence of *H. pylori* in the human body is accompanied by the pronounced immune response to bacterial invasion, which is subsequently replaced by immune tolerance. This fact may suggest that the relationship between *H. pylori* and the host is symbiotic.

H. pylori-associated diseases

The currently available data may suggest that *H. pylori* persistence in the stomach is associated with the development of gastroduodenal diseases, such as chronic gastritis, PUD, gastric adenocarcinoma, and gastric MALT lymphoma[3,28,58,59]. Recent data show a statistically significant relationship between *H. pylori* detection and pancreatic cancer development[60,61].

The risk of developing symptoms of a gastrointestinal disease depends on the degree of pathogenic properties in a persistent strain, the genetic characteristics of the host, environmental factors, and the pattern of diet[62,63]. The researchers emphasize the fact that the persistence of *H. pylori* in the gastric mucosa is constantly controlled by the immune system, as a result of which the pathogenic properties of *H. pylori* and, as a consequence, the symptoms of the disease manifest in the presence of favorable factors. Beyond that point, more and more attention is paid to the implication of *H. pylori* in the pathogenesis of extragastric diseases. Thus, the role of the microorganism in developing a number of neurological, cardiovascular, hematological, skin, and metabolic diseases is being actively investigated[62-66]. The results of the available studies are undoubtedly quite contradictory and require a more thorough study.

The meta-analysis by Wang *et al*[67] demonstrated that chronic *H. pylori* infection is a predictor for the possible development of ischemic brain injury. Reports suggesting a relationship between *H. pylori* detection and Alzheimer's disease development have been published[68,69]. Huang *et al*[70] were able to establish that the risk of Parkinson's disease was significantly higher in the *H. pylori*-positive group than in the *H. pylori*-negative (HPN) group (adjusted hazard ratio: 2.29, 95%CI: 1.44–3.66; *P* < 0.001).

Little experience has been accumulated in studying the effects of *H. pylori* on the development of cardiovascular diseases. Some studies confirm a significant relationship between the detection of *H. pylori*, the development of atherosclerotic vascular lesions, and, as a consequence, a higher risk of coronary heart disease[71-74]. Jukic *et al*[73] found that *H. pylori*-positive patients more often suffered from hypertension (*P* = 0.014), had higher systolic (*P* = 0.043) and diastolic (*P* = 0.005) blood pressure, as well as elevated plasma triglyceride levels (*P* = 0.013) and a low antiatherogenic high-density lipoprotein level (*P* = 0.01). At the same time, there was no significant difference in the severity of the disease between the two groups.

Vijayvergiya *et al*[75] described the considered hypotheses on the mechanisms of endothelial dysfunction in *H. pylori* infection. Some hypotheses state that pathophysiological changes in the microvascular bed result from a secondary increase in homocysteine levels: *H. pylori* induces vitamin B_{12} and folic acid malabsorption, by elevating the homocysteine level that negatively affects the endothelium[76,77]. The theory of cytokine-induced vascular wall injury, which in turn is the first stage of atherosclerotic changes, should also be actively studied. The work by Rasmi *et al*[78] confirmed that *H. pylori* cagA-positive patients with cardiac syndrome X were found to have increased IL-1 and TNF-α levels. The experimental data obtained by de Jesus Souza *et al*[79] showed that urease is a potent stimulus for endothelial cell production of reactive oxygen species and NO, which also leads to the enhanced production of nuclear factor kappa B, activation and upregulated expression of cyclooxygenase-2, heme oxygenase-1, IL-1β, and intercellular adhesion molecule-1. Such experimentally established changes in the pro-inflammatory molecule profile can indirectly indicate the possible pathogenetic features of *H. pylori*-induced injury to the vascular bed.

An association between *H. pylori* infection and skin diseases is being actively studied. Yu *et al*[80] provided evidence that the detection rate of *H. pylori* was 49.5% among 1038 representatives in a study group (patients diagnosed with psoriasis), while the rate was 38.8% in a control group (*n* = 703) (the pooled OR was 1.70; 95%CI: 1.15-2.52; *P* = 0.008). Onsun *et al*[81] concluded that *H. pylori* was detected in 184 (61.3%) individuals among 300 patients with psoriasis and in 89 (59.3%) representatives in a control group (among 150 healthy people). At the same time, it was noted that the disease severity, as assessed by the Psoriasis area and severity index scores, was noted to be significantly higher in *H. pylori*-positive patients. The literature provides a large number of reports on *H. pylori* detection in patients who, in addition to psoriasis, have lichen ruber planus, scabies, rosacea, Sweet's syndrome, Behcet's disease, and Schönlein-Henoch purpura[82].

It should be noted that antibacterial drug manufacturers have an impact on more attention to the pathogenic properties of *H. pylori* and mass (program) eradication therapy[3].

IS EVERYTHING SO CLEAR?

Rare development of symptoms with high prevalence in the population

Following the discoveries by R. Warren and B.J. Marshall, the concept of pathogenesis and treatment regimens for PUD implied mainly the identification and eradication of *H. pylori*. It is currently known that the occurrence of *H. pylori* is high in the healthy population (about 50% of the population worldwide and more than 70% of that in developing countries)[2]. *H. pylori* infection is usually acquired in childhood and generally persists lifelong. Thus *H. pylori* has infected the majority of the world's population for the majority of their lifetime and in most cases causes no symptoms[3,83]. The infectious process in *H. pylori* is chronic and only one in ten colonized individuals; most commonly the elderly, develop clinical manifestations years later[2]. Tsimmerman[13] reported that less than 1% of individuals infected with *H. pylori* develop various diseases and about 70% of people who are found to have the bacterium are healthy bacterial carriers. The available data show that only 5%-10% of those infected develop symptoms of gastritis or PUD[84-87]. Moreover, the review data (Araújo *et al*[88]) indicate that the detection rate of *H. pylori* infection in patients diagnosed with PUD does not differ from that of *H. pylori* in the general population. The authors also noted that in 20%-50% of cases of PUD, they are unable to identify the overarching etiological factor of an ulcerative lesion, that is to say, an idiopathic ulcer (*H. pylori* negative, non-steroidal anti-inflammatory drug-negative peptic ulcer/NSAIDs). Sidorenko[89] stated that the given facts provide a strong argument that refutes the leading role of *H. pylori* in the development of gastroduodenal diseases. The wide spread of *H. pylori* infection among individuals without signs of pathology and the low incidence rate during chronic colonization of the gastric mucosa clearly indicate that *H. pylori* is more likely to be an opportunistic or latent pathogen than a truly pathogenic bacterium.

The presented data suggest that the infectious theory of chronic gastritis, PUD, and GC seems to be rather an exception to the rule. In addition, the severity of chronic gastritis and/or PUD appears to be directly related to other etiological factors, along with the density of *H. pylori* contamination.

H. pylori and PUD

PUD is a chronic multifactorial disease characterized by an imbalance between the aggressive components of the gastroduodenal contents and the protective mechanisms of the gastric mucosa. A significant role in the pathophysiological changes characteristic of PUD is played by important components, such as hereditary predisposition, psychoemotional and psychosocial stress effects, autonomic dysfunction, local pathogenetic effects (acidity of the stomach contents), immunodeficiency state, oxidative stress, smoking, excessive alcohol consumption, and the use of steroid drugs and nonsteroidal anti-inflammatory drugs[87,90]. In their review, Malfertheiner *et al*[87] focused on the fact that the development of PUD depends on the complex influence and/or a combination of both exo- and endogenous factors. In addition to the above described exogenous factors, the most important endogenous components of ulcerogenesis are the level and adequate function of enteric hormones (gastrin, somatostatin), genetic predisposing factors (the number of parietal cells, the basal level of gastric hydrochloric acid secretion, and defects in bicarbonate secretion). Such observations show that the presence of *H. pylori* infection may be only one (but

far short of being single) component in the genesis of ulcerative disorders.

It is essential to also recall the fact that in the case of *Helicobacter* etiology, the risk of developing the disease depends on the genotype of *H. pylori*: The patients with a confirmed diagnosis of PUD were found to have *vacA*-positive and *cagA*-positive genotypes[91,92]. At the same time, the genotypes containing the *vacA* gene are known to account for about 60% of all detected forms of *Helicobacter*[93].

In addition to *H. pylori*-associated ulcers, the current classification identifies tumor ulcers, ulcerative lesions in Zollinger-Ellison syndrome, Crohn's disease, eosinophilic gastroduodenitis, radiation damage, and viral infections (cytomegalovirus or herpesvirus infection in immunocompromised patients). The idiopathic form occupies a separate place[87].

Interestingly, epidemiological studies in recent years demonstrate a progressive increase in the idiopathic forms of PUD with a decrease in the global prevalence of *H. pylori* infection[94,95]. Thus, Indian researchers have shown that 45.9% of cases of peptic ulcers of the stomach and 29.6% of those of the duodenum are idiopathic (they are unassociated with either *H. pylori* detection or a history of steroid/NSAID intake)[96].

Reshetnyak *et al*[97] presented data on the role of *H. pylori* and drugs in the development of gastric mucosal (GM) lesions in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). Endoscopic examinations of patients with SLE and APS revealed the following GM changes: antral gastritis (82.4%), erosion (24.7%), hemorrhages (8.2%), and pangastritis (8.2%). The rate of *H. pylori* infection in patients with SLE and APS corresponded to that in the general population. The authors' data showed that there was no direct correlation between the observed GM changes and *H. pylori* infection. However, therapy with glucocorticoid, low-dose acetylsalicylic acid, NSAIDs, and anticoagulants was in this case responsible for GM damage in patients with SLE and APS.

There is evidence suggesting the most favorable course of *H. pylori*-associated ulcers compared with other diagnosed types. Kanno *et al*[98] established that among 382 examinees diagnosed with PUD, the patients with a confirmed diagnosis of *H. pylori*-positive ulcer had a statistically significant increase in healing rates. In the study, the patients were divided into 4 groups: A simple *H. pylori* group; a *H. pylori* (+)/NSAIDs (+) group; a simple NSAIDs group; and an idiopathic ulcer (IPU) group. Indicators, such as healing rates at 3 mo, treatment course, and recurrence rates, were estimated. According to the data presented, the healing rates in these groups were distributed as follows: 95.0%, 94.9%, 73.3%, and 77.4%, respectively. This indicator for idiopathic forms was statistically significantly different ($P < 0.01$). The recurrence rate in the IPU group was also much higher: 13.9% in the IPU group and 2.1% in the simple *H. pylori* group ($P < 0.01$). The cumulative recurrence rates estimated by the Kaplan-Meier method were also significantly higher in the IPU group than those in the simple *H. pylori* group ($P = 0.015$).

Rasane *et al*[99] demonstrated that patients with HPN PUD had a more pronounced severe course of the disease and a more negative prognosis than those with *H. pylori*-associated forms. Thus, albumin levels in the HPN group were higher than those in the *H. pylori*-positive group: 2.97-0.96 *vs* 3.86-0.91, $P = 0.0001$. The same pattern was observed when evaluating the patients' state on admission to hospital: In the HPN group, the scores of scales, such as the American Society of Anesthesiologists scoring system and the Charlson comorbidity index, were much higher: 3.11-0.85 *vs* 2.60-0.73 ($P = 0.005$) and 4.81-2.74 *vs* 2.98-2.71 ($P = 0.004$), respectively. There were also significant differences in indicators, such as hospital length of stay: 20.20-13.82 *vs* 8.48-7.24; $P = 0.0001$) and 30 d readmission rate (11; 29.73% *vs* 5; 11.91%; $P = 0.049$).

The diversity of causes that lead to the ulcerative process allows PUD to be considered as a polyetiological and polypathogenetic disease. When *H. pylori* was discovered, there were many theories of PUD development: Vascular, stomach inflammatory, allergic, hormonal, motor-primacy, corticovisceral, neurogenic, psychosomatic, and acidopeptic theories. Each of them deserves attention, as it reflects one of the facets of this complex problem. The above data suggest that for people who are predisposed to this pathology, the emergence of an infectious theory has become an important and significant addition to the already existing etiological factors. Also, not in all cases, but only in a certain state of the macroorganism, *H. pylori* becomes a pathogen and is an additional cause of chronic gastritis, PUD, and even GC.

H. pylori and GC

GC occupies one of the leading places in the pattern of cancers. Epidemiological studies have demonstrated that GC develops in *H. pylori*-infected people 1.4-4.2 times more often than in the general population[100-102]. At the same time it should be noted that GC develops only in 1%-2% of cases with a 50% or more frequency of gastric

colonization with *Helicobacter* worldwide[13,103]. Among the population of India and Africa, where the *H. pylori* infection rates reach 90%-95%, GC is diagnosed much less frequently than in Western Europe and the United States, where the prevalence of *H. pylori* does not exceed 35%-50%[104]. The carcinogenic potential of *H. pylori* is rather ambiguous: It has been found that *H. pylori* toxins do not exert a direct mutagenic effect on gastric epithelial cells[105]. Virulence factors have been described in *H. pylori*, but the presence or absence of these factors is not critical in disease development[2]. In addition, there is evidence that *H. pylori* persistence increases the risk of developing only distal (pyloroantral) GC, whereas proximal (cardiac) GC is unassociated with *H. pylori*. Moreover, antral colonization with *H. pylori*, especially with its *cagA*-positive strains, somehow prevents the development of cardiac GC and carcinoma of the lower third of the esophagus, performing a protective function[106]. Rokkas *et al*[107] called the relationship between *H. pylori* infection and subsequent GC development an unclear epidemiological paradox.

Blaser[108] has stated his belief that there is a certain balance between the negative and positive effects of *H. pylori* on humans. Some authors consider that *H. pylori* shows its pathogenicity, by regulating the expression of different genes to the extent that is dictated by the response of a macroorganism[109,110]. Thus, the microorganism and the macroorganism create a finely tuned balance system, the resulting impairment of which develops a specific disease with certain clinical signs and prognosis[111]. In the vast majority of cases, long-lasting *H. pylori* infection induces chronic gastritis, while only some patients develop PUD and GC. For this reason, the bacterium is considered to be a risk factor for the development and recurrence of PUD and GC[112,113]. Therefore, *H. pylori* is assigned to the group of pathogenic bacteria. However, it would be more correct to treat only those individuals at high risk for GC or to establish programs for early detection of GC without implementing massive eradication programs for this bacterium that may be important to colonize the gastric stomach of young humans[2].

BENEFICIAL "PROTECTIVE ROLE" OF *H. PYLORI*

H. pylori and asthma

The literature in recent years has enough works, the results of which suggest that there is an inverse correlation between the persistence of *H. pylori* and the detection of asthma cases[8,114-117].

Chen *et al*[8] reported that the detection of *H. pylori* in young and middle-aged patients (mean age 25 years) is inversely correlated not only with asthma, but also with other atopic diseases (dermatitis, atopic rash, and eczema). These researchers found a strong inverse relationship between the detection of *H. pylori* and the early onset of asthma (≤ 5 years old): OR = 0.58; 95%CI: 0.38-0.88. The difference in the patients' current status was also statistically significant: Asthma was observed less frequently in patients with detected *H. pylori* infection (*P* = 0.03). Elias *et al*[115] showed that 25% and 40% of children were seropositive for IgG in the study and control groups, respectively (*P* = 0.03) (the children's age ranged from 4.8 to 17.3 years). Interestingly, *cagA* IgG seropositivity was associated with a low risk of asthma [adjusted OR 0.30 (95%CI: 0.10-0.87)]. However, this pattern was not found for *cagA*-negative serology [adjusted OR = 0.64 (95%CI: 0.30-1.37)]. As in a previous study, *H. pylori* seropositive children had a lower likelihood of asthma than seronegative children [adjusted OR = 0.29 (95%CI: 0.10- 0.82)].

Greek colleagues found that the detection rate of *H. pylori* was 11.1% in children aged 8.6 ± 4.5 years with asthma symptoms, while it was 29.6% in the control group of the same age without bronchial obstruction symptoms (OR = 0.1; 95%CI: 0.039-0.305; *P* = 0.026)[109]. This correlation has been confirmed by a number of other earlier studies[118,119].

Oertli *et al*[120] investigated in detail and described the mechanism of anti-atopic action of *Helicobacter*. Their study indicated that immune tolerance could be acquired due to the immune system's constant response to bacterial γ-glutamyl transpeptidase (GGT) and vacA. At the same time, there was a gradual maturation of DCs and their more targeted interaction with Treg cells, which contributed to the more targeted autoactivation of the lymphocyte pool to various antigens. Such mechanisms ultimately result in immune tolerance to benign antigens (allergens). Special attention should also be paid to the fact that isogenic *H. pylori* mutants lacking either GGT or vacA are incapable of preventing DC maturation and fail to drive DC tolerization as assessed by induction of Treg properties in cocultured naive T cells.

Pachathundikandi *et al*[121] associated the phenomenon of tolerance with the ability

of *H. pylori* antigens to activate inflammasomes and to stimulate the production of cytokines, such as IL-1b and IL-18. The authors argue that such cytokine regulation assists in reducing the hyper-reactivation of the immune system and, as a consequence, prevents the development of both asthma and inflammatory bowel diseases.

H. pylori and inflammatory bowel diseases

The negative association between *H. pylori* persistence and inflammatory bowel diseases (IBD) development has also been studied for a long time. *H. pylori* persistence may be supposed to be a potentially beneficial factor against the development of IBD. Several large meta-analyses have concluded that the risk of IBD is higher in HPN patients[122]. Wu *et al*[123] showed that 24.9% of IBD patients had *H. pylori* infection *vs* 48.3% of the controls. The pooled risk ratio for *H. pylori* infection in IBD patients compared with the controls was 0.48 (95%CI: 0.43-0.54; $P < 0.001$). Rokkas *et al*[124] obtained similar results: 26.5% (95%CI: 25.2-27.8) of IBD patients were positive for *H. pylori* infection, compared to 44.7% (43.3%-46.1%) of individuals in the control group. In the literature, there are also studies proving that *H. pylori* eradication leads to the development of intestinal lesions[125]. However, there is also a contradiction in the accumulated data, since existing studies link *H. pylori* infection with the development of colorectal cancer[126].

H. pylori and GERD

In addition to the impact of *H. pylori* infection on the development of atopic reactions, considerable attention has been paid to the detection of *H. pylori* in patients with GERD. There remain a number of controversial points around the question of how eradication therapy affects the development or progression of GERD symptoms. The available data are rather contradictory and do not give a general insight into the problem. In their studies, a number of authors prove that there is no significant difference between *H. pylori*-positive and HPN patients and the development of GERD symptoms in these patients[127,128]. Thus, on the basis of their study, Bor *et al*[127] have come to the conclusion that the detection of *H. pylori* does not affect either the development of GERD symptoms or the severity of the disease course. The detection rate of *H. pylori* was 77.1% in asymptomatic patients *vs* 71.4% in GERD patients (χ^2 = 2.6; $P = 0.27$). Xue *et al*[129] believe that eradication therapy fails to affect esophageal mucosal changes; therefore, there is no association with *H. pylori*. In their study, the investigators divided patients with endoscopically confirmed GERD into 2 groups (*H. pylori*-positive and HPN patients, respectively). The *H. pylori*-positive group received eradication therapy before treatment with proton pump inhibitors (10 d eradication, then esomeprazole 20 mg bid for 46 d). The other group was treated only with proton pump inhibitors (esomeprazole 20 mg bid therapy for 8 wk). As a result, there were 176 *H. pylori*-positive cases (with 92 eradication cases) and 180 negative cases. The healing rates in the *H. pylori*-positive eradicated group and the *H. pylori*-positive non-eradicated group reached 80.4% and 79.8%, respectively ($P = 0.911$), with reflux symptom scores of 0.22 and 0.14 ($P = 0.588$). The healing rates of esophagitis in the *H. pylori*-positive non-eradicated group and the *H. pylori*-negative group were 79.8 and 82.2%, respectively ($P = 0.848$); the reflux symptom scores were 0.14 and 0.21 ($P = 0.546$).

At the same time, contrary cases have been also described. The meta-analysis by Zhao *et al*[130] demonstrated that eradication therapy can lead to erosive GERD: The OR for the development of erosive GERD after *H. pylori* eradication was 1.67 (95%CI: 1.12-2.48; $P = 0.01$). Chung *et al*[131] revealed a clear inverse relationship between the detection of *H. pylori* and GERD: The prevalence of *H. pylori* infection was lower in cases with reflux esophagitis than in the controls (38.4% *vs* 58.2%, $P < 0.001$). The severity of esophagitis was also found to be inversely correlated with the detection of *H. pylori*. It is anticipated that *H. pylori* urease activity contributes to the neutralization of gastric acidity and, therefore, reduces the risk of acid reflux disease[132].

There are studies indicating the possible positive effect of *H. pylori* on the human body. In this connection, *H. pylori* in the majority of bacteria carriers can probably be attributed to bacteria that colonize the human body and constitute a population of commensal bacteria that use the host for their vital activity, but do not exhibit their pathogenic properties (as their persistence is under strict control by the host immune system). Such relationships between commensal bacteria and humans are typified by co-evolution, co-adaptation, and interactions[133]. Taking into account immune tolerance to *H. pylori* in the presence of long-term persistence in the host, the microorganism can also be considered as a symbiont[13].

CONCLUSION

The presented data suggest that there is clear ambiguity related to the problem of studying the mechanisms of ulcerogenesis, and the role of *H. pylori* in the processes of ulceration and carcinogenesis. On this basis, the management strategies for these inpatients are extremely difficult for clinicians. It is evident that a complete understanding of the mechanisms of inflammatory gastroduodenal mucosal injuries requires a more thorough approach, by considering the infectious and noninfectious, exogenous and endogenous factors, and an evaluation of the pathogenic and positive effects of *H. pylori* on human vital processes. Given the discussions surrounding the active eradication of *H. pylori* from the human population[134], it is more important than ever to critically assess its role within the microbiome. There is no coordinated attempt to eradicate these organisms from the human population; Malnick *et al*[3] suggested that there should not be a similar effort to eradicate *H. pylori*. Considering the growing number of publications on the potentially positive effects of the microorganism on the human body, it is not improbable that *H. pylori* is one of the bacteria in the healthy microbiome for the majority of the human population. There is a complex biological relationship between humans and commensal bacteria that is only now beginning to be understood. To better understand the mutualistic (*mutual* from Latin) role of *H. pylori* in cohorts at low risk for *H. pylori*-associated diseases, more investigations are needed to qualitatively and quantitatively estimate its benefits in healthy humans[132].

The manifestation of the pathogenic properties of *H. pylori*, which is characteristic of a smaller proportion of the human population having a genetic predisposition to develop gastrointestinal diseases, requires a reassessment of the available data on *H. pylori* infection. The "test and treat" approach to *H. pylori* does not address this issue at all[3]. It may be that the more correct way is an individualized approach to the patient according to the *H. pylori* endemic region, the presence of gastrointestinal diseases among relatives, or the impossibility of excluding nonmodifiable risk factors. Therefore, the most correct approach will be used to consider *H. pylori* persistence in terms of the possible positive role of the bacterium in the body and, therefore, to perform more individualized eradication therapy in the context of assessment of additional risk factors. Answers to such considerations should be obtained during further research.

ACKNOWLEDGEMENTS

REFERENCES

1   **Fernandes YC**, Bonatto Gda R, Bonatto MW. Recurrence rate of Helicobacter pylori in patients with peptic ulcer five years or more after successful eradication. *Arq Gastroenterol* 2016; **53**: 152-155 [PMID: 27438419 DOI: 10.1590/S0004-28032016000300006]

2   **Li J**, Perez-Perez GI. Helicobacter pylori the Latent Human Pathogen or an Ancestral Commensal Organism. *Front Microbiol* 2018; **9**: 609 [DOI: 10.3389/fmicb.2018.00609]

3   **Malnick SD**, Melzer E, Attali M, Duek G, Yahav J. Helicobacter pylori: friend or foe? *World J Gastroenterol* 2014; **20**: 8979-8985 [PMID: 25083071 DOI: 10.3748/wjg.v20.i27.8979]

4   **McColl KE**. Clinical practice. Helicobacter pylori infection. *N Engl J Med* 2010; **362**: 1597-1604 [PMID: 20427808 DOI: 10.1056/NEJMcp1001110]

5   **Crowe SE**. *Helicobacter pylori* Infection. *N Engl J Med* 2019; **380**: 1158-1165 [PMID: 30893536 DOI: 10.1056/NEJMcp1710945]

6   **Everhart JE**. Recent developments in the epidemiology of Helicobacter pylori. *Gastroenterol Clin North Am* 2000; **29**: 559-578 [PMID: 11030073 DOI: 10.1016/s0889-8553(05)70130-8]

7   **Haruma K**, Okamoto S, Kawaguchi H, Gotoh T, Kamada T, Yoshihara M, Sumii K, Kajiyama G. Reduced incidence of Helicobacter pylori infection in young Japanese persons between the 1970s and the 1990s. *J Clin Gastroenterol* 1997; **25**: 583-586 [PMID: 9451667 DOI: 10.1097/00004836-199712000-00006]

8   **Chen Y**, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis* 2008; **198**: 553-560 [PMID: 18598192 DOI: 10.1086/590158]

9   **Eder W**, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; **355**: 2226-2235 [PMID: 17124020 DOI: 10.1056/NEJMra054308]

10   **Holster IL**, Vila AM, Caudri D, den Hoed CM, Perez-Perez GI, Blaser MJ, de Jongste JC, Kuipers

EJ. The impact of Helicobacter pylori on atopic disorders in childhood. *Helicobacter* 2012; **17**: 232-237 [PMID: 22515362 DOI: 10.1111/j.1523-5378.2012.00934.x]

11   **Rothenbacher D**, Blaser MJ, Bode G, Brenner H. Inverse relationship between gastric colonization of Helicobacter pylori and diarrheal illnesses in children: results of a population-based cross-sectional study. *J Infect Dis* 2000; **182**: 1446-1449 [PMID: 11015236 DOI: 10.1086/315887]

12   **Hunt RH**, Yaghoobi M. The Esophageal and Gastric Microbiome in Health and Disease. *Gastroenterol Clin North Am* 2017; **46**: 121-141 [PMID: 28164846 DOI: 10.1016/j.gtc.2016.09.009]

13   **Tsimmerman YS**. [Critical analysis of the Helicobacter pylori-infection leading role in the development of gastroduodenal diseases]. *Clin Pharmacol Ther* 2019; **28**: 19-27

14   **Kanizaj TF**, Kunac N. Helicobacter pylori: future perspectives in therapy reflecting three decades of experience. *World J Gastroenterol* 2014; **20**: 699-705 [PMID: 24574743 DOI: 10.3748/wjg.v20.i3.699]

15   **Reshetnyak VI**, Reshetnyak TM. Significance of dormant forms of *Helicobacter pylori* in ulcerogenesis. *World J Gastroenterol* 2017; **23**: 4867-4878 [PMID: 28785141 DOI: 10.3748/wjg.v23.i27.4867]

16   **Christopher JA**, Abiodun OJ. Helicobacter pylori infection: past, present and future. *Pan Afr Med J* 2016; **23**: 216 [DOI: 10.11604/pamj.2016.23.216.8852]

17   **de Bernard M**, Josenhans C. Pathogenesis of Helicobacter pylori infection. *Helicobacter* 2014; **19** Suppl 1: 11-18 [PMID: 25167940 DOI: 10.1111/hel.12160]

18   **Stark RM**, Suleiman MS, Hassan IJ, Greenman J, Millar MR. Amino acid utilisation and deamination of glutamine and asparagine by Helicobacter pylori. *J Med Microbiol* 1997; **46**: 793-800 [PMID: 9291892 DOI: 10.1099/00222615-46-9-793]

19   **Mentis A**, Lehours P, Mégraud F. Epidemiology and Diagnosis of Helicobacter pylori infection. *Helicobacter* 2015; **20** Suppl 1: 1-7 [PMID: 26372818 DOI: 10.1111/hel.12250]

20   **Luzza F**, Suraci E, Larussa T, Leone I, Imeneo M. High exposure, spontaneous clearance, and low incidence of active Helicobacter pylori infection: the Sorbo San Basile study. *Helicobacter* 2014; **19**: 296-305 [PMID: 24758553 DOI: 10.1111/hel.12133]

21   **Burucoa C**, Axon A. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2017; **22** Suppl 1 [PMID: 28891138 DOI: 10.1111/hel.12403]

22   **Hooi JKY**, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology* 2017; **153**: 420-429 [PMID: 28456631 DOI: 10.1053/j.gastro.2017.04.022]

23   **Tsimmerman IaS**. [The problem of growing resistance of microorganisms to antibiotic therapy and prospects for Helicobacter pylori eradication]. *Klin Med (Mosk)* 2013; **91**: 14-20 [PMID: 24417061]

24   **Kayali S**, Manfredi M, Gaiani F, Bianchi L, Bizzarri B, Leandro G, Di Mario F, De' Angelis GL. Helicobacter pylori, transmission routes and recurrence of infection: state of the art. *Acta Biomed* 2018; **89**: 72-76 [PMID: 30561421 DOI: 10.23750/abm.v89i8-S.7947]

25   **Mladenova I**, Durazzo M. Transmission of Helicobacter pylori. *Minerva Gastroenterol Dietol* 2018; **64**: 251-254 [PMID: 29458239 DOI: 10.23736/S1121-421X.18.02480-7]

26   **Zamani M**, Vahedi A, Maghdouri Z, Shokri-Shirvani J. Role of food in environmental transmission of *Helicobacter pylori*. *Caspian J Intern Med* 2017; **8**: 146-152 [PMID: 28932364 DOI: 10.22088/cjim.8.3.146]

27   **Sgambato D**, Visciola G, Ferrante E, Miranda A, Romano L, Tuccillo C, Manguso F, Romano M. Prevalence of *Helicobacter pylori* infection in sexual partners of *H. pylori*-infected subjects: Role of gastroesophageal reflux. *United European Gastroenterol J* 2018; **6**: 1470-1476 [PMID: 30574317 DOI: 10.1177/2050640618800628]

28   **Kao CY**, Sheu BS, Wu JJ. Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. *Biomed J* 2016; **39**: 14-23 [DOI: 10.1016/j.bj.2015.06.002]

29   **Marcus EA**, Sachs G, Scott DR. Acid-regulated gene expression of Helicobacter pylori: Insight into acid protection and gastric colonization. *Helicobacter* 2018; **23**: e12490 [PMID: 29696729 DOI: 10.1111/hel.12490]

30   **Weeks DL**, Eskandari S, Scott DR, Sachs G. A H+-gated urea channel: the link between Helicobacter pylori urease and gastric colonization. *Science* 2000; **287**: 482-485 [PMID: 10642549 DOI: 10.1126/science.287.5452.482]

31   **Schoep TD**, Fulurija A, Good F, Lu W, Himbeck RP, Schwan C, Choi SS, Berg DE, Mittl PR, Benghezal M, Marshall BJ. Surface properties of Helicobacter pylori urease complex are essential for persistence. *PLoS One* 2010; **5**: e15042 [PMID: 21124783 DOI: 10.1371/journal.pone.0015042]

32   **Lowenthal AC**, Hill M, Sycuro LK, Mehmood K, Salama NR, Ottemann KM. Functional analysis of the Helicobacter pylori flagellar switch proteins. *J Bacteriol* 2009; **191**: 7147-7156 [PMID: 19767432 DOI: 10.1128/JB.00749-09]

33   **Gu H**. Role of Flagella in the Pathogenesis of Helicobacter pylori. *Curr Microbiol* 2017; **74**: 863-869 [PMID: 28444418 DOI: 10.1007/s00284-017-1256-4]

34   **Gupta N**, Maurya S, Verma H, Verma VK. Unraveling the factors and mechanism involved in persistence: Host-pathogen interactions in Helicobacter pylori. *J Cell Biochem* 2019; **120**: 18572-18587 [PMID: 31237031 DOI: 10.1002/jcb.29201]

35   **Hathroubi S**, Zerebinski J, Ottemann KM. Helicobacter pylori Biofilm Involves a Multigene Stress-Biased Response, Including a Structural Role for Flagella. *mBio* 2018; **9**: e01973-18 [PMID: 30377283 DOI: 10.1128/mBio.01973-18]

36   **García A**, Salas-Jara MJ, Herrera C, González C. Biofilm and Helicobacter pylori: from environment to human host. *World J Gastroenterol* 2014; **20**: 5632-5638 [PMID: 24914322 DOI: 10.3748/wjg.v20.i19.5632]

37   **Matsuo Y**, Kido Y, Yamaoka Y. Helicobacter pylori Outer Membrane Protein-Related Pathogenesis. *Toxins (Basel)* 2017; **9**: 101 [PMID: 28287480 DOI: 10.3390/toxins9030101]

38   **Chang WL**, Yeh YC, Sheu BS. The impacts of H. pylori virulence factors on the development of gastroduodenal diseases. *J Biomed Sci* 2018; **25**: 68 [PMID: 30205817 DOI: 10.1186/s12929-018-0466-9]

39   **Ricci V**, Giannouli M, Romano M, Zarrilli R. Helicobacter pylori gamma-glutamyl transpeptidase and its pathogenic role. *World J Gastroenterol* 2014; **20**: 630-638 [PMID: 24574736 DOI: 10.3748/wjg.v20.i3.630]

40   **Javed S**, Skoog EC, Solnick JV. Impact of Helicobacter pylori Virulence Factors on the Host Immune Response and Gastric Pathology. *Curr Top Microbiol Immunol* 2019; **421**: 21-52 [PMID: 31123884 DOI: 10.1007/978-3-030-15138-6_2]

41   **Tohidpour A**. CagA-mediated pathogenesis of Helicobacter pylori. *Microb Pathog* 2016; **93**: 44-55 [PMID: 26796299 DOI: 10.1016/j.micpath.2016.01.005]

42   **Ansari S**, Yamaoka Y. Survival of Helicobacter pylori in gastric acidic territory. *Helicobacter* 2017; **22**: 10.1111/hel.12386 [PMID: 28402047 DOI: 10.1111/hel.12386]

43   **Maleki Kakelar H**, Barzegari A, Dehghani J, Hanifian S, Saeedi N, Barar J, Omidi Y. Pathogenicity of Helicobacter pylori in cancer development and impacts of vaccination. *Gastric Cancer* 2019; **22**: 23-36 [PMID: 30145749 DOI: 10.1007/s10120-018-0867-1]

44   **Ohnishi N**, Yuasa H, Tanaka S, Sawa H, Miura M, Matsui A, Higashi H, Musashi M, Iwabuchi K, Suzuki M, Yamada G, Azuma T, Hatakeyama M. Transgenic expression of Helicobacter pylori CagA induces gastrointestinal and hematopoietic neoplasms in mouse. *Proc Natl Acad Sci USA* 2008; **105**: 1003-1008 [PMID: 18192401 DOI: 10.1073/pnas.0711183105]

45   **Romano M**, Ricci V, Zarrilli R. Mechanisms of disease: Helicobacter pylori-related gastric carcinogenesis--implications for chemoprevention. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 622-632 [PMID: 17068500 DOI: 10.1038/ncpgasthep0634]

46   **De Falco M**, Lucariello A, Iaquinto S, Esposito V, Guerra G, De Luca A. Molecular Mechanisms of Helicobacter pylori Pathogenesis. *J Cell Physiol* 2015; **230**: 1702-1707 [PMID: 25639461 DOI: 10.1002/jcp.24933]

47   **Rassow J**, Meinecke M. Helicobacter pylori VacA: a new perspective on an invasive chloride channel. *Microbes Infect* 2012; **14**: 1026-1033 [DOI: 10.1016/j.micinf.2012.07.002]

48   **Raju D**, Hussey S, Ang M, Terebiznik MR, Sibony M, Galindo-Mata E, Gupta V, Blanke SR, Delgado A, Romero-Gallo J, Ramjeet MS, Mascarenhas H, Peek RM, Correa P, Streutker C, Hold G, Kunstmann E, Yoshimori T, Silverberg MS, Girardin SE, Philpott DJ, El Omar E, Jones NL. Vacuolating cytotoxin and variants in Atg16L1 that disrupt autophagy promote Helicobacter pylori infection in humans. *Gastroenterology* 2012; **142**: 1160-1171 [PMID: 22333951 DOI: 10.1053/j.gastro.2012.01.043]

49   **McGee DJ**, Mobley HL. Pathogenesis of Helicobacter pylori infection. *Curr Opin Gastroenterol* 2000; **16**: 24-31 [PMID: 17024012]

50   **Suzuki T**, Kato K, Ohara S, Noguchi K, Sekine H, Nagura H, Shimosegawa T. Localization of antigen-presenting cells in Helicobacter pylori-infected gastric mucosa. *Pathol Int* 2002; **52**: 265-271 [PMID: 12031081]

51   **Figueiredo CA**, Marques CR, Costa Rdos S, da Silva HB, Alcantara-Neves NM. Cytokines, cytokine gene polymorphisms and Helicobacter pylori infection: friend or foe? *World J Gastroenterol* 2014; **20**: 5235-5243 [PMID: 24833853 DOI: 10.3748/wjg.v20.i18.5235]

52   **D'Elios MM**, Codolo G, Amedei A, Mazzi P, Berton G, Zanotti G, Del Prete G, de Bernard M. Helicobacter pylori, asthma and allergy. *FEMS Immunol Med Microbiol* 2009; **56**: 1-8 [PMID: 19220467 DOI: 10.1111/j.1574-695X.2009.00537.x]

53   **Bimczok D**, Clements RH, Waites KB, Novak L, Eckhoff DE, Mannon PJ, Smith PD, Smythies LE. Human primary gastric dendritic cells induce a Th1 response to H. pylori. *Mucosal Immunol* 2010; **3**: 260-269 [PMID: 20237463 DOI: 10.1038/mi.2010.10]

54   **Altobelli A**, Bauer M, Velez K, Cover TL, Müller A. *Helicobacter pylori* VacA Targets Myeloid Cells in the Gastric Lamina Propria To Promote Peripherally Induced Regulatory T-Cell Differentiation and Persistent Infection. *mBio* 2019; **10** [PMID: 30890606 DOI: 10.1128/mBio.00261-19]

55   **Hsu WT**, Ho SY, Jian TY, Huang HN, Lin YL, Chen CH, Lin TH, Wu MS, Wu CJ, Chan YL, Liao KW. Helicobacter pylori-derived heat shock protein 60 increases the induction of regulatory T-cells associated with persistent infection. *Microb Pathog* 2018; **119**: 152-161 [PMID: 29660522 DOI: 10.1016/j.micpath.2018.04.016]

56   **Lehours P**, Ferrero RL. Review: Helicobacter: Inflammation, immunology, and vaccines. *Helicobacter* 2019; **24** Suppl 1: e12644 [PMID: 31486236 DOI: 10.1111/hel.12644]

57   **Watanabe M**, Kato J, Inoue I, Yoshimura N, Yoshida T, Mukoubayashi C, Deguchi H, Enomoto S, Ueda K, Maekita T, Iguchi M, Tamai H, Utsunomiya H, Yamamichi N, Fujishiro M, Iwane M, Tekeshita T, Mohara O, Ushijima T, Ichinose M. Development of gastric cancer in nonatrophic stomach with highly active inflammation identified by serum levels of pepsinogen and Helicobacter pylori antibody together with endoscopic rugal hyperplastic gastritis. *Int J Cancer* 2012; **131**: 2632-2642 [PMID: 22383377 DOI: 10.1002/ijc.27514]

58   **Sokic-Milutinovic A**, Alempijevic T, Milosavljevic T. Role of Helicobacter pylori infection in gastric carcinogenesis: Current knowledge and future directions. *World J Gastroenterol* 2015; **21**: 11654-11672 [PMID: 26556993 DOI: 10.3748/wjg.v21.i41.11654]

59   **Huang JQ**, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; **359**: 14-22 [PMID: 11809181 DOI: 10.1016/S0140-6736(02)07273-2]

60   **Ertz-Archambault N**, Keim P, Von Hoff D. Microbiome and pancreatic cancer: A comprehensive topic review of literature. *World J Gastroenterol* 2017; **23**: 1899-1908 [PMID: 28348497 DOI: 10.3748/wjg.v23.i10.1899]

61   **Xiao M**, Wang Y, Gao Y. Association between Helicobacter pylori infection and pancreatic cancer development: a meta-analysis. *PLoS One* 2013; **8**: e75559 [PMID: 24086571 DOI: 10.1371/journal.pone.0075559]

62   **Otero LL**, Ruiz VE, Perez GIP. Helicobacter pylori: The balance between a role as colonizer and pathogen. *Best Pract Res Clin Gastroenterol* 2014; **28**: 1017-1029 [DOI: 10.1016/j.bpg.2014.09.003]

63   **Mentis AFA**, Boziki M, Grigoriadis N, Papavassiliou AG. Helicobacter pylori infection and gastric cancer biology: tempering a double-edged sword. *Cell Mol Life Sci* 2019; **76**: 2477-2486 [DOI: 10.1007/s00018-019-03044-1]

64   **Gravina AG**, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. *Helicobacter pylori* and extragastric diseases: A review. *World J Gastroenterol* 2018; **24**: 3204-3221 [PMID: 30090002 DOI: 10.3748/wjg.v24.i29.3204]

65   **German SV**, Bobrovnitsky IP. [New aspects of Helicobacter pylori infection: Association with metabolic disturbances]. *Ter Arkh* 2017; **89**: 102-107 [PMID: 29171479 DOI: 10.17116/terarkh20178910102-107]

66   **Maev IV**, Samsonov AA, Andreev DN, Grechushnikov VB, Korovina TI. [Clinical significance of helicobacter pylori infection]. *Clin Med* 2013; **91**: 4-12 [PMID: 24437177]

67   **Wang ZW**, Li Y, Huang LY, Guan QK, Xu DW, Zhou WK, Zhang XZ. Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. *J Neurol* 2012; **259**: 2527-2537 [PMID: 22688569 DOI: 10.1007/s00415-012-6558-7]

68   **Kountouras J**, Boziki M, Zavos C, Gavalas E, Giartza-Taxidou E, Venizelos I, Deretzi G, Grigoriadis N, Tsiaousi E, Vardaka E. A potential impact of chronic Helicobacter pylori infection on Alzheimer's disease pathobiology and course. *Neurobiol Aging* 2012; **33**: e3-e4 [PMID: 22325590 DOI: 10.1016/j.neurobiolaging.2012.01.003]

69   **Franceschi F**, Covino M, Roubaud Baudron C. Review: Helicobacter pylori and extragastric diseases. *Helicobacter* 2019; **24** Suppl 1: e12636 [PMID: 31486239 DOI: 10.1111/hel.12636]

70   **Huang HK**, Wang JH, Lei WY, Chen CL, Chang CY, Liou LS. Helicobacter pylori infection is associated with an increased risk of Parkinson's disease: A population-based retrospective cohort study. *Parkinsonism Relat Disord* 2018; **47**: 26-31 [PMID: 29174171 DOI: 10.1016/j.parkreldis.2017.11.331]

71   **Izadi M**, Fazel M, Sharubandi SH, Saadat SH, Farahani MM, Nasseri MH, Dabiri H, SafiAryan R, Esfahani AA, Ahmadi A, Jonaidi Jafari N, Ranjbar R, Jamali-Moghaddam SR, Kazemi-Saleh D, Kalantar-Motamed MH, Taheri S. Helicobacter species in the atherosclerotic plaques of patients with coronary artery disease. *Cardiovasc Pathol* 2012; **21**: 307-311 [PMID: 22104005 DOI: 10.1016/j.carpath.2011.09.011]

72   **Park MJ**, Choi SH, Kim D, Kang SJ, Chung SJ, Choi SY, Yoon DH, Lim SH, Kim YS, Yim JY, Kim JS, Jung HC. Association between Helicobacter pylori Seropositivity and the Coronary Artery Calcium Score in a Screening Population. *Gut Liver* 2011; **5**: 321-327 [PMID: 21927661 DOI: 10.5009/gnl.2011.5.3.321]

73   **Jukic A**, Bozic D, Kardum D, Becic T, Luksic B, Vrsalovic M, Ljubkovic M, Fabijanic D. *Helicobacter pylori* infection and severity of coronary atherosclerosis in patients with chronic coronary artery disease. *Ther Clin Risk Manag* 2017; **13**: 933-938 [PMID: 28794636 DOI: 10.2147/TCRM.S142193]

74   **Sharma V**, Aggarwal A. Helicobacter pylori: Does it add to risk of coronary artery disease. *World J Cardiol* 2015; **7**: 19-25 [PMID: 25632315 DOI: 10.4330/wjc.v7.i1.19]

75   **Vijayvergiya R**, Vadivelu R. Role of Helicobacter pylori infection in pathogenesis of atherosclerosis. *World J Cardiol* 2015; **7**: 134-143 [PMID: 25810813 DOI: 10.4330/wjc.v7.i3.134]

76   **Cárdenas VM**, Boller F, Román GC. *Helicobacter pylori*, Vascular Risk Factors and Cognition in U.S. Older Adults. *Brain Sci* 2019; **9**: 370 [PMID: 31842501 DOI: 10.3390/brainsci9120370]

77   **Santarelli L**, Gabrielli M, Cremonini F, Santoliquido A, Candelli M, Nista EC, Pola P, Gasbarrini G, Gasbarrini A. Atrophic gastritis as a cause of hyperhomocysteinaemia. *Aliment Pharmacol Ther* 2004; **19**: 107-111 [PMID: 14687172 DOI: 10.1046/j.1365-2036.2003.01820.x]

78   **Rasmi Y**, Raeisi S, Seyyed Mohammadzad MH. Association of inflammation and cytotoxin-associated gene a positive strains of helicobacter pylori in cardiac syndrome x. *Helicobacter* 2012; **17**: 116-120 [PMID: 22404441 DOI: 10.1111/j.1523-5378.2011.00923.x]

79   **de Jesus Souza M**, de Moraes JA, Da Silva VN, Helal-Neto E, Uberti AF, Scopel-Guerra A, Olivera-Severo D, Carlini CR, Barja-Fidalgo C. Helicobacter pylori urease induces pro-inflammatory effects and differentiation of human endothelial cells: Cellular and molecular mechanism. *Helicobacter* 2019; **24**: e12573 [PMID: 30907046 DOI: 10.1111/hel.12573]

80   **Yu M**, Zhang R, Ni P, Chen S, Duan G. *Helicobacter pylori* Infection and Psoriasis: A Systematic

Review and Meta-Analysis. *Medicina (Kaunas)* 2019; **55** [PMID: 31561576 DOI: 10.3390/medicina55100645]

81 **Onsun N**, Arda Ulusal H, Su O, Beycan I, Biyik Ozkaya D, Senocak M. Impact of Helicobacter pylori infection on severity of psoriasis and response to treatment. *Eur J Dermatol* 2012; **22**: 117-120 [PMID: 22063790 DOI: 10.1684/ejd.2011.1579]

82 **Yorulmaz A**, Kulcu SC. Helicobacter pylori and inflammatory skin diseases. *World J Dermatol* 2015; **4**: 120-128 [DOI: 10.5314/wjd.v4.i3.120]

83 **Atherton JC**, Blaser MJ. Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. *J Clin Invest* 2009; **119**: 2475-2487 [PMID: 19729845 DOI: 10.1172/JCI38605]

84 **Stein M**, Ruggiero P, Rappuoli R, Bagnoli F. Helicobacter pylori CagA: From Pathogenic Mechanisms to Its Use as an Anti-Cancer Vaccine. *Front Immunol* 2013; **4**: 328 [PMID: 24133496 DOI: 10.3389/fimmu.2013.00328]

85 **Walker MM**, Talley NJ. Review article: bacteria and pathogenesis of disease in the upper gastrointestinal tract--beyond the era of Helicobacter pylori. *Aliment Pharmacol Ther* 2014; **39**: 767-779 [PMID: 24612362 DOI: 10.1111/apt.12666]

86 **Calvet X**, Ramírez Lázaro MJ, Lehours P, Mégraud F. Diagnosis and epidemiology of Helicobacter pylori infection. *Helicobacter* 2013; **18** Suppl 1: 5-11 [PMID: 24011238 DOI: 10.1111/hel.12071]

87 **Malfertheiner P**, Chan FK, McColl KE. Peptic ulcer disease. *Lancet* 2009; **374**: 1449-1461 [PMID: 19683340 DOI: 10.1016/S0140-6736(09)60938-7]

88 **Araújo MB**, Borini P, Guimarães RC. Etiopathogenesis of peptic ulcer: back to the past? *Arq Gastroenterol* 2014; **51**: 155-161 [PMID: 25003270 DOI: 10.1590/s0004-28032014000200016]

89 **Sidorenko SV**. [Diagnosis and treatment of infections caused by Helicobacter pylori]. *Antibiot Khimioter* 2001; **46**: 23-31 [PMID: 11871316]

90 **Rosenstock S**, Jørgensen T, Bonnevie O, Andersen L. Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults. *Gut* 2003; **52**: 186-193 [PMID: 12524398 DOI: 10.1136/gut.52.2.186]

91 **Figura N**, Guglielmetti P, Rossolini A, Barberi A, Cusi G, Musmanno RA, Russi M, Quaranta S. Cytotoxin production by Campylobacter pylori strains isolated from patients with peptic ulcers and from patients with chronic gastritis only. *J Clin Microbiol* 1989; **27**: 225-226 [PMID: 2913034 DOI: 10.1128/JCM.27.1.225-226.1989]

92 **Atherton JC**, Cao P, Peek RM Jr, Tummuru MK, Blaser MJ, Cover TL. Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. *J Biol Chem* 1995; **270**: 17771-17777 [PMID: 7629077 DOI: 10.1074/jbc.270.30.17771]

93 **Atherton JC**. The clinical relevance of strain types of Helicobacter pylori. *Gut* 1997; **40**: 701-703 [PMID: 9245920 DOI: 10.1136/gut.40.6.701]

94 **Iijima K**, Kanno T, Koike T, Shimosegawa T. Helicobacter pylori-negative, non-steroidal anti-inflammatory drug: negative idiopathic ulcers in Asia. *World J Gastroenterol* 2014; **20**: 706-713 [PMID: 24574744 DOI: 10.3748/wjg.v20.i3.706]

95 **Charpignon C**, Lesgourgues B, Pariente A, Nahon S, Pelaquier A, Gatineau-Sailliant G, Roucayrol AM, Courillon-Mallet A; Group de l'Observatoire National des Ulcères de l'Association Nationale des HépatoGastroentérologues des Hôpitaux Généraux (ANGH). Peptic ulcer disease: one in five is related to neither Helicobacter pylori nor aspirin/NSAID intake. *Aliment Pharmacol Ther* 2013; **38**: 946-954 [PMID: 23981105 DOI: 10.1111/apt.12465]

96 **Goenka MK**, Majumder S, Sethy PK, Chakraborty M. Helicobacter pylori negative, non-steroidal anti-inflammatory drug-negative peptic ulcers in India. *Indian J Gastroenterol* 2011; **30**: 33-37 [PMID: 21424697 DOI: 10.1007/s12664-011-0085-9]

97 **Reshetnyak TM**, Doroshkevich IA, Seredavkina NV, Nasonov EL, Maev IV, Reshetnyak VI. The Contribution of Drugs and *Helicobacter pylori* to Gastric Mucosa Changes in Patients with Systemic Lupus Erythematosus and Antiphospholipid Syndrome. *Int J Rheumatol* 2019; **2019**: 9698086 [PMID: 31191660 DOI: 10.1155/2019/9698086]

98 **Kanno T**, Iijima K, Abe Y, Yagi M, Asonuma S, Ohyauchi M, Ito H, Koike T, Shimosegawa T. Helicobacter pylori-negative and non-steroidal anti-inflammatory drugs-negative idiopathic peptic ulcers show refractoriness and high recurrence incidence: Multicenter follow-up study of peptic ulcers in Japan. *Dig Endosc* 2016; **28**: 556-563 [PMID: 26866510 DOI: 10.1111/den.12635]

99 **Rasane RK**, Horn CB, Coleoglou Centeno AA, Fiore NB, Torres Barboza M, Zhang Q, Bochicchio KM, Punch LJ, Bochicchio GV, Ilahi ON. Are Patients with Perforated Peptic Ulcers Who are Negative for *Helicobacter pylori* at a Greater Risk? *Surg Infect (Larchmt)* 2019; **20**: 444-448 [PMID: 30939075 DOI: 10.1089/sur.2018.249]

100 **Tsimmerman YS**. [Gastric cancers: a modern approach to the problem]. *Vestnik chirurgicheskoj gastroenterologii* 2011; **2**: 77-88

101 **Laine L**, Hopkins RJ, Girardi LS. Has the impact of Helicobacter pylori therapy on ulcer recurrence in the United States been overstated? *Am J Gastroenterol* 1998; **93**: 1409-1415 [PMID: 9732917 DOI: 10.1111/j.1572-0241.1998.452_a.x]

102 **Leodolter A**, Kulig M, Brasch H, Meyer-Sabellek W, Willich SN, Malfertheiner P. A meta-analysis comparing eradication, healing and relapse rates in patients with Helicobacter pylori-associated gastric or duodenal ulcer. *Aliment Pharmacol Ther* 2001; **15**: 1949-1958 [PMID: 11736726 DOI: 10.1046/j.1365-2036.2001.01109.x]

103 **Lamb A**, Chen LF. Role of the Helicobacter pylori-induced inflammatory response in the

development of gastric cancer. *J Cell Biochem* 2013; **114**: 491-497 [PMID: 22961880 DOI: 10.1002/jcb.24389]

104   **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

105   **Danesh J**. Helicobacter pylori infection and gastric cancer: systematic review of the epidemiological studies. *Aliment Pharmacol Ther* 1999; **13**: 851-856 [PMID: 10383517 DOI: 10.1046/j.1365-2036.1999.00546.x]

106   **Hansen S**, Melby KK, Aase S, Jellum E, Vollset SE. Helicobacter pylori infection and risk of cardia cancer and non-cardia gastric cancer. A nested case-control study. *Scand J Gastroenterol* 1999; **34**: 353-360 [PMID: 10365894 DOI: 10.1080/003655299750026353]

107   **Rokkas F**. [Helicobacter pylori infection as risk factor of a carcinoma of the stomach: current evidence]. *Russ J Gastroenterol Hepatol Coloproctol* 2002; **3**: 66-70

108   **Blaser MJ**. Helicobacter pylori: Balance and inbalance. *Europ J Gastroenterol Hepatol* 1998; **10** Suppl 1: 15-18 [DOI: 10.1097/00042737-199806001-00004]

109   **Cover TL**, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009; **136**: 1863-1873 [PMID: 19457415 DOI: 10.1053/j.gastro.2009.01.073]

110   **Blaser MJ**. Helicobacter pylori and the pathogenesis of gastroduodenal inflammation. *J Infect Dis* 1990; **161**: 626-633 [PMID: 2181029 DOI: 10.1093/infdis/161.4.626]

111   **Bardakhch'ian EA**, Kharlanova NG, Kamneva NV, Lomov SIu, Saiamov SR, Golubev BP. [Coccoid forms of Helicobacter pylori and their role in human pathology]. *Eksp Klin Gastroenterol* 2003; **(6)**: 11-15, 153 [PMID: 15065521]

112   **Yamaoka Y**. Pathogenesis of Helicobacter pylori-Related Gastroduodenal Diseases from Molecular Epidemiological Studies. *Gastroenterol Res Pract* 2012; **2012**: 371503 [PMID: 22829807 DOI: 10.1155/2012/371503]

113   **Liu J**, He C, Chen M, Wang Z, Xing C, Yuan Y. Association of presence/absence and on/off patterns of Helicobacter pylori oipA gene with peptic ulcer disease and gastric cancer risks: a meta-analysis. *BMC Infect Dis* 2013; **13**: 555 [PMID: 24256489 DOI: 10.1186/1471-2334-13-555]

114   **Miftahussurur M**, Nusi IA, Graham DY, Yamaoka Y. *Helicobacter*, Hygiene, Atopy, and Asthma. *Front Microbiol* 2017; **8**: 1034 [PMID: 28642748 DOI: 10.3389/fmicb.2017.01034]

115   **Elias N**, Nasrallah E, Khoury C, Mansour B, Abu Zuher L, Asato V, Muhsen K. Associations of Helicobacter pylori seropositivity and gastric inflammation with pediatric asthma. *Pediatr Pulmonol* 2020; **55**: 2236-2245 [PMID: 32543787 DOI: 10.1002/ppul.24905]

116   **Tsigalou C**, Konstantinidis TG, Cassimos D, Karvelas A, Grapsa A, Tsalkidis A, Panopoulou M, Tsakris A. Inverse association between *Helicobacter pylori* infection and childhood asthma in Greece: a case-control study. *Germs* 2019; **9**: 182-187 [PMID: 32042724 DOI: 10.18683/germs.2019.1174]

117   **Ierardi E**, Losurdo G, Giorgio F, Di Leo A. Might helicobacter pylori play a role in allergic or cross-reaction related disorders? *Expert Rev Gastroenterol Hepatol* 2020; **14**: 643-646 [PMID: 32510247 DOI: 10.1080/17474124.2020.1780119]

118   **Amberbir A**, Medhin G, Erku W, Alem A, Simms R, Robinson K, Fogarty A, Britton J, Venn A, Davey G. Effects of Helicobacter pylori, geohelminth infection and selected commensal bacteria on the risk of allergic disease and sensitization in 3-year-old Ethiopian children. *Clin Exp Allergy* 2011; **41**: 1422-1430 [PMID: 21831135 DOI: 10.1111/j.1365-2222.2011.03831.x]

119   **Zevit N**, Balicer RD, Cohen HA, Karsh D, Niv Y, Shamir R. Inverse association between Helicobacter pylori and pediatric asthma in a high-prevalence population. *Helicobacter* 2012; **17**: 30-35 [PMID: 22221613 DOI: 10.1111/j.1523-5378.2011.00895.x]

120   **Oertli M**, Noben M, Engler DB, Semper RP, Reuter S, Maxeiner J, Gerhard M, Taube C, Müller A. Helicobacter pylori γ-glutamyl transpeptidase and vacuolating cytotoxin promote gastric persistence and immune tolerance. *Proc Natl Acad Sci USA* 2013; **110**: 3047-3052 [PMID: 23382221 DOI: 10.1073/pnas.1211248110]

121   **Pachathundikandi SK**, Müller A, Backert S. Inflammasome Activation by Helicobacter pylori and Its Implications for Persistence and Immunity. *Curr Top Microbiol Immunol* 2016; **397**: 117-131 [PMID: 27460807 DOI: 10.1007/978-3-319-41171-2_6]

122   **Kyburz A**, Müller A. Helicobacter pylori and Extragastric Diseases. *Curr Top Microbiol Immunol* 2017; **400**: 325-347 [PMID: 28124160 DOI: 10.1007/978-3-319-50520-6_14]

123   **Wu XW**, Ji HZ, Yang MF, Wu L, Wang FY. Helicobacter pylori infection and inflammatory bowel disease in Asians: a meta-analysis. *World J Gastroenterol* 2015; **21**: 4750-4756 [PMID: 25914487 DOI: 10.3748/wjg.v21.i15.4750]

124   **Rokkas T**, Gisbert JP, Niv Y, O'Morain C. The association between Helicobacter pylori infection and inflammatory bowel disease based on meta-analysis. *United European Gastroenterol J* 2015; **3**: 539-550 [PMID: 26668747 DOI: 10.1177/2050640615580889]

125   **Jovanovic IR**, Milosavjevic TN, Jankovic GP, Micev MM, Dugalic PD, Saranovic D, Ugljesic MM, Popovic DV, Bulajic MM. Clinical onset of the Crohn's disease after eradication therapy of Helicobacter pylori infection. Does Helicobacter pylori infection interact with natural history of inflammatory bowel diseases? *Med Sci Monit* 2001; **7**: 137-141 [PMID: 11208510]

126   **Papamichael K**, Konstantopoulos P, Mantzaris GJ. Helicobacter pylori infection and inflammatory bowel disease: is there a link? *World J Gastroenterol* 2014; **20**: 6374-6385 [PMID: 24914359 DOI: 10.3748/wjg.v20.i21.6374]

127   **Bor S**, Kitapcioglu G, Kasap E. Prevalence of gastroesophageal reflux disease in a country with a high occurrence of *Helicobacter pylori. World J Gastroenterol* 2017; **23**: 525-532 [PMID: 28210089 DOI: 10.3748/wjg.v23.i3.525]

128   **Mungan Z**, Pınarbaşı Şimşek B. Gastroesophageal reflux disease and the relationship with Helicobacter pylori. *Turk J Gastroenterol* 2017; **28**: S61-S67 [PMID: 29199171 DOI: 10.5152/tjg.2017.16]

129   **Xue Y**, Zhou LY, Lin SR, Hou XH, Li ZS, Chen MH, Yan XE, Meng LM, Zhang J, Lu JJ. Effect of Helicobacter pylori eradication on reflux esophagitis therapy: a multi-center randomized control study. *Chin Med J (Engl)* 2015; **128**: 995-999 [PMID: 25881589 DOI: 10.4103/0366-6999.155049]

130   **Zhao Y**, Li Y, Hu J, Wang X, Ren M, Lu G, Lu X, Zhang D, He S. The Effect of Helicobacter pylori Eradication in Patients with Gastroesophageal Reflux Disease: A Meta-Analysis of Randomized Controlled Studies. *Dig Dis* 2020; **38**: 261-268 [PMID: 32396919 DOI: 10.1159/000504086]

131   **Chung SJ**, Lim SH, Choi J, Kim D, Kim YS, Park MJ, Yim JY, Kim JS, Cho SH, Jung HC, Song IS. Helicobacter pylori Serology Inversely Correlated With the Risk and Severity of Reflux Esophagitis in Helicobacter pylori Endemic Area: A Matched Case-Control Study of 5,616 Health Check-Up Koreans. *J Neurogastroenterol Motil* 2011; **17**: 267-273 [PMID: 21860818 DOI: 10.5056/jnm.2011.17.3.267]

132   **Lin D**, Koskella B. Friend and foe: factors influencing the movement of the bacterium Helicobacter pylori along the parasitism-mutualism continuum. *Evol Appl* 2015; **8**: 9-22 [PMID: 25667600 DOI: 10.1111/eva.12231]

133   **Blaser MJ**, Falkow S. What are the consequences of the disappearing human microbiota? *Nat Rev Microbiol* 2009; **7**: 887-894 [PMID: 19898491 DOI: 10.1038/nrmicro2245]

134   **Lee YC**, Chen TH, Chiu HM, Shun CT, Chiang H, Liu TY, Wu MS, Lin JT. The benefit of mass eradication of Helicobacter pylori infection: a community-based study of gastric cancer prevention. *Gut* 2013; **62**: 676-682 [PMID: 22698649 DOI: 10.1136/gutjnl-2012-302240]

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