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Review Article

The protective effects of *Helicobacter pylori*: A comprehensive review

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Abstract

Previous reports have estimated that approximately half of the world's population is infected with *Helicobacter pylori*, the most prevalent infectious agent responsible for gastrointestinal illnesses. Due to the life-threatening effects of *H. pylori* infections, numerous studies have focused on developing medical therapies for *H. pylori* infections, while the commensal relationship and positive impacts of this bacterium on overall human health have been largely overlooked. The inhibitory efficacy of *H. pylori* on the progression of several chronic inflammatory disorders and gastrointestinal diseases has recently raised concerns about whether this bacterium should be eradicated in affected individuals or maintained in an appropriate balance depending on the patient's condition. This review investigates the beneficial effects of *H. pylori* in preventing various diseases and discusses the potential association of conditions such as inflammatory disorders with the absence of *H. pylori*.

Introduction

Spiral-shaped gram-negative bacteria, known as *Helicobacter pylori*, are frequently found in the human stomach. Most individuals infected with *H. pylori* exhibit no symptoms or serious complications.[1] However, *H. pylori* can contribute to various gastrointestinal problems. In most cases, initial childhood infections are asymptomatic, although children may occasionally experience dizziness, vomiting, and abdominal discomfort. This asymptomatic phase underscores the importance of specific antibacterial combination therapy to prevent individuals with persistent severe gastric inflammation, commonly referred to as gastritis, from experiencing symptoms throughout their lives. While the majority of infected individuals remain asymptomatic, approximately 10% may develop peptic ulcers,[2,3] and a small percentage (around 1% to 2%) may eventually develop gastric neoplasms due to the gradual progression of preneoplastic changes characterized by atrophic gastritis, intestinal metaplasia, and dysplasia.[4,5] However, it should be clarified why some patients with *H. pylori* experience these symptoms.[1] This bacterium can remain undetected in the human body for years. Its incidence varies depending on geographical location, ethnicity, and socioeconomic status, with developing countries of low socioeconomic status having higher rates of infection.[6] Bacterial colonization in saliva and tooth plaque can also facilitate transmission through oral-oral contact.[7,8] Despite *H. pylori* infection being an established cause of peptic ulcers and gastric cancer, other factors also involved in the development of *H. pylori* infections into gastric disorders.[9] Therefore, investigating the genetic and environmental factors is crucial for understanding the causes of diseases and preventive measures.

To date, the association between various stomach morphologies with quantitative traits and H. pylori infection is still unclear. On the other hand, the role of known factors on bacterial virulence such as vacuolating cytotoxin A (VacA), urease, cytotoxin-associated gene A (CagA), and blood group antigen binding adhesion 2 (BabA2), as well as environmental factors, financial status, diet, and exposure to toxic chemicals should not be underestimated.[10,11]

Since the 2015 Kyoto H. pylori Conference's agreement, there have been substantial

modifications to the strategy regarding the *H. pylori* management. In the case of *H. pylori* infection, eradication is recommended now unless there are justifiable reasons not to eradicate it. These reasons may include co-existing

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medical conditions, higher re-infection rates in the area, or other essential health considerations.[12] This strategy raises concerns due to *H. pylori* antibiotic resistance during the past decades. This issue is exacerbated by a lack of effective therapeutic options and extensive public consumption of drugs.[13,14] Additionally, *H. pylori* species exhibit an unusually high capacity for adaptation, leading to the rapid development of primary antibiotic resistance. Although treatment success rates vary by location and region, the efficacy of eradication medications has progressively declined over time.[13,15,16]

Since 2017, the World Health Organization (WHO) has classified *H. pylori* as one of the top 20 drug-resistant pathogens posing a significant threat to human health.[17] Addressing this global issue necessitates the implementation of various measures by clinicians, including the use of new treatment methods, optimization of empirical therapies, and personalized treatments.[18]

H. pylori instigates a potent immune response, leading to the release of pro-inflammatory and anti-inflammatory cytokines. These cytokines, including interleukin (IL)-17, IL-6, and transforming growth factor-β (TGF-β), are produced by immune-responsive cells such as T-helper 1 (Th1), Th2, Th17, and Treg cells.[19,20] While activation cytokines are generally considered detrimental, *H. pylori*-regulated cytokine production may play a beneficial role in certain conditions. Many studies have found that H. pylori regulates the expression of inflammatory cytokines, such as TNF-α, IL-10, and IL-1β, which play crucial roles in preventing several disorders.[21]

While studying *H. pylori* infections and treatment approaches is critical, researchers must also consider the bacterium's beneficial effects on host physiology. Eradication procedures may have more significant consequences than its presence in the human gastrointestinal system.[8] Common diseases associated with the "protective" significance of *H. pylori* infection include allergies and asthma,[22] gastroesophageal reflux disease (GERD),[21] inflammatory bowel disease (IBD),[23] autoimmune diseases,[24] allergic disorders,[25] eosinophilic esophagitis [26], and esophageal squamous cell carcinoma (ESCC).[27]

The protective effects of *Helicobacter pylori* in various diseases

Allergies and asthma

Previous research has shown a link between the incidence of allergies (e.g., asthma), environmental factors, and microbes.[28] The immune system can mature and defend against immunologically-mediated diseases when exposed to the environment and bacteria.[29] For example, studies have demonstrated that early childhood exposure to various microorganisms can help to prevent allergies later.[30]

The connection between *H. pylori* and asthma has recently gained significant attention. By modifying the ratio of Th1/Th2, Th17/regulatory T cells (Tregs), and other variables, *H. pylori* can prevent allergic asthma. Additionally, *H. pylori* can target dendritic cells to enhance immunological tolerance and the ability to prevent allergic asthma.[31-35] The *H. pylori* neutrophil-activating protein (HP-NAP) is crucial in this context.

In both *in vitro* and *in vivo* studies, HP-NAP has been shown to have protective effects in asthma, stimulating type 1 T helper (Th1) responses, and reducing Th2 reactivity in allergy-related asthma.[36-38] However, the mechanisms of asthma and *H. pylori* are not solely explained by the Th1/Th2 ratio.[39,40] In addition, Tregs and Th17 cells are associated with the pathogenesis of asthma. Moreover, the interplay between Th17 and Th2 inflammatory processes has been observed in asthma.[41] Subsequently, Th17/Tregs and Th1/Th2 interaction results in a complex and extensive network with their respective cytokines.[41,42] In turn, Th17 cells produce IL-17, which can promote inflammatory responses by stimulating neutrophil maturation, immune cell proliferation, and chemotaxis.[43] On the other hand, Tregs release IL-10 and other inhibitory cytokines that play crucial roles in regulating immune responses. For instance, Treg cells promote immune tolerance and suppress immune responses through the activation of forkhead transcription factor p3,[43,44] a protective mechanism associated with *H. pylori* in preventing asthma.[45,46]

Previous research indicates that *H. pylori* can upregulate the *Th1*, *Tregs*, and *Th17* genes in both experimental and clinical settings, potentially in terms of asthma prevention.[24] Dendritic cells (DCs) have been proposed as a target of *H. pylori* to enhance immunological resistance and protective mechanisms against allergic asthma. This mechanism mainly relies on the suppression of Tregs.[24,47] Additionally, Shiu et al. revealed that *H. pylori* can enhance cellular responses that quench inflammation, such as IRAK-M (IL-1 receptor-associated kinase M).[48] IRAK-M expression, activated by toll-like receptors (TLRs) in DCs, inhibits DC function, including the upregulation of cytokines and co-stimulatory molecules, without affecting their response to Th17 and Tregs.

Calling attention, *H. pylori* has been shown to trigger a cascade of inflammatory responses and activation of various inflammatory factors in both mouse and human immune cells.[49,50] For instance, *H. pylori*-induced IL-1β can stimulate Th17 and Th1 activation.[51] In mouse models, several receptors, including nod-like receptor family members (NLRP3), caspase-1, and TLR2, regulate the release of IL-1β induced by *H. pylori*. These receptors play a role in inhibiting hypersensitive reactions such as asthma.[49,51,52] Nucleotide-binding oligomerization domain containing 1 (NOD1) is an intracellular pattern-recognition receptor (PRR) that recognizes bacterial components and initiates inflammation pathways. Variations in the NOD1 gene have been genetically linked to asthma.[53] These gene variations are associated

with IBDs and asthma. NOD1 has been shown to induce minimal production of TNF-α, IL-10, and IL-1β from human peripheral blood while synergistically enhancing TLRs-induced responses. This synergistic effect involves the release of multiple cytokines and multiple ligands.[54,55]

Inflammatory bowel disease

IBD, which encompasses chronic inflammatory disorders of the gastrointestinal (GI) system such as ulcerative colitis (UC) and Crohn's disease (CD), has been the subject of several observational studies to investigate the possible link with *H. pylori*. Recently, the presence of *H. pylori* in the intestinal mucosa of IBD patients, colorectal neoplasms, and normal colonic mucosa has been reported.[56-58] However, a meta-analysis study has shown that individuals with IBD have a lower incidence of *H. pylori* compared to non-IBD patients.[59,60] These conflicting findings may suggest that the prevalence of *H. pylori*-related disease in individuals with IBD could be influenced by some factors like ethnicity.

Further studies declared that individuals with IBD who received antibiotics had a lower *H. pylori* infection rate compared to those without antibiotics treatment.[60,61] A study included 153 patients with severe UC showed significantly lower rates of *H. pylori* infection compared to the control group. Another study found that patients with small intestine and ileocolonic CD had remarkably lower rates of *H. pylori* infection than those in the control group.[62] However, in a different study, only 13% of IBD individuals were found to have *H. pylori*, while the frequency ranged from 39% to 67% in the control group. This finding was corroborated by Polish research involving ninety-four children with IBD, which indicated a lower prevalence of *H. pylori* in individuals with IBD.[63]

Similarly, a recent meta-analysis of thirty research projects also suggested potential protective roles of *H. pylori*, with only 27% of IBD individuals presenting signs of *H. pylori*-related disease.[64] However, the researchers emphasized that the variability in study design could affect the certainty of their conclusions. Therefore, further research is needed to fully understand the protective effects of *H. pylori* in both affected and healthy individuals.

Animal studies have also indicated that chronic infection with *H. pylori* may change the pattern of microbiota in the large intestine, potentially influencing the development of IBD.[65] Research on animal colitis models has also suggested that *H. pylori* infection could modulate immune responses, leading to the host being less susceptible to other chronic inflammatory disorders like IBD.[64-66]

In this line, Papamichael et al. suggested that *H. pylori* infection may protect against IBD through mechanisms such as elevating cytokine levels, stimulating T cells and dendritic cells, and suppressing the Th1/Th17 process.[23,67,68] A similar study has also demonstrated the protective effect of *H. pylori* on colitis due to the bacteria's chromosomal DNA, containing a high frequency of immune-regulatory sequences, which is sufficient to intercept sodium dextran sulfate-induced colitis. In the animal model, rats were treated with an oral administration of *H. pylori* DNA before being subjected to chronic and acute colitis; in both groups, the DNA-based treatment reduced virulence and other factors related to dextran sulfate sodium-induced colitis.[66] The protective effect of *H. pylori* DNA was attributed to its ability to inhibit cytokine release by dendritic cells. However, it is not yet determined whether or not *H. pylori* DNA can protect against IBD development in human or mouse models.

Gastro-oesophageal reflux disease

GERD, a common disorder, irritating the squamous epithelium of the esophagus, involves the passage of stomach contents into the esophagus.[69] On the contrary, GERD has been linked to *H. pylori* infection and Barrett's esophagus (BO), especially the cagA+ strain.[8,70] Previously, no differences in the prevalence of *H. pylori* were observed between patients with GERD and the control group. However, the coexistence of *cagE* and *cagA* genes of *H. pylori* was more common in the control group.[71] Similarly, Bor et al found that the presence of *H. pylori* had no impact on the frequency of GERD or the associated symptom profile.[72] In this respect, a methodological analysis has also indicated that the incidence of *H. pylori* is significantly lower in individuals with GERD. Despite controversial findings, it has been demonstrated that GERD incidence tends to be lower in individuals infected with *H. pylori*, potentially suggesting a protective role of *H. pylori* against GERD development.[73] Moreover, it has been posited that the occurrence of GERD escalates after the successful elimination of Helicobacter pylori.[21]

Of note, corpus-predominant gastritis caused by *H. pylori*, especially the CagA-positive strain, can reduce gastric acid secretion and prevent damage to the esophageal epithelium.[74,75] Additionally, *H. pylori* can influence the production of leptin and ghrelin in the stomach, and gastric acid release.[59,60] Furthermore, *H. pylori* DNA has been shown to systemically downregulate pro-inflammatory responses, including type 1 interferon and IL-12 cytokines, which can minimize the occurrence of erosive esophagitis (EO).[64,76,77]

Similarly, another study suggests that the elimination of *H. pylori* may result in the development of GERD. The risk of developing new GERD is approximately twofold in individuals experienced *H. pylori* eradication. However, eradicating *H. pylori* may not affect the therapeutic or recurrence rates of pre-existing GERD. Noteworthy, given the wide array of variables, including *H. pylori* virulence factors, host physiology, genetics, lifestyle, and geographical factors, further research is needed to evaluate the impact of *H. pylori* on the onset of GERD.[70]

Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is a type of immune-mediated esophageal dysfunction, characterized by esophageal dysfunction symptoms, frequent eosinophilic infiltration of the esophageal mucosa, and food impaction,[78] in which, recent studies have suggested a beneficial impact of *H. pylori* on EoE.[26] In this regard, Cheung et al. showed lower rates of *H. pylori*-related infection in Australian children with EoE compared to the control group.[79] Ronkainen et al. also found that Swedish adults with EoE were at a lower risk of severe complications related to *H. pylori* compared to the control group.[80-82]

There are two opinions regarding the protective impact of *H. pylori* in EoE patients: (1) EoE is typically characterized by a TH2-polarized allergic reaction, while the bacteria elicit a Th1 immune response, and (2) Increasing concerns suggest that the reduction in *H. pylori* incidence over the past few decades has been associated with an increase in EoE prevalence.[83-86]

Notably, H. pylori infections have been found to result in a complicated, Th1/Th17-dominated immune response rather than a purely Th1-polarized response, promoting the differentiation of anti-inflammatory Th2 cells.[87] Additionally, EoE patients with delayed onset and severe allergic inflammation have shown IL-17-positive cell expansion influenced by both Th1 and Th17 cytokine profiles.[88] Recent research in adults and children with EoE has also indicated that Th17 plays a crucial role in disease progression.[88]

Several studies have previously suggested common pathogenic factors between EoE and *H. pylori*. Galectin-3 (Gal-3) has a critical function in *H. pylori* pathogenicity in the stomach lining, immune responses, and chronic gastric consequences.[89] In this regard, Gal-3 could be a crucial host component for maintaining subclinical *H. pylori* infection and colonization levels.[89,90] In vitro studies have also demonstrated that Gal-3 is an essential factor for the activation of human basophils in IgE-dependent conditions rather than EoE.[89] Mast cells, known immune cells involved in both *H. pylori* infection virulence and EoE virulence,[91,92] are thought to play a significant role in EoE development. They can stimulate the inflammatory pathways and fibrosis in EoE through the secretion of TGF-β, which stimulates proliferation and collagen release.[93,94] TGF-β is also believed to be a facilitating factor in *H. pylori* pathogenesis. Moreover, *H. pylori*-derived VacA cytotoxin has chemotactic effects on mast cells derived from bone marrow (BMDMCs), leading to the production of pro-inflammatory cytokines, including TNF-α, which has high expression in the esophageal epithelial cells of EoE.[26,95]

During infection with *H. pylori*, the gastric epithelial cells actively engaged in signaling pathways mediated by extracellular signal-regulated kinase to intensify the production of IL-33. This intricate process was contingent upon cagA, a crucial factor, leading to heightened inflammation and an augmented bacterial load within the protective lining of the stomach. In hence, *H. pylori*-associated mast cell-associated TGF-β, TNF-α, and IL-33 may be involved in the pathophysiology of EoE, and further research is needed to explore this field.[26]

According to the literature, another granulocyte associated with EoE is basophils,[96,97] however, the exact role of *H. pylori*-derived peptides as strong basophil chemo-attractants in the severity of EoE remains to be determined.[26] Regarding *H. pylori* infection, a few studies have shown that Th1 and Th17 cells exhibit dual effects.

The anti-inflammatory effects following *H. pylori* infection can be regulated by Treg and Th2 cells. Noteworthy, reduced esophageal expression of hBD1 and hBD3 has been also identified during EoE, suggesting that the esophageal mucosa could be more vulnerable to the EoE incident.[98,99] Despite *H. pylori* can evade defensin attack, human defensins (small proteins produced by circulating white blood cells and tissue cells) may play a crucial role in *H. pylori-associated* neurodegenerative diseases, as the bacterium induces defensin release in response to persistent inflammatory tissue injury.[100,101]

Esophageal squamous cell carcinoma

ESCC ranks as the 8th fatal malignancies malignancy, accounting for 90% of the 456,000 esophageal cancers diagnosed each year.[102,103] Previous studies have suggested that *H. pylori* infection may act as a protective factor for GERD and the development of esophageal adenocarcinoma (EA).[74,104-106] Ye et al for the first time established the association between ESCC and CagA-positive *H. pylori* infections in the Swedish population via serological assessment.[107] A similar correlation was recently observed in Japan.[108] The potential mechanism of this effect may be derived from stomach atrophy, low intragastric acidity, and increased intragastric NH3 secretion following *H. pylori* infection.

Besides, Barrett's esophagus plays a substantial role in the development of EA.[109,110] A Barrett's ulcer can occur due to recurrent gastroesophageal reflux,[110] causing chronic inflammation and mucosal damage, leading to the replacement of squamous epithelium with intestinal-type epithelium in an acidic microenvironment.[111] Infection with *H. pylori*, especially cagA + strains, accelerates hypochlorhydria, and a lower pH environment results from multifocal stomach atrophy.[111] Therefore, *H. pylori's* "protective" role could be attributed to reduced gastric reflux potency in individuals with corpus-predominant gastritis or decreased esophageal movements.[112,113]

However, another study demonstrated that *H. pylori* has the potential to cause cell death in Barrett 's-derived esophageal adenocarcinoma cells through the Fas-caspase cascade.[114] The effect of *H. pylori* infection on acid secretion can vary depending on the gastritis pattern it induces.[115] *H. pylori* infection should not be considered a single

entity regarding its role in acid secretion and its impact on esophageal reflux disease and its consequences.[116] Patients with gastric ulcers typically have atrophic gastritis and normal or reduced acid secretion, while patients with duodenal ulcers often have *H. pylori* antral predominance, non-atrophic gastritis, and increased acid secretion.[117-119]

The literature suggests that patients with duodenal ulcers infected with *H. pylori* have a higher risk of developing esophageal adenocarcinoma, whereas no such relationship has been found with gastric ulcers. This observation supports the idea that *H. pylori* infection is not the sole factor responsible for inducing reflux disease. Therefore, patients with *H. pylori* infection who experience excessive acid secretion due to antral-predominant, non-atrophic gastritis may be at a higher risk of developing EA.[120]

The disparity in findings can be explained by the pattern of gastritis induced by *H. pylori* infection, which determines the potential impact on reflux disease.[120,121] Infection with *H. pylori* is associated with a higher likelihood of developing atrophic gastritis and reduced acid secretion, which may protect against reflux disease.[120,121] Conversely, the infection is typically associated with antral-predominant and non-atrophic gastritis in the West countries.[122]

Autoimmune diseases

Multiple sclerosis

Multiple sclerosis (MS) is a progressive neurological disease that affects the nervous system i.e., the brain, spinal cord, and optic nerve, and significantly influences the quality of life.[123] In MS, similar to the pathogenicity observed in IBD, the Th17 subset of helper T-cells plays a central role in chronic (neuro-) inflammation.[124] It is now widely understood that Th17 cells, previously thought to be Th1 cells, are the primary encephalitogenic population in autoimmune neuroinflammation, particularly in the experimental model of autoimmune encephalomyelitis (EAE) known as a conventional mouse model of MS.[125]

Of note, recent literature has shown that autoreactive helper T-cells expressing IFN-γ and IL-17A but lacking GM-CSF were unable to induce neuroinflammation. However, the secretion of GM-CSF by Ifng−/−Il17a−/− helper T-cells was sufficient to cause EAE. There is compelling evidence indicating that Th17-derived GM-CSF plays a dominant role in autoimmune CNS inflammation. Compelling data suggest a protective role for *H. pylori* in the development of MS.[126]

Conversely, a contradictory association between *H. pylori* infection and MS development was found among the Japanese people.[127] Some pieces of literature have suggested a higher incidence of MS in adults with a history of asthma since childhood.[128] In a study involving 105 MS patients and 85 non-MS healthy controls, individuals with MS had significantly lower seropositivity to Helicobacter pylori than those without MS.[127] These findings need further confirmation in larger cohorts and should be empirically tested in the MS EAE model. In EAE, the tail and hind limbs become sensitive to *H. pylori*-induced Treg-mediated immunoregulation due to CNS inflammation and progressive supranuclear palsy caused by myelin-specific auto aggressive T cells.[126]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE), is a syndrome characterized by dysfunction in the skin and various internal organs and is typically categorized as a group of autoimmune connective tissue diseases.[129,130] A study demonstrated that *H. pylori* urease may induce the production of anti-ssDNA in rats. It is also believed that *H. pylori* has a preventive effect on the progression of SLE.[131]

Another research study examined the prevalence of *H. pylori* seropositivity in 466 lupus patients compared to matched controls and found that fewer SLE patients were seropositive for *H. pylori*, suggesting that *H. pylori* did not contribute to the development of SLE. However, it had a protective effect against the progression of the disease.[132] Subgroup analysis revealed that African-American women seropositive for *H. pylori* were more likely to develop lupus in their later years compared to *H. pylori*-negative SLE patients.[133] However, the exact mechanism underlying this association remains unclear.

Shapira et al. also reported higher levels of anti-*H. pylori* antibodies in patients with giant cell arteritis, antiphospholipid syndrome, and primary biliary cirrhosis.[134] A study conducted in 2002 by Kalabay et al found that 82% of individuals with connective tissue diseases were infected with *H. pylori*.[135] However, another study indicated that *H. pylori* infection did not play a role in SLE development but rather involved in preventing the disease from progressing.[132]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common systemic inflammatory joint disorder.[136] The initial evidence of a link between RA and *H. pylori* infection was presented by Yamanishi et al, who demonstrated that *H. pylori* urease could stimulate B cells to produce IgM rheumatoid factor.[131] However, other studies found no association between the presence of H. pylori and RA. The rate of *H. pylori* infection was higher in the control group than in RA patients.[132,137]

Additionally, a growing body of evidence has reported a significant correlation between the eradication of *H. pylori* and the development of RA.[138-140] Recent research has shown that RA patients who use non-steroidal anti-inflammatory drugs (NSAIDs) have a higher incidence of peptic ulcers. According to Janssen et al, *H. pylori* infections are less common in RA patients who use NSAIDs.[137,141]

Systemic sclerosis

Systemic sclerosis (SS) is an autoimmune disease that affects the abnormal development of connective tissues [142]. In one study involving twelve European scleroderma patients, 42% (5 individuals) were found to have *H. pylori* infection.[143] In a larger cohort study of 124 Japanese patients with systemic sclerosis, the seroprevalence of *H. pylori* was 55.6%, significantly higher than in healthy controls.[90] Another study involving a different group of patients (n=64) in Japan suggested that *H. pylori* infection may have protective effects against the progression of reflux esophagitis in individuals with scleroderma[144] (Figure 1).

Other diseases

Celiac disease

CD is an immune-related gluten allergy that affects the small intestine, resulting in both gastrointestinal and extraintestinal symptoms.[145] Research has shown a strong inverse correlation between the presence of *H. pylori* and the development of CD in patients undergoing gastrointestinal endoscopy for various symptoms. *H. pylori* recruits T-regulatory lymphocytes, which have protective effects against allergen-induced asthma and systemic implications.[47,146,147] T-regulatory lymphocytes are also involved in the etiology of CD. In patients with CD, there is a decrease in the number of receptors for cellular responses facilitated by T-regulatory cells in the bowel wall, and these receptors are impaired or absent.[48] Therefore, lacking functional gastric T-regulatory cells and *H. pylori* may not be able to reduce the number of immune response receptors to gluten. Instead, *H. pylori* may influence the absorption of gluten by altering gastric pH or using proteases, thereby reducing its immunogenicity.[1,148,149]

Diarrheal disease

Diarrheal diseases are the most prevalent infectious causes of morbidity and mortality worldwide.[150] *H. pylori* may play protective roles against exogenous pathogens by activating specific local and systemic immunoglobulins or by secreting antibacterial peptides.[151,152] While it has not been extensively studied, many researchers suggest that *H. pylori* protects against diarrheal diseases.[150,151,153]

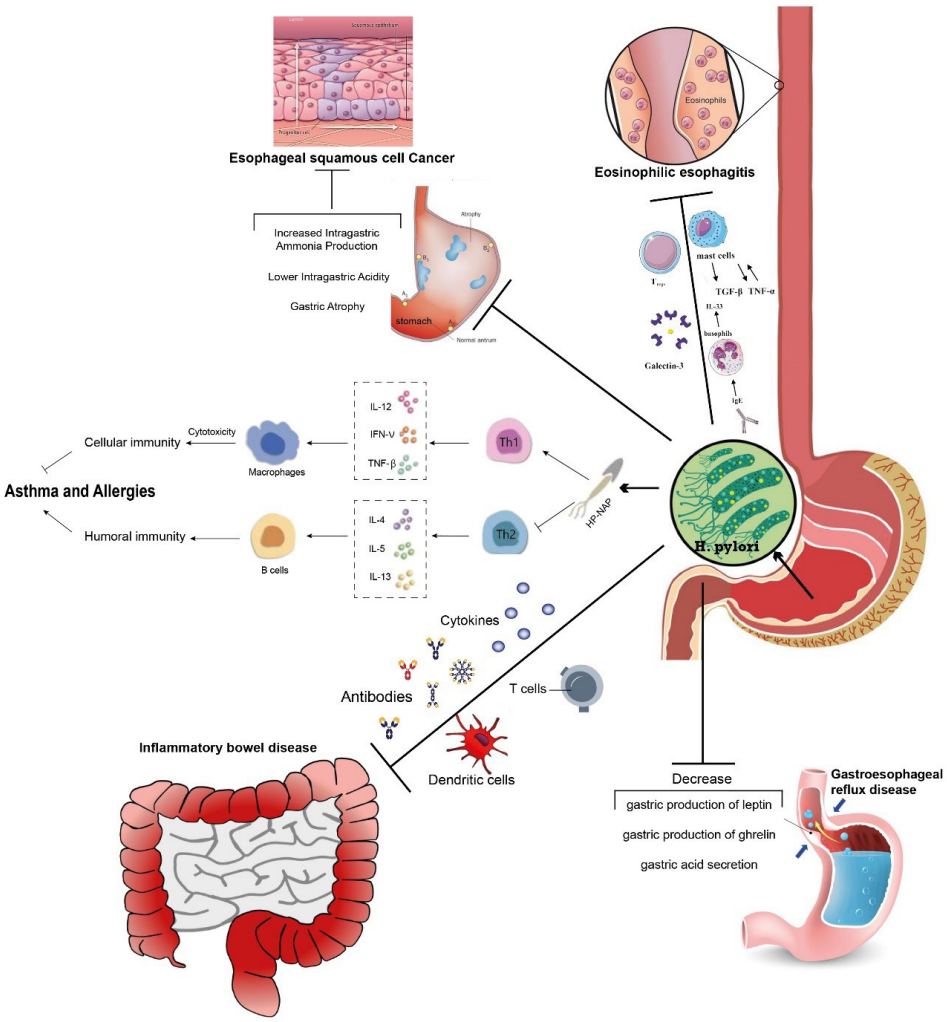

Figure 1. Probable protective mechanisms of *Helicobacter pylori* in various diseases. Abbreviations: Ig (immunoglobulin), IL (interleukin), TGF (transforming growth factor), TNF (tumor necrosis factor), Tregs (regulatory T cells), HP-NAP (*H. pylori* neutrophil-activating protein), Th1/Th2 (Helper T cells 1/2)

The protective mechanisms may involve the secretion of antibacterial peptides by either the host or *H. pylori*, immune system stimulation as an adjuvant, competition for a niche, or the maintenance of gastric acid through hypergastrinemia throughout childhood.[154] The innovation of clean water, improved quality of life, and reduced population density have led to a lower prevalence of deadly diarrheal diseases, which may be linked to reduced transmission of *H. pylori* and decreased selection for its maintenance.[155]

Tuberculosis

There is a notable inverse association between *H. pylori* infection and tuberculosis. Recent research conducted in tuberculosis-prone areas of West Africa has demonstrated that individuals with *H. pylori* infections had a lower risk of reactivating latent tuberculosis infections.[156] It is suggested that *H. pylori* infection may enhance the host's innate immune response and alter the risk of active tuberculosis in both humans and non-human primates by inducing bystander suppression characterized by ongoing inflammation and T-cell signaling.[156, 157]

Metabolism and obesity

The mammalian stomach plays a role in secreting approximately five to ten percent of the body's leptin and sixty to eighty percent of ghrelin.[158] These hormones are involved in the regulation of body weight. Multiple studies have demonstrated that individuals with *H. pylori* infection tend to have lower levels of ghrelin compared to those without the infection, and the removal of *H. pylori* has been associated with an increase in ghrelin production.[159-161] The presence or absence of *H. pylori* infection can have significant long-term metabolic effects due to ghrelin's biological functions throughout the body.[162] However, the impact on leptin function remains unclear, with seemingly conflicting results that may be influenced by risk factors such as age, medications, and the severity of gastric inflammation.[76,163]

Regardless of the specific effects, the overall energy balance in the population may be influenced by changes in ghrelin and leptin production resulting from the increasing number of children growing up without *H. pylori's* presence in stomach physiology.[164]

Conclusion

In conclusion, *H. pylori* infection is widespread and potentially dangerous, causing fatal outcomes. Given that several gastrointestinal problems, including non-cardia gastric adenocarcinoma, gastric lymphoma, and peptic ulcers, have been previously linked to *H. pylori* infection. Additionally, this infection can lead to various disorders beyond the digestive system. The text explains that *H. pylori* have the potential to offer protection within or outside the digestive system, effectively preventing the occurrence or progression of certain diseases or in the absence of this bacterium, Some disorders can be aggravated. The beneficial or detrimental effects of *H. pylori* on individuals may be influenced by various factors, including host physiology, lifestyle, *H. pylori* virulence, and genetic factors. The broad eradication of *H. pylori* in recent decades, meanwhile, is now widely acknowledged to have unanticipated and undesirable effects. Therefore, the general treatment of *H. pylori* infections may not always be useful and may even be harmful in cases of early-stage gastric illness unlikely to proceed to gastric cancer or other serious outcomes. It is highly recommended that the pathogenicity of *H. pylori* in each case should be taken into account when treating *H. pylori* infections, as well as the patient's medical history and clinical situation.

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Competing Interests

The authors declare no conflict of interest.

Ethical Approval

Not applicable.

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