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Review

Helicobacter pylori and IL-8 Signaling: Implications in Gastritis and Peptic Ulcer Disease

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Abstract

The gram-negative spiral bacterium Helicobacter pylori has many flagella to colonize the stomach mucosa. Urease neutralizes stomach acid and helps H. pylori survive. Warren and Marshall found that H. pylori causes chronic gastritis, peptic ulcer disease (PUD), gastric cancer, and mucosa-associated lymphoid tissue lymphoma. H. pylori infects 50% of the worldwide population, although only a portion develops gastroduodenal diseases due to bacterial virulence, host genetics, and environmental variables. CagA and VacA, which harm epithelial cells and stimulate the immune system, are the main virulence factors. Interleukin-8 (IL-8), a pro-inflammatory cytokine that attracts neutrophils and T cells, is released by the stomach epithelium, worsening tissue inflammation and ulcer development. The IL-8 -251 polymorphism (rs4073) increases IL-8 production and increases the risk of gastritis, peptic ulcer disease, and stomach malignancies. Bacterial virulence, host immune responses, and genetic variations are key to H. pylori-related diseases. IL-8 is crucial to stomach mucosal inflammation and may be a biomarker for H. pylori disease susceptibility and progression.

Keywords: H. pylori, rs4073, Interleukin-8, VacA, CagA, Gastric cancer.

1. Introduction

Helicobacter is a microaerophilic, gram-negative, and spiral microbe. Numerous species of Helicobacter have been identified from the digestive systems of humans and linked to a variety of diseases [1]. Helicobacter are motile and move because of the movement of their flagella, which resembles either a quick spiral or a languid wave depending on the speed at which it moves [2]. The vast majority of bacterial species have flagella that are bundled together and either polar or bipolar in distribution [3]. Helicobacter have been identified in humans, animals, and birds. In the Helicobacter genus, scientists have discovered at least 36 distinct species yet. Helicobacter genotypes have been discovered in over 142 diverse vertebrate species.

While the microorganism known as H. pylori is an infectious agent and the most pathogenic to human health. Certain NPHS were associated with abnormalities in human body function; for example, Helicobacter heilmannii, Helicobacter winghamensis, Helicobacter pullorum, and Helicobacter canis were the root cause of illnesses that affected the stomach and intestines [4–6]. There is substantial evidence that additional Helicobacter species may exist in the biliary system, intestines, and stomach. The now-recognized genus "H. heilmannii," which includes numerous species such as "H. bizzozeronii" and "H. salmonis," is occasionally found in the stomach and exhibits the same problem-causing by H. pylori . Human infection is also possible with H. cinaedi, H. pullorum, H. canis, H. canadensis, H. fennelliae, H. rappini, H. bilis, H. hepaticus, and H. suis. The majority of the previously specified species likely originated from pets and livestock [7].

2. General Characteristic of Helicobacter Pylori

H. pylori organisms, when cultivated on solid media, take on a rod-like morphology despite their gram-negative status and small dimensions (0.3–1.0 mm in width and 1.5–10.0 mm in length).

In addition, H. pylori may transition into a VBNC (viable but non-culturable) form during extended in vitro culture and exposure to unfavorable environmental circumstances such as a lack of nutrients, desiccation, an absence of oxygen protection, and the presence of antimicrobials. H. pylori will undergo a shape change, from rod to coccoid, as a result of this. In the presence of this morphological change, H. pylori cannot thrive using conventional culture techniques on agar plates; this is because the morphology of the microbes has changed [8].

Bacteria in the VBNC state keep working metabolically, may still cause disease, and can resume active regrowth if the right conditions arise [9]. It has not been determined whether H. pylori can revert to active regrowth conditions after being eliminated, but the fact that H. pylori can hold on under stressful conditions is of critical importance to public health [10].

H. pylori, which is considered a motile bacterium and owns four to six flagella encased within a unipolar sheath, may have a behavior allowing it to survive within gastric fluids. H. pylori is a fastidious organism with specific development requirements, such as a specialized environment, media with rich nutrients, high humidity, and an incubation period of five to seven days. H. pylori is a capnophilic bacterium, which means it needs an environment with a high carbon dioxide concentration (between 5 and 10 per cent) [11].

H. pylori needs a culture substrate in complex form for its growth, which may be solid or liquid. In addition, it requires a supplement, which may consist of whole sheep or equine blood, hemoglobin, serum, coal, yeast, or yolk emulsion [12]. All of these substrates are involved in its nutrition; these vitamins not only nourish the microbe but also purify its environment [13,14].

In addition, when attempting isolation from samples that already contain basic microbial flora, the media must be made selective by the addition of multiple antibiotics [15]. The agitation of liquid media, which permits gas dispersion and the incubation of the liquid in a carbon dioxide-rich environment, promotes growth in the liquid medium [16].

H. pylori can flourish at temperatures between 30 and 37 degrees Celsius, with optimal growth occurring at 37 degrees Celsius; however, it cannot grow at 25 degrees Celsius. Unpredictable development is observed at a temperature of 42 degrees Celsius [13,14]. At temperatures as low as 4 degrees Celsius, H. pylori can survive significantly longer than at ambient temperature [17]. It thrives at pH levels ranging from 4.5 to 7.3, with optimal growth occurring at pH 5 [18]. H. pylori develop normally in the presence of a specific percentage of NaCl, like 0.5% and 1%; if it reaches 2% NaCl, this will put a limitation on the bacterium's development. For growth to occur, the water activity value must be between 0.96 and 0.98 [19]. Based on these findings, it appears that this specific bacterium cannot thrive on a wide range of dietary types [20]. H. pylori is positive for both catalase and oxidase, and it is also characterized by a high level of urease activity, while the inability of H. pylori to reduce hippurate or nitrate is one of the characteristics that distinguish it from other Campylobacter species.

2.1 Virulence Factors

Several virulence factors are linked to the intensity of diseases caused by H. pylori; however, the genotype of the H. pylori strain that causes the disease plays an essential role [21]. The virulence factors generated by H. pylori are accountable for the explosion of inflammatory responses; they control and regulate them, resulting in the development of inflammation [22].

H. pylori can colonize and persist within the mucosa of the stomach due to its virulence factors. This causes further immune evasion and, ultimately, the induction of precancerous changes [23]. H. pylori possess many virulence factors, including urease, flagellum, cytotoxin-associated gene A, vacuolating cytotoxin A, catalase, and others. The number of virulence factors that H. pylori possesses is what makes it highly virulent [24–26]. Cytotoxin-associated gene A and vacuolating cytotoxin A are considered the most critical for H. pylori to develop gastric diseases, while urease is very intrinsic for H. pylori to survive within the stomach.

2.1.1 Vacuolating cytotoxin A (VacA)

VacA is a cytotoxin that is considered a type of bacterial virulence factor; this toxin is secreted by H. pylori, and it's a protein with a size of about 88 kilodaltons (kDa) [27]. This cytotoxin earned its name from its ability to induce vacuolation in the host cell. When this toxin was discovered, there was no bacterial toxin with the same action, so many studies were done to clarify its function and structure after its discovery [28,29]. In the gastric epithelium, vacuolating cytotoxin A tends to be an important factor that promotes the growth and survival of the bacteria. The 33 kDa N-terminal domain of this protein is responsible for toxicity, while the 55 kDa C-terminal domain is essential for the attachment of the bacterium to the cell surface receptors [30].

All Helicobacter pylori strains tend to appear with the VacA gene [31]. This protein binds to many receptors,

including lipoprotein receptor-related protein-1 (LRP-1), protein tyrosine phosphatase α and β (RPTPα and RPTPβ), and sphingomyelin. These are the major types of receptors that vacuolating cytotoxin A binds. There are numerous combinations of VacA genotypes, with s1, s2, m1, m2, s1m1, and s2m2 being the most common. Peptic ulceration Patients have a high likelihood of being infected with the s1 genotype of H. pylori [32]. Gastritis is distinguished by the VacA s1m1 genotype, whereas gastric cancer is distinguished by the s1 and m1 genotypes [33,34].

Vacuolating cytotoxin A is a protein that considers a multi-receptor with a pleiotropic effect, including membrane depolarization, alteration in mitochondrial function, autophagy, apoptosis, and narcosis [28,35]. VacA affects the immune cell by inhibiting the proliferation of the T and B cells and leading to apoptosis in macrophages by inhibiting the signaling of IFN-β. Also, VacA leads to the excessive release of IL-8 [36]. Furthermore, VacA stimulates the regulatory T cell and differentiates it into the effector T cell, which helps in the continuation of H. pylori infection [37] as shown in Fig. 1. VacA is able to induce cells into cell apoptosis; from the mitochondria into the cytosol, the cytochrome c will release along with the activation of Caspase 3, and these are the two recognized biochemical processes that occur during the process of apoptosis. While atrophic gastritis is most likely caused by the death of cells, which plays a significant role in its development.

Within the pH range of 1.5 to 6, VacA will be highly active without being inhibited. This protein is resistant to pepsin digestion at the pH level of 2 [38].

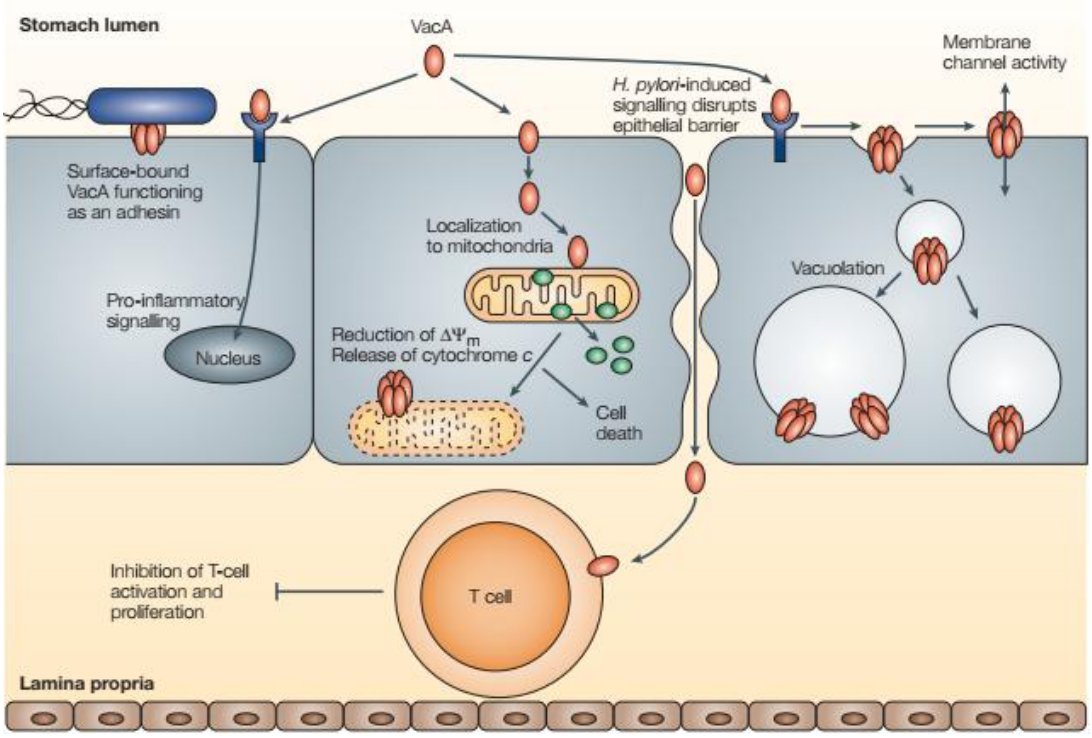

Figure 1. Several VacA actions help H. pylori in stomach colonization [39].

Some of the VacA molecules released by H. pylori and stimulated by gastric fluid may traverse the pylorus and induce vacuolation of duodenal epithelial cells before they are metabolized by gastrointestinal proteases that maintain other areas of the intestinal lumen.

2.1.2 Cytotoxin-Associated Gene A (CagA)

H. pylori CagA, which has a molecular weight ranging from 120 to 140 kDa and is known as a highly immunogenic protein, is expressed by the CagA gene, which may be found near the very end of the pathogenic island (Cag PAI) [40].

The strains that express this gene are highly virulent strains and are called CagPAI-positive strains, while the strains that lack this gene are considered less virulent strains and are called CagPAI-negative strains.

Both the type 4 secretion system (T4SS) and CagA are encoded by the cag pathogenicity island and are involved in carcinogenesis; this will result in cellular modification, proliferation, and mortality, as well as alterations to the cytoskeleton overall. CagA enters the cell via a pilus, and the T4SS contributes to the formation of this pilus. This will occur when H. pylori attach themselves to the stomach epithelium and stimulate the expression of CagA [41] as shown in Fig. 2.

CagA-positive strains are embroiled in making the risk of gastric cancer, duodenal ulcers, and active or atrophic gastritis [42,43]. When blood group antigen-binding adhesin (BabA), cytotoxin, outer inflammatory protein A (OipA), and CagA co-express, inflammatory responses are amplified [44]. The clinical outcome and the prevalence of gastrointestinal illnesses may rise as a result.

CagA-positive genotypes are less difficult to eradicate than CagA-negative infections, according to the findings of a meta-analysis by [45], CagA-positive genotypes appear to be significantly more dangerous than others.

The extent of activity of the CagA protein is associated with the types and numbers of Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs found in its C-terminal region.

The adhesions between gastric epithelial cells and H. pylori are accomplished via many adhesins, including BabA/B, SabA, OipA, HopZ, and AlpA/B, and then start to form the TFSS syringe-like (TFSS pilus). After establishing a stable attachment, H. pylori cagA-positive strains use the TFSS to transfer CagA into gastric epithelial cells [46].

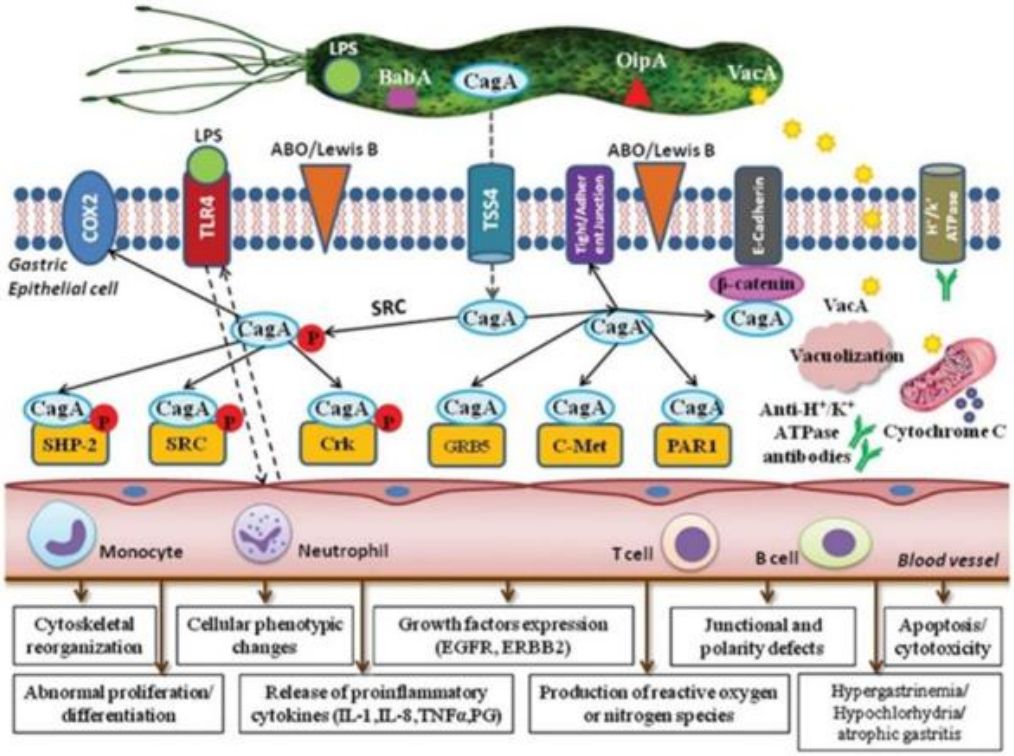

Figure 2. The interaction between Helicobacter pylori CagA and the immune system [47]**.**

2.1.3 Urease

This enzyme tends to be the most important virulence factor generated by H. pylori, and it plays a role in the colonisation of gastric mucosa and metabolism [48]. Urease may be present in either the cytoplasmic compartment or the outer layer of the bacterial cell. Depending on where they are located, enzymes are classified as either internal or external. During the process of cell lysis, the external urease is produced and is effective at pH levels between 5.0 and 8.5, whereas the internal urease is effective at pH levels between 2.5 and 6.5.

The ability of urease to hydrolyze urea into ammonia and carbamate, increasing pH, is indicative of the enzymatic reaction that this enzyme catalysis [49].

H. pylori was able to effectively colonize the stomach when the pH of the mucous climbed above 8. Additional enzymes that produce ammonia, such as aliphatic amidases E and F (AmiE and AmiF), are produced by H. pylori.

Urease is an important factor that plays a crucial role in facilitating bacterial colonization, and the urease-negative strains will fail to colonize the gastric mucosa. Besides this, urease plays a key role in protecting the bacterial surface from gastric acidity because of the release of ammonia and promotes bacteria nutrition since it leads to the release of host metabolites.

Urease can modulate the host immune response, and this is done using many mechanisms, like enhancing the chemotaxis within monocytes and neutrophils, leading to altered opsonization via interacting with the major histocompatibility complex (MHC) receptor of the class II subtype and leading to apoptosis, and it can enhance pro-inflammatory cytokine release [50].

2.1.4 Flagella

H. pylori relies on its flagellum for both chemotactic and motile qualities, which makes it an important part of the bacterium [51]. The physiological composition of H. pylori tends to possess two to six sheathed unipolar flagella; each flagellum is roughly three micrometers in length and is shielded from the acidic environment of the stomach by its surrounding sheaths.

The number of flagella is connected with the movement rate of H. pylori; however, this connection may vary from species to species [52]. The main components of the flagellar filament are the proteins FlaA and FlaB, both of which belong to the flagellin family.

Flagellum considers the factor that provides the motility for H. pylori, so it plays a crucial role in the pathogenicity of the bacterium [53]. The motility of H. pylori facilitates the colonization of the gastric mucosa, and less motile strains face difficulties in the colonization process [54].

In addition to their part in colonization, flagella also play a part in H. pylori -induced inflammation and immunological invasion. This would be in addition to their involvement in colonization. Furthermore, flagella contribute to the production of biofilms. It has been shown that HpA, FlaA, and FlaB, three types of flagellins that may be detected in bacterial flagella, can induce particular antibody responses and increase humoral immunity after an infection. According to the findings, the production of IL-8 was boosted by H. pylori strains that had higher motility.

2.2 Pathogenicity of H. pylori

H. pylori in the first place colonizes the stomach and therefore causes many gastric diseases involving gastritis, peptic ulceration, and gastric cancer [55]. Besides the stomach, this bacterium can colonize other sites, including the gallbladder, ears, nose, skin, and even eyes [56] see Fig. 3.

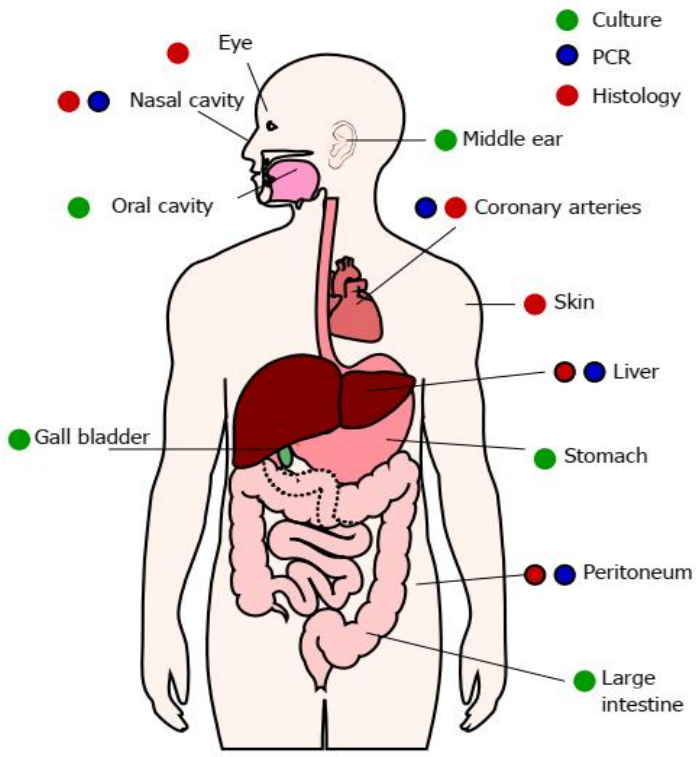

Figure 3. Sites that H. pylori colonize and the detection methods that have been used [56].

H. pylori is a contributing factor in both peptic ulcers and persistent inflammation of the mucous membranes that line the stomach, so H. pylori is considered the primary cause of both of these disorders. Additionally, an infection with H. pylori might lead to the evaluation of gastric neoplasms such as lymphomas and stomach cancer, so consider it a risk factor for such diseases.

H. pylori moderate different virulence factors and involve them in the pathogenic infection process [57]. These virulence factors, which include either an enzyme (urease, catalase, lipase, phospholipase, and proteases) or a toxin (vacuolating cytotoxin, which is encoded by the VacA gene), are produced by all H. pylori strains. The PAI also comprises genes for several virulence factors, resulting in the synthesis of pro-inflammatory cytokines in epithelial cells (mainly interleukin-8) and the assembly of proteins that deliver the CagA protein into eukaryotic cells, which is called the type 4 secretion system (T4SS).

2.2.1 Gastritis

The fact that H. pylori are considered to be the primary agent responsible for gastritis and peptic ulcers was not established until the year 1982. In that year patients with gastritis and peptic ulcers had flagellated bacteria identified from endoscopic biopsy cultures, and since then H. pylori has tended to be recognized as a pathogen that is responsible for gastric diseases like gastritis and peptic ulceration [58,59].

Gastritis infection is divided into acute or chronic, and H. pylori tends to be the most common cause of gastritis. Epithelial and lamina propria components are responsible for the formation of normal stomach gastric mucosa; the epithelial components change according to their location in the stomach and become the cardiac gland, which is the region that surrounds the esophageal (the cardia), or the fundic gland, which is represented by the body of the stomach except for the region of the cardiac gland and antral-pyloric gland, and finally, the antral-pyloric gland, which is located in the pyloric antrum (the region between the fundus and pylorus).

The mucus layer that covers the epithelial cells plays a very important role in preventing pathogens from colonizing the underlying epithelium. This layer thickness is around 300 μm, and H. pylori have to penetrate it if they want to get into the underlying epithelium. So, the spiral shape of this bacterium is very helpful in penetrating the mucus layer and its two flagellins (FlaA and FlaB), which are used in motility [60]. Even though H. pylori tends to colonize the antrum, the infection can travel to any area of the stomach and cause gastritis. When the disease is cured, migration of the bacteria occurs from the antrum to the corpus, resulting in a less severe form of antral gastritis. Early acute gastritis is distinguished by the presence of substantial neutrophilic infiltrates in the mucous pharynx and lamina propria.

Neutrophils and H. pylori both contribute to the destruction of the epithelium, which triggers the cells of the mucous neck to multiply in an attempt to replenish the cells that are being lost [61]. Chronic gastritis may affect the antrum or corpus, or it may be diffuse (also known as pangastritis or multifocal gastritis). Antrum-predominant gastritis patients tend to have normal acid secretion, and the colonization of H. pylori is bounded to the antrum, while antral gastritis tends to raise the risk of developing duodenal ulcers, and corpus-predominant gastritis tends to raise the risk of gastric ulcer development, which may lead to metaplasia and adenocarcinoma.

H. pylori can colonize the corpus of a patient with diffuse gastritis because their acid secretion is frequently substantially diminished [56] as seen in Fig. 4.

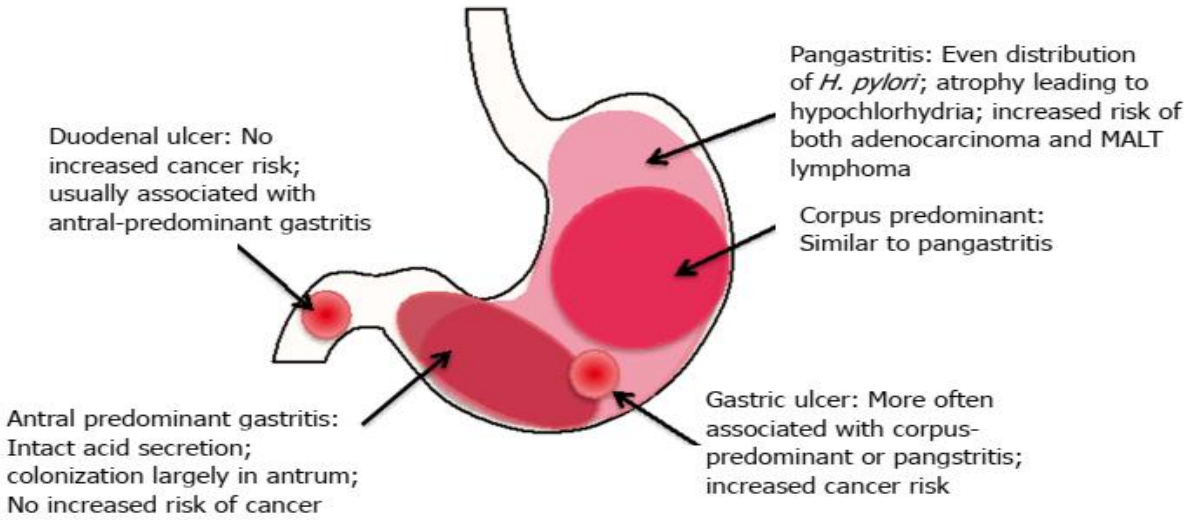

Figure 4. Types of H. pylori -related pathology within the stomach [56].

The IV Maastricht/Florence Consensus report provides the most recent clinical management along with treatment recommendations for H. pylori infection [62]. Except for high prevalence of clarithromycin resistance regions, the first line of treatment is frequently a combination of clarithromycin and proton pump inhibitors (PPIs) [63]. In this circumstance, a therapy containing quadruple bismuth would be the preferred option; however, a therapy containing no bismuth would also be a viable option. After two unsuccessful attempts to eradicate H. pylori, it is recommended to acquire a culture of the bacteria and test for drug resistance [64].

2.2.2 Peptic ulceration

Peptic ulcers are lesions within the stomach or duodenum and happen due to factors that cause damage to the mucosa, like gastric acid, Helicobacter pylori, pepsin, and non-steroidal anti-inflammatory drugs (NSAIDs). H. pylori infection is considered the main factor for both gastric and duodenal ulcers along with using NSAIDs. Approximately

10 per cent of peptic ulcers are caused by pharmaceuticals like aspirin along with NSAIDs [65]. Peptic ulcer disease and dyspepsia present the same gastrointestinal symptoms, and it's difficult to distinguish them clinically; therefore, the endoscopy diagnosis could be the best choice to distinguish them. The symptoms of these diseases are represented by epigastric pain, nausea, bloating, and belching [65].

Infection with H. pylori may result in either hyperchlorhydria or hypochlorhydria; the kind of peptic ulcer that develops depends on which one you have. Cytokines are considered major mediators for H. pylori infection which decrease parietal cell secretion; however, it is possible that modifications of the H+/K+ ATPase subunit directly occur by H. pylori activating calcitonin gene-related peptide (CGRP) sensory neurons linked with somatostatin or inhibiting the synthesis of gastrin.

Gastric ulcer development is linked to hyposecretion; 10–15% of people who are infected with H. pylori have increased gastric secretion as a result of hypergastrinemia and lower antral somatostatin concentration, while hyposecretion is linked to the development of stomach ulcers [66].

The elimination of H. pylori results in a reduction in the amount of mRNA that is expressed for gastrin and an increase in the amount of mRNA that is expressed for somatostatin [67]. Gastric ulcers are related to hypochlorhydria and mucosal atrophy in the individuals who make up the remaining majority of the patient population [68].

The primary factors that determine the location of a peptic ulcer are the severity and division of gastritis. Because bile prevents the organism's migration, H. pylori cannot ordinarily cause infections in the duodenum. Because a low pH precipitates glycine-conjugated bile acid, however, duodenal ulcers may develop if acid secretion in the duodenal bulb is sufficient to persistently reduce the pH. This permits colonization of the duodenal bulb, while by maintaining a healthy pH, duodenal ulcers can be prevented [69].

For a duodenal ulcer to exist and persist, the stomach must be capable of producing at least 12 moles of acid per hour. For this to be possible, the gastric corpus must be normal or virtually normal. Ulcers in the prepyloric region of the stomach are also associated with increased acid production in this region.

2.2.3 Gastric cancer

H. pylori infections are essential but not sufficient for H. pylori -associated gastric cancer development [70]. But consider the most prevalent cause of related malignancies, infection, which accounts for 5.5% of the world's diagnosed cancer population. Although the preponderance of H. pylori -infected individuals stay asymptomatic during their lives, virtually everyone develops chronic inflammation.

About ten percent of those who are infected with H. pylori will develop peptic ulcer disease, and between one and three percent may progress to gastric cancer (GC), and 0.1% acquire MALT lymphoma (mucosa-associated lymphoid tissue lymphoma). Atrophic gastritis is considered a serious factor for the evaluation of gastric cancer and causes the stomach to produce little or no acid, which in turn affects the stomach's microbiome [71,72].

The effect of Helicobacter pylori infection on cancers of the gastric area may vary based on anatomic location [73]. Cancers of the cardia and gastro-esophageal junction (the proximal stomach) have distinct epidemiological and pathophysiological features, and they are not common within the regions that contain a high prevalence of H. pylori. A significant correlation exists between Helicobacter pylori infection and the evaluation of gastric MALT lymphomas. Sixty to eighty per cent of those suffering from MALT lymphoma achieved complete remission after H. pylori eradication.

2.3 Host Immune Response to H. pylori

The bacterial immune response in a common way can be grouped into two distinct categories: innate and adaptive. What distinguishes the innate response to a bacterial infection from other forms of response is the initial nonspecific process; this type of reaction acts rapidly on a variety of bacterial molecules to eradicate the bacteria. The innate immune response forms the adaptive immune response, which is delayed, more specific (antigen-specific), and activates T, B, and memory cells, while the adaptive immune response is driven by the innate immune response [74].

In innate immunity, TLRs, also known as toll-like receptors, are responsible for the identification of bacterial compounds in the innate immune system. These receptors are expressed on antigen-presenting cells (APCs). When bacteria come into contact with APCs, this results in the release of proinflammatory cytokines such as IL-1 and IL-8. It has been shown that infections caused by H. pylori are linked to elevated levels of cytokines.

H. pylori infection can initiate a very strong immune response. TLR2 is considered the major innate receptor that recognizes H. pylori infection and the dominant receptor that is intact with this bacterium. Furthermore, TLR2, another receptor-like TLR4 which is called the LPS receptor, and TLR5 (flagellin receptor) are also involved in innate response towards H. pylori infection [75].

In adaptive immunity, neutrophils initiate this immune response, then lymphocytes, plasma cells, and macrophages [76]. When H. pylori attacks the gastric mucosa, the adhesion of the bacteria to the outer layers of epithelial cells activates the host's immune system. This leads to the formation of gastric ulcers.

This bacterium produces numerous antigenic compounds, including heat-shock protein (HSP), urease, and lipopolysaccharide (LPS). Lamina propria macrophages can absorb these compounds, which stimulate T-cell activity [77].

2.4 interleukins

Interleukins, also known as IL, are a type of cytokine that is known to be expressed exclusively by leukocytes [78]. However, scientists have since discovered that numerous other cell types in the body also produce IL. They are essential for immune cell activation, differentiation, proliferation, maturation, migration, and adhesion. Moreover, they display both pro-inflammatory and anti-inflammatory properties [79]. As a result, the primary function of interleukins in inflammatory and immunological responses is to act as growth, differentiation, and activation modulators.

Interleukins are comprised of a vast array of proteins that, when bound to high-affinity receptors on the surfaces of cells, can trigger an assortment of cellular and tissue responses, so they possess both autocrine and paracrine capabilities. Cytokines regulate inflammatory and immune responses to infections and antigens; the production of interleukin is self-limiting. While the majority of interleukins are synthesized transiently because messenger RNA is unstable, these molecules rapidly exit the body after production.

Several interleukins can serve similar purposes; for example, B-cell differentiation is promoted by interleukin-4 (IL-4), IL-5, and IL-13. Interleukins frequently influence one another, like IL-1 stimulates lymphocytes to generate IL-2. External signals and high-affinity receptors regulate cytokine-induced cellular responses. Pathogens stimulate B-cells, which increases cytokine receptor production [80]. It is possible to utilize the measurement of interleukin levels in the human body as a diagnostic indication of the severity or advancement of a different illness, including cancer, cardiovascular disease, and neurological problems.

2.4.1 Interleukin-8 and gene polymorphism

Interleukin-8 is responsible for a crucial function in the body, which is the regulation of inflammation. Neutrophils go from the periphery to the inflammation site to serve as the first line of defense against this inflammation. There are numerous cell types capable of releasing IL-8, including lymphocytes, monocytes, macrophages, fibroblasts, and epithelial cells. It accomplishes this by enhancing neutrophil adhesion to endothelial cells and stimulating the exocytosis of neutrophil granules, which are both followed by the release of lysosomal enzymes. These two actions have a significant impact on the regulation of polymorphonuclear leukocyte activity. During an H. pylori infection, gastric epithelial cells will secrete IL-8; this is particularly true in the cag-pathogenicity-island-positive strain of H. pylori, which is one of the most important virulence factors. In addition, the levels of the IL-8 protein in gastric cancer are ten times higher than in ordinary stomach tissue, and they connect directly with the vascularity of the lesions [81]. By recruiting neutrophils and monocytes, elevated levels of IL-8 might intensify the inflammatory response to H. pylori . This can contribute to a more severe form of gastritis, which increases a person's risk of developing gastric cancer [82].

The IL-8 gene has three different types of polymorphisms that are rather common: -251 A/T, 396 T/G, and 781 C/T. In particular, an increased level of IL-8 production is linked to the presence of the A allele in the -251 A/T polymorphism [83].

2.4.2 Interleukin 17 (IL-17) and its role in H. pylori infection

The cytokine IL-17 may be subdivided into six distinct forms, labelled IL-17A through IL-17F. Because of the possible role that IL-17A (commonly known as IL-17) might have in the immune systems of mammals, this cytokine has been the focus of a significant amount of study. In a human stomach infected with H. pylori, IL-17 production is increased not only in the gastric mucosal cells but also in the lamina propria mononuclear cells (LPMC). The excretion of IL-8 by gastric LPMC cells decreased significantly when IL-17 synthesis was inhibited. Since gastric epithelial cells and LPMC can express IL-17 receptors, IL-17 is capable of acting on these cells to stimulate the generation of IL-8. After H. pylori was eradicated, the level of IL-17 expression decreased significantly. People infected with H. pylori and suffering from a gastric ulcer have an active site of IL-17 and IL-8 secretion in the mucosa of their stomach. Through its interaction with IL-8, IL-17 may promote the expansion of gastric ulcers. This may be attributed to the role IL-8 plays in neutrophil recruitment at the ulcer site [84].

The presence of combined cells Th17/Th1 through H. pylori infection has the potential to promote the colonization of the gastrointestinal tract by H. pylori; therefore, the inflammation occurs [85].

2.4.3 Interleukin 18 (IL-18) and its role in H. pylori infection

Interleukin-18, which is also known as IL-18, has come under examination as a cytokine in both innate and acquired immune responses. And it encourages the proliferation of Th1 cells, increases IFN, and increases the natural

killer cytotoxicity. The presence of IL-18 in the body is linked with chronic inflammation, autoimmunity, and a vast array of other infectious diseases [86]. Human IL-18 is encoded by a gene in the 11q22.2-q22.3 region of the chromosome, and the IL-18 promoter gene regulates its production and function.

Infection with H. pylori elevates IL-18, and the overexpression of IL-18 increases local production of interferon-gamma (IFN-) and cell-mediated responses from the stomach mucosa, both of which contribute to H. pylori -induced gastroduodenal disease. The overexpression of IL-18 is associated with H. pylori -caused gastroduodenal disease [87].

3. Conclusion

Helicobacter pylori is a highly specialized gastric pathogen whose persistence in the acidic gastric environment depends on urease activity, motility, and adhesin-mediated colonization's pathogenicity is mostly influenced by virulence factors, including CagA and VacA, which cause epithelial damage and provoke significant inflammatory responses.Interleukin-8 (IL-8) is pivotal in orchestrating inflammation by attracting immune cells to the gastric mucosa, hence leading to gastritis, peptic ulcer disease, and, in some instances, gastric cancers. Genetic variants in IL-8, especially the -251 polymorphism, may alter cytokine production and affect illness susceptibility and severity. Comprehending the intricate relationships among H. pylori, host immunological responses, and genetic predisposition is essential for formulating focused therapy methods and identifying patients at high risk for early intervention.

Also, Helicobacter pylori infection is closely associated with gastric cancer, mostly due to the overexpression of interleukin-8 (IL-8) in gastric epithelial cells and the surrounding tumor environment. Besides facilitating chemoresistance, IL-8 promotes tumor development, angiogenesis, and metastasis, underscoring its pivotal role in cancer progression. IN chronic gastritis, the heightened production of pro-inflammatory mediators, including interleukin-1β, interleukin-8, and cyclooxygenase-2, underscores the association between H. pylori -induced inflammation and the onset of gastric cancer. Targeting IL-8 is a viable therapeutic strategy, since modulating its activity may inhibit cancer growth and improve treatment outcomes.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Varon C, Azzi-Martin L, Khalid S, Seeneevassen L, Ménard A, Spuul P. Helicobacters and cancer, not only gastric cancer? Seminars in Cancer Biology. Elsevier; 2022. pp. 1138–1154.
2. Jacob ME. Spirilla IV: Helicobacter–the Spiral Microorganisms of the Gastrointestinal Tract and Liver. Vet Microbiol. 2022; 219–224.
3. 3. Thormann KM, Beta C, Kühn MJ. Wrapped up: The motility of polarly flagellated bacteria. Annu Rev Microbiol. 2022;76: 349–367.
4. Melito PL, Munro C, Chipman PR, Woodward DL, Booth TF, Rodgers FG. Helicobacter winghamensis sp. nov., a novel Helicobacter sp. isolated from patients with gastroenteritis. J Clin Microbiol. 2001;39: 2412–2417.
5. Van den Bulck K, Decostere A, Baele M, Driessen A, Debongnie J-C, Burette A, et al. Identification of non-Helicobacter pylori spiral organisms in gastric samples from humans, dogs, and cats. J Clin Microbiol. 2005;43: 2256–2260.
6. Vukojević J, Nikolić I, Kukić B, Bogdanović B, Nikin Z. Helicobacter heilmannii associated gastritis: case report. Arch Oncol. 2011;19: 73–75.
7. Ashaolu JO, Tsai Y-J, Liu C-C, Ji D-D. Prevalence, diversity and public health implications of Helicobacter species in pet and stray dogs. One Health. 2022;15: 100430.
8. Fan J, Jia Y, Xu D, Ye Z, Zhou J, Huang J, et al. Anaerobic condition induces a viable but nonculturable state of the PCB-degrading Bacteria Rhodococcus biphenylivorans TG9. Science of The Total Environment. 2021;764: 142849.
9. Cai Y, Liu J, Li G, Wong PK, An T. Formation mechanisms of viable but nonculturable bacteria through induction by light-based disinfection and their antibiotic resistance gene transfer risk: A review. Crit Rev Environ Sci Technol. 2022;52: 3651–3688.
10. Moreno-Mesonero L, Hortelano I, Moreno Y, Ferrús MA. Evidence of viable Helicobacter pylori and other bacteria of public health interest associated with free-living amoebae in lettuce samples by next generation sequencing and other molecular techniques. Int J Food Microbiol. 2020;318: 108477.
11. Lopes AI, Vale FF, Oleastro M. Helicobacter pylori infection-recent developments in diagnosis. World journal of gastroenterology: WJG. 2014;20: 9299.
12. Hortelano I, Moreno Y, Vesga FJ, Ferrús MA. Evaluation of different culture media for detection and quantification of H. pylori in environmental and clinical samples. International Microbiology. 2020;23: 481–487.
13. Sánchez-Alonzo K, Arellano-Arriagada L, Castro-Seriche S, Parra-Sepúlveda C, Bernasconi H, Benavidez-

Hernández H, et al. Temperatures outside the optimal range for helicobacter pylori increase its harboring within candida yeast cells. Biology (Basel). 2021;10: 915.

14. Rubin EJ, Trent MS. Colonize, evade, flourish: how glyco-conjugates promote virulence of Helicobacter pylori. Gut Microbes. 2013;4: 439–453.
15. FURMANČÍKOVÁ P, ŠŤÁSTKOVÁ Z, Navratilova P, BEDNÁŘOVÁ I, VOŘÁČKOVÁ MD. Prevalence and detection of Helicobacter pylori in raw cows' and goats' milk in selected farms in the Czech Republic. Journal of Food & Nutrition Research. 2022;61.
16. Kinoshita-Daitoku R, Kiga K, Miyakoshi M, Otsubo R, Ogura Y, Sanada T, et al. A bacterial small RNA regulates the adaptation of Helicobacter pylori to the host environment. Nat Commun. 2021;12: 2085.
17. Zarzecka U, Harrer A, Zawilak-Pawlik A, Skorko-Glonek J, Backert S. Chaperone activity of serine protease HtrA of Helicobacter pylori as a crucial survival factor under stress conditions. Cell Communication and Signaling. 2019;17: 1–18.
18. Su C, Bieniek K, Liao W, Constantino MA, Decker SM, Turner BS, et al. Comparison of motility of H. pylori in broth and mucin reveals the interplay of effect of acid on bacterium and the rheology of the medium it swims in. bioRxiv. 2020; 2020–2024.
19. Patwardhan MH. Heat sensitization of human enteric viruses by plant extracts and validation of their thermal inactivation by bacterial surrogates. 2019.
20. Delgado Carreño C V, Rojas B. Helicobacter pylori in water sources and food products: A constant public health problem. 2018.
21. Roesler BM, Rabelo-Gonçalves EMA, Zeitune JMR. Virulence factors of Helicobacter pylori: a review. Clin Med Insights Gastroenterol. 2014;7: CGast-S13760.
22. Chonwerawong M, Ferrero RL. Regulation and functions of inflammasome-mediated cytokines in Helicobacter pylori infection. Microbes Infect. 2017;19: 449–458.
23. Kao C-Y, Sheu B-S, Wu J-J. Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. Biomed J. 2016;39: 14–23.
24. Blankenstein T, Coulie PG, Gilboa E, Jaffee EM. The determinants of tumour immunogenicity. Nat Rev Cancer. 2012;12: 307–313.
25. Gaddy JA, Radin JN, Loh JT, Piazuelo MB, Kehl-Fie TE, Delgado AG, et al. The host protein calprotectin modulates the Helicobacter pylori cag type IV secretion system via zinc sequestration. PLoS Pathog. 2014;10: e1004450.
26. Pozdeev OK, Pozdeeva AO, Valeeva Y V, Gulyaev PE. Mechanisms of interraction of Helicobacter pylori with epithelium of gastric mucosa. I. Pathogenic factors promoting successful colonization. Russian Journal of Infection and Immunity. 2018;8: 273–283.
27. Chew Y, Chung H-Y, Lin P-Y, Wu D-C, Huang S-K, Kao M-C. Outer membrane vesicle production by helicobacter pylori represents an approach for the delivery of virulence factors caga, VacA and urea into human gastric adenocarcinoma (Ags) cells. Int J Mol Sci. 2021;22: 3942.
28. Foegeding NJ, Caston RR, McClain MS, Ohi MD, Cover TL. An overview of Helicobacter pylori VacA toxin biology. Toxins (Basel). 2016;8: 173.
29. Cover TL, Blaser MJ. Purification and characterization of the vacuolating toxin from Helicobacter pylori. Journal of Biological Chemistry. 1992;267: 10570–10575.
30. Qiu S, Liu J, Xing F. 'Hints' in the killer protein gasdermin D: unveiling the secrets of gasdermins driving cell death. Cell Death Differ. 2017;24: 588–596.
31. Yahiro K, Hirayama T, Moss J, Noda M. Helicobacter pylori VacA toxin causes cell death by inducing accumulation of cytoplasmic connexin 43. Cell Death Dis. 2015;6: e1971.
32. Keikha M, Ali-Hassanzadeh M, Karbalaei M. Association of Helicobacter pylori VacA genotypes and peptic ulcer in Iranian population: a systematic review and meta-analysis. BMC Gastroenterol. 2020;20: 1–11.
33. Atrisco-Morales J, Martínez-Santos VI, Román-Román A, Alarcón-Millán J, De Sampedro-Reyes J, Cruz-del Carmen I, et al. VacA s1m1 genotype and cagA EPIYA-ABC pattern are predominant among Helicobacter pylori strains isolated from Mexican patients with chronic gastritis. J Med Microbiol. 2018;67: 314.
34. Román-Román A, Martínez-Carrillo DN, Atrisco-Morales J, Azúcar-Heziquio JC, Cuevas-Caballero AS, Castañón-Sánchez CA, et al. Helicobacter pylori VacA s1m1 genotype but not cagA or babA2 increase the risk of ulcer and gastric cancer in patients from Southern Mexico. Gut Pathog. 2017;9: 1–12.
35. Ricci V. Relationship between VacA toxin and host cell autophagy in Helicobacter pylori infection of the human stomach: a few answers, many questions. Toxins (Basel). 2016;8: 203.
36. Chauhan N, Tay ACY, Marshall BJ, Jain U. Helicobacter pylori VacA, a distinct toxin exerts diverse functionalities in numerous cells: An overview. Helicobacter. 2019;24: e12544.
37. Djekic A, Müller A. The immunomodulator VacA promotes immune tolerance and persistent Helicobacter pylori infection through its activities on T-cells and antigen-presenting cells. Toxins (Basel). 2016;8: 187.
38. Waldum H, Fossmark R. Gastritis, gastric polyps and gastric cancer. Int J Mol Sci. 2021;22: 6548.

39. Cover TL, Blanke SR. Helicobacter pylori VacA, a paradigm for toxin multifunctionality. Nat Rev Microbiol. 2005;3: 320–332.
40. Nejati S, Karkhah A, Darvish H, Validi M, Ebrahimpour S, Nouri HR. Influence of Helicobacter pylori virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders. Microb Pathog. 2018;117: 43–48.
41. Chowdhury R. Host Cell Contact Induces Fur-dependent Expression of Virulence Factors CagA and VacA in H elicobacter pylori. Helicobacter. 2014;19: 17–25.
42. Inagaki T, Nishiumi S, Ito Y, Yamakawa A, Yamazaki Y, Yoshida M, et al. Associations between cagA, VacA, and the clinical outcomes of Helicobacter pylori infections in Okinawa, Japan. Kobe Journal of Medical Sciences. 2017;63: E58.
43. Baidya AK, Bhattacharya S, Chowdhury R. Role of the flagellar hook-length control protein FliK and σ28 in cagA expression in gastric cell–adhered Helicobacter pylori. J Infect Dis. 2015;211: 1779–1789.
44. Miftahussurur M, Yamaoka Y, Graham DY. Helicobacter pylori as an oncogenic pathogen, revisited. Expert Rev Mol Med. 2017;19: e4.
45. Wang D, Li Q, Gong Y, Yuan Y. The association between VacA or cagA status and eradication outcome of Helicobacter pylori infection: A meta-analysis. PLoS One. 2017;12: e0177455.
46. Zorah SM, Al-Oqaili NAD. Molecular identification of Helicobacter Pylori and virulence genes (CagA and VacA) in patients with gastritis in Iraq. AIP Conference Proceedings. AIP Publishing LLC; 2024. p. 020015.
47. Conteduca V, Sansonno D, Lauletta G, Russi S, Ingravallo G, Dammacco F. H. pylori infection and gastric cancer: state of the art. Int J Oncol. 2013;42: 5–18.
48. Kalali B, Mejías-Luque R, Javaheri A, Gerhard M. H. pylori virulence factors: influence on immune system and pathology. Mediators Inflamm. 2014;2014.
49. Okwadha GDO, Li J. Optimum conditions for microbial carbonate precipitation. Chemosphere. 2010;81: 1143–1148.
50. Schmalstig AA, Benoit SL, Misra SK, Sharp JS, Maier RJ. Noncatalytic antioxidant role for Helicobacter pylori urease. J Bacteriol. 2018;200: e00124-18.
51. Gu H. Role of Flagella in the Pathogenesis of Helicobacter pylori. Curr Microbiol. 2017;74: 863–869.
52. Fagoonee S, Pellicano R. Helicobacter pylori: molecular basis for colonization and survival in gastric environment and resistance to antibiotics. A short review. Infect Dis. 2019;51: 399–408.
53. Baj J, Forma A, Sitarz M, Portincasa P, Garruti G, Krasowska D, et al. Helicobacter pylori virulence factors—mechanisms of bacterial pathogenicity in the gastric microenvironment. Cells. 2020;10: 27.
54. Rhee K-H, Park J-S, Cho M-J. Helicobacter pylori: bacterial strategy for incipient stage and persistent colonization in human gastric niches. Yonsei Med J. 2014;55: 1453–1466.
55. Noto JM, Peek Jr RM. The gastric microbiome, its interaction with Helicobacter pylori, and its potential role in the progression to stomach cancer. PLoS Pathog. 2017;13: e1006573.
56. Testerman TL, Morris J. Beyond the stomach: an updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. World journal of gastroenterology: WJG. 2014;20: 12781.
57. Ranjbar R, Behzadi P, Farshad S. Advances in diagnosis and treatment of Helicobacter pylori infection. Acta Microbiol Immunol Hung. 2017;64: 273–292.
58. Cho J, Prashar A, Jones NL, Moss SF. Helicobacter pylori infection. Gastroenterology Clinics. 2021;50: 261–282.
59. Charitos IA, D'Agostino D, Topi S, Bottalico L. 40 years of Helicobacter pylori: a revolution in biomedical thought. Gastroenterol Insights. 2021;12: 111–135.
60. Eletto D, Vllahu M, Mentucci F, Del Gaudio P, Petrella A, Porta A, et al. TFF1 induces aggregation and reduces motility of Helicobacter pylori. Int J Mol Sci. 2021;22: 1851.
61. Pellegrino C, Michele R, Chiara M, Alberto B, Florenzo M, Antonio N, et al. From Sidney to OLGA: an overview of atrophic gastritis. Acta Bio Medica: Atenei Parmensis. 2018;89: 93.
62. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou J-M, Schulz C, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022;71: 1724–1762.
63. Zullo A, De Francesco V, Gatta L. Helicobacter pylori culture: from bench to bedside. Ann Gastroenterol. 2022;35: 243.
64. Macedo Silva V, Lima Capela T, Freitas M, Boal Carvalho P, Magalhães J, Cotter J. A "new" option in Helicobacter pylori eradication: High-dose amoxicillin dual therapy outperforms bismuth quadruple therapy in a high dual resistance setting. Helicobacter. 2023;28: e12962.
65. Sverdén E, Agréus L, Dunn JM, Lagergren J. Peptic ulcer disease. Bmj. 2019;367.
66. Borao Laguna C, Lanas A. Advances in the pharmacotherapeutic management of refractory peptic ulcers. Expert Opin Pharmacother. 2023.
67. Vaillant L, Oster P, McMillan B, Orozco Fernandez E, Velin D. GM-CSF is key in the efficacy of vaccine-induced reduction of Helicobacter pylori infection. Helicobacter. 2022;27: e12875.
68. Jaswanth K, Kumar K, Venkatesh P. A review on peptic ulcer. UPI Journal of Pharmaceutical, Medical and Health

Sciences. 2022; 19–26.
69. Castro R, Pimentel-Nunes P, Dinis-Ribeiro M. Evaluation and management of gastric epithelial polyps. Best Pract Res Clin Gastroenterol. 2017;31: 381–387.
70. Graham DY. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. Gastroenterology. 2015;148: 719–731.
71. Piscione M, Mazzone M, Di Marcantonio MC, Muraro R, Mincione G. Eradication of Helicobacter pylori and gastric cancer: a controversial relationship. Front Microbiol. 2021;12: 630852.
72. Vinasco K, Mitchell HM, Kaakoush NO, Castaño-Rodríguez N. Microbial carcinogenesis: Lactic acid bacteria in gastric cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2019;1872: 188309.
73. Kim J, Cho YA, Choi IJ, Lee Y-S, Kim S-Y, Shin A, et al. Effects of interleukin-10 polymorphisms, Helicobacter pylori infection, and smoking on the risk of noncardia gastric cancer. PLoS One. 2012;7: e29643.
74. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy, Asthma & Clinical Immunology. 2018;14: 1–10.
75. Pachathundikandi SK, Tegtmeyer N, Backert S. Masking of typical TLR4 and TLR5 ligands modulates inflammation and resolution by Helicobacter pylori. Trends Microbiol. 2023.
76. Rosales C. Neutrophils at the crossroads of innate and adaptive immunity. Journal of Leucocyte Biology. 2020;108: 377–396.
77. Chmiela M, Kupcinskas J. Pathogenesis of Helicobacter pylori infection. Helicobacter. 2019;24: e12638.
78. Sikora J, Smycz-Kubańska M, Mielczarek-Palacz A, Kondera-Anasz Z. Abnormal peritoneal regulation of chemokine activation—The role of IL-8 in pathogenesis of endometriosis. American journal of reproductive immunology. 2017;77: e12622.
79. Varadé J, Magadán S, González-Fernández Á. Human immunology and immunotherapy: main achievements and challenges. Cell Mol Immunol. 2021;18: 805–828.
80. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. Journal of Allergy and Clinical Immunology. 2016;138: 984–1010.
81. Heidari Z, Moudi B, Mahmoudzadeh-Sagheb H. Immunomodulatory factors gene polymorphisms in chronic periodontitis: an overview. BMC Oral Health. 2019;19: 1–15.
82. Prata MMG, Cavalcante PA, da Silva AVA, de Medeiros PHQS, de Assis Júnior EM, Reyes MA V, et al. Alanyl-Glutamine protects against damage induced by enteroaggregative Escherichia coli strains in intestinal cells. J Pediatr Gastroenterol Nutr. 2019;68: 190–198.
83. Saha R, Islam MA, Sattar ANI, Ahmed S. The Interleukin-8-251 A Allele is Associated with Increased Risk of Different Gastroduodenal Diseases in H. pylori Infected Bangladeshi Patients. Am J Infect Dis. 2016;4: 102–106.
84. Outlioua A, Badre W, Desterke C, Echarki Z, El Hammani N, Rabhi M, et al. Gastric IL-1β, IL-8, and IL-17A expression in Moroccan patients infected with Helicobacter pylori may be a predictive signature of severe pathological stages. Cytokine. 2020;126: 154893.
85. Dewayani A, Fauzia KA, Alfaray RI, Waskito LA, Doohan D, Rezkitha YAA, et al. The roles of IL-17, IL-21, and IL-23 in the Helicobacter pylori infection and gastrointestinal inflammation: a review. Toxins (Basel). 2021;13: 315.
86. Samarani S, Allam O, Sagala P, Aldabah Z, Jenabian M-A, Mehraj V, et al. Imbalanced production of IL-18 and its antagonist in human diseases, and its implications for HIV-1 infection. Cytokine. 2016;82: 38–51.
87. Zuo ZT, Ma Y, Sun Y, Bai CQ, Ling CH, Yuan FL. The protective effects of Helicobacter pylori infection on allergic asthma. Int Arch Allergy Immunol. 2021;182: 53–64.

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