

Review on Helicobacteriosis Associated Diseases

Dhary Alewy Almashhadany^{1*}, Hero Ismael Mohammed², Abdulmunem Dherar Abdullah Aljoborey³

¹Knowledge University, College of Science, Department of Medical Laboratory Science, Erbil 44001, Iraq; E-mail: dhary.alewy@knu.edu.iq

²Cihan University-Erbil, College of Science, Department of Biomedical Sciences, Erbil 44001, Iraq.

³ Knowledge University, College of Science, Department of Medical Microbiology, Erbil 44001, Iraq

Abstracts Helicobacteriosis is a bacterial infection caused by *Helicobacter pylori* (*H.pylori*)(HP). which was discovered in 1982 by Australian scientists Barry Marshall and Robin Warren, who were later awarded the Nobel Prize in 2005. Epidemiological evidence has shown that *H.pylori* colonizes the upper gastrointestinal tract(GIT), and the infection is one of the most common human bacterial pathogens worldwide, with 4.4 billion infected individuals in 2015, but the prevalence varies according to situation and hygiene principles. Since this first isolation, it has become apparent that this organism may be one of the most common bacterial pathogens of humans, and it is one of the risk factors for adenocarcinoma. Thus, it was categorized as a group 1 carcinogen in 1994 by the World Health Organization (WHO). New infections with *H.pylori* are thought to occur as a consequence of direct human-to-human transmission, via either an oral-oral or fecal-oral route or both. *H.pylori* has been detected in stool, saliva, vomitus, and gastric refluxate, the material that has been subject to reflux, principally stomach acid that has leaked up into the esophagus. Clinically, *H. pylori* infection in humans is related to chronic gastritis, peptic ulceration, duodenal ulcer, and gastric cancer in addition to mucosa-associated lymphoid malignancies. According to the World Health Organization (WHO) estimates available at that time, it was supposed that about 4.4 billion infected individuals in 2015 were infected with *H. pylori*. These estimations can vary and are subject to change over time as recent investigations and information become obtainable. The prevalence of *H. pylori* is complex and affected by several factors, comprising age, clinical outcomes, geographical location, and socioeconomic status. A higher incidence was reported in unhygienic and economically poor areas; the rate of *H. pylori* infection in Africa, South America, and Asia was significantly higher than that in Western Europe, North America, and Australia. However, the disease spectrum of *H. pylori* infection shows a wide range of clinical aspects, including gastrointestinal diseases and extra gastric manifestations. In this review, we have described the general scope of these diseases.

Keywords: *Helicobacter pylori*, Helicobacteriosis, Gastrointestinal diseases, Extra gastric diseases

1. INTRODUCTION

Helicobacters is one of the most common bacterial infections globally, caused by *Helicobacter pylori* (*H.pylori*)(HP). This bacterium is commonly found in the stomach and can cause several categories of gastrointestinal conditions, such as gastritis, peptic ulcers, and in some circumstances, stomach cancer [1-2].

For a long time, the human stomach was a germ-free organ where no microorganisms could survive due to the highly acidic environment of the stomach. This concept changed in 1982 when Warren and Marshall were capable to isolate *H. pylori* bacteria from gastric biopsies and found that the bacteria survived in patients with active chronic gastritis, gastric ulcer, or duodenal ulcer [3-4].

The probability that peptic ulcers could not be caused by spicy food, and not stress, or other factors, but because of bacteria, was a wonder to the scientific community, and it was challenging for Warren and Marshall to change the prevailing dogma. Subsequently, the Nobel Prize was conferred upon them in 2005 in recognition of their seminal contribution to the identification of *H. pylori* and its pivotal involvement in the pathogenesis of gastritis and peptic ulcer disease. [5-6].

However, *H. pylori* were first discovered in 1982 by two Australian researchers, Barry Marshall and Robin Warren. They observed curved bacteria in biopsy samples taken from the stomach lining of patients with gastritis and peptic ulcers. Marshall and Warren's discovery challenged this concept and finally led to the acceptance that *H. pylori* is accountable for many cases of gastric disorders [7-8].

The name "*Helicobacter pylori*" reflects the characteristics of the bacterium. "*Helicobacter*" refers to its helical or spiral shape, while "*pylori*" indicates its association with the pylorus, which is the lower part of the stomach that connects to the small intestine [9].

H. pylori has specialized adhesions (proteins) on its surface that help it adhere to the epithelial cells of the stomach lining, allowing it to establish an infection. It is characterized by a unique spiral (corkscrew-like) or helical shape, which helps in its penetration and to move and burrow into the mucus layer and attach the protective lining of the stomach, where it can colonize and cause inflammation. Also, it possesses several whip-like structures (flagella) that protrude from its surface. These flagella facilitate *H. pylori* to move in the highly acidic circumstances of the stomach by circling and pushing itself. Furthermore, one of the key virulence factors of *H. pylori* is its ability to produce the enzyme urease. The bacterium employs this enzyme to counteract the acidic conditions of the stomach by catalysing the hydrolysis of urea into ammonia and carbon dioxide. *Helicobacter pylori* (*H. pylori*) possesses a significant quantity of urease enzyme, which serves to mitigate the acidic conditions within the stomach by facilitating the release of ammonia. [10-12].

Helicobacteriosis frequency varies considerably among different populations and geographic regions. Normally, it is more common in developing countries with poorer hygiene and living conditions. On the contrary, the popularity tends to be lower in developed countries where sanitation and living conditions are better.

The prevalence of *H. pylori* infection is influenced by multiple contributing factors, including living conditions, geographical location, socioeconomic level, and personal cleanliness [13-14]. The primary source of *H. pylori* is infected individuals, however a significant proportion of these infections do not exhibit any symptoms [15]. In the clinical context, it has been observed that *Helicobacter pylori* infection in the human population is associated with chronic gastritis, peptic ulcers, duodenal ulcer, gastric cancer, as well as malignancies affecting the mucosa-associated lymphoid tissue [6, 15].

According to the World Health Organization (WHO) estimates available at that time, it was supposed that about 4.4 billion infected individuals in 2015 were infected with *H. pylori*. However, these estimations can vary and are subject to change over time as recent investigations and information become obtainable. Anyway, the prevalence of *H. pylori* is complex and affected by several factors, comprising age, clinical outcomes, geographical location, and socioeconomic status. A greater prevalence was observed in unsanitary and socioeconomically disadvantaged regions; the prevalence of *H. pylori* infection in Africa, South America, and Asia exhibited a statistically significant elevation compared to Western Europe, North America, and Australia [16-18].

Helicobacter pylori (*H. pylori*) is classified as a Group 1 carcinogen and serves as the causative agent for several stomach ailments, including gastritis, ulcers, and gastric cancer. It has been shown to affect almost 50% of the global population. *H. pylori* infection is influenced by various risk factors, including socioeconomic position, lifestyle choices, and dietary patterns [19-20].

Since this first isolation, it has become apparent that this organism may be one of the most common bacterial pathogens of humans. However, *H. pylori* is one of the risk factors for adenocarcinoma. Thus, it was categorized as a carcinogen in 1994 by the World Health Organization (WHO) [21-22].

The process of acquisition primarily takes place throughout the early stages of childhood, often facilitated by immediate family members. The act of prechewing food by the parent is a potential risk factor for the transmission of *H. pylori*, however its association remains questionable. There is a favourable correlation between childhood crowding within and outside the home and the frequency of *H. pylori*. Additional potential modes of transmission encompass contaminated water and food [23].

There are two hypotheses in the transmission pathways of *H. pylori*, the first of these hypotheses highlight the supposed significance of external reservoirs, commonly either drinking or environmental water sources or foodstuffs. Many epidemiological studies have identified particularly drinking water sources as a major risk factor for

H.pylori infection [24-25]. The second of the two hypotheses instead proposes that H.pylori is spread directly from person to person, typically within the family or close communities [26-27].

H.pylori infection varies greatly worldwide, with infection rates of more than 80% in some developing countries and below 20% in some developed countries [28-29]. In general, the frequency rate of H.pylori infection varies from 10% to 90%, depending on the age, geographic location, and socioeconomic status of the population[30-31]. Also, the prevalence of H.pylori infection varies between and within the population[32-33]. While the occurrence of H.pylori in Western societies is declining, the colonisation of the stomach by H.pylori continues to be prevalent in developing regions [34].

Special attention to the good news regarding H. pylori, the early diagnosis of H. pylori infection is essential to avoid the prevalence of the infection. Detecting and treating the infection early can prevent these complications from occurring or progressing. However, the World Gastroenterology Organization (WGO), in its 2023 guideline, recommended the minimum satisfactory eradication rate of more than 80% on an intention-to-treat basis using moderate [35-36].

Before we stated the diseases associated with H. pylori infection, the good news is that H. pylori infections can certainly be successfully treated with a combination of antibiotics and acid-reducing medicines [37]. Nevertheless, the spectrum of diseases caused by H. pylori infection encompasses a diverse array of clinical presentations, encompassing both gastrointestinal disorders and indications outside of the stomach. The general spectrum of these disorders will now be discussed below [38-39].

1. Gastrointestinal diseases

H. pylori infection is primarily responsible for the development of several disorders, including chronic gastritis, gastric ulcers, duodenal ulcers, and gastric adenocarcinomas [38, 40-41].

1.1. Gastritis

Gastritis refers to inflammation of the gastric mucosa. There are many causes of gastritis; most of which can be grouped as acute or chronic gastritis. Acute H.pylori infection causes gastritis and hypochlorhydria (means low stomach acid, particularly, low hydrochloric acid (HCl)); as well as symptoms such as vomiting and dyspepsia have been associated with acquirement [42]. Chronic infection with H.pylori can lead to gastric atrophy and intestinal metaplasia [43]. However, Clinical manifestations of acute gastritis comprise sour stomach or heartburn, and transient gastric suffering, which may lead to vomiting and, in more severe conditions, to hematemesis and bleeding [7].

1.2. Peptic ulcer disease (PUD)

Since the early 1980, there has been a radical shift in thinking concerning the cause of peptic ulcers. No longer is peptic ulcer believed to result from genetic stress, susceptibility, or dietary carelessness.

Much of the familial accumulation of peptic ulcers whose expansion was previously related to genetic causes is now supposed to be due to intra-familial infection with H.pylori rather than genetic susceptibilities [44]. However, the most common forms of peptic ulcer are duodenal and gastric ulcers. Anyway, Peptic ulcer disease is widespread, about 1 in 5 peptic ulcers is related to H. pylori infection, with most of the rest due to using nonsteroidal anti-inflammatory drugs (NSAID) [45].

1.3. GASTRIC CANCER

Infection with H.pylori appears to serve as a cofactor in some types of gastric carcinomas [46]. The disease is much more common in some countries and regions, principally Japan, Central Europe, the Scandinavian countries, South and Central America, the Soviet Union, China, and Korea; and is the major cause of cancer death worldwide, gastric adenocarcinoma is the second highest cause of cancer deaths worldwide [47].

H. pylori causes gastritis and peptic ulceration and it is an essential risk factor for gastric adenocarcinoma, the second maximum cause of cancer deaths globally. The acquisition of *Helicobacter pylori* (*H. pylori*) infection throughout early childhood has been well-documented as a recognised risk factor for the development and progression of stomach cancer [48].

H. pylori infection is highly related to gastric cancer risk, and this type of cancer differs from region to region and country to country. Although the prevalence rate of gastric cancer reduced in Western countries, it is still the second most prevalent cancer type and second cause of cancer-associated death worldwide [47, 49].

In the meta-analyses of randomized controlled trials and monitoring study has concluded that moderate indication recommends that *H. pylori* eradication therapy decreases the occurrence of gastric cancer in healthy persons, with an overall risk reduction of 46% [50].

1.4. Gastric lymphoma

Lymphoma is a cancer of the lymphatic system. Primary gastric lymphoma is a general term for a type of cancer that originates within the stomach, it comprises about 3-6% of all gastric malignancies [51]. *Helicobacter pylori* is intricately associated with the development of a low-grade lymphoma known as Mucosa-Associated Lymphoid Tissue (MALT). Lymphoid tissue is typically absent in the healthy stomach, but the presence of *H.pylori* infection can lead to the development of lymphoid aggregates. Superficial mucosa-associated lymphoid tissue (MALT) can potentially be resolved through the eradication and elimination of *H.pylori* [52].

2. Extra Gastric Diseases

Given the association of *H. pylori* with many gastric ailments, including gastroenteritis, gastroduodenal ulcers, and gastric cancer, it is imperative to promptly and effectively diagnose and treat *H. pylori* infection in order to prevent its dissemination [53].

In recent decades, there are several papers related to the topic of *H. pylori* infection with diseases localized outside the stomach have been reported, including neurodegenerative, cardiovascular, hematological, ischaemic heart, metabolic syndrome, diabetes mellitus, hepatobiliary diseases, non-alcohol fatty liver disease, and allergy disorders [4, 36, 54-58]. We summarized below the general scope of these diseases.

2.1. Iron Deficiency Anaemia

Iron deficiency is widely recognized as a prevalent dietary insufficiency, impacting around 500 million individuals worldwide [59]. Given the widespread presence of *H. pylori* bacteria, it is unsurprising that researchers have directed their efforts towards establishing a causal relationship between *H. pylori* infection and iron deficiency. The association between *Helicobacter pylori* and iron deficiency anaemia was initially established by Blecker and Renders (1991)[60] in their seminal work. The individual under examination, a 15-year-old Belgian, exhibited chronic active hemorrhagic gastritis attributed to *H. pylori* infection and iron deficient anaemia. Notably, the total resolution of the conditions occurred in the absence of iron supplementation upon successful eradication of *H. pylori* [4, 60-62].

2.2. Idiopathic Thrombocytopenic Purpura (ITP)

ITP is a blood disorder characterized by lower-than-normal platelet counts in the blood. Platelets are essential for blood clotting, and when their count is reduced, it can lead to an increased risk of bleeding or bruising. The symptoms of immune thrombocytopenia (ITP) might exhibit variability, encompassing manifestations such as facile bruising, little red or purple skin lesions known as petechiae, haemorrhaging gums, epistaxis, and in more severe instances, internal haemorrhage.

In the context of immune thrombocytopenia (ITP), the immune system erroneously recognises platelets as exogenous entities and generates antibodies that target and eliminate them. This immune response can be activated by several factors, but in many cases, the exact cause remains unknown. It can affect individuals of all

ages, but it is more prevalent in children and young adults. Some studies have suggested a relationship between *H. pylori* infection and ITP, probably due to the immune system's response to the bacterium affecting platelet destruction. The study conducted by Campuzano-Maya (63), confirmed that the frequency of *H. pylori* infection was considerably higher in patients with Idiopathic Thrombocytopenic Purpura (ITP) than in controls (90.6% vs. 43.8%, $P = 0.00006$) in the Colombian study. The systematic review reported by Stasi, Sarpatwari (64), proved that among 696 ITP patients receiving *H. pylori* eradication, 42.7% attained complete response (platelet count $\geq 100 \times 10^9/L$).

2.3. Vitamin B12 Deficiency

There is evidence suggesting a link between *H. pylori* infection and vitamin B12 deficiency, though the exact mechanisms are not fully understood. *H. pylori* itself requires vitamin B12 to grow. It has been suggested that the bacteria may participate with the host for presented vitamin B12, potentially reducing the amount of vitamin B12 obtainable for the host's use. Successful *H. pylori* removal has been linked to improvements in vitamin B12 levels, according to some study, which strengthens the connection between the infection and deficiency [65-66].

Several studies have been carried out that established a link between *H. pylori* infection and vitamin B12 malabsorption, it has been found that more than half (67.4%) of patients with *H. pylori* infection also have this deficiency. A study examining people afflicted with this illness has revealed a noteworthy correlation between *H. pylori* infection and vitamin B12 insufficiency [67-69].

2.4. Asthma and Allergy

It is important to note that the research findings on this topic have been mixed, and not all studies have found a consistent association between *H. pylori* infection and asthma. Some studies have suggested a potential inverse relationship between *H. pylori* infection and the development of asthma. However, the potential relationship between *H. pylori* infection and asthma, is not yet fully understood, and more studies are needed to clarify the nature of this relationship and its potential clinical implications [70-71].

2.5. Gastro-Esophageal Reflux Disease

Gastro-oesophageal reflux disease (GORD), alternatively referred to as gastroesophageal reflux disease (GERD), is a pathological illness characterised by the retrograde movement of stomach acid into the oesophagus. This occurrence gives rise to a range of symptoms including heartburn, regurgitation, and chest discomfort. About 15% of the general population is affected by gastro-oesophageal reflux (GOR) symptoms, with a detrimental effect on the quality of life among persons who experience them, in addition to an important economic load for the community [72].

It is primarily caused by a malfunctioning of the lower esophageal sphincter (LES), a muscle that separates the esophagus from the stomach. *H. pylori* is not a direct cause of GORD, there is some evidence suggesting a probable association between *H. pylori* infection and the progress of GORD. It can infect the stomach lining, leading to several gastrointestinal disorders, containing gastritis and peptic ulcers [73].

However, the relationship between *H. pylori* and GORD is complex and not fully understood. Some studies have suggested that *H. pylori* infection might lower the risk of developing GORD. This is thought to be due to the protective effect of *H. pylori*-induced gastritis, which reduces stomach acid production. Gastritis caused by *H. pylori* can lead to thinning (atrophy) of the stomach lining and a decrease in acid-producing cells, which could potentially reduce the severity of acid reflux. On the other hand, other research has proposed that *H. pylori* infection could increase the risk of GORD by affecting the function of the LES and promoting relaxation of the sphincter, thus contributing to acid reflux [74-76].

2.6. Diabetes mellitus

Diabetes is a metabolic condition that is distinguished by elevated levels of glucose in the bloodstream due to insufficient insulin production or impaired insulin utilisation by the body. It is mainly classified into type 1 diabetes, which is an autoimmune condition, and type 2 diabetes, which is associated with insulin resistance [77].

There has been some research into the potential relationship between *H. pylori* infection and diabetes, but the exact nature of this relationship is still not fully understood and remains a subject of ongoing investigation [78]

Several studies have indicated a potential association between infection with *H. pylori* and an elevated susceptibility to the development of type 2 diabetes. It's theorized that the infection might contribute to inflammation in the body, which could potentially impact insulin sensitivity and glucose metabolism, both of which are central factors in the development of type 2 diabetes [79-80].

2.7. Chronic Urticaria (CU)

H. pylori has been linked to a variety of conditions that can affect the skin such as Chronic urticaria (CU), generalized pruritus (itch), atopic dermatitis, systemic sclerosis, and aphthous ulceration [81-82]. However, a study conducted by Dennis, Mavura (83) revealed that the aetiology of Chronic Urticaria (CU) is often not adequately acknowledged. Several investigations have demonstrated that infection caused by *Helicobacter pylori* (*H. pylori*) has a substantial role in the development of chronic urticaria CU [83-84].

2.8. Neurological Disorders

The findings of recent investigations have indicated a potential association between *H. pylori* infection and specific neurological illnesses, including Alzheimer's disease and Parkinson's disease. However, the veracity of these findings remains a subject of ongoing debate. According to Dobbs, Dobbs (85), The potential correlation between the pathogenesis of Parkinson's disease and the detrimental impact of *H. pylori* on dopaminergic cells within the nervous system has been suggested. Furthermore, Tan, Mahadeva (86), highlighted that the presence of *H. pylori* in individuals with Parkinson's disease could potentially exacerbate the severity of motor symptoms due to gastrointestinal illness. Tseng, Li (59), has been verified that the eradication of *H. pylori* in individuals with Parkinson's disease resulted in enhancements in the efficacy of clinical manifestations and overall quality of life. [59]. In contrast, some other studies have failed, to find a causal association between the eradication of *H.pylori* and the clinical consequences of Parkinson's disease [87].

2.9. Cardiovascular Diseases

Although the primary effects of *H. pylori* are associated with the digestive system, there has been some research exploring probable relations between Helicobacteriosis and cardiovascular disorders [88].

Because the *H. pylori* infection cause chronic inflammation in the stomach lining, and inflammation is a key factor in the progress of atherosclerosis, and it's potential that systemic inflammation resulting from Helicobacteriosis could participate to cardiovascular problems [89].

Several investigations have indicated a potential association between infection by *H. pylori* and an elevated susceptibility to specific cardiovascular ailments, including atherosclerosis and various forms of heart disease. Nevertheless, the evidence is not consistently robust, and further investigation is required to definitively demonstrate a causal relationship between Helicobacteriosis and cardiovascular problems [90].

2.10. pathogenesis of several respiratory diseases

The initial epidemiological studies examining the correlation between *H. pylori* infection and respiratory illnesses have been substantiated by subsequent findings from animal models. These models have demonstrated that the presence of *H. pylori* in the gastric region may be linked to lung damage, as evidenced by heightened expression of

inflammatory markers and mediators associated with endothelial dysfunction [91]. Following this, the epidemiological studies have directed their attention towards examining the association between *Helicobacter pylori* infection and respiratory illnesses [25].

2.10.1. Helicobacteriosis and Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a persistent inflammatory respiratory condition distinguished by the presence of chronic bronchitis, which can result in the development of airflow limitation [25].

The study conducted by Rosenstock, Jørgensen (92), aimed to evaluate the correlation between *H. pylori* infection and several factors including lifestyle, chronic disease, body indices, and age of menarche in a sample of 2913 adults. The researchers established a greater prevalence of chronic bronchitis among women who tested positive for *H. pylori* antibodies in comparison to women who were not infected with the bacterium.

2.10.2. Helicobacteriosis and Lung Cancer

Lung cancer is a significant public health concern and stands as the primary contributor to global cancer mortality. The primary cause of this condition is the inhalation of environmental carcinogens. However, it is worth noting that a significant proportion of cases, ranging from 10% to 15% in Western countries and up to 25% in Asia, are identified in individuals who have never smoked [93].

In the study conducted by Philippou, Koursarakos (94), and by Najafizadeh, Tafti (95), has provided evidence to support the conclusion that there is no statistically significant correlation between *H. pylori* infection and the development of lung cancer.

In contrast, alternative case-control investigations have demonstrated markedly elevated prevalence rates of seropositivity for antibodies targeting *H. pylori* among individuals afflicted with lung cancer, as compared to the control group [96-97].

2.10.3. Helicobacteriosis and Tuberculosis

Although both Helicobacteriosis and TB are bacterial infections, they are transmitted through different routes. *H. pylori* primarily infects the stomach and is transmitted through direct contact, contaminated, food, or water, while TB primarily affects the lungs and is transmitted through the air [53, 98].

According to the findings of Mitchell, Li (99) there appears to be a potential correlation between a prior occurrence of active pulmonary tuberculosis and the presence of *Helicobacter pylori* infection in the southern region of China. Contrarily, Sanaka, Kuyama (100), reported contrasting findings in a case-control research utilising serology as a diagnostic tool.

Furthermore, Tsang, Lam (101), asserted that there were no discernible disparities in the seroprevalence of *H. Pylori* between individuals who were in good health and those who were afflicted with tuberculosis.

Conclusions

Throughout this review, we concluded that *H. pylori* has harvested a great deal of concern because it is a widespread and problematical pathogen, with 4.4 billion infected individuals in 2015. Person-to-person transmission is thought to occur through the oral–oral, fecal–oral, gastric–oral, or sexual routes. There are two routes of transmission, the first is direct routes, which include oral-oral, gastro-oral, fecal-oral, and sexual routes; while the second comprises drinking of polluted water, consumption of contaminated food, and using polluted kitchen instruments.

Helicobacteriosis is commonly infecting the stomach lining and can cause gastritis, peptic ulcers, and other gastrointestinal manifestations. In recent decades, there are several papers related to the topic of *H. pylori* infection with extra gastrointestinal complications, localized outside the stomach have been reported, including metabolic

syndrome, diabetes mellitus, cardiovascular, neurodegenerative, hematological, ischaemic heart, hepatobiliary diseases, non-alcohol fatty liver disease, as well as allergy.

Therefore, in this review, we have described the general scope of these diseases, comprising gastrointestinal disorders, as well as extra gastrointestinal complications. Considering that the understanding of complications connected with Helicobacteriosis infection is significant for the prevention and early intervention of this disease, which is the key to reducing the risk of Helicobacteriosis complications.

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