

## Extragastric Manifestations of *Helicobacter Pylori* Infection: A Commentary

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### Introduction

*Helicobacter pylori* (Hp) is characterized as a gram-negative bacterium with microaerophilic metabolism, flagellated and helix-shaped that affects approximately 50% of the world population and, in some regions, this rate can exceed 80% [1,2]. Hp infection is well known to infect the epithelial tissue of the stomach, being involved with development of many stomach diseases, including gastric carcinoma [3,4]. However, less frequently, this bacterium might also be involved in the development of extragastric disorders, such as manifestations in the gastrointestinal tract, except stomach, autoimmune, dermatological, ophthalmic and cardiac diseases, in addition to neurological, respiratory and endocrine diseases [5,6]. The article titled "*Helicobacter pylori* infection: beyond gastric manifestations" shows these possibilities [7].

### Extragastric Manifestations: Manifestations of the Gastrointestinal System, Except Stomach

Inflammatory Bowel Disease (IBD), as Crohn's Disease (CD) and Ulcerative Colitis (UC), may offer a negative relationship with the infection, and some systematic reviews confirm the low prevalence of IBD in Hp positive patients, along with a positive CagA profile in these cases [8,9]. Thus, in this scenario, Hp gastric infection appears as a protective factor, since infected patients have less chance of progressing to CD or UC [10,11] and the severity of the disease can also be reduced by the infection [12]. Besides, it was also observed that gastritis by Hp infection is less often in children with IBD [13]. There are some mechanisms that explain this protection: The release of Interleukin (IL)-18 and IL-10 and decrease in the maturation of antigen-presenting cells can reduce intestinal inflammation [14]. Yet, the role of the bacterium in Gastroesophageal Reflux Disease (GERD) remains uncertain, given that depending on

the affected site, gastritis can increase or reduce acid secretion. According to what is described in the article, hyperacidity worsens GERD, while hypoacidity offers protection, and Hp cytotoxin-associated gene A (CagA) seems to play a role in this outcome. A study reported that patients with both GERD and peptic ulcers (PUs) had a higher prevalence of the infection than patients without PUs [15]. Therefore, Hp infection is capable of influencing the course of some diseases, as well as protecting patients in certain situations.

On the other hand, Hp-positive patients may have a worse prognosis in some diseases, such as Non-Alcoholic Fatty Liver Disease (NAFLD) [16,17]. These patients have increased production of Tumoral Necrosis Factor and C-reactive Protein, which enhances insulin resistance and, consequently, favors the disease. Furthermore, the infection can also reduce the production of adiponectin, a molecule that inhibits fatty acid deposition [18] and influence the release of pro-inflammatory cytokines, as well as markers, which contributes to the onset of the inflammatory status and worse prognosis. Reduced adiponectin levels favor the development of diabetes mellitus, metabolic syndrome and cardiovascular diseases, such as atherosclerosis [19]. Thus, this bacterium may be associated with other diseases of a metabolic nature and accumulation of fat in the body. However, further studies are needed to better understand these mechanisms. In addition, the connection between Hp and inflammation, hepatic fibrosis and necrosis, which contributes to carcinogenic processes, such as hepatic carcinoma, is also possible [20]. Anyway, according to the commented manuscript, bacterial translocation in the biliary tract can lead to direct tissue damage. Chronic inflammation of this tissue affects the acid secretion and leads to reduction of the dissolvability of calcium salts in bile, which predisposes to the formation of gallstones, and further cholelithiasis and cholecystitis [21], with Hp in bile being a risk factor for the second one.

B12 deficiency is also associated with this bacterium. According to the manuscript, regardless of gastric atrophy and dyspepsia, positive patients have reduced levels of cobalamin [7]. Several studies show that the malabsorption of food-cobalamin has been reported in cases of Hp gastritis [22,23]. As a result, the Maastricht V / Florence Consensus Report recommends screening for Hp patients with deficiency of this vitamin [24]. A study showed an association between lower levels of B12 vitamin and positive Hp patients, which has a 4.2 times greater risk of having low levels of cobalamin, when compared to healthy individuals [25]. Furthermore, the association of Hp infection and iron deficiency anemia, independently of tissue damage and bleeding, has been confirmed [26,27]. In this sense, it is recommended that infected patients undergo eradication therapy in cases of iron deficiency anemia, given that a bacterium is capable of using the host's iron, which decreases its bioavailability. As an additional factor, these individuals usually have higher levels of pro-inflammatory cytokines, favoring anemia. Moreover, it has been suggested that there is a relationship between iron deficiency and growth disorders in children and adolescents, which reveals the need to screen for Hp in children with unexplained anemia and growth disorder [24,28].

## **Extragastric Manifestations: Dermatological, Ophthalmic, Allergic and Respiratory Diseases**

### **Dermatological and ophthalmic diseases**

Hp infection can also cause autoimmune skin diseases. Rosacea, psoriasis, alopecia areata, urticaria and idiopathic thrombocytopenic purpura have been identified in Hp infection [6]. A possible explanation for the emergence of these autoimmune diseases is a dysregulation of the immune system in response to Hp infection, which can lead to loss of tolerance to autoantigens [29]. Furthermore, Hp cytokines can cause early stress-induced senescence of skin cells, leading to inflammatory skin diseases [28].

Regarding autoimmune diseases, the studies addressed in the article bring positive associations for Hp, which produces antigens that mimic platelet membrane proteins. This process leads to the autoimmune effect and clinical picture of idiopathic thrombocytopenic purpura. In addition, some factors, as an improvement in platelet counts of patients who eradicated the bacteria with antibiotic therapy, are still being studied and evaluated [30].

The manuscript also showed a possible association of psoriasis and its severity with the intensity of the bacterial infection. The disease is dermatological in nature and clinically presents with erythematous, papular, and scaly lesions. The pathogenesis remains uncertain, but there are some possibilities. One of them is the chronic degree of inflammation generated by the microaerophilic microorganism, which produces substances

that induce the immune system more intensely. Furthermore, the intermediation of IL-6 release by Hp may be associated, as well as the production of IL-8 by Hp CagA, which is a chemotactic factor for immune cells and is also involved in the pathogenicity process of psoriasis [6,31,32].

Even though alopecia areata is a condition associated with various organic diseases or psychiatric factors, its relationship with the bacteria is much debated. Some studies have reported a prevalence of Hp infection in patients with this type of alopecia, along with an improvement in the condition after antibiotic treatment for the infection. However, these studies still show some limitations in the management of the variables involved and, therefore, further investigations are needed [6,32].

Urticaria is another idiopathic dermatological disorder that causes skin rash, itching and papules. It is also the target of studies to determine possible correlations with the bacterium, but there is great controversy among researchers. In the article, there are references that positively and negatively supplant the interaction with Hp. In other situations, such as in bullous immune diseases, there is consistent evidence of an increased presence of antibodies to Hp, as well as infections, then in the control group, which confirms the relationship between diseases and the presence of the bacterium [6,32].

Despite this, some studies highlight the lack of evidence to prove a strong association between Hp, dermatological, autoimmune manifestations and their mechanism [33,34].

Based on the manuscript, some ophthalmologic diseases have also been associated with Hp infection, such as glaucoma, central serous chorioretinopathy, blepharitis, and dry eye. However, studies and evidence are still controversial [35,36,37].

Its expression occurs due to a systemic inflammatory reaction induced by cytokines that are able to release vasoactive and proinflammatory substances [20]. This process can provoke oxidative stress, mitochondrial dysfunction, damage to DNA, and, finally, apoptosis [37-39]. Blepharitis presents as an eyelid inflammation, with oily particles and bacteria covering the eyelid margin [40]. Rosaceablepharitis clinical signs include flushing, persistent erythema, papules and pustule, and sprays of vessels, while seborrheic blepharitis includes greasy-looking scales, crusts, increased redness, and cutaneous color variability [40,41]. Central serous chorioretinopathy expresses acute and serous detachment of the sensory retina in the macular region [42,43]. Dry eye disease occurs when tears provide insufficient lubrication to eyes, characterized by discomfort, visual disturbance, and tear film instability [44,39]. Glaucoma is a progressive optic neuropathy, with degeneration of the optic nerve and visual field damage [45]. Regarding its physiopathology, apoptosis occurs mainly in retinal ganglion cells and axonal loss within the optic nerve, which results in

elevated intraocular pressure (IOP) [46,47]. Another study analyzed the relationship between Hp infection, dry eye, and Sjogren's syndrome, which was significantly higher in the Hp positive group [48].

### Allergic and respiratory diseases

According to the manuscript, Hp infection can act as a protective factor, mostly related to CagA positivity [49,50]. Thus, the efficiency of Hp infections in reducing allergic processes and asthma occur due to its interference in Th1 and Th2 lymphocytes proportion [50-52]; there is also a PD-L1 and IFN- $\gamma$  suppression mechanism, eosinophil-mediated [48], that happens as a result of the bacterium's influence in dendritic cells (DC) through NLRP3 activation, which leads to a TLR2 / NLRP3 / IL-18 stimulation and the raising of regulatory Foxp3 + T lymphocytes, increasing allergic asthma immunotolerance [52]. Otherwise, some studies indicate that the depletion of DCs might increase the inflammation of the airways by suppressing ILC2-mediated airway hyperreactivity [52,53].

Hp is also capable of decreasing asthma inflammation through the reduction of heat shock protein 70 expression, an important stimulatory factor for antigen presentation [54], as a result of the stomach hormone alterations that affect the autonomic nervous system [55].

Research shows that Hp without type 4 secretion systems are not able to influence Th1 via eosinophils, failing to present the protective effect [51].

Concerning age influence in patients with asthma and allergic cough, a clinical observational study related that patient with <40 years old infected with Hp presented lower levels of atopy and immunoglobulin E in comparison to those who do not have the bacterium [56]. Also, younger patients who presented with Hp infection, showed a lower risk of developing respiratory disease [55].

The development of chronic obstructive pulmonary disease and chronic bronchitis, linked to positive Hp CagA infections, demonstrated twice as much pathogenicity, when compared to healthy patients and those without the factor. The increased risk of diseases may be correlated to the action of IL-1, IL-8 and tumor necrosis factor that are released during the infection and acts on the respiratory tissue [57].

### Extragastic Manifestations: Neurological, Cardiac and Vascular and Endocrine Diseases Neurological Disease

The manuscript showed a positive relation between the infection by Hp and the commitment of the nervous system. The immune response to Hp provides release of cytokines, chemokines, free radicals and pro-inflammatory factors that

arecapable of stimulating a systemic inflammation that can lead to neurotoxicity through axon and neuron damage, besides destruction of the blood-brain barrier.

Studies have demonstrated an increased risk of Parkinson's disease in Hp-positive patients, while the eradication of the bacterium doesn't seem to contribute to the reduction of the risk [58]. The overproduction of interleukin 17 (IL-17) and interferon-gamma (INF- $\gamma$ ) release can be related to reduced hippocampal neurogenesis and destruction of the myelin sheath, respectively. This neuroinflammation has been associated with the emergence of neurological symptoms, being a possible risk factor for dementias, such as Parkinson's disease [59]. Furthermore, Hp was also related to Parkinson's treatment impairment and maintenance of the motor symptoms in infected people, by reducing intestinal motility and delaying gastric emptying, which decreases the L-3,4-dihydroxyphenylalanine intestinal absorption, one of the main drugs used in the treatment. The bacterium is able to modify the gastric pH and alter the bioavailability of this drug through the liberation of the pro-inflammatory cytokine-1b [60].

Chronic atrophic gastritis caused by Hp can reduce the absorption of nutrients that are necessary for the proper functioning of the brain, such as folic acid and vitamin B12, which can lead to excessive protein digestion and neuronal degeneration, leading to Alzheimer's. Furthermore, possible cross-reactions between bacterial antigens and neuronal structures can provoke dementia conditions [61]. Reduced levels of vitamin B12 in the body are related to the development of Alzheimer's disease and higher risk of stroke, due to the increase in homocysteine levels, which contribute to an excess of free radicals, that damage blood vessels and cell membranes. Besides, hypovitaminosis can lead to the development of optic neuropathies, sensorimotor polyneuropathy and cognitive impairment, since it causes changes in the white and gray matter of the brain [5].

The Hp was responsible for causing the misfolding of a protein called tau, which is one of the proteins related to the emergence of Alzheimer's disease. In this sense, the bacterium can change the protective function of some genes in the nervous system through the action of the peptide Hp (2-20), which can change the anti-inflammatory capacity of ANXA1 gene and protective capacity of MTRNR2L2, APOE genes, stimulating neurological damages [62]. Another finding present in patients with Alzheimer's disease infected by Hp was the alteration of the blood-brain barrier. The chronic infection can stimulate a Th2 response, which is able to produce autoantibodies that are related to detection and reaction against the barrier components, causing its disruption and proportioning both the accumulation and reduction of the depuration of amyloid- $\beta$ , peptide related to Alzheimer's pathophysiology, in the brain [63].

Moreover, this mimicry between antigens of the bacterium and the components of the nervous system can contribute to autoimmune damages to host structures, and the emergence of Guillain Barre Syndrome (GBS). Studies have demonstrated a higher prevalence of IgG antibodies against Hp in the cerebrospinal fluid of people with GBS than in individuals without the syndrome, indicating that the infection and the GBS are possibly correlated [64]. The antibodies IgG against the vacuolating cytotoxin A have been related to the cross-reaction with components of the Nervous System, causing the demyelination of motor neurons and involving proximal regions of peripheral nerves [65]. On the other hand, bacterial eradication was related to the improvement of cognitive functions [61].

Lastly, researches have also reported a possible link between strokes and Hp infection, especially with strains that carry CagA, since during the immune response, there might occur a liberation of inflammatory molecules that are able to stimulate a coagulation cascade and platelet production and, consequently, increase the risk of ischemic stroke [66]. Corroborating, studies have demonstrated that after the Hp eradication, the levels of some risk factors to the stroke such as fibrinogen and low-density lipoprotein-cholesterol, were lower than in control patients [65].

Therefore, the assessment of sequelae of Hp infection, as well as its early treatment is extremely important to prevent the emergence of neurological impairments, which may contribute to health promotion worldwide and reduce the burden on health services, taking into account that this bacterium is extremely prevalent throughout the world.

### Cardiac and vascular diseases

The manuscript demonstrated that the presence of inflammatory factors related to the response to Hp could be related to the emergence of cardiovascular symptoms. Atherosclerosis is a multifactorial disorder in which inflammatory diseases, including chronic bacterial infections, could play a major role. [61] Infectious agents can induce atherosclerosis by increasing the levels of some circulating cytokines, such as interleukin-1 (IL-1), the IL-1 $\beta$  receptor and its haplotypes, interleukin-6 (IL-6) and the like, leading to stimulation of the immune system system-mediated responses, i.e., inflammation [68].

Yet, another finding evidenced a strict correlation between increased serum levels of some pro-inflammatory cytokines (IL1 $\beta$ , IL-8, TNF $\alpha$ ) and cardiovascular risk factors [69].

A recent study showed that CagA potentially stimulates foam production within macrophages, contributing to increased atherosclerotic plaque and arterial dysfunction [70].

The other study evaluated the prevalence of Hp positive CagA-strains in patients with CAD. Their studies have

demonstrated a higher prevalence of Hp CagA-positive strains in patients with CAD, compared with the control group (52% vs 43% or 43% vs 17%) [71].

Coronary artery diseases (CAD) are a major cause of disability and death worldwide [72]. The pathogenetic basis of the possible association between CAD and Hp infection may also reside in the existence of antigenic mimicry phenomena between bacterial peptides and some substances contained in the cardiac muscle and coronary wall [73].

In a meta-analysis on the association between Hp and coronary heart disease (CHD) risk, involving studies published from 1992 to 2014, it demonstrated that Hp infection increased the risk of CHD by 11% (RR 1.11; CI 1.01-1.22), especially in patients with a follow-up period of 5 years [74]. Concerning possible pathogenic mechanisms, another study showed not only a higher prevalence of Hp infection in patients with CHD but also a higher production of anti-Hp HspB IgG cross-reacting with human Hsp-60, a well-known risk factor for cardiovascular diseases (CVD) [75].

Thus, Hp infection may be another aggravating factor to cardiac and vascular diseases worldwide, in addition to various factors, such as the social determinants in health, contributing to the increased prevalence of non-communicable chronic diseases.

### Endocrine disease

The infection by Hp has been related to endocrine diseases. A study conducted in a population of Cameroon reported a higher prevalence rate of infection in diabetic patients [76]. Besides, it has been related that infected people can present higher rates of metabolic syndrome than those uninfected [77]. Studies have also showed that Hp infection has been indirectly related to control of energy capture and impact on body weight and metabolism, since it is related to the alteration of the gut microbiome, which contributes to the stimulation of gastric acid secretion, through increased production of gastrin, and further impact on the production of ghrelin and leptin, hormones related to appetite regulation [78].

Furthermore, studies with Asian patients demonstrated that CagA-positive Hp strains could provoke impairments in the glycemic control of people with type 2 Diabetes Mellitus [79]. In addition, some works have found higher seropositivity to Hp in diabetic patients, when compared to a non-diabetic population, which demonstrates that, in the first public, Hp was related to an increase of insulin resistance, possibly associated with chronic inflammation caused by the infection and alteration in the normal secretion of the gastric hormones [80]. On the other hand, the bacterium is also capable of favoring insulin resistance through the positive regulation of the suppressor of cytokine signaling 3 (SOCS3) and the c-Jun expression, both related to the suppression of miR-203

[81]. Such facts reinforce what was previously exposed in the manuscript, which demonstrates that Hp would be related to alterations in glycemic control and increase of glycosylated hemoglobin A. However, there are limitations that make it difficult to properly assess the relation between Hp and Diabetes Mellitus, since, often, variables such as the patient's economic status and age are not detailed in many studies [79].

## Conclusion

With what is exposed in this manuscript and in "Infection by *Helicobacter pylori*: beyond the gastric manifestations", it is possible to realize the wide spectrum of diseases that are, somehow, correlated to *Helicobacter Pylori*, and see the several occurrences and relationships it can exert on the host, both as a protective or pathogenic factor. According to the manuscript, an Hp infection can influence the functioning of the gastrointestinal, cardiovascular and nervous system, which can lead to hematological, autoimmune, dermatological, allergic, respiratory, endocrine and cardiovascular disorders and neurological conditions.

However, the material present in the literature needs to be improved, especially with regard to dermatological and ophthalmological diseases. Therefore, there is a need for larger and more complex studies, making the results more specific, relevant and reliable, enabling better explanations and understandings about the pathogenesis of diseases and its correlation to Hp infection.

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