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ABOUT COVER

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Helicobacter pylori infection: Beyond gastric manifestations

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Abstract

Helicobacter pylori (*H. pylori*) is a bacterium that infects more than a half of world's population. Although it is mainly related to the development of gastroduodenal diseases, several studies have shown that such infection may also influence the development and severity of various extragastric diseases. According to the current evidence, whereas this bacterium is a risk factor for some of these manifestations, it might play a protective role in other pathological conditions. In that context, when considered the gastrointestinal tract, *H. pylori* positivity have been related to Inflammatory Bowel Disease, Gastroesophageal Reflux Disease, Non-Alcoholic Fatty Liver Disease, Hepatic Carcinoma, Cholelithiasis, and Cholecystitis. Moreover, lower serum levels of iron and vitamin B12 have been found in patients with *H. pylori* infection, leading to the emergence of anemias in a portion of them. With regards to neurological manifestations, a growing number of studies have associated that bacterium with multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Guillain-Barré syndrome. Interestingly, the risk of developing cardiovascular disorders, such as atherosclerosis, is also influenced by the infection. Besides that, the *H. pylori*-associated inflammation may also lead to increased insulin resistance, leading to a higher risk of diabetes mellitus among infected individuals. Finally, the occurrence of dermatological and ophthalmic disorders have also been related to that microorganism. In this sense, this minireview aims to gather the main studies associating *H. pylori* infection with extragastric conditions, and also to explore the main mechanisms that may

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explain the role of *H. pylori* in those diseases.

Key words: *Helicobacter pylori*; Extragastric; Neurological; Cardiovascular; Autoimmune; Ophthalmic; Diabetes; Timeline; Treatment

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Core tip: *Helicobacter pylori* is a bacterium that is known to infect the gastric environment and to be related to gastroduodenal diseases, including peptic ulcer and gastric adenocarcinoma. However, since the 80s the relationship between this infection and manifestations that affect not only the gastric system has been studied, such as inflammatory bowel disease, iron and B12 deficiency, non-alcoholic fatty liver disease, hepatic carcinoma, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Guillain-Barré syndrome. In this sense, this study made a survey of these manifestations and their physiopathology.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that inhabits the gastric environment of 60.3% of the world population, and its prevalence is particularly high in countries with inferior socioeconomic conditions, exceeding 80% in some regions of the globe^[1]. This phenomenon occurs, among other reasons, due to the unsatisfactory basic sanitation and high people agglomerations observed in many underdeveloped nations, scenarios that favour the oral-oral and fecal-oral transmissions of *H. pylori*^[2]. Another possible transmission route of this pathogen currently being discussed is the sexual route^[3], since people with *H. pylori*-positive sexual partners have higher infection rates than control groups. It is well established that this microorganism is mainly related to the development of gastroduodenal disturbances, of which stand out peptic ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma^[4-6]. However, since the 1980s, growing evidence have associated such infection with several extragastric manifestations (Figure 1)^[7].

In that context, *H. pylori* infection seems to influence the onset and the severity of diseases from multiple organ systems, behaving as a risk factor for a number of disorders but also as a protective agent against some conditions^[8]. Regarding the main diseases that affect organs other than the stomach in the gastrointestinal tract (GIT), the *H. pylori* infection appears to be associated with inflammatory bowel disease (IBD), gastroesophageal reflux disease (GERD), non-alcoholic fatty liver disease (NAFLD), hepatic carcinoma, cholelithiasis, and cholecystitis^[7]. Besides that, serum vitamin B12 and iron deficiencies are known to be worsen or even caused by *H. pylori* infection. In addition, ocular, dermatological, metabolic, cardiovascular, and neurological diseases are also related to that microorganism^[8,9].

Given the background, this minireview aimed to compile evidence supporting the main associations between *H. pylori* infection and extragastric diseases (Figure 2), as well as to gather information on the supposed mechanisms that may link that bacterium to manifestations occurring in organs far from their primary infection site (Table 1)^[10]. The publications with the highest level of evidence found for each non-gastroduodenal manifestation were selected and listed at Table 2.

EXTRAGASTRIC MANIFESTATIONS

IBD

One of the most studied conditions in gastroenterology field, IBD is a set of chronic disorders that affects the digestive tract and includes Crohn's disease (CD) and

Table 1 Non-gastric manifestations of *Helicobacter pylori* and their suggested mechanisms of pathophysiology

Non-gastric manifestation	Mechanisms of pathology suggested to be correlated
Allergic diseases	Hygiene hypothesis ^[9,96]
Alzheimer's disease	Vitamin B12 deficiency leading to increased concentrations of homocysteine ^[109] Anormal hyperphosphorylation of the TAU protein caused by <i>H. pylori</i> infection ^[109] ApoE polymorphism ^[110]
Asthma	Treg pattern, suppressing Th-2-mediated allergic response ^[94]
Atherosclerosis and myocardial infarction	Stimulation of foam production inside macrophages, contributing to the magnification of the atherosclerotic plaque and arterial dysfunction ^[122]
B12 deficiency	Still to be clarified, but proven to be independent of gastric atrophy and bleeding that impair their dietary absorption ^[49]
Cholelithiasis	Presence of <i>H. pylori</i> infected bile ^[43,44]
Coronary arterial disease/systemic arterial stiffness	Increased levels of homocysteine ^[132] .
Gastroesophageal reflux disease	Hyperacidity ^[25]
Diabetes mellitus	Increased cytokine production; phosphorylation of serine residues from the insulin receptor substrate ^[136]
Hepatic carcinoma	Inflammatory, fibrotic and, consequently, necrotic process ^[37,38]
Idiopathic thrombocytopenic purpura (ITP)	CagA may stimulate the synthesis of anti-CagA antibodies that cross-react with platelet surface antigens causing ITP ^[74,75]
Inflammatory bowel disease	Reduced intestinal inflammation through release of IL-18 and development of FoxP3-positive regulatory T cells ^[16-18] Neutrophil-activating protein reducing inflammation through Toll-like receptor 2 and IL-10 stimulation ^[19,20]
Iron deficiency anemia	Still to be clarified, but proven to be independent of gastric atrophy and bleeding that impair their dietary absorption ^[49] Relationship with growth disorders in children ^[52,53]
Multiple sclerosis	Hygiene hypothesis ^[9] Inhibitory induction of <i>H. pylori</i> over the Th1 and Th17 immune response ^[103]
Non-alcoholic fatty liver disease	<i>H. pylori</i> induced insulin resistance ^[32] Reduced production of adiponectin ^[33] Liver inflammation ^[34,35]
Ophthalmic manifestations	Systemic inflammatory status; increased oxidative stress; mitochondrial dysfunction; damage to DNA ^[82]
Parkinson's disease	Increased synthesis of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ^[118] Reduced levodopa absorption ^[118]

H. pylori: *Helicobacter pylori*; CagA: Cytotoxin-associated gene A.

ulcerative colitis (UC)^[11]. Although the mechanisms involved in IBD genesis are broadly studied, they are not well understood and may include genetic, immune, and environmental interactions^[12]. Among these complex interplays, the association between microorganisms and IBD has been broadly explored, and, interestingly, researches have pointed to a protective role of *H. pylori* gastric infection in that condition. In this sense, a meta-analysis that included 60 studies found a negative association between that infection and IBD (OR = 0.43, 95%CI: 0.36-0.50, $P < 1^{-10}$). Besides that, such protection relationship was stronger in CD (OR = 0.38, 95%CI: 0.31-0.47, $P < 1^{-10}$) and in IBD unclassified (OR = 0.43, 95%CI: 0.23-0.80, $P = 0.008$) when compared to UC (OR = 0.53, 95%CI: 0.44-0.65, $P < 1^{-10}$)^[13]. In addition, a cohort carried out in Taiwan observed an increased risk of IBD development after bacterial eradication (adjusted hazard risk = 2.15; 95%CI: 1.88-2.46, $P < 0.001$)^[14]. Furthermore, *H. pylori* infection seems not only reduces the risk of IBD acquirement but also seems to minimize the clinical severity of the disease. A recent study that evaluated CD

Table 2 Levels of evidence of the risk relationship between *Helicobacter pylori* infection and each non-gastrointestinal manifestation

Manifestation	Year of publication ¹	Ref. ¹	Level of evidence
Alopecia areata	2017	Behrangi <i>et al</i> ^[72]	III
Alzheimer's disease	2016	Shindler-Itskovitch <i>et al</i> ^[107]	II
	2020	Fu <i>et al</i> ^[108]	II
Arterial hypertension	2018	Wan <i>et al</i> ^[127]	III
Asthma	2013	Wang <i>et al</i> ^[90]	II
	2017	Chen <i>et al</i> ^[91]	III
Atherosclerosis	2019	Iwai <i>et al</i> ^[124]	III
B12 deficiency	2000	Kaptan <i>et al</i> ^[47]	I
	2018	Mwafy <i>et al</i> ^[48]	III
Central serous chorioretinopathy	2006	Cotticelli <i>et al</i> ^[88]	IV
Cholecystitis and cholelithiasis	2015	Guraya <i>et al</i> ^[43]	II
	2018	Tsuchiya <i>et al</i> ^[41]	III
	2018	Cen <i>et al</i> ^[44]	III
Coronary artery disease	2016	Sun <i>et al</i> ^[131]	II
Diabetes mellitus	2019	Chen <i>et al</i> ^[135]	III
Gastroesophageal reflux disease	2016	Wang <i>et al</i> ^[26]	II
Glaucoma	2018	Zeng <i>et al</i> ^[83]	III
	2002	Kountouras <i>et al</i> ^[84]	III
Guillain-Barré syndrome	2020	Dardiotis <i>et al</i> ^[120]	III
Halitosis	2017	HajiFattahi <i>et al</i> ^[29]	III
	2019	Anbari <i>et al</i> ^[30]	III
Hepatic carcinoma	2017	Huang <i>et al</i> ^[39]	III
Idiopathic thrombocytopenic purpura	2018	Kim <i>et al</i> ^[78]	II
Inflammatory bowel disease	2017	Castaño-Rodríguez <i>et al</i> ^[13]	III
	2019	Lin <i>et al</i> ^[14]	III
Iron deficiency anemia	2018	Mwafy <i>et al</i> ^[48]	III
Myocardial infarction	2015	Liu <i>et al</i> ^[125]	III
Multiple sclerosis	2007	Li <i>et al</i> ^[100]	III
	2016	Jaruvongvanich <i>et al</i> ^[101]	III
	2016	Yao <i>et al</i> ^[102]	III
Non-alcoholic fatty liver disease	2019	Liu <i>et al</i> ^[36]	II
Parkinson's disease	2020	Wang <i>et al</i> ^[118]	III
Psoriasis	2019	Yu <i>et al</i> ^[67]	II
	2017	Mesquita <i>et al</i> ^[64]	III
Rosacea	2017	Saleh P <i>et al</i> ^[59]	III
	2017	Jørgensen <i>et al</i> ^[62]	III

Adapted from the American Society of Plastic Surgeons rating scale for risk studies, 2011^[137].

¹Publications with the higher level of evidence found for the risk relationship between *Helicobacter pylori* infection and each non-gastrointestinal manifestation. Levels of evidence: I - High-quality, multi-centered or single-centered, prospective cohort or comparative study with adequate power, or a systematic review of these studies; II - Lesser-quality prospective cohort or comparative study, retrospective cohort or comparative study, untreated controls from a randomized controlled trial, or a systematic review of these studies; III - Case-control study, or systematic review of these studies; IV - Case

series with pre/post test, or only post test; V - Expert opinion developed *via* consensus process; case report or clinical example; or evidence based on physiology, bench research or “first principles”.

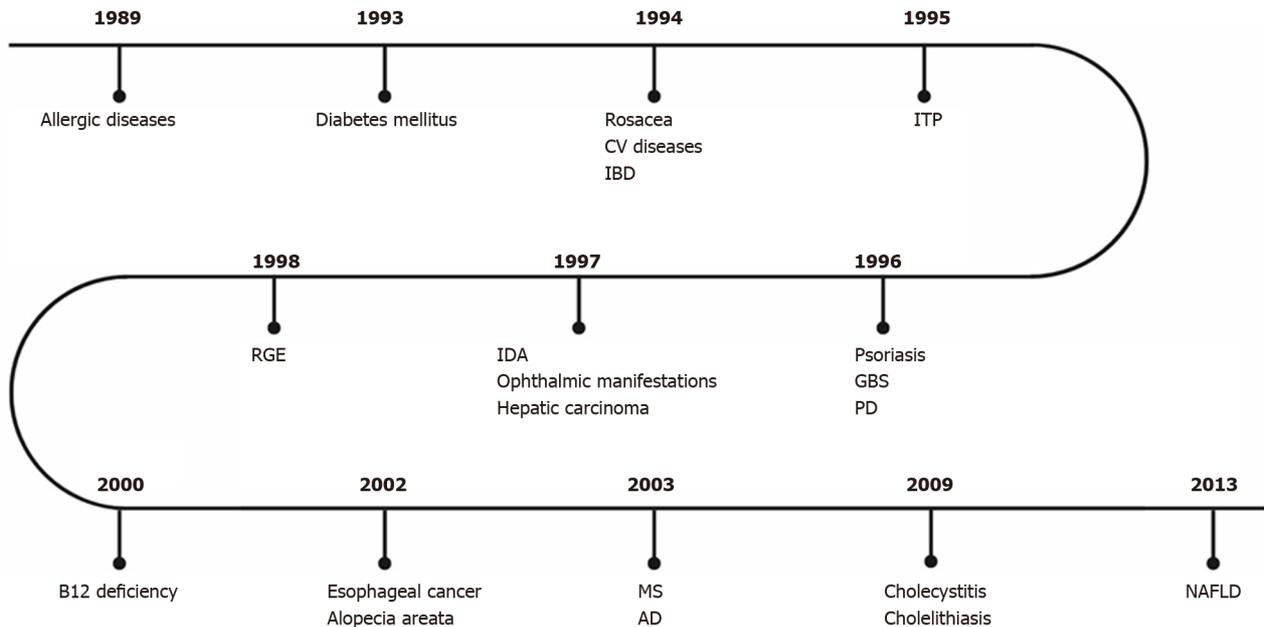


Figure 1 First studies on the association between *Helicobacter pylori* infection and extragastric manifestations over time. CV: Cardiovascular; IBD: Intestinal bowel disease; ITP: Idiopathic thrombocytopenic purpura; GBS: Guillain-Barré Syndrome; IDA: Iron deficiency anemia; RGE: Gastroesophageal reflux disease; PD: Parkinson's disease; MS: Multiple sclerosis; AD: Alzheimer's disease; NAFLD: Non-alcoholic fatty liver disease.

patients observed that *H. pylori* infection was negatively associated with fistulizing or stricturing phenotype (OR = 0.22, 95%CI: 0.06-0.97, $P = 0.022$), as well as with active colitis (OR = 0.186, 95%CI: 0.05-0.65, $P = 0.010$)^[15].

A hypothesis that can justify these findings is the fact that such infection induces interleukin (IL)-18 release, leading to the development of FoxP3-positive regulatory T cells, as well as decreases the maturation of antigen-presenting cells, what reduces intestinal inflammation^[16-18]. Another contributory mechanism may be the presence of the *H. pylori* neutrophil-activating protein that attenuate inflammation by means of the activation of toll-like receptor 2 and stimulation of IL-10 production^[19,20]. Finally, the composition of gut microbiota, which seems to play a crucial role in IBD development^[21], is significantly affected by the *H. pylori* eradication^[22]. In this sense, it is plausible to think that the changes in the intestinal microbiome may be decisive in the IBD onset after *H. pylori* treatment, although studies evaluating this proposition are not yet available.

GERD

Still regarding gastrointestinal diseases, GERD is characterized by the abnormal stomach content reflux through the esophagus, leading to damages in its organ mucosa, among other outcomes^[23]. Pyrosis, regurgitation, sore throat, cough, chest pain, and dysphagia are the most common symptoms in that condition^[24].

The role of *H. pylori* infection in GERD is controversial since its associated gastritis can lead both to an increase or to a reduction of acidic secretion, depending on the affected gastric region. On one hand, the *H. pylori*-associated antral gastritis causes hyperacidity, aggravating GERD. On the other hand, the corpus gastritis results in hypoacidity and plays a protective role against that disease. Such a protective behavior can be explained by bacterial genetic factors that influence *H. pylori* cytotoxin-associated gene A (CagA) positivity, once CagA-positive strains are associated with corpus atrophic gastritis and acidic secretion inhibition, which suggests that they may provide GERD protection^[25]. A meta-analysis conducted by Wang *et al*^[26], involving twenty randomized controlled trials, evaluated the onset of GERD-associated symptoms and esophageal lesions, comparing *H. pylori*-positive patients who underwent bacterial eradication with others who did not went through it. Their results

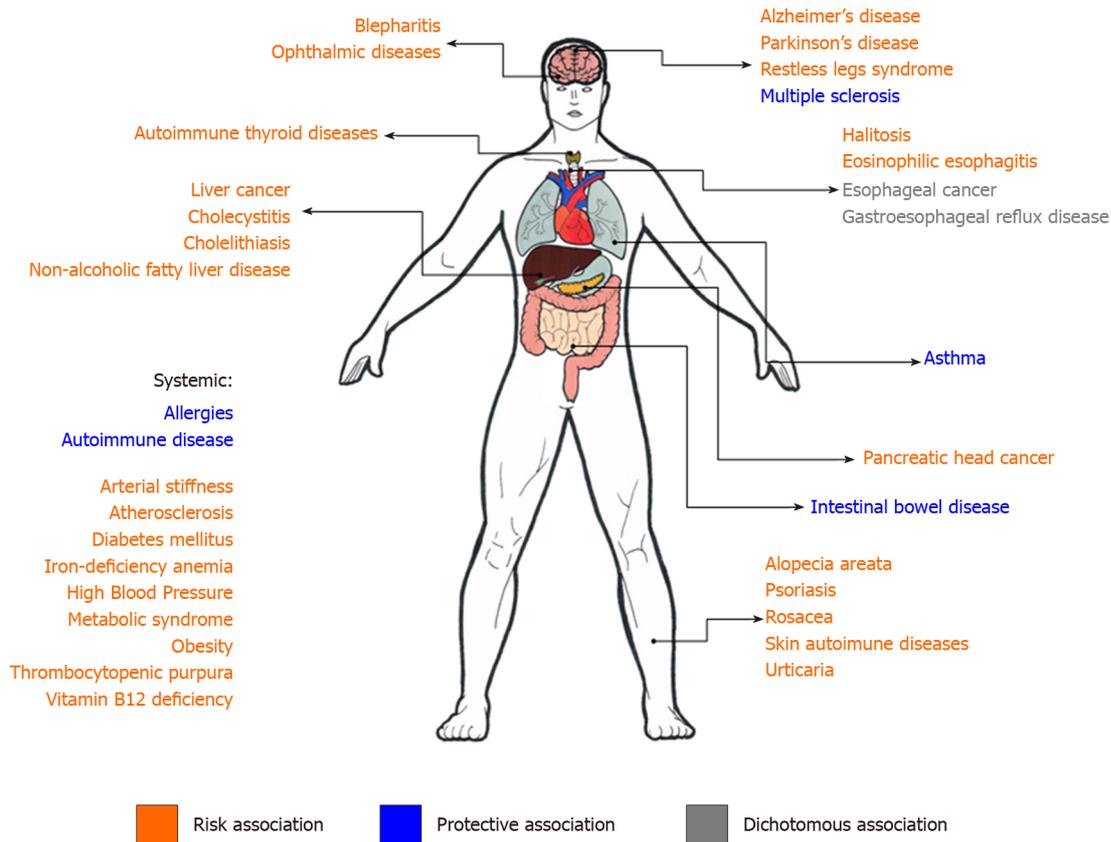


Figure 2 Summary scheme of non-gastric manifestations of *Helicobacter pylori* infection. In orange, the manifestations for which *Helicobacter pylori* (*H. pylori*) infection represents a risk association. In green, the manifestations for which *H. pylori* infection represents a protective association. In gray, the manifestations for which studies show a dichotomous association.

showed a rise in endoscopic reflux esophagitis incidence among treated patients (OR = 1.62, 95%CI: 1.20-2.19, $P = 0.002$). However, the occurrence of GERD symptoms was not significantly different between the groups (OR = 1.03, 95%CI: 0.87-1.21, $P = 0.76$), suggesting that the *H. pylori* eradication does not influence GERD symptoms onset. Regarding esophageal adenocarcinoma, which is usually due to GERD, a recent meta-analysis that included 35 studies showed that *H. pylori* infection may reduce the risk of development of that cancer (OR = 0.71, 95%CI: 0.57-0.92)^[27]. Meantime, these studies did not distinguish the patients infected by CagA-positive *H. pylori* from those colonized by CagA-negative bacteria.

Halitosis

Another non-gastric manifestation suggested to be related to *H. pylori* infection is halitosis^[28]. In 2017, HajiFattahi *et al*^[29] tried to prove this correlation, showing that among patients with halitosis, 91% were *H. pylori*-positive, against only 32% in the control group ($P < 0.001$). However, knowing that halitosis is associated with poor oral hygiene conditions, it is possible that there is a bias related to theory of hygiene in this association and, in this sense, studies have tried to prove this relationship and its pathophysiology, aiming biases exclusion^[30].

NAFLD

NAFLD refers to a range of disorders in which hepatic steatosis is observed by means of image or histology exams^[31]. It is believed that the above-mentioned condition is promoted by the insulin resistance induced by molecules whose production is stimulated by *H. pylori* infection such as tumor necrosis factor and C-reactive protein^[32]. Furthermore, a reduced production of adiponectin, a molecule that inhibits the fatty acid deposition in the liver, is observed in *H. pylori* patients^[33]. Moreover, the bacterium can reach the liver through the biliary tree and can lead to liver inflammation^[34,35]. Recently, studies have been developed in order to verify if *H. pylori* infection plays a role in that disease. Indeed, a meta-analysis that included 21 studies observed a positive association between this infection and NAFLD (OR = 1.529, 95%CI:

1.336-1.750, $P = 0.000$)^[36]. It is important to be highlighted that most available studies on this issue took place in Asian countries, so this data should be interpreted with caution when considered the Western population.

Hepatic carcinoma

Although researches have investigated the association between *H. pylori* infection and liver carcinoma, conflicting results have been found. However, it was already shown that *H. pylori* infection is associated with liver inflammation, fibrosis, and necrosis. Along with these repercussions, the bacterial translocation through the biliary tract may also lead to direct hepatic damage, predisposing or even triggering the carcinogenic process^[37,38]. The rates of *H. pylori* infection among HBV-related hepatic carcinoma patients (68.9%) and HBV-negative hepatic carcinoma (33.3%) were higher when compared to control groups ($P < 0.001$)^[39]. In this sense, studies agree with regards to the screening of *H. pylori* infection followed by the bacterial eradication in patients with liver disorders, in order to prevent the progression of the preexisting disease and the cancer onset^[39,40].

Cholecystitis and cholelithiasis

Recent research has investigated the possible risk relationship between *H. pylori* infections and the development of cholelithiasis and cholecystitis^[41,42]. Regarding the first one, studies have shown that the presence of *H. pylori* in bile may be a risk factor for its development^[43]. Moreover, among other studies, a meta-analysis demonstrated a positive association between *H. pylori* infection and chronic cholecystitis/cholelithiasis (OR = 3.022; 95% CI: 1.897-4.815; $P = 20.1\%$)^[44-46]. Among the possible explanations for that phenomenon, it is believed that *H. pylori* may infects the biliary system, causing chronic inflammation in its mucosa and, as a result, leading to the impairment of acid secretion and reduction of the dissolvability of calcium salts in bile, what predisposes the formation of gallstones^[44].

B12 deficiency

A probable risk relationship between *H. pylori* infection and pernicious anemia was also suggested^[47]. Case-control and prospective cohort studies have shown that patients with positive *H. pylori* had lower Vitamin B12 (Cobalamin) levels when compared to control groups^[47,48]. In addition, when treated with triple therapy - clarithromycin, amoxicillin and omeprazole - to eradicate *H. pylori*, patients with previous pernicious anemia obtained satisfactory levels of Vitamin B12, with mean iron levels of 262.5 ± 100.0 pg/mL among *H. pylori*-positives against 378.2 ± 160.6 pg/mL in the group of *H. pylori*-negatives, representing a difference of 30.6% between those groups, with a P value of 0.001^[48]. Corroborating to the consolidation of this association, studies have shown that there is a decrease in Cobalamin levels in *H. pylori* positive patients regardless of gastric atrophy and dyspepsia^[49]. Even though there is still a lack of studies with regard to clarifying the pathophysiological process of this risk association, the Maastricht V/Florence Consensus Report^[50] recommends that in patients with this deficiency, *H. pylori* should be sought and eradicated.

Iron deficiency anemia

Choe *et al.*^[51] conducted a randomized case-control study to test whether anemic patients positive for *H. pylori*, when underwent infection eradication therapy, have a better response of blood iron levels when compared to the control group. The results were positive for the risk association between infection and anemia. Since then, studies have tried to understand the pathophysiology behind this manifestation, in addition to evaluate its occurrence in different age groups.

In this scenario, subsequent studies confirmed this correlation, in addition to explaining that it occurs regardless of bleeding. That is, there is no need for tissue damage and hemorrhagic processes for the onset of anemia due to infection by *H. pylori*^[52]. When comparing *H. pylori* positive patients to the *H. pylori* negative ones, the first group had iron levels of 71.6 ± 24.8 µg/dL against 80.1 ± 20.7 µg/dL of the second one, a difference of 10,6%, with a t value of -3.206 and P value: 0.001^[48].

It has also been suggested that the anemia triggered by *H. pylori* infection is a causal factor for growth disorders among children and adolescents. Although this is a difficult relationship to be proven, some studies agree on the influence of anemia triggered by *H. pylori* as a causal factor for developmental gap among infants^[52,53]. In this sense, groups of children with unexplained anemia and growth disorders presenting clinical manifestations suggestive of infection by this bacterium should be screened and, if necessary, undergo *H. pylori* eradication, as recommended by current

guidelines^[50].

Dermatological and autoimmune diseases

Some studies suggest an association and possible causality of *H. pylori* infection in some dermatological diseases^[8]. Among them, rosacea and some immunological diseases such as idiopathic thrombocytopenic purpura, psoriasis, alopecia areata, and urticaria are the most studied ones. However, the evidence makes it clear that significant associative power with *H. pylori* infection only occurs in some of these diseases, whereas in many of them conflicting results have been obtained, demanding further research with more appropriate methodologies and statistical designs^[54]. As for autoimmune diseases, they are characterized by a dysregulation of the immune system, which leads to loss of tolerance to auto antigens^[55]. It is believed that these diseases have a multivariate etiology and that infectious agents can trigger them. The immunological response against *H. pylori* can generate an inflammatory condition that potentially leads to the development of cross-reactive antibodies^[56].

Rosacea is a chronic disease with skin manifestations such as facial erythema, edema, papules, telangiectasia, and pustules that are located, most of the time, in the center of the face^[57]. A risk association has been observed between *H. pylori* infection and rosacea, and the treatment of this bacterial infection dramatically decreases the severity of such dermatological disorder^[58]. Other authors observed the same associative results, and began to recommend that patients with rosacea who are positive for *H. pylori* should be treated with bacterial eradication^[59-61]. However, a meta-analysis concluded that cause-effect associations are weak between this disease and *H. pylori* infection (OR = 1.68, 95%CI: 1.100-2.84, $P = 0,052$) and that *H. pylori* eradication therapy does not reach the statistical significance necessary for its mass recommendation, (RR= 1.28, 95%CI: 0.98-1.67, $P = 0,069$)^[62]. The contrast of the results found in the literature may be related, among other things, to the big variability in methodological and statistical designs used.

Psoriasis is a chronic, non-contagious inflammatory skin disease, with genetic and autoimmune characteristics that affects the skin and joints^[63,64]. Its association with *H. pylori* infection had already been investigated with the search for antibodies against *H. pylori* in patients with psoriasis without known gastrointestinal complaints^[65]. Recently, a meta-analysis found a strong evidence demonstrating this association (OR = 1.19, 95%CI: 1.15-2.52, $P = 0.008$) and highlighted that the rate of *H. pylori* infection, interestingly, was significantly high in patients with moderate and severe psoriasis (OR = 2.27; 95%CI: 1.42-3.63, $I^2 = 27\%$) but not in patients with the milder disease (OR = 1.10; 95%CI: 0.79-1.54, $I^2 = 0\%$)^[66]. Another disease commonly associated with *H. pylori* infection is chronic urticaria, a clinical condition that presents with itchy, erythematous or swollen urticaria^[67,68]. The studies reveal conflicting evidence regarding the cause-effect association of *H. pylori* with chronic urticaria. Interestingly, a meta-analysis showed that the improvement in chronic urticaria was not directly linked to the eradication of *H. pylori*, but with the antibiotic therapy used, and, even if the treatment was not effective, a significant remission in chronic urticaria was observed in those patients^[69,70].

Alopecia areata (AA), an autoimmune disease, leads to hair loss and can present a variable course among affected individuals^[71]. There are few published studies on the association of AA with *H. pylori* infection. In an Iranian case control study, a statistically significant risk association was observed (OR = 2.263, 95%CI: 1.199-4.273); however, the study limitations such as the incapacity of controlling some confounding variables weaken this evidence^[72].

Idiopathic thrombocytopenic purpura (ITP) is a condition that results from the individual's platelet destruction mediated by antiplatelet antibodies^[73]. Several studies associate the relationship between *H. pylori* infection and ITP. Although the pathogenesis involved in this process is inconclusive, some authors suggest that CagA stimulates the synthesis of anti-CagA antibodies that cross-react with platelet surface antigens causing ITP^[74,75]. The first correlation of this possible pathogenesis observed an increase in patients' platelet count after *H. pylori* eradication^[76]. Other studies have also been conducted in order to evaluate the remission of PTI after the treatment of *H. pylori* infection. A prospective Brazilian study demonstrated an increase in platelets after bacterial eradication in part of the *H. pylori*-positive patients with ITP. In addition, a significant decrease in the levels of cytokines of the pro-inflammatory profiles Th1 and Th17 as well as an increase in anti-inflammatory cytokines linked to regulatory T cells (Treg) and Th2 were observed in infected patients with ITP in whom an increase in platelet count after *H. pylori* eradication was observed^[77]. A recently published meta-analysis corroborates the significant therapeutic effect that *H. pylori* eradication has on patients with ITP and suggests that this evidence can be taken into

account in the clinical treatment of patients with ITP (OR = 1.93, 95%CI: 1.01-3.71, $P = 0.05$)^[78]. This study presents fragilities since it included researches with a limited number of individuals, few studies with adults, and embraced a small variation of ethnicities. However, it is important to highlight that *H. pylori* infection investigation and eradication have been recommended by ITP clinical management guidelines^[79].

Ophthalmic manifestations

Ophthalmic manifestations association with *H. pylori* was firstly studied by Mindel and Rosenberg^[80], when they tried to relate the rosacea's ocular manifestations with this bacterium. The ocular and extraocular microbiomes and their influence in ophthalmic diseases have been extensively studied and although some associations with *H. pylori* infection are controversial, a set of diseases as open-angle glaucoma, central serous chorioretinopathy (CSCR), and blepharitis have been more widely studied^[81,82].

Cytokines induced by the *H. pylori* in gastric mucosa can generate a systemic inflammatory status contributing with the pathogenesis of these diseases through increased oxidative stress, causing mitochondrial dysfunction and damage to DNA. This process culminates in morphological changes and apoptosis. Oxidative stress is an important pillar in the pathogenesis of both conditions but it is a controversial causal association without large-scale studies^[82].

A meta-analysis showed a significant correlation between *H. pylori* infection and open-angle glaucoma (OR = 2.08, 95%CI: 1.42-3.04). Analyzing the subgroups, this association was present in primary open-angle glaucoma (OR = 3.06, 95%CI: 1.76-5.34; $P < 0.001$) and normal tension glaucoma (OR = 1.77, 95%CI: 1.27-2.46; $P = 0.001$), but not seen with pseudoexfoliation glaucoma (OR = 1.46, 95%CI: 0.40-5.30; $P = 0.562$)^[83]. The *H. pylori* eradication can result in an improvement of intraocular pressure ($P < 0.001$) and visual field ($P \leq 0.01$) parameters^[84]. The eradication had been either associated with the reduction of ocular rosacea symptoms in a case series^[85], improvement in patients with CSCR^[86] and better cytology results in 50% of patients with *H. pylori* and blepharitis ($n = 142$)^[87]. Regarding CSCR, studies have shown a higher prevalence of the disease among *H. pylori* positive patients (78.2%, 95%CI: 56% - 92%) when compared to the control group (43.5%, 95%CI: 23%-65%), with $P < 0.03$ and a 4.6 OR^[88].

Asthma and allergic diseases

The research on infections, microbiome and allergic diseases started with the discussion about hygiene hypothesis due to the increase of allergic diseases as allergic rhinitis or hay fever, asthma and eczema in the post industrial revolution world^[9]. The first study that aimed to determine the seroprevalence of *H. pylori* in asthma patients was performed in 2000 and had inconclusive findings^[89]. Therefore, several studies were conducted in an attempt to elucidate the association between both conditions and although some findings are controversial, meta-analyses indicate that *H. pylori* infection could be considered a protective factor for asthma especially in children and in patients with cagA-positive strains^[90,91].

The *H. pylori* infection as other microbial antigens tends to induce, especially in adults, a Th1 polarized response. This pro-Th1 balance inhibits the activation of a Th2 immune response, fundamental in the asthma and allergies pathophysiology whereas eosinophilic activation and IgE production are dependent of IL-4 and IL-5^[92]. The neutrophil-activating protein of *H. pylori* (*H. pylori*-NAP) can induce this polarization *in vivo* and *in vitro* and could be a target in the development of a treatment or a prevention strategy for asthma and others allergic diseases^[93].

In children, the *H. pylori* infection produces a predominant Treg pattern^[94] that either suppress the Th2-mediated allergic response. Furthermore, the *H. pylori* IgG titre in children was inversely correlated with asthma severity^[95]. This response triggered against bacterial antigens is strong and could suppress responses to autoantigens and allergens^[96]. Another mechanism that could explain the lower incidence of asthma in *H. pylori* carriers is that the presence of the bacteria, especially CagA+ strains, protects against gastroesophageal reflux disease (GERD), reducing GERD-related asthma and the exacerbations associated with this condition^[97].

Considering that *H. pylori* infection is associated with poor household hygiene, some authors and studies endorse that the infection should be considered a biomarker for precarious condition instead of a specific protective factor for allergic diseases^[98].

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central

nervous system (CNS), causing a multifactorial immune dysregulation that involves genetic and environmental factors^[99]. For the first time, in 2007, it was reported a negative association between *H. pylori* infection and MS^[100]. In that occasion, a Japanese study included patients with opticospinal MS (OSMS), conventional MS (CMS), and healthy controls (HC). The results showed a considerably lower *H. pylori* seropositivity in CMS patients (22.6%, $P < 0.05$) when compared to HC (42.4%, $P = 0.0180$) and OSMS individuals (51.9%, $P = 0.0019$). After that, various studies investigated such association and two meta-analyses were conducted in order to evaluate the possible protective effect of *H. pylori* infection to MS. The first one included 1902 patients and demonstrated a significantly lower infection prevalence among SM patients when compared to controls with the same age range and sex (OR = 0.59, 95% CI: 0.37–0.94, $P = 0.03$)^[101]. The second one embraced 2806 individuals and also found a reduced general prevalence of *H. pylori* infection in MS patients (24.66% vs 31.84%, OR: 0.69, 95% CI: 0.57–0.83, $P < 0.0001$)^[102].

Among the various hypothesis that try to justify the *H. pylori* infection as a protection factor for MS, the hygiene hypothesis argues that the exposition to microbial agents during childhood modulates the human immune system, avoiding the development of immune hypersensitivity during adulthood^[9]. Another mechanism that is probably associated with this process is the inhibitory induction of *H. pylori* over the Th1 and Th17 immune response by means of the FoxP3-positive regulatory cells^[103].

Interestingly, the immune response against the *H. pylori* infection also seems to be influenced by the MS. In a cohort that included 119 MS patients (most of them with acute remittent-recurrent MS), it was demonstrated that the *H. pylori* positive patients presented a reduced humoral response against the bacterial protein HP986^[104]. However, another study investigated the antibodies production against the *H. pylori* VacA (vacuolating cytotoxin A) in patients with secondary progressive MS, who presented such immunoglobulins more often when compared to healthy individuals. This suggests that the recognition of *H. pylori* antigens by antibodies is influenced not only by the positivity status for EM, but also by the forms of presentation of this autoimmune disease^[105].

Alzheimer's disease

Alzheimer disease (AD) is a neurodegenerative disturb with progressive cognitive impairment and has the gradual involvement of the sporadic memory as its commonest clinical representation^[106]. Shindler-Itskovitch *et al*^[107], 2016, conducted a meta-analysis that embraced 13 observational studies on the association between *H. pylori* and dementia. The results showed that the *H. pylori*-positive patients had higher risk of dementia when compared to the not infected ones (OR = 1.7, 95% CI: 1.17–2.49). However, when considered only AD patients, such association was not statistically significant (OR = 1.39, 95% CI: 0.76–2.52). Despite that, a more recent meta-analysis identified a significant positive association between *H. pylori* infection and AD in an Asian population (OR = 1.60, 95% CI: 1.20–2.15)^[108].

Some mechanisms are supposed to be involved in the increase of AD risk in individuals infected by *H. pylori*. The vitamin B12 deficiency due to gastric alterations induced by the infection leads to increased concentrations of homocysteine, what leads to dementia. Other hypothesized mechanism for such association is the anormal hyperphosphorylation of the TAU protein caused by *H. pylori* infection. That protein is involved in the AD-linked neurodegeneration^[109]. Besides that, Kountouras *et al*^[110], showed that the *H. pylori* infection positively influence the ApoE polymorphism known as the mais genetic risk factor for AD.

Some hypotheses affirm that *H. pylori* can reach the brain, leading to changes that trigger AD. One of them is based on the *H. pylori* ability to reach the olfactory bulb through the oral-nasal-olfactive *via*^[111]. Such bulb is responsible for the decodification of olfactive signals in the brain and its dysfunction is related to the enfecalic neurodegeneration. Other supposition is the bacterial access through the rupted hematoencephalic barrier (HEB) inside leukocytes, causing an inflammatory process with the release of chemical mediator^[112]. All of the above-mentioned *H. pylori* ways to reach CNS could allow *H. pylori* to exert its potential neurodegenerative action in that environment^[113].

Parkinson's disease

Parkinson's disease (PD) is the second most prevalent progressive neurodegenerative disturb in the world, and has tremor, postural instability, and bradykinesia as preminent outcomes^[114,115]. However, among other reverberations in the human body, gastrointestinal impairments, such as constipation, are important consequences of that

disease and they often represent the first PD manifestations^[116]. The supposed link between Parkinson's disease and gastrointestinal tract led researchers to further investigate that relationship, raising the hypothesis that microorganisms from the digestive system could influence PD pathophysiology^[117].

In that context, a recent meta-analysis that included 23 studies investigated the impact of viral, fungal, and bacterial infections in the risk of PD and found a positive association between *H. pylori* infection and that disease (pooled OR, 95%CI: 1.653, 1.426-1.915, $P < 0.001$)^[118]. Furthermore, another meta-analysis which included 7 studies found that the *H. pylori* infection is also associated with the clinical severity of the PD, since *H. pylori*-positive patients presented poorer scores when undergone Unified Parkinson Disease Rating Scale (UPDRS) evaluation [mean \pm SD, 95%CI: 6.83, 2.29-11.38, $P = 0.003$]^[119]. In addition, the last study also observed an improvement in the UPDRS-III scale in PD patients after *H. pylori* eradication (mean \pm SD, 95%CI: 6.83, 2.29-11.38, $P = 0.003$). It is important to be highlighted that these researches present some limitations. Firstly, the included studies used different diagnostic criteria of PD, and the methods performed for the detection of *H. pylori* infection also varied. The use of ELISA for *H. pylori* infection diagnosis in some of these studies may have overestimated the number of positive individuals, since that test is often reagent even when performed months following a possible *H. pylori* spontaneous eradication. Last but not least, *H. pylori* infection is closely related to various socioeconomic factors, including hygiene. Consequently, some of the associations between *H. pylori* and PD could have been correlational and not causal^[118,119].

It is known that the *H. pylori* infection increases the synthesis of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)^[118]. Such substance can cause dopamine depletion, as well as damage to the substantia nigra, what can lead to PD. Concomitantly, *H. pylori* infection has been found to reduce levodopa absorption, what potentially has the exacerbation of PD symptoms as a consequence^[118].

Guillain-Barré syndrome

The association between the Guillain-Barré syndrome and the *H. pylori* infection have been widely studied and, recently, a meta-analysis about this issue confirmed this interrelation, proceeding with the analysis of the anti-*H. pylori* antibody in serum and cerebrospinal liquid (CSL). When the first one was analyzed, the antibodies prevalence in the patients that presented GBS was significantly higher when compared to those without GBS (OR = 2.31, 95%CI: 1.30-4.11, $P = 0.004$). In the CSL analysis, there was also a strong positive association between GBS and anti-*H. pylori* IgG (OR = 42.45, 95%CI: 9.66-186.56, $Pz < 0.00001$)^[120].

Cardiovascular diseases

Atherosclerosis is a ischemic disease caused by a chronic inflammatory process in the arterial wall and that can lead to other circulatory system diseases^[121]. Yang *et al*^[122] showed, in an animal model, a positive association between *H. pylori* infection and atherosclerosis. They also observed that CagA potentially stimulates the foam production inside macrophages, what contributes to the magnification of the atherosclerotic plaque and arterial dysfunction. In addition, the *H. pylori*-infected gastric epithelial cells-derived exosomes (Hp-GES-EVs) are absorbed by the plaques and CagA is released inside them. Such event exacerbates the obstructive inflammatory process and lead to *in vitro* and *in vivo* lesions^[122]. A south korean study that evaluated the relationship between *H. pylori* and cardiovascular risk factors concluded that this bacterial infection has a atherogenic potential once it seems to influence the lipidic profile of the patient. The results pointed to higher levels of total cholesterol and low-density lipoprotein (LDL), as well as to decreased high-density lipoprotein (HDL) in *H. pylori*-positive individuals^[123]. In that context, another recent study complemented that hypothesis, showing that the *H. pylori* eradication intensely contributed to the improvement of the lipidic parameters in dyslipidemic individuals by means of an increase in HDL levels and a drop in LDL/HDL ratio, which is a parameter used in the evaluation of the atherosclerosis risk^[124].

Another meta-analysis explored the association between *H. pylori* and myocardial infarction (MI), and concluded that *H. pylori* implies a higher risk of MI (OR = 2.10, 95%CI: 1.75-2.53, $P = 0.06$)^[125]. Interestingly, a study identified that people with IL-1 polymorphisms present higher inflammatory activity and higher chances of suffering from ST-segment elevation MI (OR = 2.32, 95%CI: 1.23-4.37, $P = 0.009$)^[126].

A study conducted in a Chinese population identified a high prevalence of arterial hypertension in *H. pylori* seropositive patients (OR = 1.23; 95%CI: 1.04-1.46)^[127]. One of the mechanisms that can explain that association is the production of inflammatory cytokines such as TNF- α , interleukin-6 and c-reactive protein induced by the *H. pylori*

[128]. These cytokines lead to insulin resistance, contributing to the total peripheral vascular resistance and to the atherosclerotic process. Both phenomena are related to the hypertension^[129].

The coronary artery disease (CAD) is characterized by a heart blood flow reduction in the as a result of obstructions of the coronary arteries due to their narrowing due to an atherosclerotic and/or a thrombotic process^[130]. A meta-analysis showed that the *H. pylori* infection is significantly related to higher odds of CAD (OR = 1.11, 95%CI: 1.01-1.22, *P* = 0.24)^[131].

According Tamura *et al.*^[132], the probable hypothesis to explain the positive association between *H. pylori* and CAD may be linked to the atrophic gastritis caused by the bacterial chronic infection, leading to a decreased absorption of vitamin B12 and folic acid in the gastrointestinal tract. This absorptive deficiency causes an increase in the circulant levels of homocysteine, which potentially contribute to the CAD development. In addition, a study conducted by Kutluana and Kilciler^[133], 2019, demonstrated that the reduced absorption of above-mentioned nutrients due to atrophic gastritis and gastric intestinal metaplasia during *H. pylori* infection also lead to an increase in the arterial stiffness.

Diabetes mellitus

A positive association between *H. pylori* infection and diabetes mellitus (DM) was found in a meta-analysis of 39 studies that included more than 20 thousands patients (OR = 2.00, 95%CI: 1.82-2.20, *P* = 0.07)^[134]. Besides that, the *H. pylori* infection not only increase the risk of DM, but it also impairs the satisfactory control of glycemic levels in DM patients. A meta-analysis that included 35 studies observed that the glycated hemoglobin A levels were significantly higher in *H. pylori*-positive patients when compared to *H. pylori* negative individuals (weighted mean difference 0.50, 95%CI: 0.28-0.72, *P* < 0.001)^[135]. However, the fact that these studies do not take into account other factors that influence the glycemic control, such as obesity index and smoking status, constitute an important limitation^[134,135]. Among the hypothesis on how does *H. pylori* increases the risk of DM, it is believed that the increased cytokine production leads to the phosphorylation of serine residues from the insulin receptor substrate, whose linkage with insulin receptors turns deficient^[136].

CONCLUSION

Although *H. pylori* infection is most commonly associated with gastric manifestations, growing evidence have drawn attention to its role in extragastric diseases. The knowledge on how does that bacterium influence non-gastroduodenal disorders can elucidate little understood points about their pathophysiology and may shed light on new therapeutic targets in the management of these conditions. The *H. pylori* eradication is already a well established therapeutic alternative in some of these diseases. However, further studies are needed in order to evaluate if the bacterial elimination can be a consistent therapeutic alternative in a greater number of health problems. Finally, the beneficial association of *H. pylori* infection with some extragastric diseases should be explored by future research in order to evaluate the use of the bacterium and its products in new prophylactic and therapeutic protocols.

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