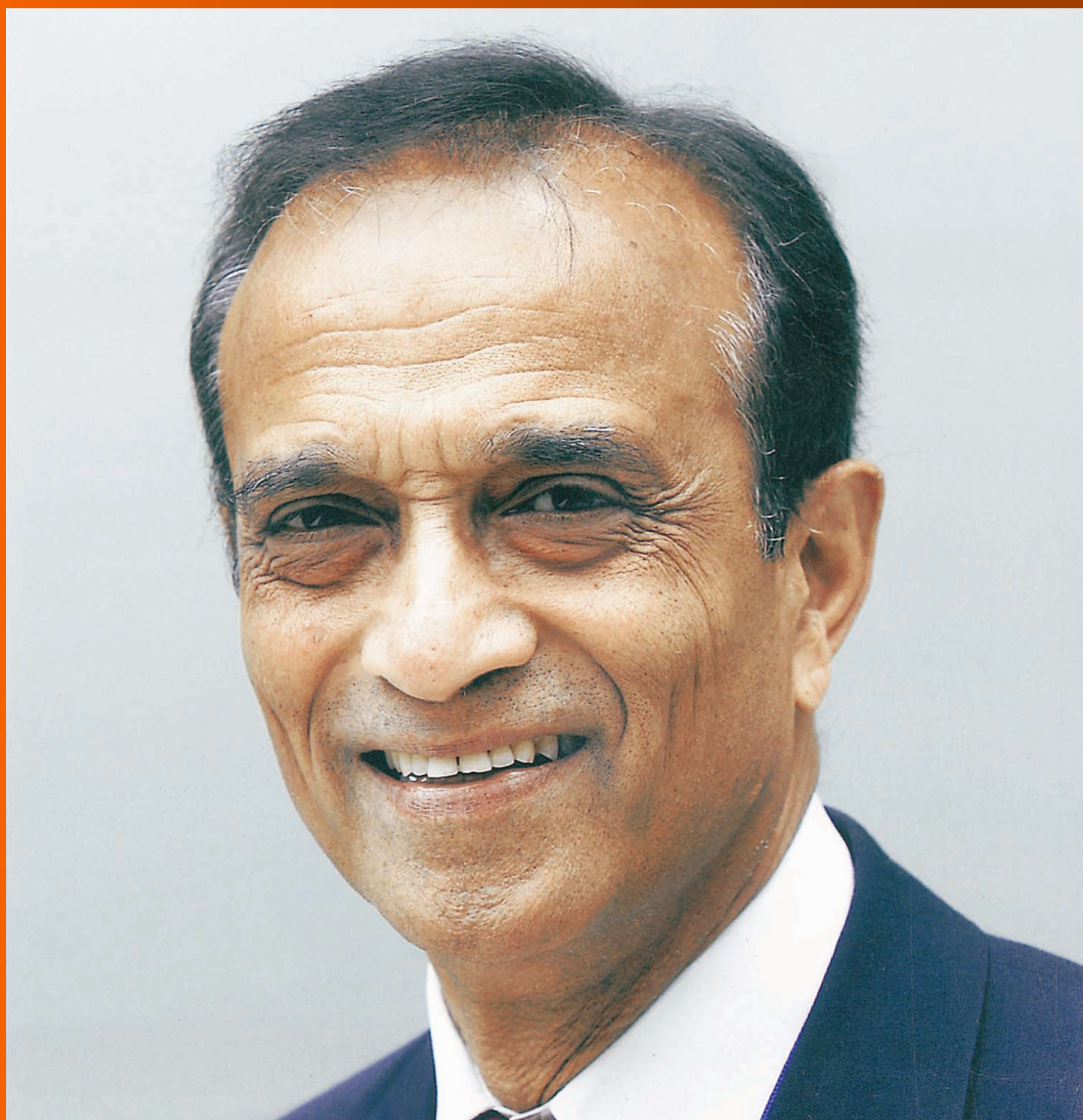


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Editorial board member of *World Journal of Gastroenterology*, Rakesh Kumar Tandon, FRCP (Hon), MD, PhD, Doctor, Professor, Department of Gastroenterology, Pushpawati Singhania Research Institute for Liver, Renal and Digestive Diseases, Sheikh Sarai-Phase II, New Delhi 110017, Delhi, India

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## ***Helicobacter pylori* and extragastric diseases: A review**

Antonietta Gerarda Gravina, Rocco Maurizio Zagari, Cristiana De Musis, Lorenzo Romano, Carmelina Loguercio, Marco Romano

Antonietta Gerarda Gravina, Cristiana De Musis, Lorenzo Romano, Carmelina Loguercio, Marco Romano, Dipartimento di “Medicina di Precisione”, UOC Epatogastroenterologia, Università della Campania “Luigi Vanvitelli”, Napoli 80131, Italy

Rocco Maurizio Zagari, Dipartimento Di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna 40138, Italy

ORCID number: Antonietta Gerarda Gravina (0000-0001-8049-0115); Rocco Maurizio Zagari (0000-0001-9949-8619); Cristiana De Musis (0000-0001-7011-5047); Lorenzo Romano (0000-0002-6581-7930); Carmelina Loguercio (0000-0002-6863-6510); Marco Romano (0000-0002-3271-349X).

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**Correspondence to:** Marco Romano, MD, PhD, Full Professor, Dipartimento di “Medicina di Precisione”, UOC Epatogastroenterologia, Università degli Studi della Campania “Luigi Vanvitelli”, Via Pansini, 5, Napoli 80131, Italy. [marco.romano@unicampania.it](mailto:marco.romano@unicampania.it)  
Telephone: +39-335-6768097

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### **Abstract**

*Helicobacter pylori* (*H. pylori*) infection is very common and affects approximately half of the world population. It causes gastric diseases, but some authors have reported an association of *H. pylori* infection with other systemic manifestations beginning in 1994. The list of potential effects of *H. pylori* outside the stomach includes a number of extragastric manifestations and we focused on neurological, dermatological, hematologic, ocular, cardiovascular, metabolic, allergic, and hepatobiliary diseases. This review discusses these important reported manifestations that are not related to the gastrointestinal tract.

**Key words:** *Helicobacter pylori*; Extragastric disease; Neurological diseases; Dermatological diseases; Hematologic diseases; Ocular diseases; Cardiovascular diseases; Metabolic diseases; Allergic diseases; Hepatobiliary diseases

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**Core tip:** *Helicobacter pylori* (*H. pylori*) infection is a common infection that can cause gastric and extragastric diseases. A considerable amount of evidence links *H. pylori* infection with extragastric diseases, and in many of these diseases there is a clear beneficial effect of eradication therapy. This review summarizes the *H. pylori*-related extragastric manifestations of major interest that have been reported in the scientific literature, such as neurological, dermatological, hematologic, ocular, cardiovascular, metabolic, allergic



and hepatobiliary disease manifestations.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a gram-negative, microaerophilic, spiral-shaped and flagellated bacterium infecting about half the world's population whose main reservoir is the human stomach. The prevalence of infection varies by geographic area, age, ethnicity and socioeconomic status; in fact, the prevalence is higher in developing countries and in those with poor socio-economic conditions<sup>[1-4]</sup>. *H. pylori* possesses microbiological characteristics that allow it to survive in extremely adverse conditions such as the gastric acidic environment. Transmission of the infection occurs mainly through the oral-fecal route<sup>[5]</sup>, in particular through contaminated water and food. Oral-oral transmission is also possible, as shown by the isolation of the bacterium in saliva and dental plaque<sup>[6]</sup>.

*H. pylori* infection is the main cause of chronic gastritis and peptic ulcer disease<sup>[7]</sup>. *H. pylori* has a determinant pathogenic role in the development of distal gastric adenocarcinoma and gastric mucosa associated lymphoid tissue (MALT) lymphoma; in fact, it can contribute to gastric carcinogenesis by stimulating gastric cell proliferation without counterbalancing with adequate apoptosis<sup>[8,9]</sup>. The spectrum of gastroduodenal diseases associated with the evolution of *H. pylori* infection is wide. A large proportion of infected subjects (approximately 80%-85%) develop mild antrum and body gastritis associated with an alteration of gastric homeostasis characterized by hypergastrinemia with normal levels of gastric acid secretion. These subjects are unlikely to develop severe clinical conditions. Approximately 10%-15% of infected individuals develop prevalent antrum gastritis, in which hypergastrinemia is associated with increased gastric secretion with the possible development of duodenal ulceration<sup>[10]</sup>. A lower percentage (approximately 1%-2%) develop a prevalent body gastritis in response to the infection that is associated with multifocal atrophic gastritis, increased gastrinemia, hypo-chlorhydria and the possible development of gastric adenocarcinoma. The reason why *H. pylori* infection is associated with different gastric phenotypes with different clinical outcomes is not fully known, but it is likely that the interaction among bacterial virulence factors (e.g., CagA, urease, VacA, and babA2), environmental factors (e.g., socioeconomic conditions, nutrition, and exposure to toxic substances) and genetic

substrates of the host [e.g., IL1B gene cluster and tumor necrosis factor- $\alpha$  (*TNF $\alpha$* ) gene polymorphism] play an important role<sup>[11]</sup>. The first reports of the association between *H. pylori* infection and extra-gastric diseases were by Mendall *et al*<sup>[12]</sup> in 1994. There are several clinical extra-gastric manifestations associated with *H. pylori* infection that have been reported to date, making this a very interesting and debated topic. We summarize the data in the literature about extra-digestive diseases associated with *H. pylori* infection and focus our attention on the following conditions that are potentially linked to *H. pylori* infection: neurological, dermatological, hematologic, ocular, cardiovascular, metabolic and allergic diseases. For some of these diseases, only one association is described without a clear explanation of the pathogenic mechanism; however, for others, as we will see later, the association is so strong and the pathogenic mechanism is so clear that guidelines for the treatment of *H. pylori* infection suggest that in these conditions, *H. pylori* infection should be determined and, if present, should be treated with eradication therapy<sup>[13]</sup>.

## NEUROLOGICAL DISEASES

Several neurological disorders are associated with *H. pylori* infection. There are studies in the literature that report a positive predictive value between *H. pylori* infection and stroke; however, in 2013, in a prospective cohort analysis performed on 9885 subjects with stroke, Chen *et al*<sup>[14]</sup> not only reported no increased mortality but actually found that people infected with *H. pylori* had a lower mortality than the general population. In a recent metanalysis, Wang *et al*<sup>[15]</sup> demonstrated that chronic *H. pylori* infection and the presence of CagA-positive strains were statistically significant risk factors for ischemic stroke. The underlying pathogenic mechanism is not yet known, but it has been hypothesized that *H. pylori* increases the expression of a number of mediators of inflammation and activates platelets and factors involved in coagulation<sup>[16]</sup>. Difference in the study population and in the methods to assess *H. pylori* infection might partially explain the discrepancy between different studies.

Another neurologic disease that has been linked to *H. pylori* infection is Alzheimer's disease (AD). There are several studies concerning *H. pylori* and dementia. Huang *et al*<sup>[17]</sup> showed a 1.6 times greater risk of developing AD in *H. pylori*-infected people than in non-infected people, supporting a possible role of *H. pylori* in the pathophysiology of AD. Roubaud Baudron *et al*<sup>[18]</sup> also reported a 1.5 times greater risk of developing dementia over a 20-year follow-up period in infected people than in non-infected people. Beydoun *et al*<sup>[19]</sup> also reported an association between *H. pylori* infection and reduced cognitive ability. There are also several studies that report that eradication of infection can positively influence the manifestations of AD<sup>[20-22]</sup>. In 2016, Kountouras *et al*<sup>[23]</sup> showed that in patients

with AD and *H. pylori* infection there was an increased prevalence of apolipoprotein E (ApoE) 4 polymorphism compared with non-infected patients. The ApoE 4 polymorphism is the strongest genetic risk factor for AD<sup>[23,24]</sup>. In 2009, the same author reported significantly higher levels of anti-*H. pylori*-specific antibodies (anti-*H. pylori* IgG) in the cerebrospinal fluid (CSF) and serum from patients with AD than that in the CSF and serum from age-matched subjects with normal cognition. The same research group demonstrated a significant correlation between the severity of disease and levels of anti-*H. pylori* IgG in the CSF of these patients<sup>[25]</sup>. One hypothesis to explain the association between *H. pylori* and AD is that *H. pylori* might access the brain via an oral-nasal-olfactory pathway thus leading to neurodegeneration. In fact, olfactory performance is reduced in 90% of patients with AD, and significant olfactory bulb atrophy, as evaluated by imaging techniques, is present in these patients<sup>[26-29]</sup>. Another hypothesis is that *H. pylori* may access the brain via monocytes infected with *H. pylori* (due to *H. pylori* replication in autophagic vesicles) through a disrupted blood-brain barrier (BBB), which is also called the "Trojan horse theory"; this may lead to increased production of inflammatory mediators, such as TNF- $\alpha$ , which in turn may cause BBB disruption by up-regulation of metalloproteinases<sup>[30]</sup>. A third hypothesis is that *H. pylori* may access to brain through a fast retrograde neural pathway from the gastrointestinal tract (GIT), leading to neurodegeneration<sup>[30]</sup>. A study conducted in Japan<sup>[31]</sup> did not confirm the association between *H. pylori* infection and AD. However the high prevalence of *H. pylori* in controls might partially explain the difference with studies conducted in Western countries where the prevalence of the infection is lower. Furthermore, Chang *et al.*<sup>[32]</sup> in partial support of a role for *H. pylori* in AD, demonstrated that eradication of the infection led to a decreased progression of the neurological disease.

Multiple sclerosis (MS) is a chronic demyelinating disease that affects the central nervous system. Mohebi *et al.*<sup>[33]</sup> showed an inverse relationship between *H. pylori* infection and MS; however, other authors have shown positivity of markers for optic neuromyelitis in *H. pylori*-positive patients. The administration of *H. pylori* SS1 antigen in an experimental model of MS [experimental autoimmune encephalomyelitis (EAE)], indicates the presence of immunomodulating properties of *H. pylori*, suggesting a possible effect of *H. pylori* infection in the pathophysiology of MS<sup>[34]</sup>. Cook *et al.*<sup>[35]</sup> showed a probable protective role of *H. pylori* against EAE by inhibiting both Th1 and Th17 responses. *H. pylori* infection seems to be a risk factor for the development of aquaporin 4 (AQP4) antibodies in MS, through molecular mimicry between AQP4 and bacterial AQP<sup>[14]</sup>. Therefore, based on these studies, whether *H. pylori* infection may cause MS is still controversial.

Another disease of great neurological interest for which an association with *H. pylori* infection has been reported is Parkinson's disease (PD). PD is caused

by the degeneration of the dopaminergic neurons of the substantia nigra pars compacta of the basal ganglia system. A meta-analysis by Shen *et al.*<sup>[36]</sup> in 2017, evaluating eight eligible studies involving 33125 participants, demonstrated that *H. pylori* infection might be associated with the risk of PD. A recent study by Huang *et al.*<sup>[37]</sup> in the general population in Taiwan demonstrated that *H. pylori* infection was significantly associated with an increased risk of PD among individuals who were  $\geq 60$  years old but not among those  $< 60$  years old. *H. pylori* infection may affect L-3,4-dihydroxyphenylalanine (L-dopa) bioavailability, which is used in the treatment of PD, by disrupting the duodenal mucosa, which is the site of absorption of L-dopa<sup>[38]</sup>. The eradication of the infection appears to be associated with greater bioavailability of L-dopa and is associated with better clinical outcomes<sup>[39,40]</sup>. Several studies have demonstrated that pro-inflammatory cytokines associated with chronic gastrointestinal disease can induce brain inflammation through a disruption of the BBB and death of dopaminergic neurons and may eventually be responsible for parkinsonism<sup>[41-43]</sup>. The association between PD and *H. pylori* infection seems, therefore, to be strongly supported by literature reports.

Guillain-Barré syndrome (GBS) is an acute autoimmune neuropathy characterized by progressive paralysis of the limbs with a distal-proximal pattern (the legs being affected first and the arms later). It can cause life-threatening complications, particularly if there is respiratory muscle involvement or autonomic nervous system involvement. The disease is usually triggered by an infection. *Campylobacter jejuni* (*C. jejuni*), the most prevalent cause of bacterial gastroenteritis, has been associated with GBS and the possible pathogenic mechanism involves molecular mimicry between peripheral nerve gangliosides and *C. jejuni* lipopolysaccharides (LPSs). In fact sialic acid, a characteristic component of human gangliosides, is present among the surface antigens of *C. jejuni*. *H. pylori* has a high-molecular weight sequence in LPSs that is detected in one third of *C. jejuni* serotypes. Therefore a molecular mimicry between *H. pylori* antigens and peripheral nerve gangliosides might be responsible for the association between *H. pylori* infection and GBS<sup>[16,44,45]</sup>. Some authors demonstrated that the presence of serum anti-*H. pylori* IgG in patients with GBS was significantly higher than that in controls. They also demonstrated that the CSF was positive for anti-*H. pylori* IgG in 80% of patients and in only 20% of controls<sup>[16]</sup>. Chiba *et al.*<sup>[46]</sup> demonstrated IgG antibodies to vacuolating cytotoxin A (VacA) of *H. pylori* in the CSF of patients with GBS. In this study, the authors found sequence homology between VacA and the human ATPase A subunit, suggesting that antibodies to VacA might bind to ion channels in Schwann cells, resulting in the demyelination of motor neurons in these patients. A limitation of all these studies is the small sample size and, for this reason, studies with a greater sample size are needed to demonstrate a real cause-

effect relationship between *H. pylori* and GBS.

## DERMATOLOGICAL DISEASES

Rosacea is the most common dermatological disease associated with *H. pylori* infection. It is a chronic facial dermatitis that manifests as erythema and cutaneous lesions characterized by much dilated red superficial capillaries, called telangiectasia, and its etiology remains unknown. Although the etiopathogenesis is not fully known, an element commonly found in patients with rosacea is the presence of gastrointestinal disorders. Several studies have suggested a potential relationship to *H. pylori* infection; however, the correlation between *H. pylori* infection and rosacea is still debated. Our group has demonstrated *H. pylori* infection in 48.9% of patients with rosacea, while only 26.7% of patients in the control group were infected with *H. pylori*. We demonstrated an improvement with partial or total regression of rosacea skin lesions after successful *H. pylori* eradication in 96.9% of patients<sup>[47]</sup>. Argenziano *et al*<sup>[48]</sup> reported *H. pylori* infection in 81% of patients with rosacea, and almost all of the patients housed CagA-positive strains. El-Khalawany *et al*<sup>[49]</sup> demonstrated that papular rosacea responded better to eradication therapy than erythematous rosacea did. Based on the majority of studies one may therefore suggest to test for and eradicate *H. pylori* infection in patients with rosacea.

Psoriasis is an autoimmune chronic inflammatory disease of the skin that is not infectious or contagious and is usually of a chronic and recurring nature. The association between *H. pylori* infection and psoriasis is still controversial. In fact some authors demonstrated neither a significant relationship between psoriasis and *H. pylori*<sup>[50,51]</sup>, nor a significant relationship between psoriasis severity and the serum levels of IgG anti-*H. pylori*<sup>[51]</sup>. However, other authors demonstrated that *H. pylori* infection is more common in patients with psoriasis than in healthy controls<sup>[52,53]</sup> and that prevalence of *H. pylori* infection was higher in patients with severe psoriasis (79%) compared to those with moderate (69.5%) or mild (46.2%) disease<sup>[53,54]</sup>. Finally, in support of a causative role for *H. pylori* in psoriasis, an interventional study by Onsun *et al*<sup>[55]</sup> demonstrated that eradication of *H. pylori* infection caused more rapid improvement than treatment with acitretin alone.

Chronic urticaria (CU) is characterized by the appearance of a more or less itchy rash, and its unique lesion is the wheal. Some research groups have reported a higher prevalence of *H. pylori* infection in patients with CU<sup>[56,57]</sup>. Campanati *et al*<sup>[58]</sup> demonstrated no difference in the presence of *H. pylori* infection between patients with CU and apparently healthy people, but they reported a significant improvement in skin lesions after eradication therapy. Yoshimasu *et al*<sup>[59]</sup> demonstrated that patients with CU infected with *H. pylori* had a cure rate of approximately 56% and that

none of the patients with *H. pylori* infection were cured if they were treated with antihistamine therapy alone.

Data regarding the association between alopecia aerata (AA) and *H. pylori* infection are discordant. In fact, some authors have reported a higher prevalence of infection in patients with AA, but other authors did not confirm this association<sup>[60,61]</sup>. Differences in methodology might account for the discrepancy of results related to the role of *H. pylori* in CU or AA and, therefore, larger population studies and controlled trials to obtain more accurate evidence about these associations are needed.

Autoimmune bullous diseases (AIBD) are a group of dermatological diseases including pemphigus, pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, and linear immunoglobulin A disease<sup>[62,63]</sup>. Very few published studies have investigated the association between AIBD and *H. pylori* infection. Sagi *et al*<sup>[64]</sup> and Mortazavi *et al*<sup>[65]</sup> demonstrated that anti-*H. pylori* IgG was higher in patients with AIBD than in controls. In the Mortazavi *et al*<sup>[65]</sup> study, the prevalence of *H. pylori* infection was as high as 79.3% in the AIBD group.

Schöenlein-Henoch purpura (SHP) is an immune condition characterized by the deposition of immunoglobulin A in the skin and in other organs, such as the kidneys, joints, and gastrointestinal tract. The onset of this disease is characterized by the appearance of purple skin lesions. There are a few reports that support the association between *H. pylori* infection and SHP, demonstrating an improvement in skin lesions following the successful eradication of the infection<sup>[66-68]</sup>. Clinical studies with a great sample size are necessary prior to draw a firm conclusion regarding the role of *H. pylori* in SHP.

## HEMATOLOGIC DISEASES

Iron deficiency anemia (IDA) is well known to be associated with *H. pylori* infection. In 1991, Blecker *et al*<sup>[69]</sup> described a case of hemorrhagic gastritis linked to *H. pylori* infection and showed a possible relationship between *H. pylori* infection and IDA. Subsequently, 5 meta-analyses concluded that there was a close association between infection and IDA<sup>[70-74]</sup>. Guidelines for the treatment of *H. pylori* infection indicate that the infection should be eradicated in cases of IDA<sup>[13]</sup>. The reason why IDA is not always associated with *H. pylori* infection is not known. Azab *et al*<sup>[75]</sup> studied the role of hepcidin, which is a small protein responsible for regulating iron recycling and the balance of iron in the body. Hepcidin, which is produced in the liver, regulates the absorption of iron from enterocytes and its release from macrophages<sup>[76]</sup>. *H. pylori* infection upregulates hepcidin serum levels, thus attenuating the response to iron therapy<sup>[77]</sup>. Senkovich *et al*<sup>[78]</sup> demonstrated that *H. pylori* is able to acquire iron from host transferrin and lactoferrin. Yokota *et al*<sup>[79]</sup> demonstrated that some polymorphisms within the *H. pylori* neutrophil-

activating protein were more frequent in strains from IDA patients than in those from non-IDA patients. *H. pylori* that harbors these polymorphisms internalizes iron more rapidly than other strains<sup>[79]</sup>. Inorganic iron dissolves best in a highly acidic environment, and *H. pylori* infection may reduce the bioavailability of dietary iron. Patients infected with CagA-positive strains and those with refractory IDA have high serum levels of TNF $\alpha$ , which is a pro-inflammatory cytokine that can induce anemia<sup>[80,81]</sup>. Hershko *et al.*<sup>[82]</sup> demonstrated that 64%-75% of patients with IDA and *H. pylori* infections had a complete disappearance of IDA after *H. pylori* eradication. Other possible causes of IDA in patients with *H. pylori* infections are chronic or acute bleeding due to erosive gastritis or concomitant therapy with non-steroidal anti-inflammatory drugs including aspirin<sup>[83-86]</sup>.

Vitamin B<sub>12</sub> is the coenzyme of many important enzymatic reactions in the human body that lead to DNA synthesis<sup>[87]</sup>. Lahner *et al.*<sup>[88]</sup> showed an association between low serum levels of vitamin B<sub>12</sub> and *H. pylori* infection in a systematic review evaluating 17 studies involving 2454 patients. Homocysteine is a component of the vitamin B<sub>12</sub> metabolic pathway<sup>[89]</sup>, and some authors have demonstrated a relationship between low serum levels of vitamin B<sub>12</sub> and increases in serum homocysteine associated with *H. pylori* infection<sup>[90]</sup>. Increased serum levels of vitamin B<sub>12</sub> and decreased serum levels of homocysteine have been reported after *H. pylori* eradication<sup>[87]</sup>. The pathophysiological mechanism of the association between vitamin B<sub>12</sub> deficiency and *H. pylori* infection is also unknown. The absorption of vitamin B<sub>12</sub> may be compromised in corpus-predominant *H. pylori*-related gastritis. Chronic vitamin B<sub>12</sub> deficiency can cause a pernicious anemia and peripheral neuropathy and lesions of the spinal cord<sup>[91]</sup>.

Primary immune thrombocytopenia (ITP), which was previously called idiopathic thrombocytopenic purpura and autoimmune thrombocytopenic purpura, is an autoimmune disorder characterized by an isolated thrombocytopenia (a peripheral blood platelet count of  $100 \times 10^9/L$ ) in the absence of other causes<sup>[87]</sup>. The first case of association between *H. pylori* infection and ITP was described in Spain in 1999<sup>[92]</sup>. In the world literature, there are many authors who have reported this association, and a significant increase in platelet count following the eradication of *H. pylori* infection varies from 32% to 100% in Italian studies<sup>[93,94]</sup> and from 26% to 100% in the overall literature<sup>[95,96]</sup>. There are only a few published studies that do not describe a positive association between *H. pylori* infection and ITP, but this may be explained by the low prevalence of the infection in these countries<sup>[97-100]</sup>. *H. pylori*-infected patients who have a particular polymorphism in IL- $\beta$ , the IL- $\beta$  (-511) T allele, are more likely to develop ITP than uninfected ITP patients<sup>[80,101]</sup>. The pathogenesis of ITP associated with *H. pylori* infection is most likely multifactorial. Various mechanisms involved in this autoimmune process in patients with *H. pylori* infection

have been described, and one mechanism does not exclude the other. One of these mechanisms is the modulation of the Fc $\gamma$  receptor balance, which is related to the activation of monocytes/macrophages and the relationship to the inhibitory receptor Fc $\gamma$ RIIB. Monocytes from *H. pylori*-infected patients exhibited an enhanced phagocytic capacity and low levels of inhibitory Fc $\gamma$ RIIB, leading to increased monocyte function with autoreactivity with B and T lymphocytes. This may cause the production of autoantibodies by lymphocyte B against circulating platelets. Eradication of *H. pylori* in ITP causes an upregulation of Fc $\gamma$ RIIB expression in monocytes, increased platelet recovery and suppression of antigen presentation by macrophages with the subsequent inhibition of T- and B-cell responses to platelet antigens<sup>[87,102]</sup>. Another mechanism potentially involved in *H. pylori*-associated ITP is molecular mimicry between platelet surface glycoproteins, including glycoprotein IIIa, and amino acid sequences of virulence factors, such as VacA, CagA and urease B<sup>[87,103]</sup>. Anti-*H. pylori* IgG can induce opsonization of platelets by binding to *H. pylori*, von Willebrand's factor, and GPIb<sup>[102,104]</sup>.

The putative mechanisms responsible for the association between *H. pylori* infection, IDA, Vitamin B<sub>12</sub> deficiency and ITP are summarized in Figure 1.

Other unrecognized hematologic disorders that are associated with *H. pylori* infection are autoimmune neutropenia (AN), anti-phospholipid syndrome (AS), and plasma cell dyscrasias (PCD). The association between AN and *H. pylori* infection was described for the first time by Cicconi *et al.*<sup>[105]</sup> in 2001 and was subsequently described by other authors<sup>[105,106]</sup>. AN (defined as 400 neutrophils per  $\mu L$ ) may dramatically improve after *H. pylori* eradication<sup>[87,107,108]</sup>. The association between *H. pylori* infection and PCD, including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, solitary plasmacytomas, plasma cell leukemia, Waldenstrom macroglobulinemia and other chronic myeloproliferative diseases of B lymphocytes, is supported by some authors but not by others<sup>[107,109-111]</sup>. This relationship maybe a result of chronic antigenic stimulation of B lymphocytes by *H. pylori*<sup>[84]</sup>.

## OCULAR DISEASES

Ocular diseases described in association with *H. pylori* infection are open-angle glaucoma (OAG), central serous chorioretinitis (CSC) and blepharitis (B). There are studies that show a prevalence of *H. pylori* infection that is approximately two-fold higher in patients with OAG than in controls. However, other authors including Galloway *et al.*<sup>[112]</sup> and Kurtz *et al.*<sup>[113]</sup> did not find a higher prevalence of infection in patients with open-angle glaucoma. Zeng *et al.*<sup>[114]</sup> published a meta-analysis about this association, evaluating ten studies, and suggested a statistically significant association between *H. pylori* infection and OAG. In further support of an association between *H. pylori* infection and



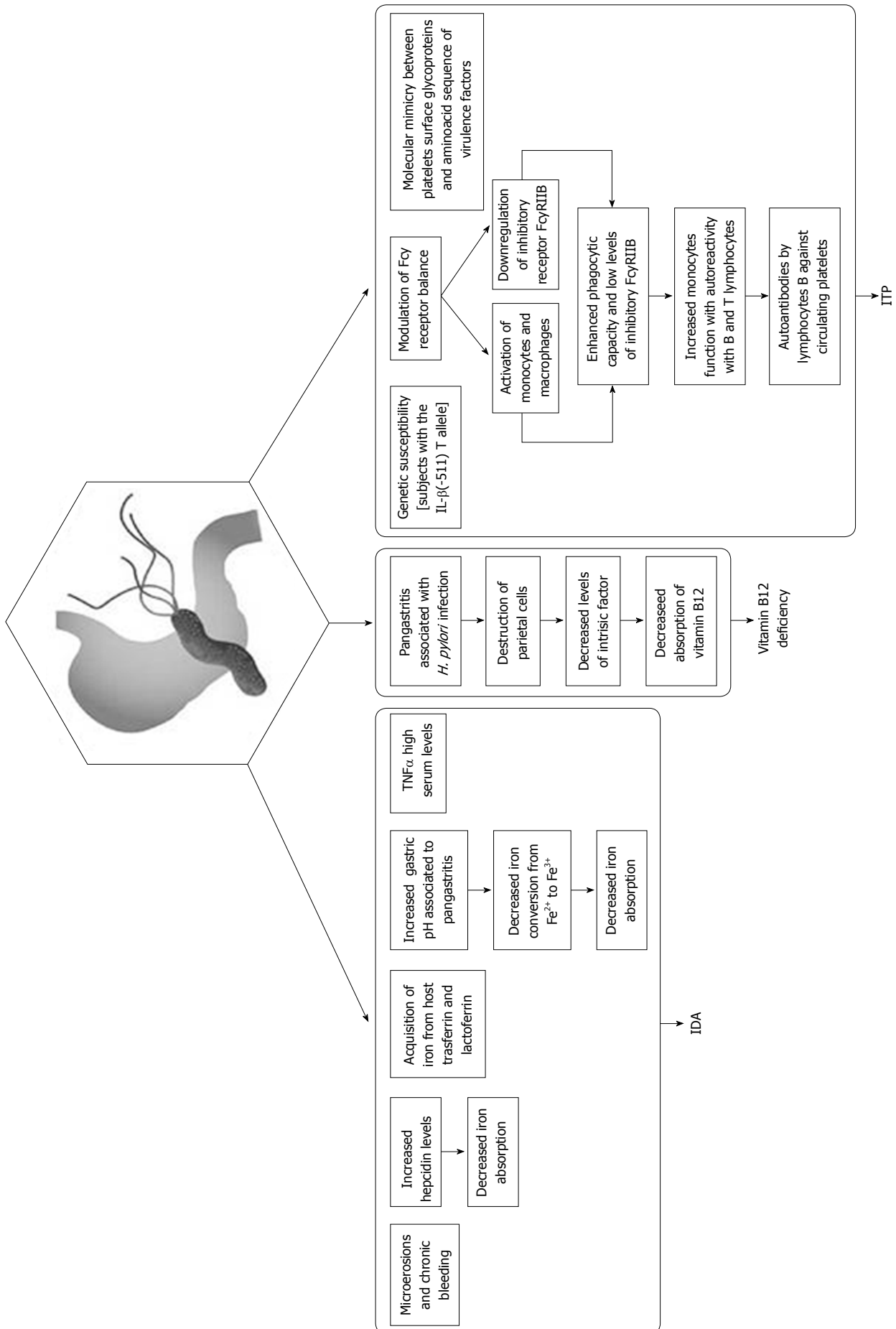


Figure 1 Hematologic diseases associated to *Helicobacter pylori* infection.

OAG, successful eradication of the infection has been reported to lead to an improvement in ocular pressure parameters in treated patients compared with the patients who do not have the infection eradicated<sup>[80]</sup>.

CSC is an ocular disease that causes a temporary reduction in central vision and usually affects only one eye. In the different phases of activity, it is characterized by the presence of liquid passing under the retina, which tends to accumulate under the macula. This results in blurred or distorted vision, with a reduction in visual acuity that can persist even after reabsorption of the fluid if it does not take place rapidly<sup>[115]</sup>. In a systematic review and meta-analysis about the risk factors for CSC published in 2016, Liu *et al.*<sup>[116]</sup> concluded that *H. pylori* infection was a possible risk factor for the occurrence of CSC. Our research group also evaluated this association in a retrospective observational case series and demonstrated that the prevalence of *H. pylori* infection was 78.2% in CSC patients and 43.5% in control subjects<sup>[117]</sup>. *H. pylori* eradication may lead to an improvement in CSC<sup>[115,118,119]</sup>. In particular, Zavoloka *et al.*<sup>[120]</sup> demonstrated that *H. pylori* eradication caused a decrease in the disease duration of 3 mo and in the recurrence frequency of 45.6 % and led to an improved long term prognosis. In fact, after two years, the visual acuity increased, the scotoma frequency decreased and the metamorphopsia frequency decreased.

Blepharitis is characterized by non-granulomatous inflammation of the eyelid margin. It remains difficult to ascertain whether its association with *H. pylori* infection is real because the data are highly discordant<sup>[121,122]</sup>.

## CARDIOVASCULAR DISEASES

The association of *H. pylori* infection with cardiovascular diseases (CD) represents one of the fields of study that has attracted the most attention in the scientific community, despite the evident difficulties in identifying the specific role of *H. pylori* in the pathogenic processes of CD, including coronary atherosclerotic disease (CAD), stroke and myocardial infarction. Mendall *et al.*<sup>[121]</sup> were the first to describe a significant association between *H. pylori* infection and the development of CAD in male subjects aged 45-65 years in a prospective study. CAD is due to dysfunction of the vessel endothelium associated with a simultaneous remodeling of the vessel wall, which is accompanied by an increase in blood pressure, a local inflammatory state and blood clotting; these are all phenomena that overall converge towards the formation of atherosclerotic plaques that are frequently unstable and susceptible to breakage. A possible rupture may compromise the blood circulation and lead to a myocardial infarction (MI). There are multiple causal factors that are involved in the pathogenesis during the initial stages of disease progression, including smoking, arterial hypertension, the presence of mixed dyslipidemia (alterations in total cholesterol levels, low density lipoprotein (LDL) and triglycerides) associated with a simultaneous reduction in high density lipoprotein

(HDL) cholesterol, obesity, diabetes mellitus, and the presence of hyperhomocysteinemia and increased coagulation factors<sup>[123,124]</sup>. The hypothesis that infectious factors may play a role in the pathogenesis of CAD has developed only recently, probably stimulated by evidence that, despite the predisposing factor pattern, there is still a part of the population affected by CAD in which the origin and progression of the disease is inexplicable. Indeed, Lai *et al.*<sup>[125]</sup> have shown that *H. pylori* infection increases the risk of acute coronary artery disease, even in the absence (or after the removal) of risk factors. The most likely pathogenic mechanism of the relationship between *H. pylori* and CAD is the initiation of a chronic inflammatory process associated with infection; however, it should be clarified if the role of *H. pylori* is to trigger the disease or only to accelerate its clinical course. The particular role of *H. pylori* in the pathogenesis of CAD is thought to be related to its ability to trigger a persistent chronic inflammatory state that is established within the gastric epithelium but that can also cause systemic inflammatory effects<sup>[126]</sup>. In the stomach, VacA and urease contribute to the destruction of tight junctions, and this may allow the bacterial agents that breach the lamina propria to come into contact with the cells of the immune system<sup>[127]</sup>. *H. pylori* antigens can either interact directly with the vascular endothelium or may form complexes with LDL/oxLDL cholesterol<sup>[128]</sup>. The subacute inflammation present in chronic diseases, such as CAD, can be determined by the activation of the cells of the immune system or epithelial cells, through pattern recognition receptors (PRRs) that specifically recognize pathogen-associated molecular pattern<sup>[129]</sup>. Both endothelial cells and macrophages present in atherosclerotic lesions show an overexpression of PRRs, such as TLR4, CD14 and TLR2, that are specialized for recognizing bacterial LPS<sup>[130,131]</sup>. Xu *et al.*<sup>[131]</sup> suggested a possible pathophysiological link between lipids, *H. pylori* infection, inflammatory status and CAD based on the overexpression of TLR4 on the surface of macrophages induced by pro-oxidant oxidized LDL. The inflammatory hypothesis was confirmed by several studies conducted with the intent of identifying an association between the increase in inflammatory markers and CAD. Li *et al.*<sup>[132]</sup> and Libby *et al.*<sup>[133]</sup> have highlighted a relationship between CAD and some of the most important inflammation markers, such as C-reactive protein (CRP), interleukin-6 (IL-6) and TNF- $\alpha$ , which are all expressed at higher levels in patients with atherosclerosis than in controls. CRP is an important acute phase protein that is associated with infectious and inflammatory processes or tissue damage; therefore, it is a reliable marker of endothelial dysfunction in CAD<sup>[134,135]</sup>. A second hypothesis about the relationship between *H. pylori* infection and the pathogenesis of CAD is that bacterial antigens can induce T- and B-cell expansion and cause self-reactive antibody production by molecular mimicry. As an example of molecular mimicry, Matsuura *et al.*<sup>[136]</sup> proposed that heat shock protein 60 derived from *H.*

*pylori* (Hp-HSP60) may potentially be related to the pathogenesis of CAD through the stimulation of Th1 lymphocytes, which are induced to produce INF- $\gamma$  and IL-12, or through the activation of macrophages important in forming atherosclerotic plaques. An analysis of the literature clearly shows that serum positivity for CagA is closely associated with heart disease, including atherosclerosis, unstable angina, cardiac syndrome X and coronary artery disease<sup>[137-139]</sup>. CagA is the most important virulence factor of *H. pylori*. CagA-positive strains are associated with increased IL-8 production, which is a marker of inflammation<sup>[140]</sup>. The atherosclerotic cascade is notoriously characterized by an increase in the expression levels of inflammation markers, such as CRP and some interleukins. Discordant data about the association between *H. pylori* infection and CAD are present in the literature. In fact, Manolakis *et al.*<sup>[141]</sup> did not find a correlation between CRP levels and *H. pylori* infection. Similarly, Carter *et al.*<sup>[142]</sup> did not find any correlation between *H. pylori* infection and fibrinogen or von Willebrand's factor levels.

Discordant data about the relationship between *H. pylori* and myocardial infarction (MI) also exist. In 2013, Ikeda *et al.*<sup>[143]</sup> demonstrated that only CagA-positive *H. pylori* strains were associated with an increased risk of MI. In a meta-analysis of 26000 patients, Liu *et al.*<sup>[144]</sup> demonstrated the existence of a significant association between *H. pylori* infection and the risk of MI, whereas Hughes *et al.*<sup>[145]</sup> showed a parallel decline of MI and duodenal ulcers in people born from 1930 to 1980. This study showed that the decline in MI was temporally related to a decline in duodenal ulcers and, by inference, *H. pylori* infection. The discordant data make it impossible to provide an unambiguous definition of *H. pylori* as a causal factor for cardiovascular diseases.

## METABOLIC DISEASES

*H. pylori* infection has also been identified as related to alterations in glycolipid metabolism. The role of *H. pylori* infection in diabetes mellitus (DM), insulin resistance syndrome (IR), and metabolic syndrome (SMet) is still rather controversial, and in some cases, appears to bear marginal weight.

The association between *H. pylori* infection and DM has been suggested recently but still appears rather unclear<sup>[146]</sup>. In a study of a Chinese population, Hsieh *et al.*<sup>[147]</sup> demonstrated how high levels of glycated hemoglobin (HbA1c) were significantly associated with *H. pylori* infection in patients aged > 65 years. Bégué *et al.*<sup>[148]</sup> demonstrated that eradication of *H. pylori* infection in patients with type 1 DM might be associated with better control of glycemia by evaluating HbA1c, which is an important indicator of long-term glycemic control, within two years after the eradication of the infection. In contrast, in 141 patients with type 2 DM, Demir *et al.*<sup>[149]</sup> demonstrated no significant differences in either blood glucose levels or HbA1c values in patients

with *H. pylori* infections compared with controls. In a cross-sectional study including 1285 subjects aged 19-85 years, Yang *et al.*<sup>[150]</sup> suggested the existence of a correlation between *H. pylori* infection and DM. According to Horikawa *et al.*<sup>[151]</sup>, the glycemic control of patients with DM was worse in the presence of *H. pylori* infections, in particular in infections with CagA-positive strains. A few studies demonstrated that eradication could lead to a benefit for glycemic control<sup>[152,153]</sup>. This has not been confirmed by other studies<sup>[154]</sup>. A meta-analysis by Wang *et al.*<sup>[155]</sup> demonstrated the presence of higher levels of inflammatory markers in diabetic patients than in controls. Jeon *et al.*<sup>[156]</sup> demonstrated that IL-6 levels and CRP levels, when used as inflammatory markers, appeared to be very similar in patients with DM, both in patients who were *H. pylori* positive and in those who were negative. As it is now known, chronic *H. pylori* infection is responsible for a low-level inflammatory state of the gastric mucosa, which is defined as the biological response of the mucosa to pathogens, that can involve different regions depending on the host phenotype. Chronic gastritis, such as that found in type 2 DM, atherosclerosis and SMet, is associated with an increase in circulating pro-inflammatory cytokine levels that are capable of interfering with both local and systemic metabolic processes<sup>[157]</sup>. Studies have also been conducted evaluating complications associated with DM. Wang *et al.*<sup>[158]</sup> described a possible correlation between *H. pylori* infection and the risk of nephropathy or neuropathy in an Asian population; however, some other authors did not confirm this correlation<sup>[159]</sup>. Vafaeimanesh *et al.*<sup>[160]</sup> have demonstrated the existence of an association between diabetic patients with microalbuminuria and *H. pylori* infection. Microalbuminuria, as well as neuropathy and heart disease, are very common complications in patients with DM, and patients with CagA-positive *H. pylori* infection are at a greater risk of developing these complications<sup>[152,161]</sup>.

Vafaeimanesh *et al.*<sup>[160]</sup> also focused on the possible correlation between *H. pylori* infection and the development of IR. IR and *H. pylori* infection share pathogenic mediators that are potentially involved in the pathophysiology of the SMet<sup>[161]</sup>. Zhou *et al.*<sup>[162]</sup> showed that *H. pylori* may induce hepatic IR by interfering with the c-Jun/miR-203/SOCS3 pathway, both in humans and in animal models. An analysis of the literature shows that *H. pylori* eradication can improve IR, although this resolution seems to be associated with a progressive increase in BMI and cholesterol levels, as *H. pylori* suppresses ghrelin, which is the hormone responsible for increased appetite, which may explain the weight gain associated with the eradication of infection<sup>[154]</sup>. However, one can hypothesize that the resolution of the symptoms related to infection may lead to recovery of a normal weight. HOMA-IR, which is a model for measuring insulin homeostasis, is higher in patients with *H. pylori* infection than in control<sup>[163-165]</sup>. However, this finding has not been confirmed by other

studies<sup>[166]</sup>.

Considering the aforementioned role of *H. pylori* in IR, there have been several studies in the literature that demonstrate a higher prevalence of SMet in patients with *H. pylori* infection<sup>[167]</sup>. Some studies have revealed changes in the lipid profiles of patients associated with the low-level inflammatory status induced by *H. pylori* infection; this has been demonstrated by Niemelä *et al.*<sup>[168]</sup> in a study involving a Finnish population, in which serum cholesterol and triglyceride levels were higher in infected male subjects. Several studies have demonstrated the presence of these serum lipid profile alterations that can promote atherogenic processes<sup>[169]</sup>.

## ALLERGIC DISEASES

In the literature, a number of studies and meta-analyses have reported an inverse association between *H. pylori* infection and asthma, worldwide<sup>[170-172]</sup>. Blaser *et al.*<sup>[173]</sup> showed the existence of an inverse relationship between *H. pylori* infection and the development of asthma or other allergic diseases, particularly in children and young people with an early onset of allergies. This relationship is controversial in adults, however, and has been confirmed mainly in cases in which the *H. pylori* strains are CagA-positive. Amberbir *et al.*<sup>[174]</sup> showed that the relationship between *H. pylori* and rhinitis is not always inverse. *H. pylori* can almost completely protect against airway hyper-reactivity, broncho-alveolar eosinophilia, and lung inflammation, but this protection, which is strongly dependent on regulatory T (Treg) lymphocytes, is impaired by the complete eradication of the infection through antibiotic therapy<sup>[170]</sup>. The functionality of T reg cells depends on IL-18 production by dendritic cells (DCs) following exposure to *H. pylori*, in the absence of which, a neonatal tolerance to infection is not established. Treg cells are derived from cells with an IL-18 -/- or an IL-18R -/- phenotype that have no protective capabilities against asthma; moreover, IL-18 is fundamental for the conversion of CD4+ T-cells into CD25+ Foxp3+ Treg cells<sup>[175]</sup>. VacA toxin is the most important factor involved in protection against allergies. It appears to disrupt the T helper cell response to Treg cells. It stimulates Treg cells, but it also has the ability to interfere with antigen presentation and T-cell inhibition<sup>[176]</sup>. *H. pylori* strains expressing the active form of VacA are usually also CagA positive<sup>[177]</sup>. Most likely, CagA-positive strains elicit a greater response through modulation of inflammation by Treg cells, but it seems plausible that there is also a pronounced effect on the migration of Treg cells<sup>[178]</sup>. To validate this hypothesis, Engler *et al.*<sup>[179]</sup> demonstrated that the administration of VacA to mouse models was able to provide allergy protection that was comparable to that of active infection. However, these effects seem to be more pronounced if this administration is carried out during the neonatal stage of life, probably because this represents a crucial period during which antigenic

tolerance develops, both in mice and in humans. *H. pylori* influences the immune system by shifting the balance of cytokines to the Th1 type, which suppresses allergic diseases that are dependent on the Th2 cytotype<sup>[180,181]</sup>, protecting infected individuals from developing atopic disease. This might also explain the low prevalence of eosinophilic esophagitis in *H. pylori*-infected subjects<sup>[182]</sup>. When analyzing the association between *H. pylori* infection and allergies one should take into account the hygiene hypothesis and the reduced prevalence of allergic diseases in pet owners. In fact, *H. pylori* infection is associated with poor hygiene, crowding and low socio-economic status. Poor hygiene conditions and low socioeconomic status together with pet ownership may expose to other bacteria or antigens which may reduce the risk of allergic diseases. Therefore, in the interpretation of epidemiologic studies between *H. pylori* infection and allergies, possible confounding factors should be considered before drawing conclusions on putative cause-effect relationship<sup>[180-182]</sup>.

## HEPATOBIILIARY DISEASES

Recent studies have shown the involvement of *H. pylori* in the etiopathogenesis of a number of liver diseases<sup>[183,184]</sup>. Polyzos *et al.*<sup>[185]</sup> showed a higher serum level of anti-*H. pylori* IgG in patients with nonalcoholic fatty liver disease (NAFLD) than in non-NAFLD patients. Many other studies have shown an association between NAFLD and *H. pylori*<sup>[186,187]</sup>. *H. pylori* could be related to a worsening of the inflammatory status of the liver, regardless of the etiology of the underlying liver disease<sup>[184]</sup>. Fukuda *et al.*<sup>[188]</sup> have proposed that because of the increase in gastric and intestinal mucosal permeability, *H. pylori* antigens could have access to the blood stream and reach the liver through the portal vein, thus causing liver damage. Some authors, such as Sumida *et al.*<sup>[189]</sup>, suggest that the eradication of *H. pylori* may play an important role in the treatment of nonalcoholic steatohepatitis (NASH), through the decrease of TNF $\alpha$ , one of the pro-inflammatory cytokines that, together with IL-1 $\beta$ , IL-6 and IL-8, is also directly correlated with the etiopathogenesis of IR, and of NASH<sup>[190,191]</sup>. Adiponectin is also involved in the etiopathogenesis of NAFLD. In fact adiponectin deficiency is associated with a pro-inflammatory condition, as it is observed in obesity and other metabolic disorders<sup>[192]</sup>. According to Polyzos *et al.*<sup>[185]</sup> a higher prevalence of low levels of circulating adiponectin, as well as of higher levels of anti-*H. pylori* IgG and elevated TNF $\alpha$  are observed in NAFLD patients compared to controls.

The correlation between *H. pylori* and hepatic fibrosis was analyzed mostly in animal models. Ki *et al.*<sup>[193]</sup> demonstrated in a murine model that *H. pylori* infection may accelerate hepatic fibrosis through increased TGF- $\beta$ 1-induced pro-inflammatory signaling pathways in hepatic stellate cells and that *H. pylori* infection might increase the risk of TGF- $\beta$  1-mediated tumorigenesis



[illegible]

Allergic diseases	Pro	Con
		Chen <i>et al</i> <sup>[170]</sup>
		Wang <i>et al</i> <sup>[171]</sup>
		Zhou <i>et al</i> <sup>[172]</sup>
		Blaser <i>et al</i> <sup>[173]</sup>
		Amberbir <i>et al</i> <sup>[174]</sup>
		Oertli <i>et al</i> <sup>[175]</sup>
		Oertli <i>et al</i> <sup>[176]</sup>
		Cook <i>et al</i> <sup>[178]</sup>
		Engler <i>et al</i> <sup>[179]</sup>
		Grad <i>et al</i> <sup>[180]</sup>
		Sheikh <i>et al</i> <sup>[181]</sup>
		Molina-Infante <i>et al</i> <sup>[182]</sup>

by disturbing the balance between apoptosis and proliferation of hepatocytes. Senescence marker protein-30, a protein that prevents oxidative stress and hepatic cell apoptosis<sup>[194]</sup> is reduced in the liver of mice treated with CCL4 and *H. pylori* compared to those treated with CCL4 only<sup>[195]</sup>.

*H. pylori* has been considered as putative a triggering factor for autoimmune extragastric conditions<sup>[196,197]</sup>. Goo *et al*<sup>[198]</sup> in 2008 showed that C57BL/6 mouse infected with *H. pylori* developed a form of primary biliary cirrhosis (PBC) very similar to that described in humans. Because of the high serum levels of IgG against *H. pylori* VacA, the authors suggested that anti-VacA antibodies might play a role in the development of PBC. Shapira *et al*<sup>[199]</sup> found higher prevalence of anti-*H. pylori* IgG in patients with PBC compared to controls. Nilsson *et al*<sup>[200]</sup> evaluated 24 liver biopsies obtained from patients with PBC and primary sclerosing cholangitis (PSC) and found that *H. pylori* was present in 20/24 patients. The authors suggested that the pathogenic link between *H. pylori* infection and autoimmune liver diseases might be a form of molecular mimicry between *H. pylori* and liver antigens. In fact, a similar amino acid sequence homology between the main mitochondrial autoepitopic region from the E2 subunit of the pyruvate dehydrogenase complex and the *H. pylori* urease was found. However Bogdanos *et al*<sup>[201]</sup> showed that the existence of this homology does not necessarily imply cross-reactivity. *H. pylori* DNA was detected in biliary epithelium in PSC patients compared to controls, corroborating the hypothesis that biliary reflux could lead to *H. pylori* contamination of the proximal biliary system, contributing to the development and / or progression of PSC in some patients<sup>[202]</sup>. Patients with PSC may also suffer from ulcerative colitis (UC). It has therefore been suggested that an increased intestinal permeability in UC patients may promote the translocation of *H. pylori* into the hepatobiliary system, thus triggering autoimmunity mechanisms<sup>[203]</sup>.

The role of *H. pylori* in hepatic carcinogenesis is controversial. There are several known risk factors for HCC, such as alcoholism, PCB, PSC and chronic viral infections<sup>[204]</sup>. The finding of *H. pylori* in hepatic biopsies of patients with HCC led to the hypothesis that *H. pylori* might be playing a role also in the development of this infection<sup>[205]</sup>. In several studies, liver biopsies of

patients with HCC or even cholangiocarcinoma were positive for *H. pylori*<sup>[206,207]</sup>. Dore *et al*<sup>[208]</sup> demonstrated *H. pylori* presence in patients with HCC, liver cirrhosis and chronic hepatitis, using both PCR on liver tissue and serology. Prevalence of *H. pylori* infection was as high as 73% in patients with HCC. Verhoef *et al*<sup>[209]</sup> and Pellicano *et al*<sup>[210]</sup> also found positivity for *H. pylori* in 45% of patients with HCC vs 10% of controls, and in 85% of patients with HCC vs 33% of controls, respectively. Finally, it has been suggested that infection by CagA positive *H. pylori* strains might play a major role in the development of *H. pylori*-associated liver diseases<sup>[211]</sup>.

To date, there is no sufficient evidence to draw a firm conclusion on the relationship between *H. pylori* infection and liver diseases.

## CONCLUSION

*H. pylori* is the cause of a number of gastroduodenal diseases including peptic ulcer disease and gastric adenocarcinoma which are the results of an interaction between bacterial virulence factors, host and environmental factors. Many extra-gastric manifestations have been reported to be linked to *H. pylori* infection (Table 1). However, most evidences derive from epidemiological studies where a number of confounding factors have not been analyzed in depth, thus making it impossible to establish a cause-effect correlation. As a result of this, to date, according to the last Consensus Report on the management of *H. pylori* infection (*i.e.*, Maastricht V/Florence Guidelines<sup>[13]</sup>) *H. pylori* infection should be sought and, if present, eradicated only in patients with IDA, ITP and vitamin B12 deficiency.

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