

World Journal of *Gastroenterology*

World J Gastroenterol 2018 July 28; 24(28): 3055-3200



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World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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PUBLICATION DATE
July 28, 2018

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Helicobacter pylori in human health and disease: Mechanisms for local gastric and systemic effects

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Author contributions: Bravo D, Hoare A, Soto C, Valenzuela MA and Quest AF contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version; Bravo D, Hoare A and Soto C were involved in the design of Table 1 and Figure 1.

Supported by Comisión Nacional de Investigación Científica y Tecnológica-Fondos de Financiamiento de Centros de Investigación en Áreas Prioritarias, No. 15130011 (to Quest AF); Fondo Nacional de Desarrollo Científico y Tecnológico, No. 1170925 (to Quest AF) and No. 1171615 (to Valenzuela MA); Fondo para la Investigación en Odontología Universidad de Chile, No. 17/020 (to Bravo D).

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

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Manuscript source: Invited manuscript

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Received: April 10, 2018

Peer-review started: April 10, 2018

First decision: April 26, 2018

Revised: May 17, 2018

Accepted: June 27, 2018

Article in press: June 27, 2018

Published online: July 28, 2018

Abstract

Helicobacter pylori (*H. pylori*) is present in roughly 50% of the human population worldwide and infection levels reach over 70% in developing countries. The infection has classically been associated with different gastro-intestinal diseases, but also with extra gastric diseases. Despite such associations, the bacterium frequently persists in the human host without inducing disease, and it has been suggested that *H. pylori* may also play a beneficial role in health. To understand how *H. pylori* can produce such diverse effects in the human host, several studies have focused on understanding the local and systemic effects triggered by this bacterium. One of the main mechanisms by which *H. pylori* is thought to damage the host is by inducing local and systemic inflammation. However, more recently, studies are beginning to focus on the effects of *H. pylori* and its metabolism on the gastric and intestinal microbiome. The objective of this review is to discuss how *H. pylori* has co-evolved with humans, how *H. pylori* presence is associated with positive and negative effects

in human health and how inflammation and/or changes in the microbiome are associated with the observed outcomes.

Key words: *Helicobacter pylori*; Co-evolution; Extragastric diseases; Inflammation; Microbiome

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Core tip: This review focuses on discussing how *Helicobacter pylori* (*H. pylori*) has co-evolved with humans, potential mechanisms that may explain both positive and negative correlations in population-based studies between *H. pylori* infection and the development of several diseases, as well as how inflammation and/or changes in the microbiome might be linked to the respective outcomes. Our analysis of the literature reveals that human infection by *H. pylori* has a longstanding history, whereby the consequences therefore are extremely complex and not always detrimental to the human host. Thus, future research should focus on determining how potentially beneficial consequences of this interaction could be promoted all the while preventing the disease-causing effects in humans.

Bravo D, Hoare A, Soto C, Valenzuela MA, Quest AF. *Helicobacter pylori* in human health and disease: Mechanisms for local gastric and systemic effects. *World J Gastroenterol* 2018; 24(28): 3071-3089 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i28/3071.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i28.3071>

INTRODUCTION

Helicobacter pylori (*H. pylori*) infects approximately 50% of the human population worldwide and the infection could reach more than 70% in developing countries^[1,2]. The consequences of infection have been associated with the development of different gastro-intestinal diseases, such as gastric ulcers, gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma and biliary tract cancer^[3]. Moreover, *H. pylori* infection has also been associated with extra gastric diseases, such as ischemic heart diseases^[4], type 2 diabetes mellitus^[5], anemia^[6], adverse metabolic traits in obese subjects^[7] and insulin resistance^[8], to mention but a few.

Despite the existence of such associations, these diseases occur only in a small percentage of infected people, suggesting that the bacteria frequently persists in the human host without inducing any obvious signs of disease, and it has been suggested that *H. pylori* may also play a beneficial role in human health^[9-14]. Indeed, recent studies indicate that the decreasing incidence of *H. pylori* in the developing world is paralleled by an increase in the incidence of allergies and autoimmune diseases^[15]. Furthermore, the absence of *H. pylori* has

been linked to elevated incidence of diseases, such as multiple sclerosis and celiac disease, among others^[16-18].

Several studies have focused on understanding the local and systemic effects triggered by this bacterium in order to understand how *H. pylori* can produce such diverse effects in the human host. One of the best-characterized mechanisms involved in such effects is likely to be the damage to the host induced by local and systemic inflammation^[19]. However, more recently, studies are beginning to focus on the effects of *H. pylori* and its metabolism on the gastric and intestinal microbiome^[20-23]. This emerging field of interest could explain, at least in part, the wide variety of effects that are currently attributed to the presence of *H. pylori* in the human body.

In this review, we discuss such gastric and extragastric effects of *H. pylori* and the possible mechanisms involved.

H. PYLORI AND THE CO-EVOLUTION WITH HUMANS: NEGATIVE AND POSITIVE EFFECTS

H. pylori is a Gram-negative bacterium whose presence in the stomach of infected individuals is linked to the development of several gastric diseases, such as chronic gastritis. Although it is estimated that 50% of the world population is infected by *H. pylori*, only a small percentage of infected patients develop more severe pathologies, such as ulcers (10%-15%) and stomach adenocarcinomas (less than 1%)^[1,2], the latter representing 15.4% of the cancers produced by infectious agents worldwide in 2012^[24]. These values suggest that while relevant to the development of severe diseases, including gastric cancer, this pathogen could also play other roles in the human host.

It is now well established that *H. pylori* has been a highly prevalent pathogen in humans for over sixty thousand years and that infection occurs mainly in the intimate family environment or through vertical transmission^[25]. These continuous infections and contact with other bacterial strains promoted the existence of a large number of mutations and genetic variability among bacteria due to horizontal transfer of information^[26-28]. The emerging differences have been characterized particularly with respect to geographic distribution and such studies have revealed that the observed genomic alterations allow *H. pylori* to survive in different microenvironments^[29,30]. Moreover, these genetic modifications are thought to have led to the emergence of less virulent strains, which may explain the low percentage of patients affected with serious pathologies, such as adenocarcinomas^[31].

The events during human evolution associated with initial acquisition *H. pylori* are thought to have been the development of agrarian practices, as evidenced by the presence of DNA remnants in the *H. pylori* genome, such

as the *vir* genes of *Agrobacterium tumefaciens*^[32]. Also population migration is likely to have contributed to the acquisition of genes or genomic islands important for *H. pylori* virulence. One of them is the *cagPAI* genomic island, where *cagA* is one of the most important virulence genes associated with an increase in the activation of pro-inflammatory pathways and the production of pro-inflammatory cytokines in the stomach mucosa^[33,34]. According to genomic analyses of *H. pylori*, European colonization trips to South America may have contributed to the acquisition of *cagA* by indigenous people living in the Andes, who possessed *H. pylori* without a functional *cagA* gene^[30,35]. Moreover, other studies analyzing South American populations, such as the Colombians, have determined that the mountain people with greater similarity to the native people of that region have a higher incidence of gastric cancer compared with residents of coastal towns, who were more strongly influenced by the colonization of African migrant populations. Currently, this sector of the population has a low incidence of gastric cancer associated with *H. pylori* infection^[36,37].

However, it has been observed that although in certain populations positive CagA strains are more numerous (as in parts of Eastern Asia), there are specific characteristics that make it unlikely for them to spread to the rest of the world, such as Western countries, with fewer positive CagA strains. These observations suggest that "fitness traits" exist, which aid in the survival of the bacteria in different hosts, in addition to other well-known factors, like difference in the lifestyles, socioeconomic levels and diet of the host population^[38]. Japan, for example, has the highest rate of gastric cancer worldwide, associated with the highest presence of CagA (57%); however a lower seroprevalence is observed compared to other populations^[39]. In contrast, despite the high prevalence of *H. pylori* in India, a low rate of gastric cancer is registered (known as the "Indian Enigma"). One of the main hypotheses seeking to explain this enigma is that the higher rate of enteric infections in more poorly developed countries could boost the immune system and limit the consequences of *H. pylori* infection. In addition, the high diet content of peppers, which represent an important ingredient in the Indian diet, may protect against *H. pylori* infection^[40]. In conjunction, these examples support the hypothesis that a variety of factors contribute to the fitness of *H. pylori* in different human host populations.

Therefore, bacterial and host fitness are very relevant in *H. pylori* infection. In particular, host genetics likely affect the progression of pathologies associated with *H. pylori* infection. Indeed, specific polymorphisms in genes coding for cytokines, such as IL-1 β , IL-8, IL-10 and TNF- α , are associated with an increase in the pro-inflammatory responses, greater colonization and infection, as well as an increased risk of gastric cancer^[41-45]. Also, polymorphisms in innate immunity genes, such as the toll-like receptor 4 (TLR4), are relevant because TLR4 is implicated as a receptor responsible for *H. pylori* induced signaling in gastric

epithelial cells. Moreover, epigenetic changes due to hypermethylation in the promoter regions of tumor suppressor genes, such as *LOX*, *HAND1* and *APC*, and the alteration as well as deregulation of microRNAs (miRs) are associated with a higher prevalence of gastric cancer following *H. pylori* infection^[46,47].

Despite clearly representing a human pathogen, evidence is available suggesting that this bacterium could also be considered a commensal bacteria in the human host. This notion is supported by the simple observation that the bacteria is present in so many individuals, yet generates relatively few symptoms or pathologies. This raises the issue as to whether to refer to *H. pylori* as a commensal or pathogen, because pathologies are likely not only to be associated with specific traits of *H. pylori*, but also with a series of specific conditions in the human host.

H. pylori has been found as part of the normal oral microbiota and part of the microbiota of the stomach in the absence of inflammation^[48,49]. In addition, it has been reported that *H. pylori* infection is not associated with the onset of the gastric cancer, but rather with its recurrence and chronicity^[50]. Moreover, the presence of *H. pylori* in the stomach microbiota may result in changes in the normal microbiota^[21,23].

In this context, it is worth mentioning that several studies have attributed positive effects to *H. pylori* infection. These include the suppression of bacteria that cause tuberculosis (*Mycobacterium tuberculosis*), protection against asthma, Crohn's disease, esophageal reflux, diarrheal diseases, as well as esophageal cancer^[9-14]. This controversy has led to the discussion whether eradication of *H. pylori* is recommendable to help restore the host's health status, or if alternative strategies should be developed to control virulence of the bacteria, thereby avoiding the appearance of ulcers and adenocarcinomas without eliminating the positive effects that this bacterium may have^[51]. With this in mind, it is not surprising that *H. pylori* is so widely studied and considered a relevant target in many therapies.

H. PYLORI COLONIZATION: PROTECTION AND PROMOTION OF INFLAMMATORY DISEASES

Protective effect of *H. pylori* colonization

H. pylori infection is inversely associated with the development of some diseases, suggesting that the presence of these bacteria may also be beneficial to the host, as is the case for reducing the risk of obesity, childhood asthma, inflammatory bowel disease and celiac disease among others. In some cases the data available strongly support the notion that *H. pylori* presence is beneficial, while for others convincing data still remains at large (Figure 1 and Table 1).

Asthma: Asthma is characterized by a chronic hyper-responsiveness to specific and non-specific stimuli that

Table 1 Association of different diseases with the presence or absence of *Helicobacter pylori*

Disease	Association	Reference	Type/model of study	Sample size	Statistical analysis	<i>H. pylori</i> detection	Diagnosis of the pathology
Asthma	NA	Holster <i>et al</i> ^[53] , 2012	Cohort study	545 childrens	Chi-square and <i>t</i> -tests. Univariate and multiple logistic regression analyses ^a	Serum anti- <i>H. pylori</i> immunoglobulin G, and CagA by ELISA	Positive diagnosed asthma by a medical questionnaire
	Positive	Den Hollander ^[54] , 2016	Cohort study	3797 childrens	Chi-square test. Multivariate logistic regression analysis. Odd ratios 95%CI ^b	immunoglobulin G levels in serum	Positive diagnosed asthma by a medical questionnaire
	Inverse	Chen and Blaser ^[50] , 2007	Cohort study	7663 adults	Unconditional logistic regression models. Odd ratios 95%CI ^b	immunoglobulin G levels in serum	Positive diagnosed asthma by a medical questionnaire
		Chen and Blaser ^[55] , 2008	Case-control study	7412 individuals	Chi-square and <i>t</i> -tests ^b	Wampole ELISA	Positive diagnosed asthma by a medical questionnaire
Inflammatory Bowel Disease		Sommer <i>et al</i> ^[57] , 1998	<i>Ex vivo</i> study. Isolated T cells from gastric biopsy	Biopsies from 30 patients	Not mentioned	Histological detection	Endoscopic examination
		Bamford <i>et al</i> ^[58] , 1998	<i>Ex vivo</i> study. Isolated T cells from gastric biopsy	<i>n</i> patients = 5, <i>n</i> control = 3	<i>t</i> -test ^b	Rapid urease test (RUT) or histopathology	-
		Oertli <i>et al</i> ^[59] , 2013	<i>In vitro</i> study. C57BL/6 mice	60 mice	Chi-square. Mann Whitney <i>U</i> -test and Kruskal-Wallis test ^a	CFU from homogenised tissues	-
		De la Pena-Ponce <i>et al</i> ^[60] , 2017	<i>In vitro</i> study. Airway epithelial cells	Between <i>n</i> = 3 to <i>n</i> = 10	One way ANOVA ^a	CagA detection by western blot	-
	Inverse	Higgins <i>et al</i> ^[61] , 2011	Meta-analysis and <i>In vitro</i> study. C57BL/6 mice	Between <i>n</i> = 3 to <i>n</i> = 9	Odd ratios 95%CI. <i>P</i> -value < 0.1. One way ANOVA and <i>t</i> -test ^b	Not mentioned	-
Celiac Disease		Lord <i>et al</i> ^[62] , 2018	Cross-sectional study	704 individuals	Odd ratios 95%CI ^b	Not mentioned	Not mentioned
		Castano-Rodriguez <i>et al</i> ^[63] , 2017	Meta analysis	6130 patients and 74659 controls	Chi-square, <i>t</i> -test, fixed effect model and odd ratios 95%CI ^b	Histology, culture, rapid urease test, serology and/or urea breath test (UBT)	Not mentioned but differentiated among Crohn's disease, ulcerative colitis, IBD, and unclassified
	Inverse	Lebwohl <i>et al</i> ^[65] , 2013	Cross-sectional study	136179 individuals	Odd ratios and 95%CI ^b	Polyclonal immunochemical stain	Duodenal and gastric biopsies
Multiple Sclerosis		Narang <i>et al</i> ^[18] , 2017	Cross-sectional study	324 childrens	Chi-square test or Fisher exact test, and odd ratio and 95%CI ^a	Giemsa staining and rapid urease test (RUT)	Serum levels of immunoglobulin A-tissue transglutaminase antibodies (IgA-tTG > 18 U/mL = CD+). Further analysis by upper gastrointestinal endoscopy for biopsies to confirm
		Lucero <i>et al</i> ^[17] , 2017	Case-control study	66 patients and 50 controls	Chi-square test or Fisher exact test, and odd ratio and 95%CI ^b	Rapid urease test (RUT), histological evaluation and PCR	Duodenal histopathology and immunoglobulin A-tissue transglutaminase (IgA-tTG) serology
	Inverse	Yao <i>et al</i> ^[67] , 2016	Meta analysis	1553 patients and 1253 controls	Chi-square test, odd ratio and 95%CI ^b	ELISA, immunofluorescence and latex agglutination tests	Not mentioned
Positive		Jaruvongvanich ^[68] , 2016	Meta analysis	1902 individuals	Chi-square test, odd ratios, multivariate models and random-effect models ^a	Urea breath test (UBT), rapid urease test, PCR and ELISA	Diagnosed by neurologist using the McDonald criteria (based on clinical presentations, finding on magnetic resonance imaging and cerebrospinal fluid profile)
		Efthymiou <i>et al</i> ^[16] , 2016	Cohort study	129 patients, 49 controls	Two-tailed <i>t</i> -test ^a	Serum anti- <i>H. pylori</i> , anti-VacA, anti-CagA, anti-Hsp60 ELISA	Not mentioned, but relapsing remitting MS (RRMS) and secondary progressive MS (SPMS) are differentiated

Ischemic Heart Diseases	Positive	Liu <i>et al</i> ^[4] , 2015	Meta analysis	5829 patients and ~16000 controls	Fixed and random effect models. Odd ratios and 95%CI. <i>P</i> -value = 0.06	Not mentioned	Medical records
		Shmueli <i>et al</i> ^[3] , 2014	Cohort study	173 patients and 127 controls	Multivariate analysis. Odd ratios 95%CI. <i>t</i> -test and ANOVA ^a	Serum anti- <i>H. pylori</i> immunoglobulin G, and CagA by ELISA	Myocardial perfusion imaging in patients with angina symptoms, chest pain, suspected CAD, cardiac related symptoms or risk stratifications in patients with known CAD
Anemia	Positive	Huang <i>et al</i> ^[72] , 2014	Retrospective cohort study	17332 patients and 69328 controls	Chi-square and <i>t</i> -tests ^a	Not mentioned	Ischemic stroke
		Xu <i>et al</i> ^[6] , 2017	Retrospective study	17791 individuals 7804 Hp positive	Chi-square and <i>t</i> -tests. Odd ratios 95%CI ^a	Serum anti- <i>H. pylori</i> immunoglobulin G and immunoglobulin M ELISA	Using haemoglobin level
		Flores <i>et al</i> ^[76] , 2015	<i>In vitro</i> study. AGS human gastric adenocarcinoma cell line	<i>n</i> = 7 experiments	One way ANOVA or non-parametric <i>t</i> -test ^b	CFU from homogenised cells	-
		Flores <i>et al</i> ^[75] , 2017	<i>In vitro</i> study. AGS human gastric adenocarcinoma cell line	<i>n</i> = 3 experiments	One way ANOVA or non-parametric <i>t</i> -test ^a	CFU from homogenised cells	-
NAFLD	Positive	Kato <i>et al</i> ^[77] , 2017	<i>In vitro</i> study. Isolated <i>H. pylori</i> strains from patients and controls (whole genome sequencing)	4 patients and 4 controls	<i>t</i> -test ^b	Biopsy directly inoculated in growth medium	Measuring serum iron and ferritin
		Chen <i>et al</i> ^[7] , 2017	Cohort study	2263 individuals	Chi-square and <i>t</i> -tests ^a	13C-labeled urea breath test (UBT)	Using the NALFD criteria suggested by the Chinese Liver Disease Association and the Clinical Diagnosis Standards
Insulin resistance	Positive	Huang <i>et al</i> ^[78] , 2009	<i>In vivo</i> study. C57BL/6 mice	<i>n</i> = 20	Chi-square test ^a	Gram staining, PCR and urease/catalase reactions	Histopathology and immunochemical analysis
		Aydemir <i>et al</i> ^[62] , 2005	Cross-sectional Study	63 patients	<i>t</i> -test ^b	Giemsa staining	HOMA-IR
		Gunji <i>et al</i> ^[83] , 2009	Cross-sectional Study	1107 participants (1008 IR- y 99 IR+)	Chi-square and <i>t</i> -tests ^a	Serum anti- <i>H. pylori</i> immunoglobulin G ELISA	HOMA-IR
		Chen <i>et al</i> ^[84] , 2015	Cohort study	811 individuals	Chi-square or Fisher exact test ^a	Serum anti- <i>H. pylori</i> immunoglobulin G ELISA	HOMA-IR
		Polyzos <i>et al</i> ^[86] , 2011	Meta analysis	2120 participants	<i>t</i> -test ^a	Gastric mucosa histologic examination for <i>H. pylori</i> presence, gastric mucosa rapid urease test (CLO test), serum <i>H. pylori</i> -specific immunoglobulin G antibody concentration (ELISA), serum <i>H. pylori</i> -specific immunoglobulin G antibody concentration (chemiluminescence)	HOMA-IR
		Yildirim <i>et al</i> ^[89] , 2016	Cohort study	41 patients and 27 controls	<i>t</i> -test ^b	13C-labeled urea breath test (UBT) and gastroscopy	HOMA-IR
		Upala <i>et al</i> ^[8] , 2016	Meta analysis	27544 participants	Chi-square. Odd ratio 95%CI ^a	Urea breath test (UBT), rapid urease test (RUT), PCR and ELISA	HOMA-IR

Type 2 Diabetes Mellitus	NA	Anastasios <i>et al</i> ^[61] , 2002	Cross-sectional study	67 patients and 105 controls	Chi-square. <i>P</i> -value < 0.05 Fixed and random effect models. Odd ratios and 95% CI ^a	Giemsa staining 13C or 14C urea breath test, stool antigen test, anti- <i>H. pylori</i> antibody, rapid urease test, histology or biopsy, culture Serum anti- <i>H. pylori</i> immunoglobulin G and immunoglobulin A ELISA Stool <i>H. pylori</i> -antigen detection by Enzyme immunoassay (EIA)	Previously diagnosed patients Not mentioned
		Li <i>et al</i> ^[5] , 2017	Meta analysis	57397 participants			
		Bener <i>et al</i> ^[61] , 2007	Case-control study	210 patients	<i>t</i> -test ^a		
	Positive	Devrajani <i>et al</i> ^[62] , 2010	Case-control study	74 patients and 74 controls	Chi-square ^a	Using venous blood glucose values or currently taking diabetic medication Fasting blood sugar (FBS) level, random blood sugar (RBS) level and hemoglobin A1c	Using venous blood glucose values or currently taking diabetic medication Fasting blood sugar (FBS) level, random blood sugar (RBS) level and hemoglobin A1c
		Aslan <i>et al</i> ^[63] , 2006	Cross-sectional Study	103 patients	<i>t</i> -test ^a	Rapid urease test (RUT) and histopathologic examination	
Periodontitis	Positive	Nasif <i>et al</i> ^[64] , 2016	Cross-sectional Study	100 patients	<i>t</i> -test, Mann Whitney <i>U</i> -test ^a	Serum anti- <i>H. pylori</i> IgG ELISA	Postprandial glucose level, glycated hemoglobin (HbA1c) and body mass index (BMI). Serum 8-OHdG and Ox-LDL
		Sujatha <i>et al</i> ^[106] , 2015	Cohort study	40 patients	Fisher exact test ^a	Rapid urease test, histopathological examination	Periodontal examination
		Pei <i>et al</i> ^[102] , 2015	Cross-sectional study	70 patients and 70 controls	The ratios were compared using χ^2 test and χ^2 statistics was adjusted. <i>t</i> -test ^a	PCR for urease C gene	Probing depth (PD), plaque index (PI) and bleeding index (BI)
		Hu <i>et al</i> ^[107] , 2016	<i>In vitro</i> study. THP-1 cells	28 samples from 14 patients	One way ANOVA ^a	real-time PCR	Probing depth (PD), plaque index (PI), bleeding index (BI), attachment loss (AL)

Different studies were analyzed considering the association of Helicobacter pylori (*H. pylori*) presence/absence with the corresponding disease (type of association), the type of study and model, the sample size, the type of statistical analysis employed, the method used for *H. pylori* detection and the method used for the disease diagnosis. Positive and inverse associations are indicated. ^a*p* < 0.05, ^b*p* < 0.01. NA: Indicates no association; IBD: Inflammatory bowel disease; IR: Insulin resistance.

favor obstruction of the airways, characterized by increased serum immunoglobulin E (IgE) levels combined with infiltration of the lungs by eosinophils, mast cells and activated CD4⁺ T-cells, a process orchestrated by effector T-helper 2 cells, implying the participation of the cytokines IL-4, IL-13, IL-5 and IL-9 in these events^[52]. Several studies have proposed an inverse association between the presence of *H. pylori* infection and asthma, although this association is still controversial. While Holster *et al*^[53] showed in a cohort of 545 children that there are no significant differences in *H. pylori* prevalence between children with asthma (7.1% vs 9.4%), others have shown either positive or negative effects. Significantly higher prevalence of asthma was reported in *H. pylori* positive compared to *H. pylori* negative children, based on a cohort study of 3759 children^[54]. In contrast, studies involving more than 7000 adults^[10,55] showed that *H. pylori* presence and also the CagA protein were inversely correlated with the development of asthma. More recently, Miftahussunur *et al*^[15] reviewed several studies, surveys, cohort studies and meta-analyses in different European countries and in the United States of America (USA), involving a large number of persons. They concluded that there is a significant but weak inverse correlation between *H. pylori* infection, allergies and asthma, suggesting that *H. pylori* infection may have a beneficial protective role against development of these diseases^[15].

The proposed mechanism involves the bacterial induction of naïve T cells, mainly in T helper 1 (Th1) rather than helper 2 (Th2) subsets^[56,57]. On the other hand, it has also been observed that T-regulatory (Treg) cells are increased in the gastric mucosa of *H. pylori*-infected humans^[58]. Moreover, the *H. pylori* virulence factors γ -glutamyl transpeptidase and VacA, induced Treg cells in the mouse gastric mucosa, resulting in the development of tolerance and a reduction in allergic responses^[59]. Also, in a recent study using infant and adult airway epithelial cells infected with *H. pylori*, IL-8 synthesis increased 4-fold in infant versus adult cultures, suggesting that the infant epithelium elicits a higher immune response than the adult tissue. This mechanism is mediated by the *H. pylori* type IV secretion system and stimulation of the p38 MAP kinase pathway^[60], and VacA was found to potentially also contribute to this mechanism.

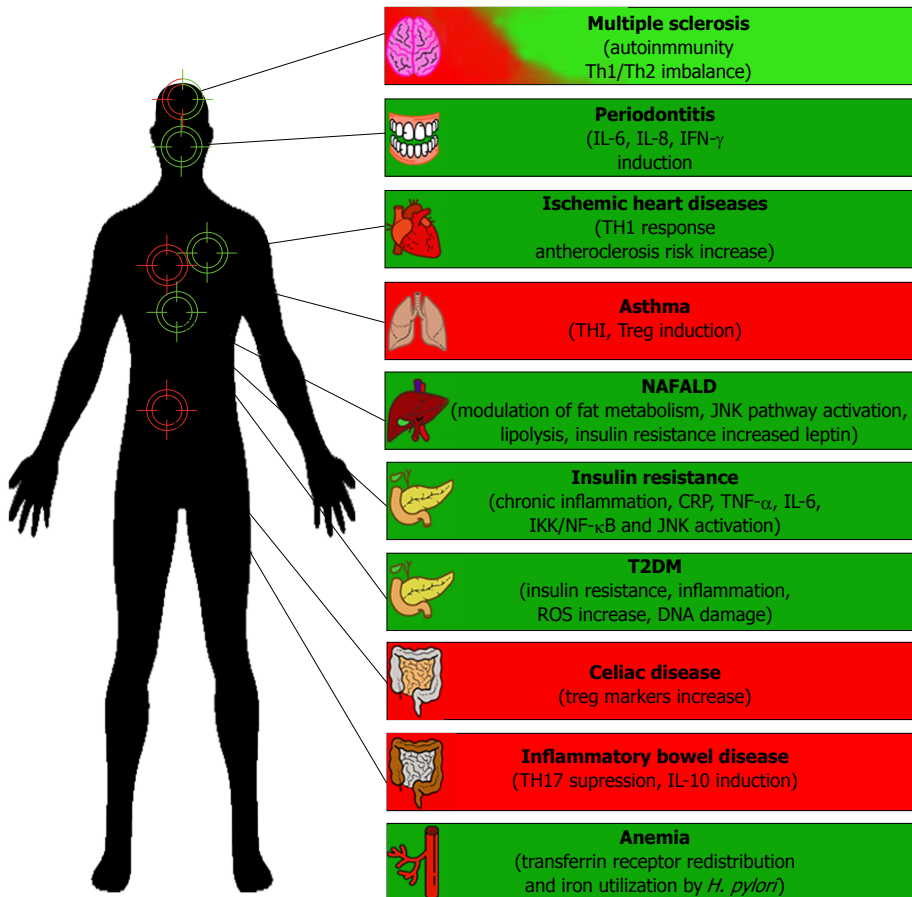


Figure 1 *Helicobacter pylori* and extra-gastric disease association. Green squares represent positive correlations between *Helicobacter pylori* (*H. pylori*) and the disease, while red squares represent inverse correlations between *H. pylori* and the disease. Multiple sclerosis is shown in red and green because there is information suggesting both positive and inverse correlations. NAFALD: Non-alcoholic fatty acid liver disease; T2DM: Type 2 diabetes mellitus.

Inflammatory bowel disease: Inflammatory bowel disease (IBD) is a chronic inflammatory intestinal disease that develops as the consequence of a deregulated immune response. Interestingly, several studies have sought to establish a relationship between *H. pylori* infection and IBD. Higgins *et al.*^[61] demonstrated the effect of gastric *H. pylori* colonization on a distant bacterial-host immune system interaction in an experimental model of colitis. Also, *H. pylori* was shown to suppress the Th17 response to *S. Typhimurium* infection, but did not alter the Th2 or Treg response. Moreover, the authors showed that the co-infection by *H. pylori*/*S. Typhimurium* decreases inflammation in both the cecum and the stomach and that *H. pylori* infection induces IL-10 in the mesenteric lymph nodes, suggesting an extra-gastric mechanism for immunomodulation. Also, IBD protection is suggested to be linked to the *cagA*-positive status of the strain^[62]. More recently, a meta-analysis performed by Castaño-Rodríguez *et al.*^[63] also revealed that *H. pylori* may exert an immunomodulatory effect and thereby favor the development of IBD.

Celiac disease: Celiac disease (CD) is an autoimmune disease whose prevalence in the USA has increased up to 4-fold in the past 50 years^[64]. A cross-sectional study of

patients who underwent esophago-gastroduodenoscopy with analysis of gastric and duodenal biopsies during a 4.5-year period showed that *H. pylori* prevalence was lower in patients with CD (4.4%) than in those without CD^[65], indicating an inverse association between CD and *H. pylori* infection.

In the same context, a recent study including 324 children with confirmed CD, the *H. pylori* prevalence was compared with a reference group of non-celiac children referred for endoscopy. The results showed that the prevalence of *H. pylori* in patients without CD was significantly higher^[18], indicating that CD and gastric *H. pylori* infection are inversely correlated.

The mechanistic link between *H. pylori* infection and CD remains to be elucidated. However, recently, Lucero *et al.*^[17] demonstrated that infection by *CagA* positive *H. pylori* induced Treg markers and that this may be protective against CD progression.

Multiple sclerosis: Emerging evidence suggests that *H. pylori* may also be inversely associated with neurodegenerative diseases. In this context, several studies have sought to establish an association between *H. pylori* infection and multiple sclerosis (MS), a chronic autoimmune, inflammatory and neurodegenerative disorder

of the central nervous system^[66].

In a meta-analysis of nine studies involving 2806 cases (1553 patients with MS and 1253 controls), Yao *et al.*^[67] found that the prevalence of *H. pylori* infection in MS patients was lower than that in control groups. Another meta-analysis of six observational studies involving 1902 participants showed also a statistically significant lower prevalence of *H. pylori* infection in patients with MS^[68].

In spite of these studies, Efthymiou *et al.*^[16] in a cohort study of 129 patients and 49 controls, showed that anti-*H. pylori* antibody titers were higher in 129 MS patients than in 48 healthy controls. Additionally, anti-*H. pylori* hsp 60 seropositivity correlated with age at disease onset, suggesting a possible role of this factor in the pathogenesis of MS^[16].

In this context, it has been proposed that the inflammatory mediators induced by *H. pylori* infection might impact on the nervous system and induce damage^[69]. Additionally, circulating pro-inflammatory cytokines, such as IL-17, and reactive oxygen species (ROS) can reach the CNS and induce damage^[70]. Moreover, recent reports implicate the Galectin-3 receptor, a leptin receptor that is stimulated by *H. pylori*, in inducing a pro-inflammatory response *via* TLRs. Activation of these receptors in the CNS, triggers an inflammatory response mediated by interferon (IFN)- γ and TNF- α that is associated with neuro-pathophysiological changes^[70].

Negative effect of *H. pylori* colonization

Despite these observations suggesting a protective role for *H. pylori* against several diseases, there is a large body of literature associating *H. pylori* infection with the development of gastric diseases, such as peptic ulcer diseases, gastric adenocarcinoma, MALT lymphoma and biliary tract^[71]. Moreover, the positive correlations between *H. pylori* and disease conditions have also been noted for extra-intestinal diseases, such as dermatological diseases, heart diseases, obesity, anemia, insulin resistance and non-alcoholic fatty liver disease, among others (Figure 1 and Table 1). In most of these cases, disease development is associated with the chronic inflammatory response that the infection triggers in the host.

Ischemic heart diseases: *H. pylori* has been suggested to contribute to the development of coronary heart diseases (CAD). In a meta-analysis of 26 studies, including more than 20000 patients, Liu *et al.*^[4] observed a significant association between *H. pylori* infection and the risk of myocardial infarction. In the same context, Shmueli *et al.*^[3] in a cohort study of 173 patients and 127 controls, observed that *H. pylori* infection was significantly higher in CAD-positive patients than in CAD-negative subjects, suggesting a positive correlation between *H. pylori* seropositivity and CAD. In addition, in a retrospective cohort study by Huang *et al.*^[72], involving 17332 patients with *H. pylori* infection and 69328 randomly selected age- and gender-matched

controls, a more specific association between chronic *H. pylori* infection and ischemic stroke was observed since patients diagnosed with *H. pylori* infection exhibited a higher incidence rate of ischemic stroke. Despite such observations suggesting that the presence of *H. pylori* favors the development of heart disease, the mechanisms involved remain to be determined. However, because chronic inflammation is believed to be associated with an increased risk of atherosclerosis^[73], this may in an indirect manner explain the augmented risk of heart disease associated with *H. pylori* infection.

Anemia: An association between *H. pylori* infection and iron deficiency was proposed based on studies showing that for individuals with idiopathic iron deficiency anemia of unknown origin and no evidence of bleeding due to lesions, iron deficiency anemia was no longer observed in any of the follow-up examinations following eradication of *H. pylori*^[74]. In a recent retrospective cohort study, Xu *et al.*^[6] evaluated the relationship between anemia and *H. pylori* infection in 17791 subjects. They observed a higher probability for anemia in *H. pylori* positive populations coincident with lower hemoglobin levels.

Recent studies suggest that the mechanism involves changes in the intracellular iron distribution associated with the uptake and trafficking of *H. pylori* through the cells^[75], since *H. pylori* uptake by gastric cells is associated with an increase in total cellular iron content and its homeostasis depends on the transferrin receptor^[76]. Indeed, a study by Flores *et al.*^[75] showed that *H. pylori* infection is associated with an increase in the total intracellular iron levels, redistribution of the transferrin receptor from the cell cytosol to the cell surface, and increased levels of ferritin. Moreover, Kato *et al.*^[77] showed that the SabA gene is highly expressed in bacterial isolates from iron deficient anemia patients, suggesting a role for this virulence factor in the development of anemia.

Non-alcoholic fatty liver disease: Non-alcoholic fatty acid disease (NAFLD) has also been suggested to be associated with *H. pylori* infection. In this context, a large number of reports, including cross-sectional studies, case reports and randomized-controlled studies have revealed a strong association between NAFLD and *H. pylori* infection^[7]. In addition, it has been demonstrated in an animal model of *H. pylori* infection that the orally inoculated bacterium can reach the liver and cause hepatitis^[78].

H. pylori infection may induce NAFLD by producing chronic systemic inflammation, increasing the levels of inflammatory cytokines, such as IL-6 and TNF- α , and activating NF- κ B pathway, which induce insulin resistance (IR)^[79]. The mechanisms of the pathogenesis of *H. pylori*-related inflammation in NAFLD involve directly reducing hepatocyte glycogen levels *via* a JNK signaling pathway^[80], which in turn can down-regulate the expression of key genes involved in glucose metabolism and

accelerating lipolysis^[81], thereby contributing indirectly to the development of IR. In addition, *H. pylori* may also induce white adipose tissue to release leptin, and then promote liver stearyl- CoA desaturase, favoring the accumulation of fat deposits in the liver tissue^[79].

Insulin resistance: Several studies have revealed a strong association between *H. pylori* and IR. In 2005, Aydemir et al^[82] confirmed the existence of a positive correlation between chronic *H. pylori* infection and IR by showing that the homeostasis model assessment (HOMA-IR) of *H. pylori* positive subjects was significantly higher compared with *H. pylori* negative individuals. In another large cross-sectional study including 1,107 subjects, *H. pylori* seropositivity was significantly higher for patients with IR (HOMA-IR ≥ 2.5)^[83]. Subsequent studies also confirmed the causal relationship between *H. pylori* and IR^[84-86].

Mechanistically, *H. pylori*-induced IR may be caused indirectly by chronic inflammation or directly by activating certain signaling pathways. Several reports have confirmed that chronic inflammation is important for IR onset^[87] and *H. pylori*-mediated chronic inflammation may increase the expression of C-reactive protein, TNF- α , and IL-6^[88,89]. These cytokines activate IKK/NF- κ B and JNK pathways, which may trigger IR by increasing insulin receptor phosphorylation on serine^[81] or by inhibition of insulin receptor substrate-1 phosphorylation on tyrosine residues^[90].

Despite such evidence, a recent systematic review revealed that *H. pylori* eradication does not improve insulin resistance, but may increase body weight (BW) and the body mass index (BMI), suggesting that further studies are needed to clarify the effect of *H. pylori* eradication on metabolism^[8].

Type 2 diabetes mellitus: The association between Type 2 diabetes mellitus (T2DM) and *H. pylori* infection is controversial. Some studies indicate that the prevalence of *H. pylori* is higher in diabetic compared with non-diabetic patients^[91,92], while others indicate that there are no differences between those groups^[93]. Nevertheless, more recently, He et al^[94] discussed the possibility that this controversy is likely due to inconsistencies in the methods used to define *H. pylori* positivity, diabetic status and the reduced sample sizes, among other limitations. More recently, a meta-analysis including 57397 individuals showed that there is significantly higher prevalence of *H. pylori* infection in diabetic type 2 patients as compared with healthy individuals^[5].

The possible mechanisms linking *H. pylori* to diabetes include alterations in IR signaling, inflammation, accumulation of ROS and oxidative DNA damage in the gastric mucosa. It has been reported that ROS levels and oxidative DNA damage increase due to neutrophil infiltration in *H. pylori*-infected patients^[95]. Moreover, a recent study performed in 100 patients showed increased serum levels of oxidative DNA damage (8-OHdG) and

oxidized low-density lipoprotein in T2DM patients positive for *H. pylori* infection^[96].

Periodontitis: Periodontitis is characterized by the accumulation of bacterial plaque at the gingival margin, which induces an inflammatory response that leads to destruction of the connective tissue attachments to teeth, alveolar bone resorption and tooth loss^[97]. The recent Global Burden of Disease Study (1990-2010) indicates that severe periodontitis is the 6th most prevalent disease worldwide, with an overall prevalence of 11.2%, although mild forms of this disease may reach over 90% of the population in developing countries^[98]. Remarkably, periodontitis has also been linked to an increased risk in developing atherosclerosis, diabetes, rheumatoid arthritis and cancer^[99-103].

Moreover, the oral cavity might represent a reservoir for *H. pylori*^[104]. In a recent cross-sectional study that included 70 patients and 70 controls it was reported that the presence of *H. pylori* in dental plaque correlates with periodontitis and that the correlation appears to be better in severe forms of the disease^[105]. Additionally, a study involving 40 patients (32 periodontitis and 8 controls) showed that periodontal disease positively correlates with gastric and oral *H. pylori* ($P < 0.005$)^[106]. In this study, in spite of the small number of controls, it was shown that 70% of periodontitis patients have biopsies positive for *H. pylori*. Also, it is important to mention that 81% of periodontitis patients were positive for *H. pylori* in oral plaques.

Recently, Hu et al^[107] demonstrated that *H. pylori* infected patients have worse periodontal parameters than non-infected individuals, suggesting that infection correlates the progression of the disease. This study also showed that the presence of periodontitis-associated bacteria was significantly higher in subjects with *H. pylori* infection than those without *H. pylori* infection. Moreover, the expression of inflammatory molecules, such as IL-8, IL-6 and IFN- γ significantly increased after *H. pylori* infection. Interestingly, those effects were associated with the presence of CagA^[107].

ROLE OF INFLAMMATION IN *H. PYLORI* MEDIATED DISEASES

H. pylori infection triggers several adaptive cellular mechanisms in host cells that may favor gastric cancer development and progression^[108]. However, whether the disease develops or not and the final outcome are thought to depend largely on the extent of inflammation promoted by the bacteria in the host during the pre-neoplastic process^[109]. Indeed, chronic inflammation is a common causative event associated with the development of several types of cancer^[110,111] and, as was demonstrated in animal models, *H. pylori* infection is considered the major factor responsible for gastric epithelial damage and deregulation of signaling leading to irreversible epigenetic changes in the gastric mucosa, a consistent hallmark

observed during the gastric carcinogenic cascade^[19,109]. Initially, *H. pylori*-related studies focused on identifying the virulence factors implicated in these processes. Those factors epidemiologically associated with a higher risk of developing gastric cancer were tested *in vitro* and shown to induce signaling pathways associated with exacerbated inflammatory responses. For example, strains harboring particular *vacA* and *cagA* allele variants were found to induce elevated inflammatory responses in infected cells^[112]. However, this seemingly simple scenario rapidly transited to a more complex one when epidemiological data revealed that in certain ubiquitously infected populations no correlation with elevated gastric cancer incidence was detected, as is the case for the so-called African enigma^[113] where only a minor percentage of infected patients progress to develop cancer. To date, experimental studies have clarified that final disease outcome depends not only on the contribution of certain bacterial virulence factors, but also on host susceptibility, diet and environmental factors^[114]. Here, it is important to mention that co-existence with the bacteria is not only to be viewed negatively (see previous and following chapters), bearing in mind that since the prevalence of the infection has declined in developed countries over the last decades, several disorders have emerged as a consequence of the lack of exposure to *H. pylori*^[115]. Human beings have co-evolved with the bacterium and gastric as well as extra-gastric physiology has been conditioned to such association^[116]. In order to persist in the gastric niche, *H. pylori* have evolved mechanisms necessary to evade and to attenuate the innate and adaptive immune systems by several mechanisms, including those implicated in evasion of recognition by pattern recognition receptors, inhibition of phagocytic killing, inhibition of killing by ROS and nitric oxide, among others^[117]. Particularly, antigenic phase variation, modulation of adhesion molecules, immune inhibition by VacA protein and lipopolysaccharide (LPS) have been widely described^[118]. Moreover, additional mitigating local mechanisms mediated by bacterial enzymes exist. For instance, it was recently reported that the expression of a cholesterol- α -glucosyltransferase reduced cholesterol levels in gastric epithelial cells, blocking IFN- γ signaling, a classical Th1 cytokine^[119]. Notably, this enzyme is present in most *Helicobacter* species and cholesteryl α -glucosides are also involved in resistance to antibiotics^[120], interference with phagosome trafficking^[121], *H. pylori* type IV secretion system function^[122] and immune evasion by inhibiting T-cell activation^[123]. On the other hand, *H. pylori* superoxide dismutase (SOD) has been shown to suppress the production of pro-inflammatory cytokines during *in vivo* infection by reducing oxidative stress. Thus, SOD from *H. pylori* can inhibit the production of pro-inflammatory cytokines during *in vivo* infection^[124].

Additionally, *H. pylori* deregulates adaptive immune responses by interfering with antigen presentation and modulation of T-cell responses^[117,118]. Eradication of *H. pylori* has revealed the importance of this modulation of the immune response in preventing the development

of extra-gastric immune and inflammatory disorders, such as gastroesophageal reflux disease, childhood asthma and allergy, as well as metabolic disorders^[15,52,54]. Although in most of the cases correlations are derived from cross-sectional studies, the most experimentally validated preventive association is the appearance of childhood asthma^[115,125]. Moreover, innate immune responses are also involved, given that bronchial epithelial cells, mast cells, basophils, natural killer T cells and dendritic cells (DC) also produce inflammatory mediators^[52]. This harmful effector response is modulated by CD24+CD25+ regulatory cells (Treg) present in the lung, which secrete anti-inflammatory cytokines, such as IL-10 and transforming growth factor beta (TGF- β), preventing or modulating the Th2 responses to allergens^[126]. Tregs of healthy individuals shift allergen-specific immune responses toward tolerance, thereby preventing the development of asthma and other allergic disorders^[52]. Also in animal models of infection, the importance of dendritic cells in *H. pylori*-specific adaptive immune responses was noted. Particularly tolerance induction^[52,127], Treg skewing and Th17 suppression observed in mice occurred in a *cagA*- and *vacA*-independent manner^[128]. Chronic exposure to *H. pylori* impairs dendritic cell function and inhibits Th1 development^[129]. Also, *H. pylori*-mediated protection was linked to IL-10-secretion by peripheral blood Treg cells^[130].

The importance of these immune cells has been validated in experimental animal models of infection or induced asthma. For instance, blocking CD24+CD25+ Treg cells by a CD25-neutralizing antibody abrogated Treg cell tolerance promoted by *H. pylori* infection and enhanced pulmonary inflammation following albumin induced asthma^[131]. Also, KO animals for IL-10, TGF- β or animals depleted of Tregs, develop gastritis to an elevated extent in response to *H. pylori* infection. Although these animals are able to clear the infection, pre-neoplastic lesions develop since Th1 responses predominate^[52]. Together, these results indicate that tolerance rather than immunity protects against *H. pylori*-induced gastric pre-neoplastic lesions^[132]. Accordingly, decreased Treg cell function is associated with an increase in peptic ulcer development upon *H. pylori* infection^[133].

A currently unresolved question is how *H. pylori* promotes tolerance in distant organs such as the lung? A recent study showed that systemic and mucosal pre-administration of recombinant neutrophil-activating protein prevented ovalbumin-induced allergic asthma in mice, indicating that secreted virulence factors may be responsible^[134]. What determines the balance between tolerance or elimination of an exacerbated Th1 type chronic inflammation could be explained in part by host hyperreactivity to allergens or bacterial infection. In this respect, pro-inflammatory cytokine polymorphisms are generally thought to participate in the genesis of gastric and other types of cancer^[109] and interleukin family cytokines, like IL-1 β and IL-18, have emerged as central mediators of mucosal inflammation^[135]. On

the other hand, virulence factors can determine the type of response. For instance, blocking the TLR4 in a mouse model using a specific antibody prior to *H. pylori* infection, was shown to reduce the number of T-cell effectors (Th1 and Th17) and diminish the immune response^[136]. In agreement with this observation, activation of TLR4 signaling was reported to be associated with gastric cancer progression by inducing mitochondrial ROS production^[137]. Moreover, type I *H. pylori* (*cag* PAI+ and vacuolating toxin A+, VacA+) LPS exhibited a stimulatory effect on TLR4 signaling followed by mitogen oxidase 1 activation in cultured gastric pit cells through the lipid A portion of LPS^[138]. In a similar study, LPS from some *H. pylori* strains were shown to act as TLR4 antagonists, which may contribute to more beneficial clinical outcomes of *H. pylori* infection in host individuals^[139]. Additionally, *H. pylori* LPS from type I, but not type II strains, promotes cytotoxicity in cultured gastric mucosal cells^[140]. Conversely, TLR2 mediates *H. pylori*-induced tolerogenic immune responses^[141] and TLR9 signaling has anti-inflammatory effects during the early phase of *H. pylori*-induced gastritis in mice^[142]. Also, additional virulence factors have been implicated in immune response suppression or tolerance, such as the suppression of dendritic cells by OipA *in vitro*^[143], promotion of immune tolerance by VacA-mediated inhibition of T-cell proliferation and antigen-presentation^[59]. Also, bacterial gamma-glutamyl transpeptidase^[59] and outer membrane vesicles inhibit T-cell responses^[144,145]. Furthermore, *H. pylori* infection has been associated inversely with IBD. Experimental immuno-regulatory properties of the *H. pylori* genome and particularly the immuno-regulatory sequence TTAGGG was demonstrated to down-regulate dendritic cell-mediated production of pro-inflammatory cytokines both in an *in vitro* and *in vivo* model^[146].

H. PYLORI COLONIZATION AND ITS ASSOCIATION WITH MICROBIOME SHIFTS

As discussed above, *H. pylori* infection has been associated both positively and negatively with the development of gastric and non-gastric diseases. Disease development is often linked to chronic inflammatory responses induced by *H. pylori*, as was discussed in the previous section. However, it is now becoming increasingly clear that *H. pylori* also induces changes in the host by altering the microbiome. This aspect will be covered in the following paragraphs.

The harsh gastric environment is thought to represent a key limitation to the complexity of the stomach microbiota^[147]. This assumption, together with limitations imposed by culture-dependent strategies for bacterial identification, has historically led to an underestimation of the biodiversity in the stomach. In this context, the gastric microbiota was initially considered to include only a very select group of taxa,

including mainly *Veillonella* spp., *Lactobacillus* spp., and *Clostridium* spp., besides -of course- *H. pylori*^[148-151]. Nonetheless, with the development of more sophisticated 16S rRNA-based bacterial identification techniques, we now have gleaned deeper insight to the complexity of the gastric microbiome. Accordingly, an increasing number of publications describe greater ecosystem diversity in the stomach and, importantly, correlate the presence of *H. pylori* with variations in the composition of the microbiome^[23,48,152-156]. Bik et al^[152] identified taxa, such as *Caulobacter*, *Actinobacillus*, *Corynebacterium*, *Rothia*, *Gemella*, *Leptotrichia*, *Porphyromonas*, *Capnocytophaga*, TM7, *Flexistipes*, and *Deinococcus* in the normal microbiome. Alternatively, Li et al^[155] showed that the most common genera in gastric biopsies from both normal and non-*H. pylori* gastritis individuals were *Prevotella*, *Neisseria*, *Haemophilus*, and *Porphyromonas*. Later, Delgado et al^[153] also identified *Propionibacterium*, *Lactobacillus* and *Streptococcus* as dominant genera in healthy samples.

Regarding the effect of *H. pylori* on the gastric microbiome, there is still some controversy. No effect on either diversity and/or evenness in community members between *H. pylori*-positive vs *H. pylori*-negative samples were observed at the phylum level^[152]. Likewise, in a mouse model of *H. pylori* infection, neither acute nor chronic *H. pylori* infection altered the murine gastric microbiota^[157]. Similarly, others described that, although when present *H. pylori* dominates the microbiome, only minor differences in community structure were observed in stomach biopsies from *H. pylori*-positive and negative subjects^[158]. However, others have shown that the presence of *H. pylori* dramatically reduces the diversity of the gastric microbiota^[20,21,23] and modifies the microbiome by increasing the relative abundance of *Proteobacteria*, *Spirochetes* and *Acidobacteria*, while decreasing *Actinobacteria*, *Bacteroidetes* and *Firmicutes*^[156]. Similar results were reported by Thorell et al^[30], who performed a meta-transcriptomic analysis and reported higher levels of *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* in subjects with low levels of *H. pylori*. Such discrepancies might be due to inter-subject variations, since the gastric microbiome seems to be sensitive to exogenous factors, such as diet and lifestyle, as has been shown by the analysis of monozygotic twins^[159].

Interestingly, while the experimental inoculation of *H. pylori* into an established community in rhesus monkeys, did not affect the community membership or structure^[160], pre-infection of mice with *H. pylori* did alter the microbiota structure in the stomach^[22]. Therefore, the time-point in life when *H. pylori* is acquired is another aspect to be considered in the discrepancies reported for *H. pylori*-associated microbiome variations. Differences in both diversity and community composition were also observed in the stomachs of *H. pylori*-infected vs *H. pylori*-negative children and also in comparison to adults, regardless of the *H. pylori* status^[161]. Thus, early acquisition of the bacterium is likely to shape the microbiome by inducing local modifications in the

stomach environment. One of these effects is driven by the production of ammonia and bicarbonate from urea^[162,163]. Such compounds may serve as substrates for other bacteria^[164], in addition to altering the stomach pH^[162,163], which facilitates the colonization by other species, such as nitrogen-reducing bacteria^[165]. Moreover, *H. pylori*-induced increases in the stomach pH favor the migration to the stomach of some bacterial taxa that are usually restricted to the intestinal tract (*Bacteroides* and *Clostridia*) in mice^[166]. Interestingly, the effect of *H. pylori* on acid secretion depends on the pattern of gastritis that is induced^[167]. In predominantly antral gastritis, the production of gastric acid is increased (hyperchlorhydria)^[168], while in predominantly corpus gastritis, acid production decreases (hypochlorhydria)^[169]. Thus, microbiome shifts may differ in both cases. In fact, hyperchlorhydria increases microbial diversity in the stomach^[170] and it has been implicated in the development and progression of cancer (reviewed by Espinoza *et al* 2018^[171]). Additionally, the viscosity of the gastric mucus layer decreases when the pH increases^[172], making it easier for other microorganisms to colonize the epithelium. Finally, *H. pylori* can directly alter the mucus barrier by modulating the expression of stomach mucins^[173].

As illustrated above, all these environmental modifications in the stomach may impact on the local microbiome, as well as induce changes in the entire gastrointestinal tract, since these are dynamic compartments between which fluids are exchanged and therefore microbes can easily migrate from one gastrointestinal segment to another^[174]. Some of these *H. pylori*-mediated downstream effects in other compartments include impairment in the absorption of iron and vitamin B12 in the intestine^[175,176], and alterations in carbohydrate and amino acid metabolism of the host^[177]. Interestingly, besides the direct effect of *H. pylori* in the stomach/intestine, also the immune response triggered by the bacterium could affect the local microbiome, as well as bacterial populations at more distal sites in the human body.

Regarding the effect of *H. pylori*-mediated immune mediators in the microbiome, there are some contradictory reports. No statistically significant differences in the microbiota were found in CagA-positive ($n = 10$) compared to CagA-negative ($n = 10$) biopsies from human subjects^[178]. Therefore, the increased production of pro-inflammatory cytokines mediated by CagA appears not to have an effect on the microbiome in this model. Nonetheless, as the sample cohort was small in that study, this question probably needs to be re-evaluated in larger groups of samples. In contrast, in a transgenic *Drosophila* model of CagA expression, CagA was sufficient to alter midgut host microbiota^[179]. Additionally, a series of reports demonstrated differences in the intestinal microbiome related to the presence of *H. pylori* both in humans^[180] and mice^[22]. Moreover Schulz *et al*^[158] correlated the presence of *H. pylori* in human individuals with modifications in the microbiome of the duodenum and the oral cavity. More specifically,

Heimesaat *et al*^[181] demonstrated that chronic infection of Mongolian gerbils with *H. pylori* resulted in changes in some specific genera, including increased abundance in the large intestine of *Akkermansia*, which is involved in mucus degradation. These changes were accompanied by variations in the expression of immunity-related genes in both the stomach and the lung, with stronger effects in the former. The authors speculated that early community shifts could reflect changes in the niche microenvironment (e.g., altered gastric pH), while later shifts might be driven by the cumulative changes in the immune/inflammatory response triggered by *H. pylori*. These effects could also be observed at distant sites in the host organism and be driven by other members of the *Helicobacter* genus. For instance, natural colonization of the mouse digestive tract with *Helicobacter hepaticus* leads to a shift in gut microbiota, which generates sub-clinical inflammation and a drastic impairment of the control of *Mycobacterium tuberculosis* growth by the immune system^[182].

It is likely that *H. pylori* might affect mucosal diseases at distant sites *via* its effects on immune cells that traffic through lymphatic vessels. *H. pylori* also induces a shift in the immune response toward an induction of Treg cells, mediated by VacA and GGT^[59,161,183,184]. Treg cell responses are important in differentiating between self and foreign antigens, *i.e.*, immunological tolerance. This effect could be involved in *H. pylori* persistence in the stomach, and also could contribute to suppressing gastric inflammation, which may explain reduced gastric disease severity in *H. pylori*-positive children compared to *H. pylori*-positive adults^[161]. Such effects have been linked to alterations in the stomach physiology and its microbiota, as well as to progression of extra-gastric diseases, such as asthma^[59], celiac disease^[17], ischemic heart diseases, insulin resistance, Type 2 diabetes mellitus, periodontal diseases, among others (see previous sections and references listed in Table 1).

Interestingly, as was stated above, *H. pylori* is part of a complex microbiota in the stomach and its presence has been linked to modifications in the microbiome at other sites in the body. Therefore, it is reasonable to speculate that other community members could also contribute to changes observed following *H. pylori* infection of the host. Indeed, direct bacteria-bacteria interaction was described by Khosravi *et al*^[185] between *H. pylori* and *Streptococcus mitis*, in which *H. pylori* transit from spiral to coccoid-shaped cells that are more resistant to stressing conditions. The exact effect of this conversion on disease progression remains to be elucidated. Also, antimicrobial molecules produced by *Lactobacillus spp* have been shown to be active against *H. pylori* strains^[186-189]. Therefore, bidirectional communication and modulation between *H. pylori* and other community members occur, and the combination of all these interactions will be reflected in the host health status. The question as to how the microbiota shapes the immune system and how this affects its response to some diseases has been broadly discussed in the literature (see for instance,

Hooper et al^[190] 2012). Therefore, modifications in the microbiome induced by early acquisition of *H. pylori*^[161] may also determine the host immune status and, as a consequence, the development of a number of systemic diseases. This is relevant, since Rolig et al^[191] reported that when the microbiota is altered by antibiotic treatment, the *H. pylori*-triggered inflammation is reduced.

CONCLUSION

In summary, *H. pylori* has a strong effect in the stomach microenvironment and also on the host immunological status, leading to shifts in the microbiome at different sites of the body. These shifts are involved not only in the pathogenesis of gastric diseases, but also in some of the non-gastric *H. pylori*-related diseases that were discussed in this review. The question as to whether the bacterium is acquired early on or later in life is a key point when analyzing such effects, as *H. pylori* has been reported to co-evolve with its host, shaping the immune system and consequently, the microbiome. Therefore, a better understanding of the exact mechanisms involved in such effects, as well as the *H. pylori*-induced microbiome shifts that may be related to the development of specific diseases, will likely be useful to predict and hopefully prevent *H. pylori*-associated diseases. Ideally, one would aspire to achieving this goal while at the same time preserving the beneficial effects that *H. pylori*-host cohabitation appears also to offer.

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P- Reviewer: Caruso R, Martini F **S- Editor:** Wang JL **L- Editor:** A
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ISSN 1007-9327

