Helicobacter pylori and hematologic diseases

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Abstract

Helicobacter pylori are Gram negative spiral bacteria that colonize human gastric epithelia. Their association with many gastric diseases, including roles in the pathogenesis of chronic gastritis, peptic ulcers, dyspepsia, MALT and gastric cancer is well known. In addition increasing amounts of evidence indicate that they are associated various extragastric entities such as colon cancer, neurodegenerative diseases, liver diseases, coronary artery disease, hematologic diseases and others. Of these, three hematologic diseases have clear associations with strong evidence: iron deficiency anemia when there is no other explanation, Vitamin B12 (cobalamin) deficiency and immune thrombocytopenic purpura. Many pathogenic mechanisms have been proposed for these three disorders, and there are many studies that support these associations. In this article we review the role of *Helicobacter pylori* and its pathogenetic mechanisms in the development of these three hematologic diseases.

Keywords

Helicobacter, purpura, anemia, iron.

INTRODUCTION

Helicobacter pylori (H. pylori) has accompanied humans for at least 58,000 years, (1) but its role as a pathogen was only established in 1984 when by Warren and Marshall in Australia successfully cultured the bacteria and associated it with chronic gastritis and Peptic ulcers. (2) Nowadays, it is considered that it infects 50% of the world's population. (3, 4) Nevertheless, its prevalence varies significantly among different populations. It is as high as 91% in certain African populations and as low as 7% in some studies in the United States. (5, 6) Also, there is evidence of marked differences according to ethnic group, age range and economic status within any given geographic area: its prevalence is higher among Hispanics, African-Americans, older people and low-income populations. (7-9) Ten years after its discovery, the WHO categorized it as a type I carcinogen. (10) Today is considered to be the primary cause of demonstrated chronic gastritis, peptic ulcers, gastric MALT lymphoma and gastric cancer (GC). (11, 12) In all cases of infection, it produces chronic gastritis, (13) but in most patients this gastric inflammation is asymptomatic. A clinical entity is manifested in less than 20% of the infected population: peptic ulcers in 15% to 18%, CG in 2% to 3%, gastric cancer and gastric MALT lymphoma in less than 0.1%. (11-13) Nevertheless, these numbers are not exact because only a fifth of those infected develop a disease caused by the infection. This is likely to be due to genetic factors, virulence of the bacteria and environmental factors. The risk for developing GC that is attributable to *H. pylori* is 75%, in other words, the infection is responsible for at least 75% of these tumors. Besides these gastroduodenal diseases, there are strong indications that *H. pylori* are positively associated with adenomatous polyps and colon

cancer and even stronger indications that the bacteria have an association with distal cancers (Figure 1). (14-20) In addition to this infection's participation in the conditions mentioned, there is increasing evidence of a link between *H. pylori* and various extra-gastric diseases such as blood, coronary, hepatic, and neurodegenerative diseases and even the development of type 2 diabetes mellitus. (21-27) However, current evidence only supports causal associations with iron deficiency anemia, vitamin B12 deficiency and immune thrombocytopenic purpura. (28) For this reason it is recommended that the infection be eliminated in these scenarios in accordance with the recently ratified Maastricht consensus. (29, 30, 31) Given the importance of this organism in the conditions mentioned above, we propose to review their relationships and the pathophysiological mechanisms involved.

METHODOLOGY

We performed a literature search in the PubMed database using the following strategy (((((Vitamin B 12 OR B 12, Vitamin B12 OR OR Vitamin B12, Vitamin Cyanovitamin B12 OR OR OR Vitamin B12 OR erythron vitamin B12s [Title/Abstract])) OR (Anemia, Iron-Deficiency Anemia OR, OR Iron-Deficiency Iron Deficiency Anemia Iron Deficiency Anemia OR OR OR Iron-Deficiency Anemia Iron Deficiency Anemia Anemia OR, OR Iron-Deficiency Anemia, Iron Deficiency [Title/Abstract])) OR (Purpura, Thrombocytopenic, Idiopathic OR Idiopathic Thrombocytopenic Purpura OR Idiopathic Thrombocytopenic PURPLE OR Purpura, Idiopathic Thrombocytopenic OR PURPLE, Idiopathic Thrombocytopenic OR Thrombocytopenic Purpura, Idiopathic OR Thrombocytopenic purple, Idiopathic OR Werlhof's Disease OR Disease, Werlhof's OR Werlhof's Disease OR Purpura, Thrombocytopenic, OR Autoimmune Thrombocytopenic Purpura Autoimmune Disease OR OR Werlhof Disease, Autoimmune Thrombocytopenic Purpura Werlhof OR OR OR PURPLE Autoimmune Thrombocytopenic Purpura Autoimmune Thrombocytopenic OR purple OR Immune Thrombocytopenic Autoimmune Thrombocytopenic Purpura Autoimmune Thrombocytopenia OR OR OR thrombocytopenias Autoimmune Thrombocytopenia, Autoimmune OR thrombocytopenias, Autoimmune [Title/Abstract])) AND (OR Campylobacter pylori Helicobacter pylori [Title/Abstract])). The search was limited to articles from the past five years. The titles and
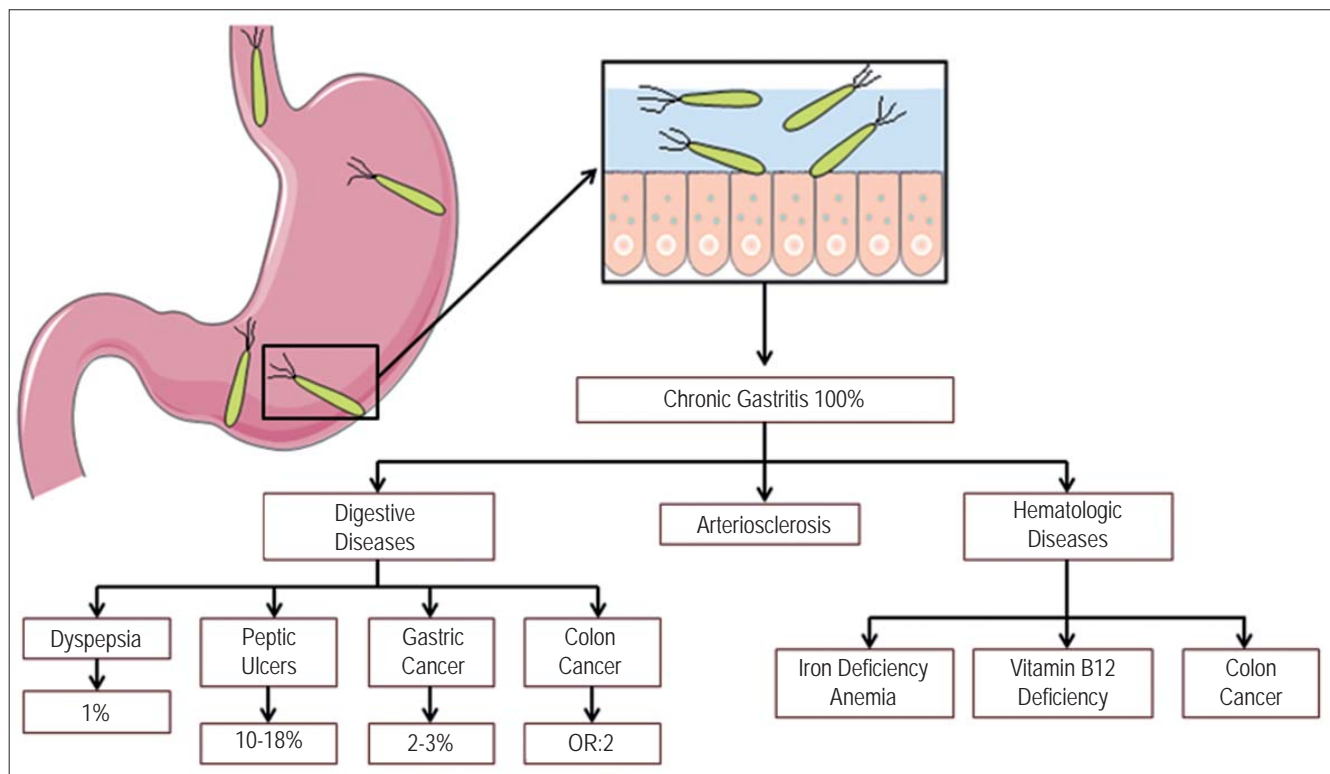
Figure 1. Diseases produced by *H. pylori*. Illustration produced from individual images created with Servier Medical Art in accordance with its conditions of use.

abstracts were reviewed and, according to the opinions of the authors, those that were relevant and provide useful information for this review were selected. We excluded those with information that repeated information found in other articles reviewed. In addition, the authors some of the articles mentioned in the bibliographies of the publications selected in the initial search.

IMMUNE THROMBOCYTOPENIC PURPURA

The prevalence of *H. pylori* in patients with immune thrombocytopenic purpura (ITP) is similar to the prevalence in controls matched for age and geographic area. (32) It ranges from levels as low as 20% to levels as high as 80% at different ages and in different areas. (33-36) However, multiple studies have shown a clear association between eradication of H. pylori in patients with ITP and improvements in their platelet counts. (30, 37, 38)

One possible mechanism for the development of ITP in patients infected with *H. pylori* is cross-reactivity between antibodies directed against these bacteria, specifically against the CagA protein and proteins on the surface of platelets. (39) In fact, the differences between success rates for treatments of patients with ITP by the eradica-

tion of *H. pylori* in Japan and the United States could be explained by this mechanism, since Japan has been more successful with this treatment and has a greater prevalence of H pylori CagA + whereas eradication of *H. pylori* has been less successful as a treatment of ITP in the USA where the prevalence of H pylori CagA + is less than in Asia. (30, 40) In addition, it has been found that this bacterial infection decreases Fcy receptor IIB inhibitor levels on monocytes while increasing Fcy receptor levels leading to a phenotype with increased monocyte phagocytic activity. One study has shown that elements of *H. pylori,* particularly urease, promote the activation of B-1 cells. These cells are a subpopulation of B cells associated with the production of auto-antibodies which could injure the platelets during an infection with *H. pylori* (Figure 2). (41, 42)

H. PYLORI TREATMENT IN PATIENTS WITH IMMUNE THROMBOCYTOPENIC PURPURA

Eradication of *H. pylori* in patients with ITP increases platelet counts in approximately 50% of patients. (30, 37, 38) The meta-analysis of Stasi and colleagues showed that the response is more successful in populations with high prevalences of *H. pylori* and among patients with
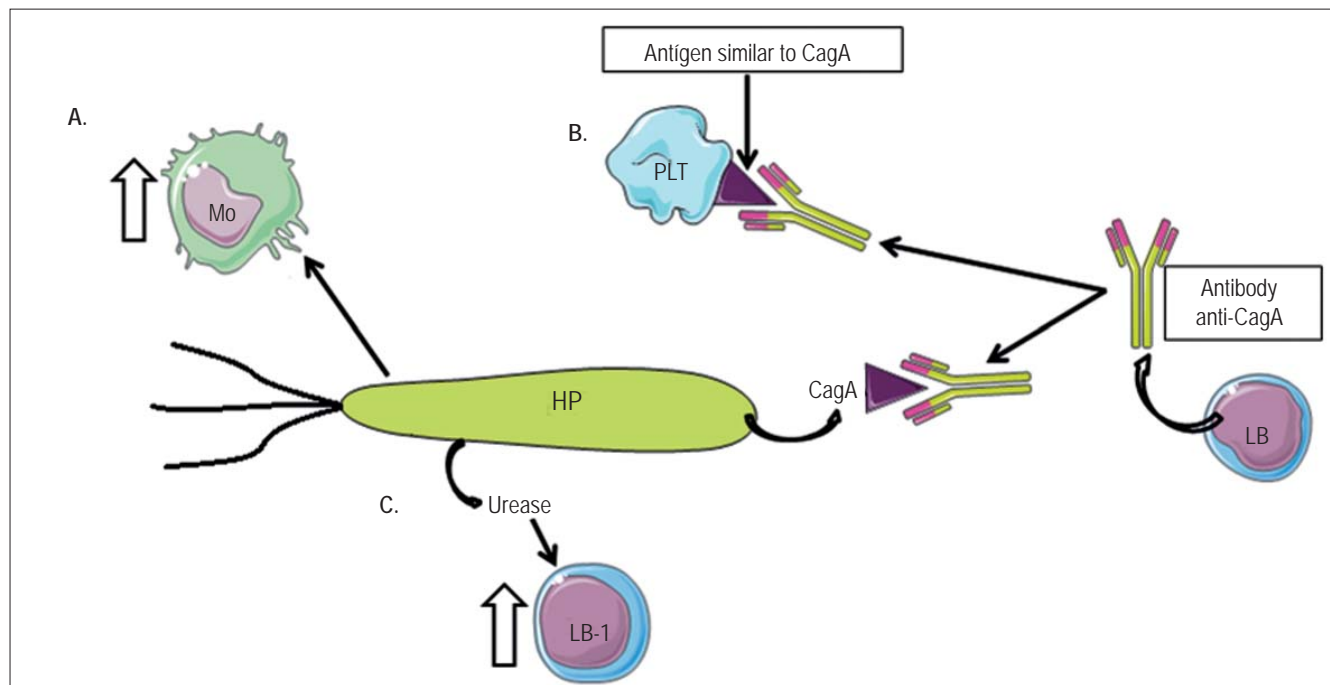
Figure 2. Primary mechanisms involved in the association between *H. pylori* and ITP. A) H. pylori (HP) favor a monocytic phenotype (Mo) with enhanced phagocytic activity. B) Antibodies directed against the CagA protein produced by H. pylori cross-react with proteins on the surface of platelets (PLT). C) Urease promotes B-1 cell activation (BL-1) associated with the production of auto-antibodies. Illustration produced from individual images created with Servier Medical Art in accordance with its conditions of use.

mild levels of thrombocytopenia. In this meta-analysis, 57.9% of patients in studies conducted in Japan had platelet count response compared to only 38.3% of patients in other countries. (37) Furthermore, 35.2% of patients with counts under 30×10^9 / L had platelet count responses whereas improvement occurred in 50.3% of patients with higher platelet counts.

A meta-analysis on the effects of H pylori eradication in patients with ITP which included 11 studies found that eradication was successful for 166 (81.0%) of 205 H. pylori positive patients. (30) Patients were treated with 750-1500 mg of amoxicillin twice daily and 200-400 clarithromycin mg twice daily. PPIs were administered for seven days, except in one study in which it was administered for fourteen days.

IRON DEFICIENCY ANEMIA

As ferric iron is absorbed the acidic pH of the stomach, it is reduced by ascorbic acid to ferrous iron. (43-45) Decreased levels of ascorbic acid and stomach acidity secondary to inflammatory histopathological changes caused by *H. pylori* can participate in producing inadequate iron absorption and thus in the pathogenesis of iron deficiency anemia. (46-51) It is well known that gastritis, regardless of its degree, leads to the predominance of the oxidized, biologically inactive form of ascorbic acid in the gastric juice. (45) This also decreases the absorption of iron. On the other hand bacteria need iron for growth and sometimes even compete with their host for it. (52) Thus, the very presence of *H. pylori,* even when asymptomatic, can reduce iron absorbed from the diet. By taking iron directly from the contents of the stomach the bacteria can reduce the amount available to the host. (53-56) In addition, it has been demonstrated that *H. pylori* can sequester lactoferrin from the gastric mucosa of the host, primarily from neutrophils and glands, (57) and that it can express a receptor for lactoferrin in its membrane through which it can directly take iron. (58-60) Bleeding peptic ulcers, hemorrhagic gastritis and tumors are other possible mechanisms that can cause or contribute to iron deficiency. (49, 53) A study of a population in Alaska attributed iron deficiency to occult gastrointestinal bleeding (detected by hemoglobin in feces) produced by chronic gastritis in *H. pylori* infected patients. (61) Other studies have found ulceration endoscopically. (62) Finally, a mechanism related to the regulation of iron metabolism through hepcidin has been proposed. Hepcidin is a peptide synthesized in the liver which acts as a regulator of absorption and systemic availability of intestinal iron. (63) Hepcidin binds to ferroportin a transmembrane protein found primarily in macrophages and enterocytes. This allows passage of intracellular iron to the extracellular space

for systemic availability. (64) This binding leads to internalization and degradation of intracellular Ferroportin resulting in iron retention in both enterocytes and macrophages. (64) One possible mechanism through which *H. pylori* infections may impact this process is through the inflammatory response which is primarily mediated by IL6. (65) This increases circulating levels of host hepcidin and leads to anemia through decreased absorption of iron and by blocking the release of the iron by the inflammatory cells as in chronic inflammatory diseases. In a study by Lee and colleagues levels of prohepcidin, the precursor of hepcidin, (66) decreased after treatment of patients with iron deficiency anemia and *H. pylori* regardless of whether they received oral iron therapy, *H. pylori* eradication or both. Also Beutler has suggested that the systemic inflammatory response to *H. pylori* was not intense enough to generate a sufficiently large increase in hepcidin production to cause anemia. Instead, Beutler suggested that while there was no increase of hepcidin, (67) some molecules generated by *H. pylori* may mimic hepcidin. However, more recent evidence actually supports a positive association between H. pylori infection and increased serum levels of hepcidin. (68, 69) In either case, a mechanism in which *H. pylori* leads to decreased systemic iron availability through downregulation of Ferroportin appears feasible. It is necessary to note that iron deficiency anemia can only be attributed to *H. pylori* when other common causes have been ruled out. (49) Therefore, *H. pylori* are not considered to be a major or frequent cause of iron deficiency anemia. (Figure 3).

H. PYLORI TREATMENT IN PATIENTS WITH IRON DEFICIENCY ANEMIA

Five randomized clinical trials (RCTs) were selected in the meta-analysis by Qu and colleagues. (28) Their comparison of changes in hemoglobin and serum ferritin in patients with iron deficiency anemia who received iron and *H. pylori* eradication treatment with patients with iron deficiency anemia who received only iron found a weighted mean difference (WMD) for hemoglobin of 4.06 g / L and a weighted mean difference for serum ferritin of 9.47 mg / L. This is not a very important increase. Subgroup analysis showed a better response in serum ferritin levels and hemoglobin among adolescents and adults than among children: the WMD for Hb was 0.65 g / L in children and 25.03 g / L in adolescents and adults while the WMD for serum ferritin was 0.70 mg / L in children and 14.79 mg / L in adolescents and adults. Each of the 5 RCTs used triple therapy for eradication of *H. pylori.* Bismuth triple therapy showed better results than PPI triple therapy, with the WMD for serum ferritin of 11.55 mg / L in the first

and 7.15 mg / L in the second. The authors of this study attributed this difference to two factors caused by the use of PPIs: decreased concentrations of ascorbic acid in the gastric juice which decreases the absorption of non-heme iron; and decreased absorption of vitamin B12 which also contributes to the absorption of iron. (70, 71)
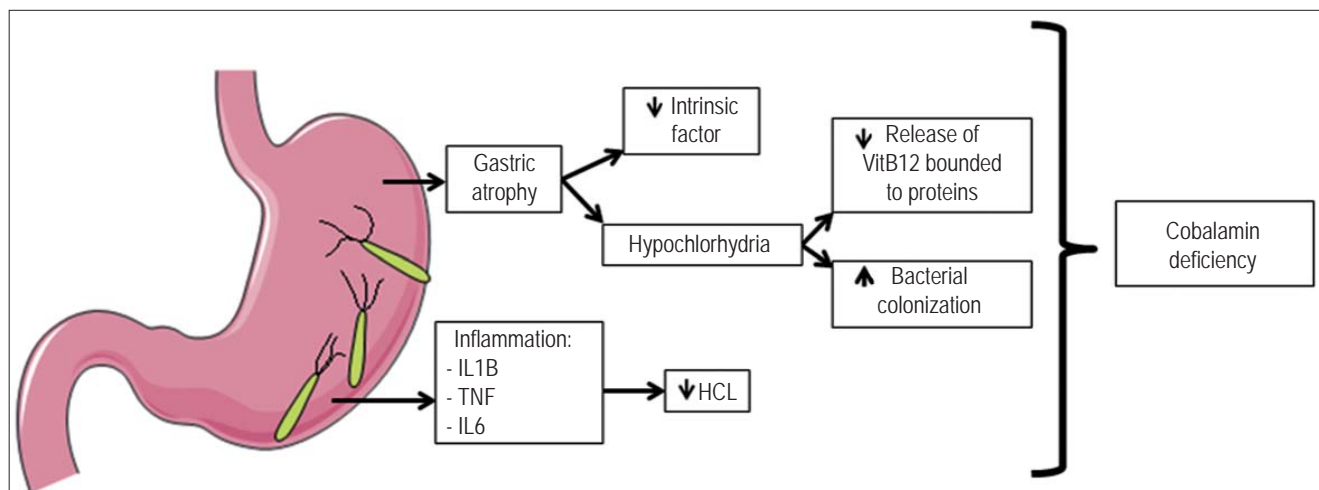
VITAMIN B12 DEFICIENCY

A mechanism that has been proposed to explain this association is that the action of *H. pylori* decreases gastric acid secretions which leads to hypochlorhydria. (72) The action of gastric acid in the stomach is required to release protein bounded vitamin B12 on the one hand while hypochlorhydria itself leads to an increase in the bacterial population of the stomach and intestines. These bacteria may in turn make use of the vitamin B12 themselves. (73) This mechanism is supported decreased vitamin B12 levels secondary to chronic use of PPIs. (71, 74) In addition, it has been proposed that vitamin B12 deficiency is secondary to decreased production of intrinsic factor due to atrophic gastritis (pernicious anemia) which results from chronic *H. pylori* infections. (29, 75, 76) However, one study has concluded that the association between *H. pylori* and vitamin B12 deficiency is independent of atrophic gastritis (Figure 4). (77)

Despite this, the systematic review of Lahner and colleagues conclude that there is insufficient evidence to arrive at conclusions about the actual mechanisms of vitamin B12 deficiency secondary to infection with H. pylori. (29)
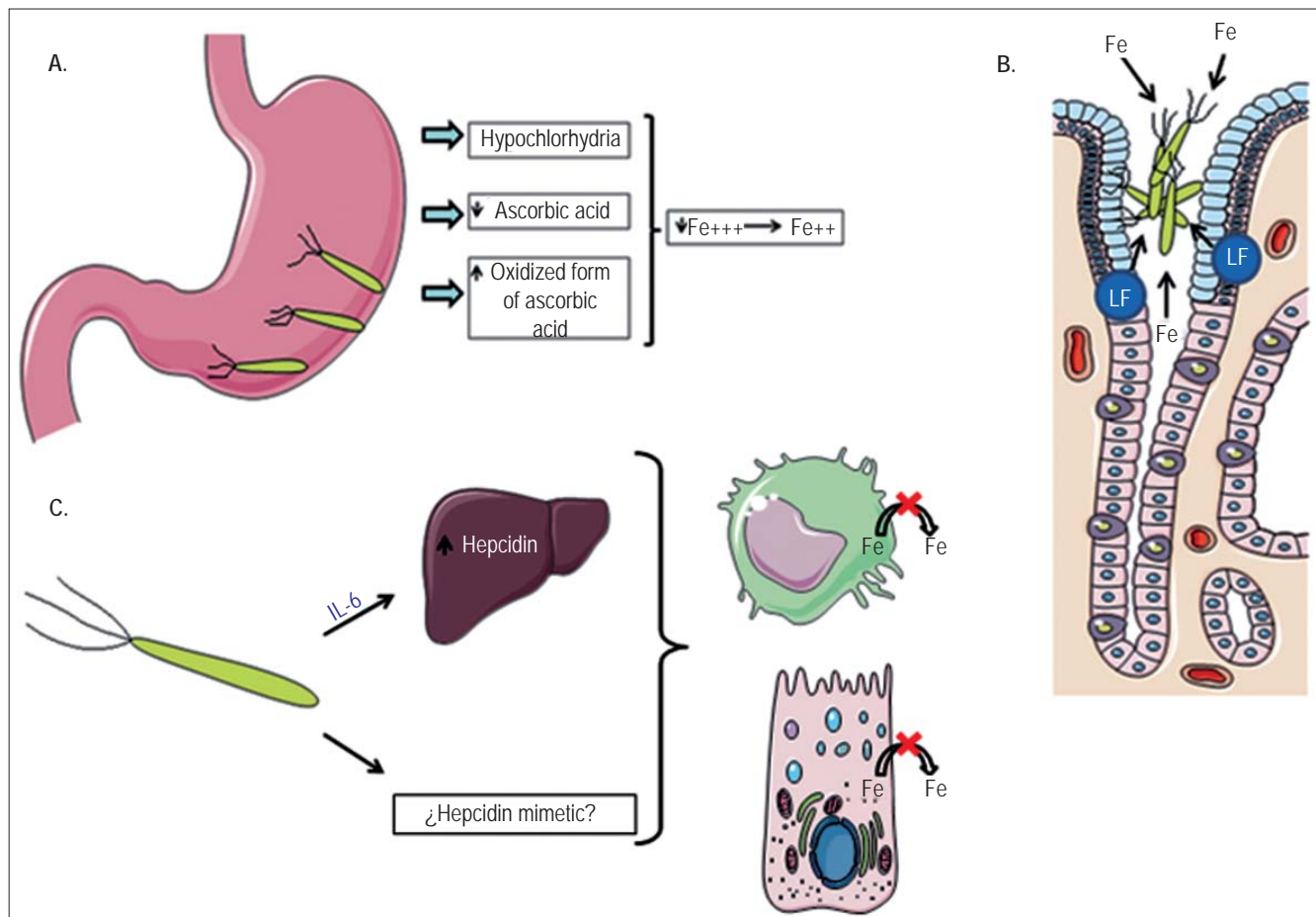
Figure 3. Primary mechanisms by which by *H. pylori* contributes to the development of iron deficiency anemia. **A)** Hypochlorhydria, decreased levels of ascorbic acid and the predominance of the oxidized form of ascorbic acid (biologically inactive) decrease the reduction of ferric iron to ferrous iron, the form absorbed by the intestines. **B)** *H. pylori* uses iron to proliferate and can compete with the host by capturing iron in its free form or via accumulation and uptake by lactoferrin (LF). **C)** Increased hepcidin production secondary to infection by *H. pylori* decreases the release of iron from macrophages and from enterocytes. Illustration produced from individual images created with Servier Medical Art in accordance with its conditions of use.

Figure 4. Mechanisms involved in the association between *H. pylori* and vitamin B12 deficiency. Hypochlorhydria leads to increased bacterial colonization. Bacteria compete with the host for vitamin B12. Hypochlorhydria also reduces release of vitamin B12 bounded to proteins thereby preventing binding to intrinsic factor and absorption. Intrinsic factor decreases due to atrophy of the gastric mucosa which decreases the ability to absorb vitamin B12 in the intestines. Illustration produced from individual images created with Servier Medical Art in accordance with its conditions of use.

TREATMENT OF *H. PYLORI* IN PATIENTS WITH VITAMIN B12 DEFICIENCY

A meta-analysis that included five studies evaluating vitamin B12 levels before and after eradication of *H. pylori* in a total of 283 *H. pylori* positive patients found that the treatment was effective in 173 patients (61.1%) with an average follow-up period of a month (0.25 to 12 months). (29) The eradication treatment used in one study combined a PPI, amoxicillin, clarithromycin and metronidazole, (78) two studies combined a PPI, clarithromycin and amoxicillin, (77, 79) another study combined a PPI and clarithromycin, and the other used only metronidazole. (80, 81) The meta-analysis showed an increase in vitamin B12 levels among patients for whom *H. pylori* was eradicated.

CONCLUSIONS

H. pylori are bacteria that have accompanied us through a large part of human history. (1) There association with gastric diseases has been shown since ancient times, but only recently has an association with extragastric diseases been demonstrated. (2, 21-27) *H. pylori* have been causally associated with vitamin B12 deficiency, immune thrombocytopenic purpura and iron deficiency anemia without another explanation. It has been recommended that physicians look for and treat *H. pylori* in patients with these three conditions. (31) Nevertheless, there are several other extragastric pathologies in which this bacterium may play a role. These include colon cancer, type 2 diabetes mellitus, neurodegenerative diseases, heart disease and liver fibrosis. (14-24, 26)

In the case of ITP, one of the primary pathogenic mechanisms is the production of antibodies against antigens produced by *H. pylori* (primarily CagA protein). These antigens cross-react against CagA similar antigens on the surface of platelets. (39) Three mechanisms are involved in the association *H. pylori* with iron deficiency anemia: 1) decreased reduction of ferric iron to ferrous iron due to histopathological changes in the stomach produced by *H. pylori* leading to decreased intestinal absorption of this mineral; (46-51) 2) *H. pylori* competes with the host for iron consumption because the bacteria need it to proliferate, (53-56, 58-60) and 3) *H. pylori* increases hepcidin production which reduces intestinal iron absorption and reduces the release of iron recycled by macrophages. (68, 69) Finally, for the case of vitamin B12 deficiency, the primary pathogenic mechanism involves reducing the release of the vitamin from proteins ingested by the host due to hypochlorhydria triggered by *H. pylori* infections. (72, 73)

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