Chapter 3

Helicobacter pylori and Hematologic Diseases

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62971

Abstract

Helicobacter pylori infection is the most common infection of the human species, with developing countries displaying a marked disadvantage in contrast to developing countries. While *H. pylori* infection is asymptomatic in most infected individuals, it is intimately related to malignant diseases of the stomach, such as gastric cancer and gastric MALT lymphoma, as well as benign diseases, for example chronic gastritis and duodenal and gastric peptic ulcers. Since the discovery that gastric mucosa could be colonized by bacteria, evidence of greater than 50 extragastric manifestations has been reported, linking *H. pylori* infection and the development of diseases associated with cardiology, dermatology, endocrinology, obstetrics and gynecology, hematology, pneumology, neurology, odontology, ophthalmology, otorhinolaryngology, and pediatrics. This chapter presents the extragastric manifestations of *H. pylori* infection expressed through hematologic diseases; particularly those included in the international consensus, and discusses guidelines for the management of *H. pylori* infection, such as iron deficiency, vitamin B_{12} (cobalamin) deficiency, and immune thrombocytopenia. Other manifestations reviewed include immune neutropenia, antiphospholipid syndrome, and plasma cell dyscrasias, such us monoclonal gammopathy of undetermined significance, multiple myeloma, and Henoch–Schönlein purpura.

Keywords: *Helicobacter pylori*, iron deficiency, immune thrombocytopenia, mucosa-associated lymphoid tissue lymphoma, vitamin B_{12} deficiency

1. Introduction

Helicobacter pylori infects greater than 50% of the world population's stomachs, therefore constituting the most common infection of the human species [1]. A marked disadvantage exists between developed countries, where the prevalence ranges between 30% and 50%, and developing countries, where the prevalence ranges between 80% and 90% [2]. Since the discovery in 1983 that the stomach could be colonized by bacteria [3], sufficient evidence has

accumulated implicating *H. pylori* as a pathogen intimately related to benign stomach diseases, such us chronic gastritis and duodenal and gastric peptic ulcers [3], and malignant diseases, for example gastric cancer [4] and gastric MALT lymphoma [5]. Furthermore, during the last three decades following the discovery [3], approximately 50 extragastric diseases have been reported in medical specialties such as cardiology, dermatology, endocrinology, obstetrics and gynecology, pneumology, neurology, odontology, ophthalmology, otorhinolaryngology, pediatrics, and hematology [6-20], the last of which is the subject of this review.

From a practical standpoint, hematological associations with *H. pylori* infection can be arbitrarily divided into two groups: (1) hematological diseases with sufficient scientific evidence to be recognized by the consensus and guidelines for the management of *H. pylori* among the indications of study and eradication and (2) hematological diseases where there is suspicion, with greater or lesser scientific evidence, of an association with *H. pylori* infection. Table 1 presents the hematological diseases associated with or possibly associated with *H. pylori* infection.

Recognized manifestations
Iron deficiency
Vitamin B_{12} deficiency
Immune thrombocytopenia
Gastric MALT lymphoma
Unrecognized manifestations
Autoimmune neutropenia
Antiphospholipid syndrome
Plasma cell dyscrasias
Henoch–Schönlein purpura
Other manifestations: acute leukemia, myelodysplastic syndrome, thrombocytosis

Table 1. Hematologic manifestations of *H. pylori* infection

2. Hematological diseases recognized as related to *H. pylori*

Until September 2015, the scientific community has recognized three hematologic diseases as extragastric manifestations of *H. pylori* infection: iron deficiency [21-30], vitamin B_{12} deficiency [27, 29], and immune thrombocytopenia (ITP) [21, 23-31]. These will be carefully analyzed in the following subsections. Gastric MALT lymphoma, although considered a disease in the oncohematologic field and is associated with *H. pylori* infection, is not presented in this review because it is recognized as gastric manifestation.

2.1. Iron deficiency

Iron deficiency, with or without anemia (*anemia sine anemia*), is a serious public health problem, which affects approximately 25% of the world's population (greater than two billion people),

according to the World Health Organization (WHO). Importantly, it mainly affects disadvantaged populations, such as children and women of gestational age [32, 33]. Iron deficiency, with or without anemia, is associated with increased morbidity due to high susceptibility to infections, decreased labor productivity, delayed weight–height and cognitive development, and other conditions [34].

It is important to note that iron deficiency is a chronic process: an iron imbalance can take several years to become established and manifest clinically or through hemogram (blood cell count) parameters, such as morphological alterations of erythrocytes or anemia, according to the WHO criteria [32]. Three stages of iron deficiency are clearly established: prelatent (Stage 1), when serum ferritin is between 12 μg/L and 30 μg/L; latent (Stage 2), when serum ferritin is below 12 μg/L; and iron deficiency anemia (Stage 3), when anemia is observed in addition to diminished or depleted iron storage levels determined by serum ferritin [35].

2.1.1. H. pylori and iron deficiency

In 1991, in Belgium, Blecker et al. described the first association between iron deficiency and *H. pylori* infection. The patient was a 15-year-old young with iron deficiency anemia (hemoglobin 8.5 g/dL) secondary to chronic active hemorrhagic gastritis, positive to *H. pylori*, without prior gastrointestinal manifestations, in whom after *H. pylori* eradication the hematologic parameters and ferrokinetics test returned to normal without requiring supplemental iron treatment [36]. Two years later, in France, Bruel et al. reported a second case of iron deficiency anemia (hemoglobin 5.6 g/dL), in an 11-year-old child, which manifested as an upper gastrointestinal hemorrhage with documented infection with *H. pylori*. The anemia was resolved after eradication of the infection, again without supplemental iron treatment [37]. In the same year, in Italy, Dufour et al. presented the case of a 7-year-old boy diagnosed with refractory iron deficiency anemia (hemoglobin 5.1 g/dL), who had been treated with oral iron, the presence of *H. pylori* was reported and was asymptomatic from the viewpoint of gastrointestinal manifestations. As in the preceding cases, the infection was eradicated without supplementary iron treatment and the hematologic parameters, including hemoglobin (13.0 g/dL), returned to normal after 6 months [38].

After these first reports, where iron deficiency disappeared after the eradication of *H. pylori* [36-38], new isolated cases were published in last century [39-43], which as the first series demonstrate the association of *H. pylori* with iron deficiency and iron deficiency anemia [40, 44, 45]. The first decade of the twenty-first century provided most of the studies that currently support the five meta-analyses associating *H. pylori* infection with iron deficiency and the resolution of disease following infection eradication [46-50] in children [51-60], in pubescent males and females [61, 62], in prepubertal girls [63], in adult men and women [40, 45, 64-75], in seniors [76], in pregnant women [63], and in non-pregnant women [77]. In addition, these studies have provided scientific support to the different consensus and guidelines for incorporating iron deficiency into the medical management of *H. pylori* infection as an extragastric manifestation and indication for eradication [21-30].

2.1.2. Pathophysiology of iron deficiency by H. pylori

The pathophysiological mechanisms through which *H. pylori* is associated with the etiology of iron deficiency, with or without anemia, has not been fully elucidated, and more questions remain than answers. Possible explanations proposed to clarify the association between *H. pylori* and iron deficiency will be enunciated. However, it is not yet known why this association exists in some patients but not in others, where a different association is presented or the infection is asymptomatic, as happens in most cases [78].

In the past decade, *H. pylori* infection and iron deficiency have been linked through a recently discovered hormone called hepcidin [79]. Hepcidin is a hormone of hepatic origin that regulates iron absorption at the enterocyte level in the small intestine and the liberation of stored iron from the macrophages of reticuloendothelial system [80]. Hepcidin is elevated, as an acute phase reactant, in response to inflammation in the gastric mucosa. This in turn translates into a physiological iron deficiency, known clinically as anemia of chronic inflammation [81-85]. Preliminary studies show that serum hepcidina levels are elevated in patients infected with *H. pylori* [85-87] and return to normal after eradication of the infection [88], thereby permitting iron absorption in enterocytes and liberation from entrapment in the macrophage reticuloendothelial system.

Other possible causes of iron imbalance in patients infected with *H. pylori* can result from chronic gastritis, which occurs in all infected individuals [78]. This condition can generate bleeding when transforms into erosive gastritis [89], especially in patients with bleeding duodenal or gastric peptic ulcers [90, 91] and in patients who chronically consume non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, for the purpose of cardioprotection [92-95]. Other mechanisms invoked to explain iron deficiency in patients infected with *H. pylori* are related to changes in gastric physiology, particularly changes in gastric pH and the presence of achlorhydria, which significantly reduces the solubility and intestinal absorption of inorganic iron [40].

Beyond the aforementioned evidence, certain highly virulent strains of *H. pylori*, such as those with cytotoxin-associated gene A (CagA) and vacuolating cytotoxin gene A (VacA), which act through molecular mimicry mechanisms, are more likely to develop or magnify iron deficiency in infected patients, compared with infected patients with strains not carrying these genes [71, 96-98]. This situation could explain, in part, the marked differences from one region to another and the large discrepancies observed in different studies.

2.1.3. Management of iron deficiency in the post-Helicobacter era

Regarding to the management of iron deficiency in the post-*Helicobacter* era, it is important to clarify that *H. pylori* is not the only cause of iron deficiency, and its incorporation into the consensus and management guidelines of *H. pylori* as an indication to investigate and eradicate the infection is not a substitute for an adequate study of the most common causes of iron deficiency. These situations are particular to each region, according to prevalence of iron deficiency and *H. pylori* infection, which vary from place to place. Thanks to over 250 referenced studies in the literature aiming to clarify different aspects of the association between *H.*

pylori and the development of iron deficiency, five meta-analyses are now available that demonstrate the impact of infection on the development of iron deficiency and that infection eradication improves hematological parameters and ferrokinetics [46-50]. These analyses have enabled the scientific community, particularly the consensus and management guides, to incorporate iron deficiency of unexplained origin as an indication to evaluate and eradicate *H. pylori* infection, when present, in adults as well as children [21-30].

Before initiating treatment for a patient with iron deficiency, an assessment of the prevalence of *H. pylori* infection should be performed according to region. Generally, the prevalence is low in developed countries; these cases should proceed with conventional management of iron deficiency [32, 35]. In developing countries, the rate of *H. pylori* infection is high; in these cases or when the patient, despite living in a country where infection rates are low, comes from a country where the infection rates are high, it should proceed to determine the status of *H. pylori* through a non-invasive test, ideally the ^{13}C-urea breath test [27]. If the patient is negative for *H. pylori*, it is necessary to investigate other causes of the iron deficiency and treat the patient conventionally [32, 35], whereas if the patient is positive for *H. pylori*, it is indispensable to eradicate the infection [27].

After 6–8 weeks of treatment, the infection eradication must be confirmed using a non-invasive test, ideally with ^{13}C-urea breath test [27]. If eradication is not achieved, it is mandatory to establish a new therapy scheme until eradication is achieved. Once *H. pylori* eradication is achieved and an improvement in hematological parameters and ferrokinetics (complete or partial remission) is obtained, it is important to periodically evaluate the clinical hematological parameters and the indicators of iron levels. If there is no response, it must establish a conventional management of iron deficiency [32, 35].

Figure 1 shows a diagnostic and management algorithm of iron deficiency in the post-*Helicobacter* era, taking into account the prevalence of infection and *H. pylori* status.

2.2. Vitamin B_{12} deficiency

Vitamin B_{12}, also known as cobalamin, is a coenzyme necessary for the metabolism of amino acids, such as methionine, threonine, and valine, and for DNA synthesis through the conversion of methyl-tetrahydrofolate to tetrahydrofolate [99]. Vitamin B_{12} is synthesized in mammals, but for humans, their provision depends exclusively of diet intake of animal products [99].

Again, as with iron deficiency, it should be noted that vitamin B_{12} deficiency is a chronic process, with very slow establishment. It may manifest clinically through neuropsychiatric symptoms or through hemogram parameters, such as morphological alterations of erythrocytes or anemia, according to the WHO criteria [32]. Four stages of vitamin B_{12} deficiency are clearly established: Stage I, reduction of vitamin B_{12} levels in blood; Stage II, low amount of vitamin B_{12} cellular levels and metabolic disorders; Stage III, increase in homocysteine and methylmalonic acid levels and decrease in DNA synthesis with onset of neuropsychiatric symptoms; and Stage IV, macrocytic anemia [100].

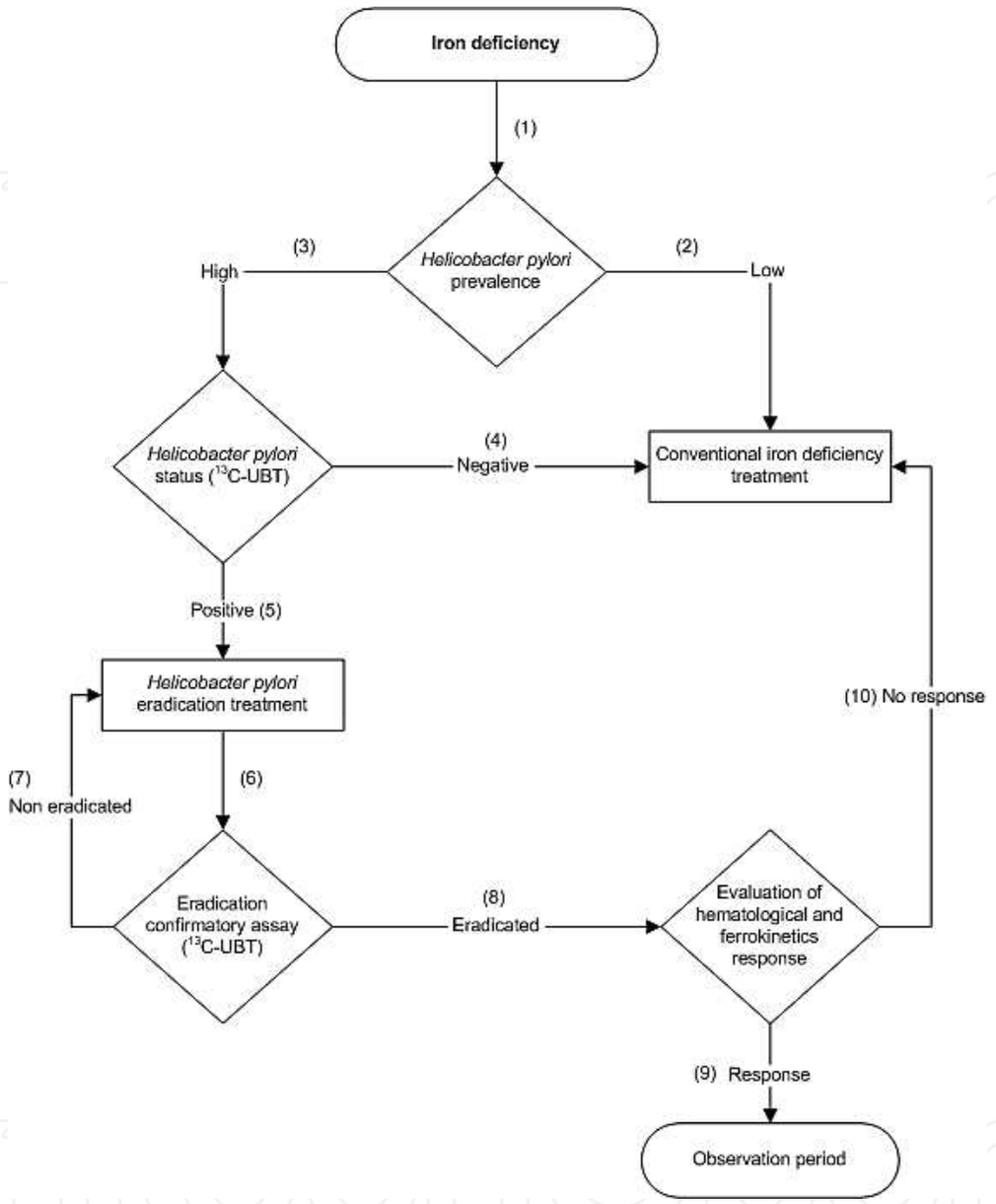

Figure 1. Algorithm for the study and management of iron deficiency, with or without anemia, in the post-*Helicobacter* era. (1) Before initiating treatment for a patient with iron deficiency, an assessment of the prevalence of *H. pylori* infection should be performed in each region. Generally, it is high in developing countries and low in developed countries [1]. (2) If the rates of *H. pylori* infection are low, proceed with a conventional management of iron deficiency [32, 35]. (3) If the rates of *H. pylori* infection are high or the patient, despite living in a country where infection rates are low, comes from a country where the infection rates are high, proceed to determine the status of *H. pylori* through a non-invasive test, ideally the ^{13}C-urea breath test (^{13}C-BUT) [27]. (4) If the patient is negative for *H. pylori*, investigate other causes of the iron deficiency and treat conventionally [32, 35]. (5) If the patient is positive for *H. pylori*, proceed with eradication of the infection [27]. (6) Confirm infection eradication 6–8 weeks after the treatment using a non-invasive test, ideally with the ^{13}C-urea breath test [27]. (7) If eradication is not achieved, establish a new scheme of eradication therapy until it is achieved. (8) Once *H. pylori* eradication is achieved, (9) if a response is obtained in the hematological parameters and ferrokinetics (complete or partial remission), periodically evaluate the clinical hematological parameters and indicators of iron. (10) If there is no response, proceed with a conventional management of iron deficiency [32, 35].

Vitamin B_{12} deficiency is defined in terms of the serum values of vitamin B_{12} and two components of its metabolic pathway, homocysteine and methylmalonic acid [101]. The diagnosis of vitamin B_{12} deficiency is established in accordance with the following criteria: (1) serum vitamin B_{12} < 150 pmol/L (< 200 pg/mL) with clinical manifestations and/or hematological alterations related to vitamin B_{12} deficiency; (2) serum vitamin B_{12} < 150 pmol/L, measured on two separate occasions; (3) serum vitamin B_{12} < 150 pmol/L and serum homocysteine > 13 mmol/L or urinary methylmalonic acid > 0.4 mmol/L (in the absence of renal failure, folic acid deficiency, and vitamin B_6 deficiency); and (4) levels of serum holotranscobalamin < 35 pmol/L [102].

The prevalence of vitamin B_{12} deficiency is highly variable and represents a serious public health problem, depending on the populations analyzed. Epidemiologic studies show that, in the general population of industrialized countries, vitamin B_{12} deficiency has a prevalence of approximately 20%, with a range between 5% and 60%, depending on the definition of vitamin B_{12} deficiency that is utilized [101, 102]. The prevalence of vitamin B_{12} deficiency expressed as pernicious anemia is higher in Latin American countries than in the rest of the world; furthermore, in Latin America, the disease occurs in younger persons [103], while it is associated with advanced age in remaining countries [104].

In addition to its close association to the etiology of pernicious anemia [105] and subacute combined degeneration [106], vitamin B_{12} deficiency is related, through homocysteine, with dissimilar diseases such as Alzheimer's disease [107, 108], dementia [109, 110], depression [111], stroke [112, 113], pulmonary embolism [114, 115], acute myocardial infarction, and coronary heart disease [116].

2.2.1. H. pylori and vitamin B_{12} deficiency

The possibility that pernicious anemia, rather than vitamin B_{12} deficiency, was associated with *H. pylori* was the first extragastric association postulated within the scientific community. This postulation was made by O'Connor et al. in 1984 [117], a year after Warren and Marshall inform the scientific community that the stomach could be colonized by bacteria [3]. Despite this premature interest, the association has been difficult to sustain and, rather, has been denied by many authors. Fong and colleagues performed what is considered the first well-founded study to clarify the probable link between *H. pylori* infection and pernicious anemia. In this study, the authors concluded that patients that suffer pernicious anemia are protected against *H. pylori* infection and that the bacteria not invade the inflamed mucosa by isolated processes [118]. These data were ratified in a Japanese study made by Saito et al. [119] and have been shared by other authors, however, with the wrong conclusion [120].

It is currently known that when vitamin B_{12} deficiency becomes clinically relevant, the bacteria are no longer at the site of the lesion due to changes in the gastric mucosa that result in a hostile environmental niche. In cases of vitamin B_{12} deficiency and pernicious anemia, *H. pylori* disappears as a result of changes mediated by the immunological response. These changes can be evidenced by the presence of antibodies against parietal cells and intrinsic factor after the bacteria have left the gastric mucosa [121, 122]. Moreover, H+/K+ ATPase autoantibodies, which are closely linked to classical autoimmune gastritis, are also important indicators of

mucosal atrophy in *H. pylori* chronic gastritis [123]. *H. pylori* also disappears from the gastric mucosa as a result of the histological and physiological changes induced by chronic atrophy in the case of gastric cancer [124].

Infection with *H. pylori* can also cause malabsorption of different micronutrients [125] like vitamin B_{12} [125-127]. A systematic review and meta-analysis of 17 studies with 2454 patients demonstrated a significant reduction in serum vitamin B_{12} levels in patients infected with *H. pylori* when compared with uninfected persons [128]. Marino et al. demonstrated a correlation between the decrease in serum vitamin B_{12} levels and the increase in serum homocysteine due to *H. pylori* infection in 62 older patients: in these same patients, following infection eradication, an increase in serum vitamin B_{12} levels and a decrease in serum homocysteine levels occurred until normalization was reached [127].

The intimately association of pernicious anemia with the probability to develop stomach cancer was widely recognized by scientific community many years before the relationship between *H. pylori* and stomach cancer was known [129-132]. Recently, Vanella et al. validated this association through a systematic review and meta-analysis, establishing that patients with pernicious anemia (vitamin B_{12} deficiency) have a relative risk of developing gastric cancer of 6.8 (95% CI: 2.6–18.1) [133].

2.2.2. Pathophysiology of vitamin B_{12} deficiency

The pathophysiological mechanism by which *H. pylori* is related to the etiology of vitamin B_{12} deficiency has not been fully clarified, and many questions remain. Possible explanations aiming to clarify the association of *H. pylori* with vitamin B_{12} deficiency are described below. It is not yet known why this association occurs in some patients but not in others, where a different association is presented or the course of the infection is asymptomatic, as happens in most cases [78].

Vitamin B_{12} deficiency manifests as antibodies against intrinsic factor and the parietal cells in the stomach, achlorhydria, and decreased pepsinogen I and gastrin, thereby presenting an histological picture of chronic type A gastritis (autoimmune) [105]. The lack of intrinsic factor, which occurs as result of these changes in the gastric mucosa, reduces the absorption and transport of vitamin B_{12} that comes from the diet. Chronic atrophic gastritis, induced immunologically, evolves over a period of 10–30 years, until reaching gastric atrophy and the development of pernicious anemia, to the extent that the stores of vitamin B_{12} are depleted [105]. Vitamin B_{12} deficiency, parallel to the development of pernicious anemia, causes peripheral neuropathy and lesions in the posterior and lateral columns of the spinal cord, known as subacute combined degeneration, that progresses with demyelination and axial degeneration and eventually neural death [105].

2.2.3. Management of vitamin B_{12} deficiency in the post-Helicobacter era

Respect to the management of vitamin B_{12} deficiency in the post-*Helicobacter* era, it must be clarified that *H. pylori* is not the only cause of vitamin B_{12} deficiency, and its incorporation into the consensus and management guidelines of *H. pylori* as an indication to investigate and

eradicate the infection is not a substitute for an adequate study of the most common causes of vitamin B_{12} deficiency. These situations are particular to each region, according to the prevalence of vitamin B_{12} deficiency and *H. pylori* infection, which vary from place to place.

A recent systematic review and meta-analysis with the aim of clarifying the association between *H. pylori* and the vitamin B_{12} deficiency evaluated the serum vitamin B_{12} levels from 17 studies involving a total of 2454 patients, infected or not with *H. pylori*. This study revealed that serum vitamin B_{12} levels are significantly lower in infected patients than in uninfected patients and that *H. pylori* eradication significantly increases vitamin B_{12} levels [128]. This has enabled the inclusion of vitamin B_{12} deficiency in the consensus and management guides of *H. pylori* infection as an indication to evaluate and eradicate the bacteria [27, 29].

Before initiating treatment for a patient with vitamin B_{12} deficiency, an assessment of the prevalence of *H. pylori* infection should be performed according to region. Generally, the prevalence is low in developed countries; in these cases should proceed with conventional management of vitamin B_{12} deficiency [134]. In developing countries, the rate of *H. pylori* infection is high; these cases or when the patient, despite living in a country where infection rates are low, comes from a country where the infection rates are high, it should proceed to determine the status of *H. pylori* through a non-invasive test, ideally the ^{13}C-urea breath test [27]. If the patient is negative for *H. pylori*, it is necessary to investigate other causes of the vitamin B_{12} deficiency and treat the patient conventionally [134], whereas if the patient is positive for *H. pylori*, it is indispensable to eradicate the infection [27].

After 6–8 weeks of the treatment, the infection eradication must be confirmed using a non-invasive test, ideally with ^{13}C-urea breath test [27]. If eradication is not achieved, it is mandatory to establish a new therapy scheme until eradication is achieved. Once *H. pylori* eradication is achieved and an improvement in hematological parameters and vitamin B_{12} levels (complete or partial remission) is obtained, it is important to evaluate them for a certain time. If there is no response, it must establish a conventional management of vitamin B_{12} deficiency [134].

Figure 2 shows a diagnostic and management algorithm of vitamin B_{12} deficiency in the post-*Helicobacter* era, taking into account the prevalence of the infection and *H. pylori* status.

2.3. Immune thrombocytopenia (ITP)

ITP is the most frequent immunological disease in hematology [135]. The annual incidence of ITP is 5.5 per 100000 persons when the platelet count cut-off point is 100×10^9/L and 3.2 per 100000 persons when the platelet count cut-off point is 50×10^9/L [136]. The chronic form of ITP increases with age, being twice as high in people older than 60 years with respect to those younger than 60 years [136, 137], with a higher incidence in women (2:1) than in men (3:1) [138].

Primary ITP, formerly known as idiopathic thrombocytopenic purpura (ITP) and autoimmune thrombocytopenic purpura, has recently been redefined and adjusted in light of new knowledge represented in the Vicenza Consensus [139]. ITP was established as an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count below 100×10^9/L) in the absence of another possible causes or conditions related to thrombocytopenia [139]. Primary ITP diagnosis continues to be one of the exclusions due to current lack of robust

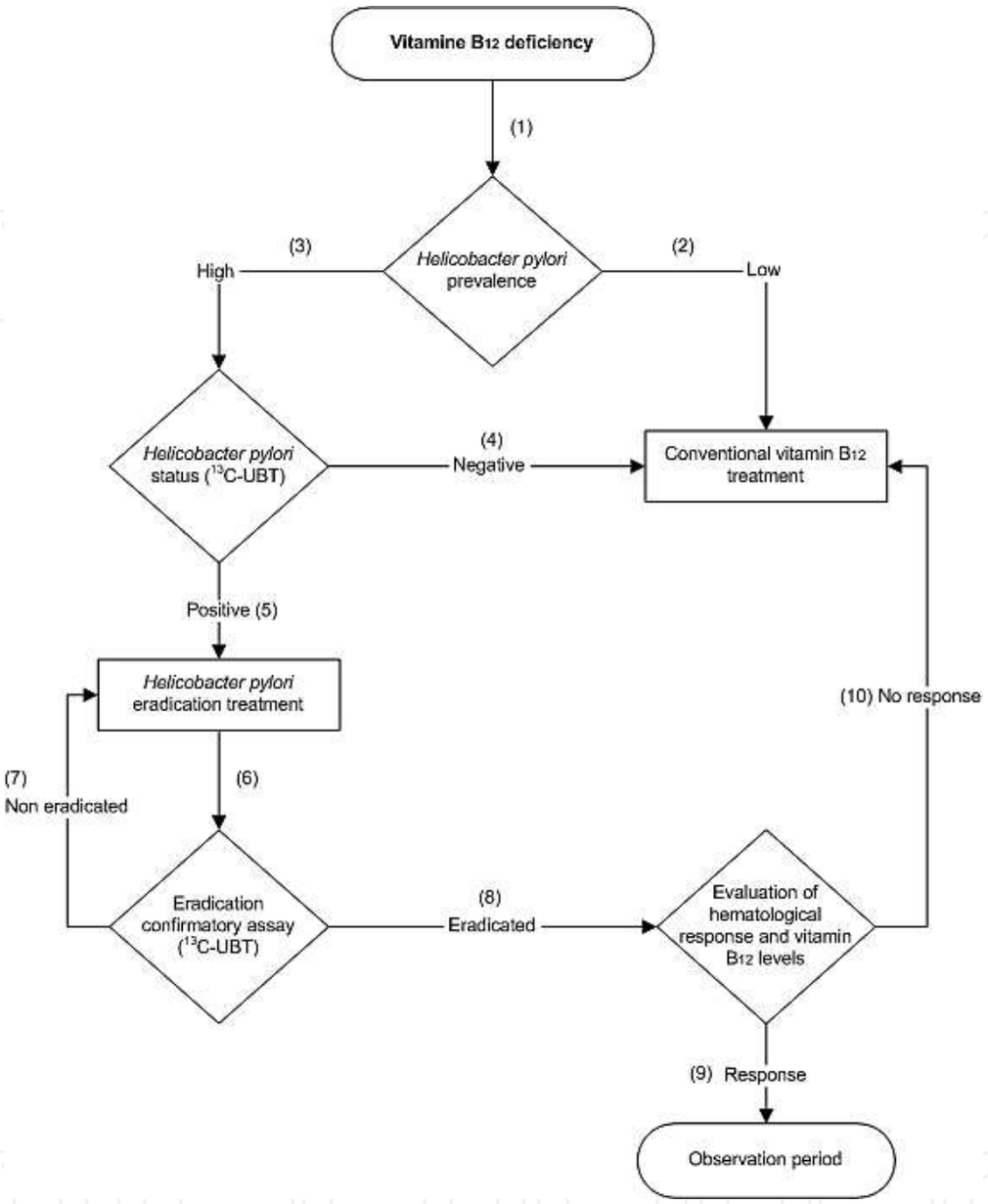

Figure 2. Algorithm for the study and management of vitamin B_{12} deficiency in the post-*Helicobacter* era. (1) Before initiating treatment for a patient with vitamin B_{12} deficiency, an assessment of the prevalence of *H. pylori* infection should be performed in each region. Generally, prevalence is high in developing countries and low in developed countries [1]. (2) If the rates of *H. pylori* infection are low, proceed with a conventional management of vitamin B_{12} deficiency [134]. (3) If the rates of *H. pylori* infection are high or the patient, despite living in a country where infection rates are low, comes from a country where the infection rates are high, proceed to determine the status of *H. pylori* through a non-invasive test, ideally the ^{13}C-urea breath test (^{13}C-BUT) [27]. (4) If the patient is negative for *H. pylori*, investigate other causes of vitamin B_{12} deficiency and treat conventionally [134]. (5) If the patient is positive for *H. pylori*, proceed with eradication of the infection [27]. (6) Confirm infection eradication 6–8 weeks after treatment using a non-invasive test, ideally the ^{13}C-urea breath test [27]. (7) If eradication is not achieved, establish a new scheme of eradication therapy until it is achieved. (8) Once *H. pylori* eradication is achieved, (9) if a response is obtained in the hematological parameters and the serum levels of vitamin B_{12} and homocysteine (complete or partial remission), periodically evaluate the clinical hematological parameters and indicators of vitamin B_{12}. (10) If there is no response, proceed with a conventional management of vitamin B_{12} deficiency [134].

clinical and laboratory parameters, with high accuracy to establish its diagnosis [139]. The main clinical concern of primary ITP is the elevated risk of bleeding; however, bleeding symptoms are not present all the time [139].

H. pylori infection is included as a new disease at the list of diseases potentially associated with the development of ITP; therefore, it must be ruled out in cases where thrombocytopenia by *H. pylori* infection is suspected [139], according to the establishment by the British Society for Haematology at beginning of 2003 [140]. In addition, the Vicenza Consensus conserved the acronym ITP to refer to the disease itself to avoid confusion and chose the term "primary immune thrombocytopenia" or "primary ITP" as a substitute name for ITP (idiopathic thrombocytopenic purpura) or autoimmune thrombocytopenic purpura, referring to cases where any associated causes are excluded. For cases where an underlying disease is present, it is recommended to use the term "secondary immune thrombocytopenia" or "secondary ITP," followed by the name of the associated condition. For example, for the cases possibly initiated by *H. pylori* infection, it must be used with the extent "secondary ITP *H. pylori*–associated," which required the demonstration of complete resolution of ITP after proving the eradication of the bacteria. This form in clinical practice could be called "ITP *H. pylori*–associated" [139].

2.3.1. H. pylori and immune thrombocytopenia

The association of *H. pylori* with ITP was first reported by Garcia-Perez et al. in Spain in 1993; this report described a patient whose platelet count returned to normal values after eradication of *H. pylori* [141]. The medical literature subsequently reported similar cases in Japan [142-146], Italy [147-149], and Turkey [150].

In Italy, in 1998, Gasbarrini et al. presented the first series of cases demonstrating the association of *H. pylori* with adult ITP, reporting a recovery in platelet counts with disappearance of autoantibodies against platelets in six of eight ITP patients infected with *H. pylori*, after successful eradication of the bacteria [151]. Including this first series [151], 40 series have been described in the medical literature until now, and these reports consistently demonstrate the association between *H. pylori* infection and platelet count recovery following eradication. Ten of these series were reported in Europe: eight in Italy [151-158], one in Turkey [159], and one in Serbia [160], with a total of 495 ITP patients, 288 (58.2%) of whom were infected with *H. pylori*. Of these, 242 received eradication therapy. Successful eradication was achieved in 222 (91.7%) patients, and a platelet response was observed in 108 (48.6%) patients. Asian countries have provided 28 published series: 23 in Japan [161-183], two in China [184, 185], two in Iran [186, 187], and one in South Korea [188], with 1525 total ITP patients, 1089 (71.4%) of whom were infected with *H. pylori*. A total of 929 patients received eradication therapy, it was successful in 811 (87.3%) and 472 (58.2%) patients demonstrated a platelet response. In America, only two series have reported an association between *H. pylori* and ITP: the first in Colombia [189] and the second in Canada [190]. The series in Colombia presented 32 patients with ITP, 29 (90.6%) of whom were infected with *H. pylori*. Those 29 patients received eradication therapy, and it was successful in 26 (89.7%) and 21 (80.8%) patients demonstrated a platelet response [189]. The association of *H. pylori* infection with ITP has not been reported in adults or children from Oceania or the continent of Africa.

A consolidated analysis of the 40 series reported worldwide reveals a total of 2074 patients with ITP, 1410 (68.0%) of whom are *H. pylori*-positive. A total of 1204 received eradication therapy, which succeeded in 1062 (88.2%); 604 (56.9%) of these patients demonstrated a platelet response. In general, Europe has a mean infection rate of 59.2% in patients with ITP and a mean platelet response in 48.6% of those patients; respective rates in Asia are 70.7% and 58.2%, and those in America (Colombia) are 90.6% and 80.8%. When consolidated, the 40 series exhibit a mean infection rate of 68.0% in patients with ITP, with a mean platelet response in 56.9% of those patients [191]. Table 2 summarizes the results of these series demonstrating an association between *H. pylori* infection and ITP development in adults and its response to *H. pylori* eradication [191]. Nevertheless, additional studies in Spain [192], France [193], the United States [193, 194], and Mexico [195] found no association between *H. pylori* infection and adult chronic ITP, explainable, at least in part, by the low prevalence of infection in these countries and insufficient samples.

Continent	Number of series	Number of patients with ITP	Number of *H. pylori*- infected ITP patients (%)	Number of treated patients	Number *H. pylori*-eradicated patients (%)	Number of patients with platelet response (%)
Europe	10 [151-160]	495	288 (58.2)	242	222 (91.7)	108 (48.6)
Asia	28 [161-188]	1525	1089 (71.4)	929	811 (87.3)	472 (58.2)
America	2 [189, 190]	54	33 (90.6)	33	29 (87.9)	24 (82.8)
Worldwide total	40 [151-190]	2074	1410 (68.0)	1204	1062 (88.2)	604 (56.9)

Source: Modified from Campuzano et al. [191]

Table 2. *Helicobacter pylori* and immune thrombocytopenia in adults

Regarding to the association of *H. pylori* infection with ITP in children, it is important to clarify that childhood ITP has a different course than ITP in adults [135]. The few studies that have thus far addressed the relationship between ITP and *H. pylori* in children are contradictory: certain groups in China [196], Japan [197], Iran [198], Finland [199], Netherlands [200], and Italy [201, 202] have identified an association between infection and ITP in children, with platelet count recovery in an average of 35.2% of the patients [191]. This rate is much lower than the response rate observed in adult patients with ITP, which is greater than 50% [151-190]. Meanwhile, other groups in Turkey [203], Italy [204, 205], Thailand [206], and Hungary [207] found no association and the response to eradication ranged from none [203, 204, 208] to very poor [205, 207].

2.3.2. Pathophysiology of secondary ITP (associated with H. pylori infection)

The origin of primary ITP is associated with congenital or acquired immune changes that lead to an immune system response against platelets or megakaryocytes that cannot be attributed to other causal changes. In secondary ITP, alternative primary events are identified that lead to the development of this autoimmune response [209]. In the case of *H. pylori* as causal agent

of this disease, several mechanisms have been described that contribute to the development of the autoimmune response. One of these mechanisms is a change in the balance of Fcγ receptors, involved in the activation of monocytes, and their relation to the inhibitory Fc receptor FcγRIIB. *H. pylori* infection decreases the levels of FcγRIIB, leading to increased activated monocytes through Fcγ receptors, with elevated non-specific phagocytosis, resulting in overactivation of B and T lymphocytes. These results were confirmed by reversing monocyte activation following *H. pylori* eradication treatment, with reducing generation of autoantibodies by B lymphocytes and overactivation of innate and acquired autoimmune response, and increasing the amount of circulating platelets [179].

In conjunction with the overeactivation of monocytes, autoantibody production has also been described in ITP, which can opsonize the platelets and induce antibody-mediated phagocytosis by the reticuloendothelial system in the spleen. This response is attributed to molecular mimicry of infection-related bacterial proteins. The principal antigens associated with the autoimmune response against the platelets include the amino acid sequences of virulence factors such as VacA, CagA [17, 178] and urease B, which are present during *H. pylori* infection [210]. The similarities shared between these antigens and platelet surface glycoproteins, like the glycoprotein IIIa among other platelet antigens not yet identified, are associated with anti-CagA antibody production [178] and demonstrate the importance of *H. pylori* infection in ITP.

2.3.3. Management of ITP in the post-Helicobacter era

Concerning to the management of ITP in the post-*Helicobacter* era, it is important to clarify that *H. pylori* is not the only cause of thrombocytopenia, and although the indication, investigation, and treatment of infection should be considered, it is no substitute for an adequate study of the etiologies more frequently associated with thrombocytopenia, which are particular to each region. The 40 series of cases previously discussed, a meta-analysis [211] and two systematic reviews [212, 213] demonstrated the burden of *H. pylori* infection on the development of ITP and that eradicating the infection improves the platelet count in more than 50% of the adult patients with chronic ITP [211-213]. This has permitted the scientific community, in particular the consensus and management guides of *H. pylori* infection, to include ITP as an indication for evaluating and eradicating the infection prior to proceeding with other traditional interventions in both adults and children [21, 23-30].

The American Society of Hematology (ASH) recognized *H. pylori* as a new cause of ITP and established to investigate and eradicate the bacteria during the basic evaluation of patients before applying conventional treatments for the disease [209]. In addition, the International Working Group for standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children, of the same Society, created a new ITP-associated group denominated "secondary ITP *H. pylori*–associated" [139]. Likewise, since 2003, the British Society for Haematology incorporated the study and eradication of *H. pylori* into their ITP management guidelines [140].

Before initiating treatment for a patient with ITP, an assessment of the prevalence of *H. pylori* infection should be performed according to the region. Generally, the prevalence is low in developed countries; these cases should proceed with conventional management of ITP

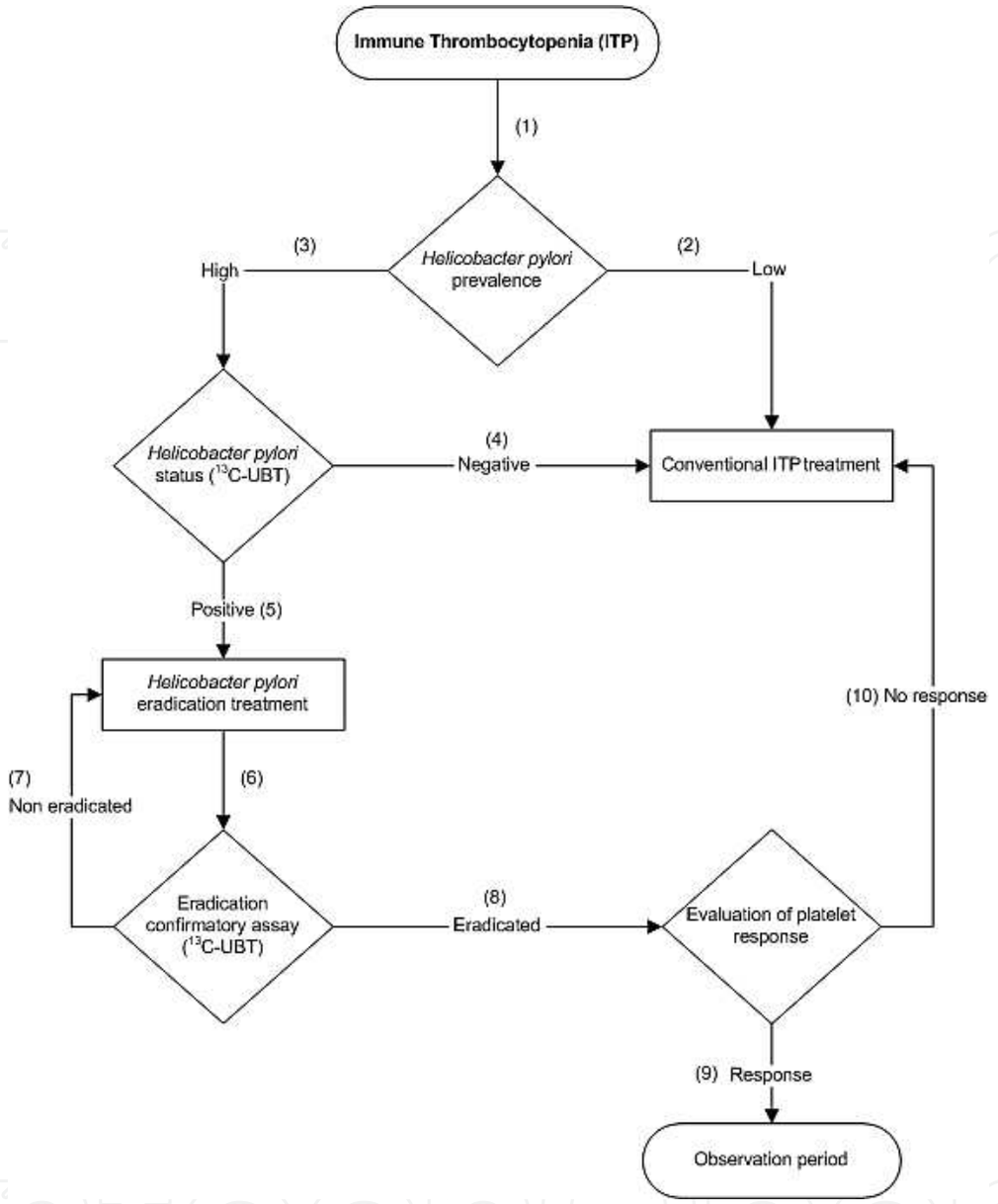

Figure 3. Algorithm for the study and management of immune thrombocytopenia (ITP) in the post-*Helicobacter* era. (1) Before initiating treatment for a patient with ITP, an assessment of the prevalence of *H. pylori* infection should be performed in each region. Generally, prevalence is high in developing countries and low in developed countries [1]. (2) If the rates of *H. pylori* infection are low, proceed with a conventional management of ITP [140, 209]. (3) If the rates of *H. pylori* infection are high or the patient, despite living in a country where infection rates are low, comes from a country where the infection rates are high, proceed to determine the status of *H. pylori* through a non-invasive test, ideally a ^{13}C-urea breath test (^{13}C-BUT) [27]. (4) If the patient is negative for *H. pylori*, investigate other causes of thrombocytopenia and treat conventionally [140, 209]. (5) If the patient is positive for *H. pylori*, proceed with eradication of the infection [27]. (6) Confirm infection eradication 6–8 weeks after treatment using a non-invasive test, ideally a ^{13}C-urea breath test [27]. (7) If eradication is not achieved, establish a new scheme of eradication therapy and continue treatment until it is achieved. (8) Once *H. pylori* eradication is achieved, (9) if a platelet response is obtained (complete or partial remission), periodically evaluate the platelet count. (10) If there is no platelet response, proceed with a conventional management of ITP [140, 209]. Reprinted from "Proof of an association between *Helicobacter pylori* and idiopathic thrombocytopenic purpura in Latin America" by G. Campuzano-Maya, 2007, *Helicobacter*, 12, p. 270. Copyright 1999–2015 by John Wiley & Sons, Inc. Reprinted with author permission [189].

[140, 209]. In developing countries, the rate of *H. pylori* infection is high; in these cases or when the patient, despite living in a country where infection rates are low, comes from a country where the infection rates are high, it should proceed to determine the status of *H. pylori* through a non-invasive test, ideally the ^{13}C-urea breath test [27]. If the patient is negative for *H. pylori*, it is necessary to investigate other causes of thrombocytopenia and treat the patient conventionally [140, 209], whereas if the patient is positive for *H. pylori* it is indispensable to eradicate the infection [27].

After 6–8 weeks of treatment, the infection eradication must be confirmed using a non-invasive test, ideally with ^{13}C-urea breath test [27]. If eradication is not achieved, it is mandatory to establish a new therapy scheme until eradication is achieved. Once *H. pylori* eradication is achieved and obtained a platelet response (complete or partial remission), it is important to periodically evaluate platelet count. If there is no platelet response, it must establish a conventional management of ITP [140, 209].

Figure 3 shows a diagnostic and management algorithm for ITP in the post-*Helicobacter* era, taking into account the prevalence and status of *H. pylori* infection [189].

3. Hematological diseases not recognized as related to *H. pylori*

This group includes autoimmune neutropenia, antiphospholipid syndrome, Henoch–Schönlein purpura, plasma cell dyscrasias, such as monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma, and other diseases possibly associated or implicated, such as leukemia and hemorrhagic manifestations with hematologic origin, like congenital and acquired coagulopathies and anticoagulation.

3.1. Immune neutropenia

This association was first proposed in 2002 by Gupta et al. in England, who reported the case of a patient with neutropenia (400 neutrophils/μL) that rapidly returned to normal values following the eradication of *H. pylori* infection [214]. Since then, two new studies have been reported, which include eight and 69 patients [215, 216] and coincide with the original report of Gupta et al. [214]. In the future, it is recommended that in patients with neutropenia that is suspected of being immunological the *H. pylori* status be established and proceed to eradicate if positive [214] as part of good medical practice.

3.2. Antiphospholipid syndrome

Similarly to immune neutropenia, antiphospholipid syndrome, a coagulation disorder of immunologic origin characterized by both arterial and venous thrombosis and associated with pregnancy complications, such as abortion, premature childbirth, and pre-eclampsia [217], was proposed as an extragastric association of *H. pylori* infection in 2001 by Cicconi et al. in Italy. These authors reported the case of a woman in whom antiphospholipid syndrome disappeared after the eradication of *H. pylori* infection [218]. At the moment, there are no new reports of

this association in the medical literature possibly only because it is not being considered or investigated. However, it is worth recalling that antiphospholipid syndrome has been associated with other diseases of immunologic origin that in turn are associated with *H. pylori* infection, such as ITP [189, 219, 220], systemic lupus erythematosus [221], and central serous chorioretinitis [222, 223].

3.3. Henoch–Schönlein purpura

Henoch–Schönlein purpura is an immunologic disease of unknown etiology manifested by small vessel leukocytoclastic vasculitis with deposits of immunoglobulin A (IgA) in the skin, joints, gastrointestinal tract, and kidneys [224]. Henoch–Schönlein purpura is included in this review because it is part of the differential diagnosis of thrombocytopenia, particularly ITP discussed previously, which manifests as purpuric lesions on the skin. The association of *H. pylori* with Henoch–Schönlein purpura was proposed in the case of a 21-year-old man by Rainauer et al. in Germany in 1996 [225]. Since then, many studies have confirmed the association in adults [226-231], children, and adolescents [229, 232, 233], with the disappearance of clinical manifestations in *H. pylori*-positive cases after eradication [229-231].

3.4. Plasma cell dyscrasias

Plasma cell dyscrasias are among the most frequent clonal diseases in elderly persons and include MGUS, multiple myeloma, solitary plasmacytoma, plasma cell leukemia, Waldenström's macroglobulinemia, and other chronic myeloproliferative syndromes of B lymphocytes [234]. Plasma cell dyscrasias may present an asymptomatic course or pass from one disease to another; for example, MGUS, a completely benign and asymptomatic condition that does not require treatment, can transform into a more severe and potentially fatal disease, such as multiple myeloma [234].

The association of plasma cell dyscrasias with stomach diseases has been known for many years, before the discovery that the stomach could be colonized by bacteria [3]. Gastrointestinal plasmacytomas were documented by the father of modern medicine, Sir William Osler, in 1920 [235], and for many years, the association of these and multiple myeloma with pernicious anemia [236, 237] and gastric cancer [238-242], entities clearly correlated with *H. pylori* infection, has been known. Perhaps, the most important evidence of the association of *H. pylori* infection with plasma cell dyscrasias is that some plasmacytomas disappear after the eradication of *H. pylori*. The authors who have analyzed this facet of infection by *H. pylori* have agreed to recommending that in all patients with these manifestations be offered the opportunity of evaluated and eradicate the infection if present [243-245]. Other associations described include a clear interaction between MALT lymphoma of the stomach and MGUS [246] as well as Waldenström's disease and MALT [247].

The relation of multiple myeloma with gastric MALT type lymphomas [248-254] was identified many years before *H. pylori* was known. Today, it is known that in MALT lymphoma, *H. pylori* antigens can also stimulate plasma cells. The plasmacytomas discussed previously could be the expression of a localized myeloma, and once disseminated, it would not be possible to

differentiate one from another. Wöhrer at al. have shown an association of gastric lymphomas with gastric myelomas [255]; besides, they described a case of plasmacytoma of the orbit, which completely remitted after the eradication of *H. pylori* [256]. Therefore, it is logical that all patients with a disease diagnosis related to plasma cells should be studied for *H. pylori* and if positive, be treated with eradication therapy prior to starting conventional treatment.

According to Malik et al., MGUS, important in the study of patients with plasma cell dyscrasia, may be related to *H. pylori* as result of chronic antigenic stimulation of B lymphocytes in the gastric mucosa by the bacteria. Resolution of the gammopathy is observed in up to 30% of cases by eradicating the bacteria [257], a relationship confirmed by some authors [246, 258] but not by others [215, 259].

3.5. Other hematologic manifestations

According to the medical literature, other hematologic manifestations demonstrate possible associations with *H. pylori* infection, which despite the low abundance of information entailed important clinical implications. Lehtine et al. reported that in Iceland, anti-*H. pylori* immunoglobulin G was associated with increased risk of childhood leukemia in offspring (OR = 2.8, 95% CI: 1.1–6.9), whereas in Finland, it is not associated. Because anti-*H. pylori* immunoglobulin G indicates chronic carriage of the bacteria, early colonization of the offspring probably differs between Iceland and Finland, two affluent countries [260]. This type of study should be replicated at other sites, especially those where the prevalence of *H. pylori* is high, such as in Asian countries and Latin America. Diamantidis et al. reported that although there is no evidence for a causal relationship between *H. pylori* infection and myelodysplastic syndrome (MDS), an increased prevalence of *H. pylori* infection among MDS patients has been found. This is an interesting finding that deserves further investigation because it may indicate a common factor causing susceptibilities to both MDS and *H. pylori* infection or that *H. pylori* might influence the pathophysiology of MDS [261]. Recently, Kawamata et al. described the case of a patient with *H. pylori*-induced thrombocytosis clinically indistinguishable from essential thrombocythemia, which disappeared after the eradication of the infection [262].

Another problem emerging in clinical practice is the inherent increased risk of hemorrhage in patients with hematologic diseases; *H. pylori*, according to preliminary studies, would be a risk factor for the occurrence of these events. This is the case for patients with acute leukemia who are infected with *H. pylori*: the risk of gastrointestinal hemorrhaging during treatment is greater than in non-infected patients. This would be reduced if all patients with leukemia are offered the screening and eradication of *H. pylori* when treatment begins [263]. In patients with potentially hemorrhagic diseases, such as hemophilia (A and B) and von Willebrand's disease, *H. pylori* infection should be considered as an important cause of upper gastrointestinal bleeding. It is recommended a stool antigen test as a new and non-invasive screening test for diagnosis of *H. pylori* infection in all patients with hereditary hemorrhagic disorders [264]. These procedures are cost efficient for the health system, if one takes into account that the screening, followed by treatment of all infected patients, yields a reduction of direct costs over a 5-year period of 130 US$ per screened patient [265]. Therefore, due to increased bleeding complications, *H. pylori* screening and therapy appear mandatory in patients with bleeding

disorders [266]. This conduct would also be applicable for patients undergoing prophylactic anticoagulation therapy [267] like aspirin [95]. The study and eradication of *H. pylori* in patients with chronic idiopathic neutropenia are also suggested, wherein splenomegaly, it is probably associated with *H. pylori*, as evidenced by correlation between splenic volume and infection period [215, 216].

4. Conclusions

The recognition of hematologic diseases associated with *H. pylori* infection and its incorporation as an indication for study and eradication in the consensus and management guides for *H. pylori* infection represent a profound paradigm shift in the management of these diseases and a great advance for humanity. In addition to the benefits that eradication brings to the infected people, especially those related to gastric cancer [4] and peptic ulcer disease [3], the paradigm shifts introduced into medical practice and the medico-social impact expected from these new paradigms are summarized in the following paragraphs.

4.1. Iron deficiency

The management of iron deficiency is palliative and based on iron supplementation [32], where there is often no impact on the direct cause associated with ferropenia [35]. With the incorporation of iron deficiency, with or without anemia, into the consensus and management guides for *H. pylori* infection as an indication to investigate and eradicate the bacteria [21-30], a new paradigm was generated, where the etiology of ferropenia can be infectious and the eradication of *H. pylori* may be sufficient to cure the deficiency, in the strict sense of the word [46-50]. Under the new paradigm, where eradication of the infection corrects the iron deficiency, in addition to restoring health [46-50] and increasing productivity [32], the prevalence of *H. pylori* infection and the diseases associated with it, such as gastric cancer [4] and gastric acid disease [3], decreases.

4.2. Vitamin B_{12} deficiency

The management of vitamin B_{12} deficiency is also palliative and based on vitamin supplementation, where there is little impact on the initial cause of the deficiency [134]. With the incorporation of vitamin B_{12} deficiency into the consensus and management guides for *H. pylori* infection as an indication to investigate and eradicate the bacteria [27, 29], a new paradigm was generated, where the etiology of vitamin B_{12} deficiency can be infectious and the eradication of *H. pylori* may be sufficient to correct it [127]. Under this new paradigm, where eradication of infection corrects the vitamin B_{12} deficiency by a curative rather than palliative treatment [127], the patient is released from a chronic disease [134] closely related to gastric cancer and from diverse diseases such as Alzheimer's disease [107, 108], depression [111], stroke [112, 113], pulmonary embolism [114], acute myocardial infarction, and coronary heart disease [116], which are regulated through homocysteine and generate high morbidity, mortality, and costs for health systems.

4.3. Immune thrombocytopenia

The treatment of ITP is palliative, not curative, and is oriented toward controlling the production of antibodies against platelets using medication or through the removal of organs that sequester platelets, such as the spleen [140, 209]. With the incorporation of ITP into the consensus and management guides for *H. pylori* infection as an indication to investigate and eradicate the bacteria [21, 23-30], a new paradigm was generated, where the etiology of ITP can be infectious and the eradication of *H. pylori* may be sufficient to cure it, in the strict sense of the word [151-190]. Under the new paradigm, where the eradication of infection leads to correction of the platelet count with definitive cure of ITP, the patient is freed from a chronic disease [140, 209] by a curative rather than palliative treatment [151-190]. Furthermore, the eradication of the infection in these patients reduces the prevalence of gastric cancer and peptic acid disease, with which it is closely related and which contribute to high morbidity, mortality, and costs for health systems.

Acknowledgements

The author gratefully acknowledges to Verónica Tangarife-Castaño for her insightful discussions and help with the English translation as well as the willingness and collaboration.

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