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TOPIC HIGHLIGHT

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Hematologic manifestations of *Helicobacter pylori* infection

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Abstract

Helicobacter pylori (*H. pylori*) is the most common infection in humans, with a marked disparity between developed and developing countries. Although *H. pylori* infections are asymptomatic in most infected individuals, they are intimately related to malignant gastric conditions such as gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma and to benign diseases such as gastritis and duodenal and gastric peptic ulcers. Since it was learned that bacteria could colonize the gastric mucosa, there have been reports in the medical literature of over 50 extragastric manifestations involving a variety medical areas of specialization. These areas include cardiology, dermatology, endocrinology, gynecology and obstetrics, hematology, pneumology, odontology, ophthalmology, otorhinolaryngology and pediatrics, and they encompass conditions with a range of clear evidence between the *H. pylori* infection and development of the disease. This literature review covers extragastric manifestations of *H. pylori* infection in the hematology field. It focuses on conditions that are included in international consensus and management guides for *H. pylori* infection, specifically iron deficiency, vitamin B12 (cobalamin) deficiency, immune thrombocytopenia, and MALT lymphoma. In addition, there is discussion of other conditions that are not included in international consensus and management guides on *H. pylori*, including auto-immune neutropenia, antiphospholipid syndrome, plasma cell dyscrasias, and other hematologic diseases.

Key words: *Helicobacter pylori*; Iron deficiency; Immune thrombocytopenia; Mucosa-associated lymphoid tissue lymphoma; Vitamin B12 deficiency

Core tip: *Helicobacter pylori* (*H. pylori*) infections are intimately related to malignant gastric condictions and benign diseases in the stomach, nevertheless there are extragastric manifestations closely related with *H. pylori* infection. This review focuses on hematologic diseases included in international consensus and management guides for *H. pylori* infection; specifically iron deficiency, vitamin B12 (cobalamin) deficiency, immune thrombocytopenia, and extranodal marginal zone mucosa-associated lymphoid tissue lymphoma. In addition of other hematologic diseases not included in guides and consensus as auto-immune neutropenia, antiphospholipid syndrome, and plasma cell dyscrasias.

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INTRODUCTION

Helicobacter pylori (H. pylori) is present in over 50% of all stomachs in the world population, making it the most frequent infection in humans[1]. It displays a marked disparity in occurrence between developed countries, where its prevalence oscillates between 30% and 50%, and developing countries, where its prevalence ranges between 80% and 90%[2].

After 1983, when it was discovered that the stomach could be colonized by bacteria[3], increasing evidence has shown that *H. pylori* is a pathogen closely related to a variety of gastric conditions. These range from benign stomach diseases such as chronic gastritis, duodenal peptic ulcers and gastric peptic ulcers[3] to malignant diseases such as gastric cancer[4] and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[5]. In the 30 years that have elapsed since its discovery, more than 50 extragastric manifestations of *H. pylori* infection have been reported, involving a range of medical specializations including cardiology, dermatology, endocrinology, gynecology and obstetrics, pneumology, neurology, odontology, ophthalmology, otorhinolaryngology, pediatrics, and hematology[6-18]. Hematological manifestations are the subject of this review.

For practical purposes, this review was divided arbitrarily into two groups. The first is made up of hematological diseases that are recognized as extragastric manifestations of *H. pylori* infection by the scientific community and have been incorporated into international consensus and management guides on *H. pylori* infection. The second is made up of hematological diseases that are not included in the international consensus and management guides on *H. pylori* infection (Table 1). Despite the existence of publications that link these diseases to *H. pylori* infections, they are not recognized by the scientific community due to a lack of either new evidence or further analysis.

HEMATOLOGICAL DISEASES RECOGNIZED AS EXTRAGASTRIC MANIFESTATIONS OF *H. PYLORI* INFECTION

As of May 2014, the following conditions fulfill the criteria to be hematological diseases that are recognized in international consensus and management guides on *H. pylori* infection: (1) Unexplained iron deficiency included in the Maastricht Ⅲ Consensus-2007[19] and subsequently ratified in several international consensus and management guides on *H. pylori* infection[20-28]; (2) Unexplained vitamin B_{12} (cobalamin) deficiency included in Maastricht Ⅳ/Florence Consensus-2012[25] and recently ratified in the Ⅲ Spanish Consensus Conference on *H. pylori* infection carried out in 2013[27]; (3) Primary immune thrombocytopenic purpura included in the Maastricht Ⅲ Consensus-2007[19] and subsequently ratified in several international consensus and management guides of *H. pylori* infection[21-28]; and (4) Gastric MALT lymphoma included in the first Maastricht Consensus[29] and subsequently ratified in all international consensus and management guides created for *H. pylori* infection[19-28,30-37].

It is important to note that of the extragastric diseases described in the medical literature that are possibly associated with *H. pylori*, only three such conditions have been incorporated into the guidelines: iron deficiency[19-28], vitamin B_{12} deficiency[25,27], and primary immune thrombocytopenic purpura[19,21-28].

Iron deficiency

Iron deficiency (ID) is a serious public health issue, regardless of whether it is associated with anemia. It affects a quarter of the world's population, over two billion people, according to the World Health Organization (WHO). Importantly, ID seriously affects at-risk populations such as children and pregnant women[38,39]. ID is associated with an increase in morbidity, including increased susceptibility to infections, decreased labor productivity, and impaired physical and cognitive development, even without an associated anemia[40].

It is especially important to remember that ID is a chronic process with a slow onset, in which the iron imbalance may take several years to establish and manifest clinically. One of the consequences can be observed through blood characteristics such as morphological alterations of erythrocytes or the presence of anemia, according to the criteria of the WHO[38]. ID occurs in three stages: pre-latent (stage 1), in which ferritin is between 12 and 30 μg/L, latent (stage 2) when the ferritin falls below 12 μg/L, and ID anemia (stage 3) when anemia is present in addition to diminished or depleted reservoir iron levels (determined by serum ferritin)[41].

***H. pylori* and iron deficiency:** The relationship between *H. pylori* and ID, regardless of whether the latter is accompanied by anemia, was first described by Blecker *et al*[42] in 1991 in Belgium. This case described a 15-year-old patient with ID anemia due to *H. pylori*-positive chronic active hemorrhagic gastritis, without prior gastrointestinal manifestations. After the infection was eradicated, the hematological parameters and ferrokinetics returned to normal values, and it was not necessary to administer supplementary iron treatments[42]. Two years later in France, Bruel *et al*[43] discovered a second case of ID anemia (hemoglobin 5.6 g/dL) in an 11-year-old child with a severe digestive hemorrhage who was diagnosed with an *H. pylori* infection. The anemia resolved after the eradication of the *H. pylori* infection, without supplementary iron treatment. In the same year in Italy, Dufour *et al*[44] presented the case of a 7-year-old child diagnosed with refractory ID anemia (hemoglobin 5.1 g/dL) who received oral iron treatment. The presence of *H. pylori* was described as in the preceding cases; however, it was asymptomatic from the gastrointestinal perspective. The infection was eradicated, and without supplementary iron treatment, there were improved hematological parameters (hemoglobin 13 g/dL) six months later.

After these pioneering reports of resolution of ID with treatment of the infection[42-44], additional isolated cases appeared during the 1990s in the medical literature[45-49] in both adolescents and adults that corroborated the association and therapeutic response after *H. pylori* eradication[46,50,51]. The volume of cases in the literature by the first decade of the 21st century supported the publi-

Table 1 Hematological manifestation of *Helicobacter pylori* infection

Recognized as extragastric manifestation
Iron deficiency[19-28]
Vitamin B12 (cobalamina) deficiency[25,27]
Immune thrombocytopenia[19,21-28]
Gastric MALT lymphoma[19-37]
Unrecognized as extragastric manifestation
Autoimmune neutropenia[263-265]
Antiphospholipid syndrome[267]
Plasma cell dyscrasias[284-286]
Schöenlein-Henoch purpura[302-310]
Other hematologic manifestation (childhood leukemia[311], myelo dysplastic syndrome[312], thrombocytosis[313])

MALT: Mucosa-associated lymphoid tissue.

cation of five meta-analyses[52-56], that showed an association between *H. pylori* and ID with resolution of *H. pylori*-associated disease after eradication in children[57-65], male and females in puberty[66,67], prepubertal girls[68], adult men and women[46,51,69-80], older adults[81], pregnant women[68] and nonpregnant women[82]. All of these publications have lent scientific support to the different international consensus and management guidelines that indicate that *H. pylori* should be sought and eradicated in ID cases[19-28].

Pathophysiology of iron deficiency by *H. pylori*: The pathophysiologic mechanisms by which *H. pylori* is associated with the development of ID and ID anemia are not fully understood, and more questions than answers remain. Here, we summarize the proposed explanations to explain the association of *H. pylori* with ID and ID anemia. It is still not known why some patients manifest this association and why in other patients it is not present, or there are other associations; or why some of the infections are asymptomatic[83].

Over the past decade, it has been linked *H. pylori* and ID development with a recently discovered hormone called hepcidin[84]. This hormone is produced in the liver and regulates iron metabolism in enterocytes and releases stored iron from macrophages of the reticuloendothelial system[85]. Hepcidin rises after *H. pylori* infection, acting as an acute phase reactant in response to the inflammation produced in the gastric mucosa, resulting in pathology known as "anemia of inflammation or chronic disease"[86-90]. Preliminary studies show that serum hepcidin is elevated in patients infected with *H. pylori*[90] and these levels are normalized after eradication of the infection[91], allowing that the iron to be absorbed by the enterocytes and released from macrophages of the reticuloendothelial system, where they are confined.

Other possible causes of iron imbalance in patients infected with *H. pylori* are chronic gastritis, which occurs in all individuals infected with *H. pylori*[83]. This can cause bleeding when it becomes erosive gastritis[92], especially in patients with active bleeding peptic ulcers[93,94] and in patients who chronically ingest non-steroidal anti-inflammatory drug including aspirin[95-98]. Similar to activities of other bacteria, mechanisms that have been hypothesized to explain ID in patients infected by *H. pylori* are related to changes in gastric physiology, including changes in pH, and especially in the presence of achlorhydria, which significantly reduces the solubility of inorganic iron and thus its intestinal absorption[46].

Furthermore, highly virulent strains such as *H. pylori* with the cytotoxin-associated gene A (CagA) and the vacuolating cytotoxin A (VacA), act through molecular mimicry mechanisms to produce or magnify ID in patients compared with patients infected with other less virulent strains[76,99-101]. This finding could partially explain the marked differences from one region to another and the large discrepancies observed in the different studies.

Management of iron deficiency in the post-helicobacter era: It is important to note that *H. pylori* is not the only cause of ID, and its inclusion in the international consensus and guidelines for managing *H. pylori* is an indication that it "should be sought and eradicated" but does not substitute for the adequate study of the most common causes of ID. These situations are specific to each region, due to the prevalence of ID, which varies with that of *H. pylori* infection and is a variable problem from one area to another. More than 250 studies referenced in the medical literature have tried to clarify the relationship of *H. pylori* in the development of ID, along with five meta-analyses that have all shown the association of infection in the development of ID and resolution after eradication[52-56]. The recovery of hematological and ferrokinetic parameters in ID after *H. pylori* eradication has enabled its inclusion as an unexplained origin of ID in the international consensus and management guides of *H. pylori* infection put forth by the scientific community and to indicate that it should be sought and eradicated in both adults and children[19-28].

Vitamin B12 deficiency

Vitamin B12 is required as a coenzyme for the metabolism of the amino acids methionine, threonine and valine and for the transformation of methyl-tetrahydrofolate to tetrahydrofolate, which is necessary for DNA synthesis[102]. Vitamin B12 is produced by mammals, and the consumption of animal products is required for incorporation in the human body[102].

Vitamin B12 deficiency, also known as cobalamin deficiency, is defined by low serum values of vitamin B12 and both homocysteine and methylmalonic acid, two components of the vitamin B12 metabolic pathway[103]. The diagnosis of vitamin B12 deficiency is established in accordance with the following criteria: (1) serum vitamin B12 levels < 150 pmol/L (< 200 pg/mL) with clinical features and/or hematological anomalies related to vitamin B12 deficiency; (2) serum vitamin B12 levels < 150 pmol/L on two separate occasions; (3) serum vitamin B12 levels < 150 pmol/L and total serum homocysteine levels > 13 μmol/L or methylmalonic acid levels > 0.4 μmol/L (in the absence of renal failure and folate and vitamin B6 de-

ficiencies); and (4) serum holotranscobalamin levels < 35 pmol/L[104].

It is important to remember that vitamin B12 deficiency is a chronic process with slow onset, in which the vitamin B12 imbalance may take several years to establish and manifest clinically in blood count parameters such as erythrocyte morphological alterations or anemia, according to the criteria of the WHO[38]. Vitamin B12 deficiency occurs in four stages: (1) decreased levels of vitamin in blood (stage Ⅰ); (2) low concentration of vitamin in the cell and metabolic abnormalities (stage Ⅱ); (3) increased levels of homocysteine and methylmalonic acid and decrease of DNA synthesis, with the emergence of neuropsychiatric symptoms (stage Ⅲ); and (4) macrocytic anemia (stage Ⅳ)[105].

Vitamin B12 deficiency represents a serious public health problem, and its prevalence is highly variable, depending on the ages and populations analyzed. Epidemiological studies show that in general population, vitamin B12 deficiency has a prevalence of approximately 20% in industrialized countries, with a range between 5% and 60%, depending on the vitamin B12 deficiency definition that is used[103,104]. For several years, it has been known that the prevalence of vitamin B12 deficiency, specifically pernicious anemia, is higher in Latin America than it is in the rest of the world. It also occurs in younger people[106], whereas in the rest of the world, it is a disease related to old age[107].

The etiology of pernicious anemia and subacute combined degeneration are closely related to vitamin B12 deficiency, but other diseases are also linked with the elevated homocysteine levels that are observed in vitamin B12 deficiency, such as Alzheimer's disease[108,109], dementia[110,111], depression[112], cerebral stroke[113,114], pulmonary embolism[115,116] and coronary heart disease[117].

***H. pylori* and vitamin B12 deficiency:** Pernicious anemia, as a stage of chronic vitamin B12 deficiency, was the first extragastric disease to be associated with *H. pylori* infection, as postulated in the scientific community by O´Connor *et al*[118]. One year later, Warren and Marshall reported to the scientific community that the stomach could be colonized by bacteria[3]. In 1991, Fong *et al*[119] carried out the first well-controlled study to clarify a possible association between pernicious anemia and *H. pylori* infection, after which they concluded that "patients with pernicious anemia are protected from infection with *H. pylori*, and *H. pylori* does not passively colonize mucosa inflamed by an unrelated process". These findings were confirmed by Saito *et al*[120] in Japan in 2008.

Nevertheless, when the vitamin B12 deficiency becomes clinically relevant, the bacteria are not found on the site of the lesion. *H. pylori* disappears as a result of histological and physiological changes induced by the chronic atrophy of the gastric mucosa in the case of gastric cancer[121] and the changes mediated by the immunological response on the gastric mucosa in the case of vitamin B12 deficiency and pernicious anemia. This can be evidenced by the presence of antibodies against intrinsic factor and parietal cells, despite to disappearance of *H. pylori* on gastric mucosa at diagnosis[122,123]. Moreover, H^+/K^+ ATPase autoantibodies, which are closely linked to classical autoimmune gastritis, are also significant indicators for mucosa atrophy in chronic *H. pylori* gastritis[124,125].

H. pylori infection can cause malabsorption of different micronutrients[126] among which included the vitamin B12[127-129]. A systematic review and meta-analysis in 17 studies involving 2454 patients showed a significantly reduction of serum levels of vitamin B12 in *H. pylori* infected patients than in non-infected[130]. Marino *et al*[131] demonstrated in 62 older patients a relationship between the decrease in serum levels of vitamin B12 and increase of serum homocysteine due to *H. pylori* infection. Likewise, *H. pylori* eradication in vitamin B12 deficiency patients is followed by increasing of serum levels of vitamin B12 and decreased serum levels of homocysteine.

Moreover, it was known that there was an association of *H. pylori* with stomach cancer, and it was already widely recognized by the scientific community that pernicious anemia was closely related to the development of stomach cancer[132-135]. This association was recently verified by Vanella *et al*[136] after a systematic review and meta-analysis showed that the relative risk to develop gastric cancer in patients with pernicious anemia was elevated at 6.8 (95%CI: 2.6-18.1).

Pathophysiology of vitamin B12 deficiency: The pathophysiological mechanisms by which *H. pylori* infection is related to the etiology of vitamin B12 deficiency are not fully clarified at this time. It is still not known why some patients manifest this association while others may show different *H. pylori*-associated conditions or none at all or why some of the infections are asymptomatic[83]. Below, we describe explanations that have been proposed to clarify the association between *H. pylori* and vitamin B12 deficiency.

Vitamin B12 deficiency occurs as a result of antibodies directed against gastric parietal cells and intrinsic factor, in addition to achlorhydria and a decrease in pepsinogen I and gastrin. These changes result in a histopathologic entity known as chronic gastritis type A or autoimmune[137]. The lack of intrinsic factor, which occurs due to changes in the gastric mucosa, reduces the absorption and transport of vitamin B12 from the diet. Chronic atrophic gastritis that induced by the immune response reaches gastric atrophy and pernicious anemia over a period of 10-30 years, depleting reservoirs of vitamin B12[137]. Additionally, chronic vitamin B12 deficiency can cause peripheral neuropathy and lesions in the lateral and posterior columns of the spinal cord; this is known as subacute combined degeneration and progresses to axial demyelination, neural degeneration, and eventually death[137].

Vitamin B12 deficiency management in the post-helicobacter era: Similar to ID, it is important to clarify that *H. pylori* is not the only cause of vitamin B12 deficiency

in the post-helicobacter era of vitamin B12 deficiency. Inclusion in the international consensus and management guides is an indication to seek and eradicate *H. pylori* in cases of vitamin B12 deficiency, but this does not replace a proper study of the specific epidemiologic causes in each region. A recent systematic review and meta-analysis evaluated the association of *H. pylori* and serum levels of vitamin B12 in 17 studies involving 2454 patients. This study showed that serum vitamin B12 levels were significantly lower in infected patients than in uninfected, and *H. pylori* eradication revealed a significant increase in the levels of vitamin B12 after successful treatment[130]. These publications have enabled the inclusion of vitamin B12 deficiency in the international consensus and management guides on *H. pylori* infection as an indication for which "*H. pylori* should be sought and eradicated" prior to other traditional interventions[25,27].

Immune thrombocytopenia

Primary immune thrombocytopenia (ITP), previously called idiopathic thrombocytopenic purpura and autoimmune thrombocytopenic purpura, has been defined and described in the Vicenza Consensus[138]. ITP has been redefined as "an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count 100×10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy. The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present"[138]. In this consensus statement, it was ratified that ITP is a diagnosis of exclusion, and it is necessary to exclude causal diseases such as systemic lupus erythematous and human immunodeficiency virus/acquired immunodeficiency syndrome prior to diagnosis. In addition, it included infection by *H. pylori* as a new disease in the list of diseases that must be ruled out in ITP[138], as previously recommended by the British Society for Haematology (BSH) in 2003[139]. Likewise, Vicenza Consensus established as substitute name for idiopathic thrombocytopenic purpura or autoimmune thrombocytopenic purpura, the term "immune thrombocytopenia" maintaining the acronym ITP to refer to the disease. Additionally, it called "primary immune thrombocytopenia" the in cases where is excluded the diseases associated, giving the name "secondary immune thrombocytopenia", for example, in the case of infection with *H. pylori*. The extension "secondary immune thrombocytopenia *H. pylori*-associated" or "ITP *H. pylori*-associated" would require the demonstration of complete resolution of ITP after proven eradication of the bacteria[138].

ITP is the most common immune disease in hematology[140]. The annual incidence of ITP is 5.5 per 100000 persons, when the cutoff point is 50 platelets per 10^9/L and 3.2 per 100000 persons, when the cutoff is 50 platelets per 10^9/L[141]. The chronic form of ITP increases with age, being double in people above 60 years compared to those under 60 years[141,142], as well as with a higher incidence in women than in men, with a ratio of 2:1 to 3:1[143].

***H. pylori* and adult immune thrombocytopenia:** García Pérez *et al*[144] described the relationship of *H. pylori* with ITP for the first time in 1993 in Spain, reporting a patient with ITP in whom the platelet count was normalized after eradication of *H. pylori*. After this publication, the medical literature presented several case reports of ITP patients with platelet counts recovering after the eradication of *H. pylori*, particularly in Japan[145-149] and European countries such as Italy[150-152] and Turkey[153].

Since the first series corroborated the relationship of *H. pylori* infection with ITP[154], it is possible to find 40 additional case series in the medical literature in 2014 that consistently show the relationship of *H. pylori* eradication with the recovery of platelet counts. On the European continent, there are 10 reported cases: eight in Italy[154-160], one in Turkey[161] and one in Serbia[162]. The total number was 495 ITP patients, 288 (58.2%) of whom were infected with *H. pylori*, of which 242 received eradication treatment. This achieved a successful eradication in 222 (91.7%) patients and a platelet response in 108 (48.6%) patients. On the Asian continent, there are 28 reported case series: Twenty-three in Japan,[163-185], two in China[186,187], two in Iran[188,189] and one in South Korea[190], with a total number of 1525 ITP patients, of whom 1089 (71.4%) were infected *with H. pylori*. Eradication treatment was received by 929 patients and it was successful in 811 (87.3%), of whom 472 (58.2%) had a platelet response. On the Americas, there are reported two case series: one in Colombia[191] and one in Canada[192], with a total number of 54 ITP patients, of whom 33 (90.6%) were infected *with H. pylori*. Eradication treatment was received by 33 patients and it was successful in 29 (87.9%), of whom 24 (82.8%) had a platelet response.

The consolidated analysis of all 41 worldwide reported series shows a total of 2074 ITP patients; 1410 (68.0%) were infected with *H. pylori*, and from this group, 1204 received eradication treatment. Eradication was successful in 1062 (88.2%) and platelet recovery was observed in 604 (56.9%). Further analysis shows that in almost every series where there was a platelet response after *H. pylori* eradication treatment, the *H. pylori* infection rate in ITP patients was relatively higher than in those where no association was found. Overall, the European continent showed a mean infection rate of 58.2% in ITP patients and a mean platelet response in 48.6% of them. The Asian continent showed an infection rate of 71.4% and 58.2% in the platelet response, while the Americas had both the highest prevalence of *H. pylori* infection (90.6%) and the highest platelet response (82.8%) of all reported series. Thus, the worldwide summary of 40 cases series showed an infection rate of 68.0% in ITP patients and a platelet response in 56.9% of the eradicated patients, as shown in Table 2.

Table 2 Association between immune thrombocytopenia and *Helicobacter pylori* infection in adults *n* (%)

Ref.	Year	Country	Patients with ITP	*H. pylori*-infected ITP patients	Treated patients	*H. pylori*-eradicated patients	Patients with platelet response
Gasbarrini *et al*[154]	1998	Italy	18	11 (61.1)	11	8 (72.7)	8 (100)
Emilia *et al*[155]	2001	Italy	30	13 (43.3)	13	12 (92.3)	6 (50.0)
Emilia *et al*[156]	2002	Italy	7	3 (42.9)	3	3 (100)	2 (66.7)
Veneri *et al*[157]	2002	Italy	35	25 (71.4)	16	15 (93.8)	11 (73.3)
Veneri *et al*[158]	2005	Italy	43	43 (100)	43	41 (95.3)	20 (48.8)
Stasi *et al*[159]	2005	Italy	137	64 (46.7)	52	52 (100)	17 (32.7)
Suvajdzic *et al*[162]	2006	Serbia	54	39 (72.2)	30	23 (76.7)	6 (26.1)
Sayan[161]	2006	Turkey	34	20 (58.8)	20	18 (90.0)	8 (44.0)
Emilia *et al*[160]	2007	Italy	75	38 (50.7)	38	34 (89.5)	23 (67.6)
Scandellari *et al*[204]	2009	Italy	62	32 (51.6)	16	16 (100)	7 (43.8)
Subtotal European continent			495	288 (58.2)	242	222 (91.7)	108 (48.6)
Kohda *et al*[163]	2002	Japan	40	25 (62.5)	19	19 (100)	12 (63.2)
Kohda *et al*[164]	2003	Japan	51	31 (60.8)	26	24 (92.3)	14 (58.3)
Ando *et al*[165]	2003	Japan	61	50 (82.0)	29	27 (93.1)	13 (48.1)
Hashino *et al*[166]	2003	Japan	22	14 (63.6)	14	13 (92.9)	5 (38.5)
Hino *et al*[167]	2003	Japan	30	21 (70.0)	21	18 (85.7)	10 (55.6)
Kato *et al*[168]	2004	Japan	20	20 (100)	20	17 (85.0)	11 (64.7)
Ando *et al*[169]	2004	Japan	20	17 (85.0)	17	15 (88.2)	10 (66.7)
Nomura *et al*[170]	2004	Japan	42	28 (66.7)	28	28 (100)	15 (53.6)
Sato *et al*[171]	2004	Japan	53	39 (73.6)	32	27 (84.4)	15 (55.6)
Takahashi *et al*[172]	2004	Japan	20	15 (75.0)	15	13 (86.7)	7 (53.8)
Fujimura *et al*[173]	2005	Japan	435	300 (69.0)	228	161 (70.6)	101 (62.7)
Inaba *et al*[174]	2005	Japan	35	25 (71.4)	25	25 (100)	11 (44.0)
Tsutsumi[175]	2005	Japan	25	17 (68.0)	9	9 (100)	6 (66.7)
Suzuki *et al*[176]	2005	Japan	36	25 (69.4)	13	11 (84.6)	6 (54.5)
Asahi *et al*[177]	2006	Japan	37	26 (70.3)	26	26 (100)	16 (61.5)
Ishiyama *et al*[178]	2006	Japan	14	14 (100)	14	14 (100)	8 (57.1)
Satake *et al*[179]	2007	Japan	38	26 (68.4)	26	23 (88.5)	13 (56.5)
Kodama *et al*[180]	2007	Japan	116	67 (57.8)	52	44 (84.6)	27 (61.4)
Kong *et al*[186]	2008	China	31	31 (100)	31	31 (100)	23 (74.2)
Rostami *et al*[188]	2008	Iran	129	79 (61.2)	71	62 (87.3)	30 (48.4)
Asahi *et al*[181]	2008	Japan	34	23 (67.6)	23	23 (100)	14 (60.9)
Suzuki *et al*[182]	2008	Japan	36	36 (100)	36	31 (86.1)	20 (64.5)
Wu *et al*[187]	2009	Chine	31	31 (100)	31	31 (100)	21 (67.7)
Tsumoto *et al*[183]	2009	Japan	30	21 (70.0)	21	20 (95.2)	10 (50.0)
Tag *et al*[190]	2010	South Korea	25	23 (92.0)	23	23 (100)	11 (47.8)
Sato *et al*[184]	2011	Japan	31	31 (100)	31	31 (100)	18 (58.1)
Kikuchi *et al*[185]	2011	Japan	31	19 (61.3)	19	19 (100)	10 (52.6)
Payandeh *et al*[189]	2012	Iran	52	35 (67.3)	29	26 (89.7)	15 (57.7)
Subtotal Asian continent			1525	1089 (71.4)	929	811 (87.3)	472 (58.2)
Campuzano-Maya[191]	2007	Colombia	32	29 (90.6)	29	26 (89.7)	21 (80.8)
Jackson *et al*[192]	2008	Canada	22	4 (18.2)	4	3 (75.0)	3 (100)
Subtotal American continent			54	33 (90.6)	33	29 (87.9)	24 (82.8)
Total worldwide			2074	1410 (68.0)	1204	1062 (88.2)	604 (56.9)

H. pylori: *Helicobacter pylori*; ITP: Immune thrombocytopenic purpura.

There are a few studies did not find any association between ITP and *H. pylori* infection that occurred in Spain[193], France[194], United States[195] and Mexico[196]. This lack of association can be explained by the low prevalence of infection in countries where studies were performed because the sample was insufficient or for other unmentioned reasons.

***H. pylori* and immune thrombocytopenia in children:** Studies of the relationship between *H. pylori* and ITP in children are few and contradictory. Some groups have shown a beneficial effect of *H. pylori* eradication in Asian countries such as China[197], Japan[198] and Iran[199] and in European countries such as Finland[200], Netherlands[201] and Italy[202,203]. These studies found a relationship between infection and ITP in children, with platelet count recovery in an average of 35.2% of the patients, as shown in Table 3. The platelet response was lower than the response rate observed in adult patients with ITP, which was above 50%[154-192,204]. However, groups in Turkey[205], Italy[206,207], Hungary[208] and Thailand[208] found a low response to eradication[207,208] or did not find a response[205,206,209]. It is important to clarify that the ITP in children has different characteristics than the clinical form of adult ITP[140].

Pathophysiology of secondary ITP (*H. pylori*-associated): Primary ITP is associated with congenital or acquired immune disorders, leading to an autoimmune response against platelets or megakaryocytes and charac-

Table 3 Association between immune thrombocytopenia and *Helicobacter pylori* infection in children *n* (%)

Ref.	Year	Country	Patients with ITP	*H. pylori*-infected ITP patients	Treated patients	*H. pylori*-eradicated patients	Patients with platelet response
Rajantie *et al*[200]	2003	Finland	17	9 (52.9)	9	9 (100)	5 (55.6)
Neefjes *et al*[201]	2007	Netherlands	47	3 (6.4)	3	3 (100)	3 (100)
Ferrara *et al*[202]	2009	Italy	24	8 (33.3)	8	8 (100)	8 (100)
Russo *et al*[203]	2011	Italy	244	50 (20.5)	37	33 (89.2)	13 (39.4)
Subtotal European continent			332	70 (21.1)	57	53 (93.0)	29 (54.7)
Jaing *et al*[197]	2003	Taiwan	22	9 (40.9)	9	9 (100)	5 (55.6)
Hayashi *et al*[198]	2005	Japan	10	2 (20.0)	2	1 (50.0)	1 (100)
Hamidieh *et al*[199]	2008	Iran	31	4 (12.9)	4	4 (100)	1 (25.0)
Subtotal Asian continent			63	15 (23.8)	15	14 (93.3)	7 (50.0)
Total worldwide			395	85 (21.5)	72	67 (93.1)	36 (53.7)

H. pylori: *Helicobacter pylori*; ITP: Immune thrombocytopenic purpura.

terized because it is not associated with other alterations. Often found in patients with ITP are events that can lead to the development of an autoimmune response[210]. In the case of *H. pylori* as a causative agent of ITP, various mechanisms involved in the development of the autoimmune response have been described. One mechanism is the change in the Fcγ receptor balance related to the activation of monocytes and their relation to the inhibitory receptor FcγR Ⅱ B. It has been reported that *H. pylori* infection decreases levels of the inhibitory receptor FcγR Ⅱ B in monocytes, leading to increased monocyte function with nonspecific phagocytosis and autoreactivity with B and T lymphocytes. These results were corroborated by finding a reversing effect after bacteria eradication. This finding can link *H. pylori* infection to autoantibody production by B-lymphocytes and the overactivation of the innate and acquired immune response against circulating platelets[181].

Along with monocyte overactivation, the production of autoantibodies that can opsonize platelets and induce phagocytosis mediated by antibodies in the reticuloendothelial system by spleen macrophages has been described in ITP. The molecular mimicry of bacterial infection-related proteins is responsible for this response. Amino acid sequences of virulence factors (VacA and CagA)[17,180] and urease B are present in *H. pylori* infection and are the major antigens associated with autoimmune response against platelets. The homology of these antigens with platelet surface glycoproteins including glycoprotein Ⅲa and other platelet antigens associated with antibodies anti CagA[180] show the importance of *H. pylori* infection in ITP.

ITP management in the post-*Helicobacter* era: It is important to clarify that *H. pylori* is not the only cause of thrombocytopenia, and the indication that it "should be sought and eradicated" does not replace a proper study of the etiologies that are most frequently associated with the study of thrombocytopenia in each region. The 40 cases series previously described, a meta-analysis[211] and two systematic reviews[212,213] have all shown the importance of *H. pylori* infection in the development of ITP and that eradicating the infection improves the platelet count by more than 50% in adult patients with chronic ITP[211-213]. Similarly, these publications have enabled the inclusion of ITP in the international consensus and management guides on *H. pylori* infection as an indication, wherein "*H. pylori* should be sought and eradicated" prior to other traditional interventions both in adults and children[19,21-28].

The American Society of Hematology (ASH) proposed a new name for idiopathic thrombocytopenia purpura or autoimmune thrombocytopenia purpura, changing it to primary immune thrombocytopenia and keeping the same acronym, ITP. The international working group of standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children created a new group for disease-associated immune thrombocytopenia, which in this case is called "secondary ITP (*H. pylori*-associated)"[138]. Moreover, ASH and BSH recognized *H. pylori* as a new cause for ITP and noted that the presence of *H. pylori* should be treated and eradicated in positive cases before attempting conventional treatments for ITP in both adults and children[139,210].

Gastric MALT lymphoma

Gastric MALT lymphoma is a rare form of non-Hodgkin lymphoma that affects B lymphocytes and typically develops in lymphoid tissue associated with mucous membranes and rarely in lymph nodes. It represents approximately 5% of all diagnosed non-Hodgkin lymphomas. Its annual incidence is estimated at approximately 1/313000, with a female predominance[214], and mainly affects adults over 50 years (mean 65 years)[215], as it is quite rare in children[216].

MALT lymphoma is an extranodal non-Hodgkin's B-cell lymphoma: Extranodal marginal zone lymphoma, better known by the acronym MALT lymphoma, is defined as a low-grade malignant lymphoma of the stomach originating from B cells and is associated with chronic infection by *H. pylori*[217]. Gastric MALT lymphoma was described in 1983 by Isaacson *et al*[218], four months after the description of bacterial colonization of the gastric mucosa by *H. pylori*[3]. Eight years later, it was proven to be in-

timately related to that lymphoma, when Wotherspoon *et al*[219], in 1991, proved their causal relationship for the first time. Two years later, the same authors proved that the eradication of *H. pylori* infection provided a complete cure of the lymphoma in up to 75% of the patients[220] and that this remission was maintained over time without conventional anticancer therapy[221].

The first fact that showed a relationship between *H. pylori* and gastric MALT lymphoma was the observation that lymphoid tissue lesions in the gastric mucosa are pathognomonic with *H. pylori* infection and are not a normal finding in gastric mucosa without infection[222,223]. Lymphoid follicles have been described in 27% to 100% of *H. pylori*-infected patients[219,222-224], and this percentage would be 100% if the number and depth of biopsies were appropriate[224]. Additionally, after eradicating the infection, these lymphoid aggregates disappear in all patients[225].

Pathophysiology of gastric MALT lymphoma: The mechanisms by which *H. pylori* produces the appearance of a lymphoma similar to gastric carcinogenesis[226-234] has not been fully clarified, but it is likely that environmental, host, and bacterial-related factors must be involved[235-240]. According to Isaacson[241], *H. pylori* infection leads to development of MALT lymphoma and can take the following course. First, the infection gives rise to a lymphocyte response that conditions a polyclonal B lymphocyte response and MALT formation through antibody production. Then, different lymphocyte populations would maintain the response provoked by the bacteria. In the polyclonal MALT proliferation, a monoclonal population of B-cells could appear and accumulate cytogenetic changes such as translocations, mutations, microsatellite instabilities, eventually evolving into a low-grade MALT lymphoma that is dependent on *H. pylori*-related antigen stimuli. Finally, new cytogenetic changes such as translocations, suppressor gene deactivation (*p53* and *p16*, among others), and *c-myc* activation would make this neoplastic population of monoclonal B-cells escape from its dependence on T lymphocytes and *H. pylori* antigens and favor its transformation into a high-grade lymphoma. As a result of this sequence of events, a low- or high-grade lymphoma would ultimately develop.

There are cases of extra-gastric MALT lymphoma where the presence of *H. pylori* has been found and where infection eradication is followed by full remission. These include the conjunctiva[242,243], duodenum[244-246], salivary gland (parotid)[247,248] associated with Sjögren's syndrome and *H. pylori* infection[249], larynx[250], nasal mucosa[251], lung (and respiratory tract)[252], rectum[253,254], liver[255], urinary bladder[256,257], jejunum[258], patients with Sjögren's syndrome[249,259] and in patients with previous heart transplants[260] or liver transplants[259].

Management of gastric MALT lymphoma patients in the post-helicobacter era: The medical scientific community agrees that the therapy for gastric MALT lymphoma is *H. pylori* eradication and long-term observation[220,261,262]. Most of the international consensus and management guides on *H. pylori* infection recommend study and eradication as an indication in all patients with a histological diagnosis of gastric MALT lymphoma[19-37]. However, extra-gastric MALT lymphomas may also respond to eradication in infected patients, though the guides and consensus do not include them as an absolute indication. Physicians should eradicate the infection in such patients as good medical practice. All *H. pylori* infection management guides and consensus include an indication for eradication in any individual where infection is known and eradication is desired[19-37].

UNRECOGNIZED HEMATOLOGIC MANIFESTATIONS WITH *H. PYLORI* INFECTION

This group includes autoimmune neutropenia, antiphospholipid syndrome, plasma cell dyscrasia including monoclonal gammopathy of undetermined significance and multiple myeloma, Shöenlein-Henoch purpura, and other possible associations with diseases such as leukemia and hemorrhagic manifestations with a hematological origin, including congenital coagulopathies and bleeding disorders.

Autoimmune neutropenia

Gupta *et al*[263] initially proposed the relationship between *H. pylori* infection and autoimmune neutropenia in 2002 in England, when they reported the case of a patient with neutropenia (400 neutrophils per μL) that normalized quickly after eradicating *H. pylori* infection. After this work, two new studies have been reported with eight and 69 patients[264,265] that corroborated the Gupta *et al*[263] report. In the future, it is important that patients with suspected autoimmune neutropenia receive the option of determining their *H. pylori* status and treating a present infection as part of the management of their condition and good medical practice[263].

Antiphospholipid syndrome

Antiphospholipid syndrome is an immunological hypercoagulable disorder characterized by both arterial and venous thrombosis and pregnancy-related comorbidities such as abortions, premature birth, and preeclampsia[266]. It was proposed as an extra-gastric disease associated with *H. pylori* in 2001 by Cicconi *et al*[267] in Italy, who published the case of a woman in which antiphospholipid syndrome disappeared after the eradication of an infection with *H. pylori*. There are no additional reports of this finding in the medical literature, most likely because it is not being considered and subsequently not studied. However, it is worth remembering that antiphospholipid syndrome has been associated with other *H. pylori* infection-related diseases including ITP[191,268,269], systemic erythematous lupus[270], and central serous chorioretinitis[271,272].

Plasma cell dyscrasias

Plasma cell dyscrasias (PCD) are one of the most frequent clonal diseases in the elderly and include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, solitary plasmacytomas, plasma cell leukemia, Waldenstrom macroglobulinemia and other chronic myeloproliferative diseases of B lymphocytes[273]. PCDs can be asymptomatic and can transform from one disease into another. For example, a fully benign and asymptomatic MGUS that does not require treatment can transform into another more serious and potentially lethal condition such as multiple myeloma[273].

The association of these diseases with gastric alterations was known many years before the discovery that the stomach could be colonized by bacteria[3]. Gastrointestinal plasmacytomas were documented in 1920 by the father of modern medicine, Osler *et al*[274]. The relationship between plasmacytomas and multiple myeloma with pernicious anemia[275,276] and gastric cancer[277-281] has been known for many years, both of which are entities intimately related to *H. pylori* infection. Furthermore, from a histological view, gastric MALT lymphoma can be difficult to distinguish from gastrointestinal plasmacytomas[282,283]. The most important evidence of the relationship of *H. pylori* infection with PCD is the fact that certain plasmacytomas disappear after *H. pylori* eradication. The authors who have analyzed this feature of *H. pylori*-infection recommend that all patients with these manifestations are indicated for infection studies and eradication therapy if it is found to be positive[284-286]. Gastric MALT lymphoma, a clearly recognized *H. pylori* associated disease, has additionally been associated with MGUS[287] and Waldenstrom disease[288].

The concurrence of multiple myeloma with gastric MALT lymphoma[289-295] is a finding that was known for many years before any knowledge of *H. pylori* existed. Today, with the knowledge that MALT also contains plasmocytes that can be stimulated by *H. pylori* antigens, this association is understandable. In the case of plasmacytomas, it could be said that they are an expression of localized myeloma and if they disseminated, it would not be possible to differentiate between one and the other. Wöhrer *et al*[296] demonstrated the association of gastric lymphoma with gastric myeloma. They also described the case of a plasmacytomas of the orbit that entered into full remission after *H. pylori* eradication[297]. With this background, it is logical that any patient diagnosed with a plasma cell-related disease should be studied for *H. pylori* infection and, if positive, receive eradication treatment for *H. pylori* before beginning conventional treatment.

Monoclonal gammopathy is important for studying patients with PCD, and according to the work of Malik *et al*[298], it could be related to *H. pylori* infections as a result of chronic antigen stimulation of B lymphocytes in the gastric mucosa by the bacteria. They further suggest that gammopathy could resolve in up to 30% of cases after eradicating the bacteria. This debated relationship is supported by certain authors[287,299] but refuted by others[264,300].

Schöenlein-Henoch purpura

Schöenlein-Henoch purpura is an immune condition of unknown etiology that presents as small vessel leukocytoclastic vasculitis with immunoglobulin A (IgA) deposits in skin, joints, gastrointestinal tract, and kidneys[301]. Schöenlein-Henoch purpura is included in this review because it is part of the differential diagnosis of thrombocytopenia that manifests as purple skin lesions, similar to ITP, which was previously discussed. The association of Schönlein-Henoch purpura (or Henoch-Schönlein purpura) with *H. pylori* was described in Germany in 1996 by Rainauer *et al*[302] in a 2-year-old male. After that report, additional case series have been published supporting the association both in adults[303-308] and in children and adolescents[306,309,310], with the disappearance of clinical manifestations in cases where *H. pylori* was eradicated[306-308].

Other hematologic manifestations

According to the medical literature, other clinically relevant hematologic manifestations are possibly associated with *H. pylori* infection that are no less important, despite little published data. Lehtine *et al*[311] reported that "in Iceland, *H. pylori* immunoglobulin G was associated with increased risk of childhood leukemia in offspring (OR = 2.8, 95%CI: 1.1-6.9). Since *H. pylori* immunoglobulin G indicates chronic carriage of the microorganism, early colonization of the offspring probably differs between Iceland and Finland, two affluent countries". This study should be replicated in other countries, especially in areas with a high prevalence of *H. pylori* such as Asia and Latin America. Diamantidis *et al*[312] reported in patients with myelodysplastic syndrome (MDS) that, "although there is no evidence for a causal relationship between *H. pylori*-positive and MDS, the increased prevalence of *H. pylori*-positive among the MDS patients is an interesting finding that deserves further investigation as it may indicate a common factor causing susceptibilities to both MDS and *H. pylori*-positive or that *H. pylori* might influence the pathophysiology of MDS". Recently, Kawamata *et al*[313] described a patient in whom there was "*H. pylori*-induced thrombocytosis clinically indistinguishable from essential thrombocythemia", which disappeared after the infection was eradicated.

Another problem that arises in clinical practice is an increased risk of hemorrhage in patients with hematological diseases that carry a greater inherent risk of bleeding. *H. pylori*, according to preliminary studies, could be a risk factor for the occurrence of these events. This is the case of patients with acute leukemia who, if infected with *H. pylori*, have a greater risk of gastrointestinal hemorrhage during treatment compared with uninfected patients. This risk would be reduced if all leukemia patients were offered *H. pylori* screening and eradication, if found to be infected, upon starting leukemia treatment[314]. In patients with potentially hemorrhagic genetic diseases such as hemophilias (A and B) and Von Willebrand disease, it has been observed that *H. pylori* infection "should be considered as an important cause of upper gastrointes-

Table 4 Paradigm changes in the management of hematologic diseases related to *Helicobacter pylori* infection and its medical and social impact

Disease	Accepted paradigm	New paradigm	Medical and social impact
Iron deficiency[1]	The management of ID is palliative and is based on iron supplementation[38], but it often does not treat the immediate cause of ID[41]	With the incorporation of ID in the international consensus and management guides on *H. pylori* infection as an indication to "seek and eradicate"[19-28], a new paradigm was generated. The etiology of ID can be infectious and eradication of *H. pylori* can be enough to "cure" in the strict sense of the word[52-56]	Under the new paradigm, eradication of the infection can correct ID, in addition to restoring health[52-56] and increase the productivity of the infected people[38]. It also reduces the prevalence of *H. pylori* infection and associated diseases such as gastric cancer[4], and peptic acid disease[3]
Vitamin B_{12} deficiency[2]	Vitamin B_{12} deficiency management is palliative and is based on the supplementation of vitamin[38], but often it does not treat the underlying cause of deficiency of vitamin B_{12}[320]	With the incorporation of vitamin B_{12} deficiency in the international consensus and management guides on *H. pylori* infection as an indication to "seek and eradicate"[25,27] a new paradigm was generated. The etiology of vitamin B_{12} deficiency can be infectious, and the eradication of *H. pylori* can be enough to "correct" in the strict sense of the word[52-56,131]	Under the new paradigm, eradication of the infection can correct the vitamin B_{12} deficiency, and the patient can avoid palliative treatment[131] associated with chronic disease[38]. These include the closely related gastric cancer and diverse diseases such as Alzheimer's disease[108,109], dementia[110,111], depression[112], cerebral stroke[113,114] pulmonary embolism[115,116], acute myocardial infarction and coronary heart disease[117]. Additionally, it can prevent other manifestations of vitamin B_{12} deficiency and in the homocysteine pathway, which can generate high morbidity and mortality with elevated costs for health systems
Immune thrombocytopenia[3]	Treatment of immune thrombocytopenia is palliative, not curative. It is aimed to control the production of antibodies against platelets by medication or removal of organs that destroy platelets, such as the spleen[140,321]	With the incorporation of immune thrombocytopenia in the international consensus and management guides on *H. pylori* infection as an indication to "seek and eradicate"[19,21-28] a new paradigm was generated. The etiology of immune thrombocytopenia can be infectious and eradication of *H. pylori* can be enough to "cure" in the strict sense of word[154-192,204]	Under the new paradigm, where the eradication of the infection corrects the platelet count and is a definitive cure for immune thrombocytopenia, the patient avoids chronic disease[38] and non-curative and palliative treatment[131]. Moreover, eradication of infection in these patients reduces the prevalence of gastric cancer and peptic ulcer disease, which are closely related to high morbidity, mortality and high costs for health systems
Gastric MALT lymphoma	Gastric lymphoma is a manifestation of extranodal non-Hodgkin lymphoma. Treatment includes radical gastrectomy supplemented with total abdominal radiotherapy and chemotherapy, similar to the treatment that administered for other non-Hodgkin lymphomas[322]	With the incorporation of gastric MALT lymphoma in the international consensus and management guides on *H. pylori* infection as an indication to "investigate and eradicate"[19-37] a new paradigm was generated. The etiology of gastric MALT lymphoma can be infectious and eradication of *H. pylori* may be sufficient for "cure" in the strict sense of the word[220,261,262]	Under the new paradigm, whereby the eradication of the infection induced a complete remission with a definitive cure of gastric MALT lymphoma immune, the patient avoids a chronic disease[38], with non-curative and palliative treatment[322]. This change transforms a neoplastic disease with difficult and expensive management into an infectious disease with an excellent prognosis and low treatment cost[323]

[1]With or without anemia; [2]Cobalamine; [3]Previously called idiopathic thrombocytopenic purpura and autoimmune thrombocytopenic purpura[138]. *H. pylori*: *Helicobacter pylori*; ITP: Immune thrombocytopenic purpura; MALT: Mucosa-associated lymphoid tissue.

tinal bleeding in patients with hemophilia. We would recommend stool antigen test as a new and noninvasive screening test for diagnosis of *H. pylori* infection in all patients with hereditary hemorrhagic disorders"[315]. This policy is cost-efficient for health systems if one considers that "screening, followed by treatment of all infected patients, yielded a reduction of direct costs over a 5-year period of 130 US-$ per screened patient"[316] and, in consequence, "due to increased bleeding complications, *H. pylori* screening and therapy appears mandatory in patients with bleeding disorders"[317]. This protocol would also be applicable for patients undergoing prophylactic anticoagulation[318], including aspirin[98], as analyzed previously. There is also support for its study and eradication in patients with chronic idiopathic neutropenia, in which splenomegaly is most likely associated with *H. pylori* and increased infection periods have been observed in patients infected by *H. pylori*[264,265].

CONCLUSION

The recognition of hematologic diseases associated with *H. pylori* infection and their inclusion as indications for study and eradication in the international consensus and management guides on *H. pylori* infection, represents a deep change in the management paradigm of these

diseases and a great breakthrough for humanity. Many benefits can be brought by eradiation of the infection, especially those related to gastric cancer[4] and peptic acid disease[29,267,319]. Table 4 summarizes the paradigm shifts that are discussed in this review and are being introduced into medical practice, as well as the social impact expected from these new paradigms derived from *H. pylori* eradication.

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