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Extraintestinal Manifestations in *Helicobacter pylori* Infection – Iron Deficiency Anemia and *Helicobacter pylori*

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Additional information is available at the end of the chapter

Abstract

Iron is an essential element for all living organisms. Iron metabolism is mainly controlled by its absorption. Iron deficiency (ID) is the most common nutritional deficiency, causing important clinical outcomes. One of the most common results of ID is iron deficiency anemia (IDA). The ID results from increased physiological needs, blood losses, inadequate intake, and diminished absorption. *Helicobacter pylori* (*H. pylori)* infection is one of the important causes of IDA, especially in undetermined and refractory cases.

In the literature, case series, sero-epidemiological studies, and meta-analyses showed robust evidence about the relationship between IDA and *H. pylori*. Several mechanisms have been proposed for IDA in *H. pylori* infection. In this chapter, we review clinical evidence regarding the relationships between *H. pylori* and IDA, iron metabolism, possible mechanisms of IDA in *H. pylori* infection, factors involved in IDA development in *H. pylori* infection, and IDA management in *H. pylori* infection.

Keywords: *Helicobacter pylori,*, iron deficiency anemia, hepcidin

1. Introduction

Iron (Fe) is an essential element for hemoglobin synthesis, oxidation–reduction reactions, and cellular proliferation. The term iron deficiency (ID) describes a deficit in total body iron, resulting in reduction of serum ferritin levels below normal limit [1]. ID is the most frequent nutritional deficiency worldwide.

ID is associated with impaired cognitive function, diminished work productivity, and behavioral problems in adults and children. In pregnant women, ID has been linked with increased risk for low birth weight, prematurity, and maternal morbidity [2].

Iron deficiency anemia (IDA) is defined as low hemoglobin and plasma ferritin values caused by further decrease in iron stores. IDA is the most common form of anemia worldwide with a prevalence varying from 2% to 8% in developed countries. IDA may occur at all stages of the life cycle, but it is more prevalent in mothers and young children [3].

The known causes of ID are inadequate dietary intake, increased physiological needs as seen in pregnancy and children during rapid growth, increased losses such as bleeding or hemolysis, and diminished iron absorption as seen in celiac disease and chronic inflammatory diseases [4, 5]. Because IDA can result from both physiological and pathological events, the etiology underlying IDA should be determined. The exact cause could not be identified in 20% of cases, despite all routine examinations including gastrointestinal endoscopy and serologic markers for celiac disease [3].

Helicobacter pylori (*H. pylori*) infection has been proven as a cause of IDA, especially in undetermined cases. Exact mechanism for IDA in *H. pylori* infection is still unclear. However, several mechanisms have been proposed to explain the relationship between *H. pylori* infection and IDA, including gastrointestinal bleeding and bacterial competition for dietary iron and subversion of the human iron regulatory mechanism [6]. In this chapter, we review clinical evidence regarding the relationship between *H. pylori* and IDA, iron metabolism, possible mechanisms of IDA in *H. pylori* infection, factors involved in the development of IDA in *H. pylori* infection, and IDA management in *H. pylori* infection

2. Clinical evidences on the relationship between iron deficiency anemia and *H. pylori*

The relationship between *H. pylori* and IDA was first described by Blecker et al. in 1991. Authors described a 15-year-old patient with IDA due to *H. pylori*-positive chronic active hemorrhagic gastritis without prior gastrointestinal manifestations. Hemoglobin value and serum ferritin level of the patient returned to normal limits unless administration of supplementary iron, after the infection was eradicated [7]. Subsequently, Bruel et al. in 1993 reported a second IDA case (hemoglobin 5.6 g/dL) in an 11-year-old child with *H. pylori* infection complicated with severe digestive hemorrhage. The anemia resolved after the eradication of the *H. pylori* infection without iron replacement [8]. In the same year, the first case with refractory IDA without the symptomatic gastrointestinal pathology was reported in a 7-year-old child by Dufour et al., in which *H. pylori* infection was diagnosed. After the infection was eradicated without supplementary iron treatment, improvement in hematological parameters was observed on month six [9].

Following above-mentioned reports [7-9], further isolated case reports were published in both adolescents and adults in the literature during the 1990s, indicating an association between IDA and *H. pylori* with therapeutic response after *H. pylori* eradication [10-13].

These preliminary case series in the literature encouraged the epidemiologic studies regarding the association between *H. pylori* and IDA. While some studies showed an association between *H. pylori and IDA* among women [14], the other studies showed differences in serum iron levels among *H. pylori*-infected men [15]. In another large cross-sectional study, it was found that *H. pylori* infection was associated with reduction in serum ferritin levels and that this association seemed stronger among adolescents and women at childbearing age [16]. Most epidemiologic studies had cross-sectional design. However, national health surveys enhanced the results of previous reports. Among these, a German study [17] on adult population found a decrease in serum ferritin levels by 16% in individuals infected with *H. pylori* [17]. In addition, children and adolescents were also studied in population-based surveys in South Korea [18-20]. Likewise, these studies showed an association between *H. pylori* and ID. A recent German study on pregnant women reported an association between current *H. pylori* infection and hemoglobin levels [21].

In this category, the largest study was conducted on 7,462 participants aged >3 years from the 1999–2000 National Health and Nutrition Examination Survey (NHANES). The study showed that *H. pylori* infection diagnosed by serology is associated with an increase by 40% in the prevalence of ID in the United States [22].

Finally, meta-analyses have supported the association between *H. pylori* infection and IDA [23-27]. Furthermore, resolution of iron deficiency anemia has been shown following the successful eradication of *H. pylori* [26].

All these publications have supported the relationship between *H. pylori* and IDA.

3. Regulation of iron balance

Steps in iron metabolism and contributing molecules are important for understanding effect of *H. pylori* infection on IDA.

Body iron metabolism is a semi-closed system and is critically regulated by several factors. The total amount of body iron is approximately 3–4 g. Two thirds of iron is found in the pool of red blood cell (RBC) and recycled by RBC destruction; the remainder is stored. Only 1–2 mg of iron is absorbed from intestinal tract and circulated in the blood. Since, there is no active mechanism to excrete iron from the body, iron balance is controlled by absorption [1].

Nearly all absorption of dietary iron occurs in the duodenum. Steps involved in iron metabolism include the reduction of iron into a ferrous state (Fe^{2+}), apical uptake, intracellular storage or transcellular trafficking, and basolateral release. Several proteins play a role in these steps [Table 1].

Function	Protein
Enzyme	Ferri-reductase
	Hemeoxygenase-1 (HO-1)
Transport	Divalent metal transporter-1 (DMT-1)
	Lipocalin-2
	Ferroportin-1
	Heme-carrier protein-1
	Transferrin
	Transferrin receptor 1 / 2
	Natural resistance associated macrophage protein-1
	Hephaestin
Storage	Hemosiderin
	Ferritin
	Lactoferrin
Regulatory	Iron regulatory protein 1/2 (IRP)
	Iron regulatory elements (IRE)
	Hepcidin

Table 1. Proteins Involved in Iron Metabolism

Dietary iron is found in two forms; heme iron (10%) that is derived from meat and bound to hemoglobin (Hb) and myoglobin and nonheme iron (90%) that is ionic and inorganic in form derived from plants (Figure 1). Both iron forms are absorbed at the apical surface of duodenal cells through different mechanisms.

Nonheme iron taken on a diet presents initially in oxidized (ferric-Fe^{3+}) form. This form of iron is not bioavailable, and before it is absorbed by an enterocyte it needs to be reduced to the Fe^{2+} form via ferri-reductase enzyme [28]. Fe^{3+} reduction is optimized by low gastric pH. Gastric acid, dietary ascorbic acid, and luminal reductases enhance the iron absorption [29]. Iron is transported across the intestinal epithelium by a transporter called divalent metal transporter-1 (DMT-1) that also transports other metal ions by a proton-coupled mechanism [30] (Figure 1). There is also a siderophore-like iron uptake pathway mediated by lipocalin-2 that seems to exert an innate immune response against bacterial infection by sequestrating iron. However, physiological role of lipocalin-2 has not been fully elucidated.

Heme iron is better absorbed than nonheme form. Heme iron is absorbed into enterocytes by heme carrier protein-1 that is a membrane protein found in the proximal intestine [31] (Figure 1). Heme iron is degraded by hemeoxygenase-1 (HO-1) within enterocyte [32] (Figure 1).

In the intestinal epithelial cell, iron can follow two pathways. Firstly, it may remain in the cell to be used or stored. This iron is excreted when intestinal cells demise and are molted into the lumen. Secondly, iron is transported into circulation from basolateral membrane of the enterocyte. This part is called absorbed iron. Ferroportin-1 is the sole supposed iron exporter that has been defined so far. Fe^{2+} is transported from the basal membrane via ferroportin-1;

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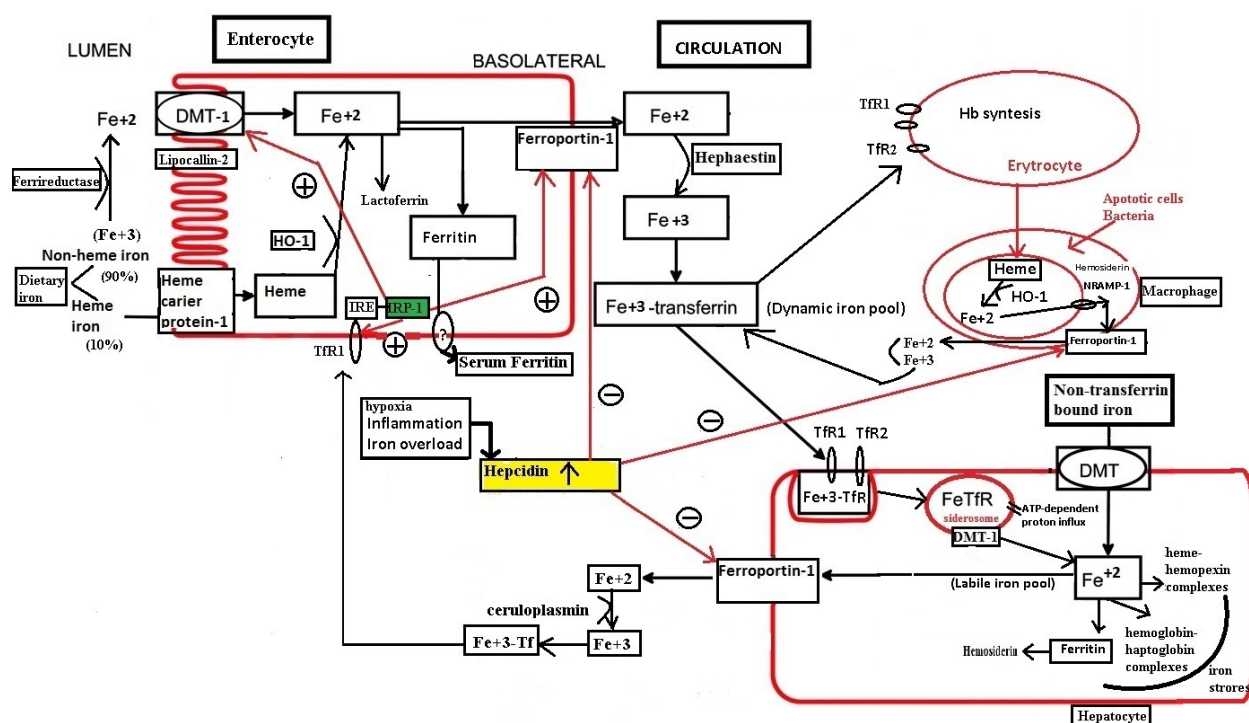
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Figure 1. Regulation of Iron Balance

thereafter, it is oxidized into Fe^{3+} by a multi-copper-oxidase protein called hephaestin, an enzymatic protein similar to plasma ceruloplasmin, before being bound by plasma transferrin (Tf). Ferroportin-1 is also the putative iron exporter in macrophages and hepatocytes [1, 28].

Iron absorption, mediated by two models, is up-regulated by iron deficiency and increased erythropoiesis or down-regulated in inflammation and iron repletion. These two models can be entitled as crypt programming model and the hepcidin model.

The crypt programming model: The intracellular iron level of the duodenal crypt cells intercommunicate with the iron deposits of the body, which, in turn, establishes the amount of iron absorbed from the intestinal lumen. The crypt cells express both transferrin receptor-1 (TfR1) and TfR2. The cellular uptake of Tf-bound iron from plasma is mediated by these receptors [28, 33].

TfR1 is expressed pervasively and Tf-mediated iron uptake is proposed to take place in majority of the cell types. Despite that, expression of TfR2 is limited in hepatocytes, duodenal crypt cells, and erythroid cells, suggesting a more privatized mission in iron balance.

Iron regulatory elements (IREs) act as iron sensors and regulate translation or stability of mRNA-encoding proteins. The intracellular iron level commands the interaction of IREs with cytosolic iron regulatory proteins (IRPs) 1 and 2. In the absence of iron, IRP1 binds to IREs of TfR1, DMT-1, and ferroportin-1 mRNA; then, syntheses of these proteins begin in the duodenum and dietary iron absorption is increased. Thus, increased IRP-binding activity represents decreased body iron stores [28].

The hepcidin model: Liver hepcidin is a 25-amino-acid cysteine-rich peptide. Numerous factors contribute to the regulation of hepcidin level. Liver iron levels, inflammation, hypoxia, and anemia can be counted among these factors. Hepcidin regulates the rate of iron absorption by controlling the expression of ferroportin-1 at basolateral membranes of enterocytes. Internalization of ferroportin-1 and loss of its function occur after the binding of hepcidin to ferroportin-1. Ferroportin-1 molecules take place also in macrophages and liver. Hence, it is suggested that iron release from intestinal crypt cells, liver, and macrophages is reduced, when hepcidin levels are increased in iron overload or inflammation (*via* IL-6). In contrast, it is likely that ferroportin-1 expression and iron release is increased when hepcidin levels are reduced as is the case in ID, anemia or hypoxia [34].

Iron released into the circulation binds to Tf and is transported to sites of use and storage. Three forms of Tf can be found in plasma: apo-transferrin that contains no iron, monoferric-transferrin, and diferric-transferrin. About 30–40% of these iron-binding Tf sites are occupied under normal physiological conditions. Tf-bound iron is the most important dynamic iron pool [35]. Tf-bound iron enters into target cells, mainly erythroid cells, but also immune and hepatic cells via a process of receptor-mediated endocytosis [28]. Tf binds to receptor, which is called TfR and located on the plasma membrane. Siderosomes, clathrin-coated endosomes, are formed by invagination of Tf and receptor–ligand complexes at the cell-surface membrane [35]. After that, the siderosomes are acidified by an ATP-dependent proton influx. This process leads to conformational changes in Tf and TFR1, and promotes iron release of Fe^{3+} from Tf. Then, Fe^{3+} is converted to Fe^{2+} through a ferri-reductase and moved to the cytoplasm by the DMT-1, while the TfR is appraised at the cell membrane again and Tf is drained back to the circulation [28, 36]. Production of hemoglobin by the erythron accounts for most iron use. High-level expression of TfR1 in erythroid precursors ensures the uptake of iron into this compartment.

Hemoglobin iron has an important cycle, as aging erythrocytes undergo phagocytosis. In the phagocytic vesicles of reticuloendothelial system macrophages, heme is metabolized through heme oxygenase-1 (HO-1). Then, iron is released to the cytoplasm by natural-resistance-associated macrophage protein-1, a transport protein similar to DMT-1. Macrophages are also able to gain iron from other apoptotic cells and bacteria [1]. Iron is stored in two forms in the cell: as ferritin in the cytosol and as hemosiderin originated from degradation of ferritin within the lysosomes. Hemosiderin is a very small part of body iron stores. It is found mostly in macrophages and increases in iron overload [35]. Iron export from macrophages to Tf is accomplished primarily by ferroportin-1, the same iron-export protein expressed in duodenal enterocytes, and hephaestin [28] (Figure 1). The amount of iron required for daily production of 300 billion RBCs (20–30 mg) is mostly provided by recycling of iron by macrophages [1].

The liver is a major storage organ of iron, in which excess iron is stored as ferritin and hemosiderin. The uptake of Tf-bound iron by the liver from plasma is mediated by TfR1 and TfR2. In iron overload states, Tf is saturated and redundant iron is found in the form of non-Tf-bound iron. This form of iron is transported along with the hepatocyte membrane through a carrier-mediated process compatible with DMT-1. The hepatocytes can also warehouse iron as ferritin, hemoglobin–haptoglobin complexes, and heme–hemopexin complexes. Whereas,

ferroportin-1 is known to be the only protein that mediates the iron transport from hepatocytes. Iron is oxidized by ceruloplasmin and attached to Tf after being released from hepatocytes [1, 28] (Figure 1).

Iron is also found at mucosal surfaces as lactoferrin. In addition to these proteins, an additional fraction of free iron is present in the form of the labile iron pool within cells.

4. Possible mechanisms of iron deficiency in *H. pylori* infection

The mechanisms by which *H. pylori* infection contributes to IDA remain unclear. Several studies have suggested different biologic mechanisms by which infection with *H. pylori* may induce depletion in the iron stores of the host. Four explanations can be posted: 1) overt or occult blood loss due to gastroduodenal lesions [37]; 2) decreased iron absorption due to hypo- or achlorhydria [38]; 3) increased iron consumption by *H. pylori* [39]; and 4) iron sequestration into the gastric mucosa [40,Table 2].

Mechanism	Findings
Blood loss	Peptic ulcer diseases
	Gastric carcinoma
	Gastric lymphoma
	Chronic erosive esophagitis,
	Chronic erosive gastritis
	Chronic erosive duodenitis
Malabsorption of iron	Atrophic gastritis
	Reversible hypoclorhydria
Bacterial competition for iron	
Changing molecular mechanisms	Elevated hepcidin level
in iron metabolism	Decreased hemeoxygenase-1
	Mislocalization of transferrin receptor

Table 2. Possible Mechanisms of Iron Deficiency in *Helicobacter pylori* Infection

4.1. Blood loss from gastrointestinal lesions

Blood loss is the most important cause of iron deficiency in adults. Each milliliter of blood loss (if Hb is 15 g/dL) results in loss of 0.5 mg of iron approximately. Gastrointestinal blood loss is the most important cause in postmenopausal women and men. While menstrual blood loss commonly causes IDA in premenopausal women, coexistent gastrointestinal lesions have often been identified [3].

IDA resulting from gastrointestinal bleeding is a common feature of many gastrointestinal conditions. The most common cause of upper gastrointestinal bleeding is peptic ulcer bleeding, which is responsible for about 50% of all cases, followed by esophagitis and erosive disease [41].

H. pylori infection is associated with both duodenal and gastric ulcer disease. Subjects infected with *H. pylori* have an average lifetime risk of 10–20% for the occurrence of peptic ulcer disease. This risk is at least three- to fourfold higher than in noninfected individuals. The bacteria can be determined in 90–100% of subjects with duodenal ulcer and in 60–100% of subjects with gastric ulcer. Individuals infected with bacterial strain producing a cytotoxin, or owning cytotoxin-associated gene A (cagA), have a higher risk of development of peptic ulcer disease. Other factors affecting the risk of peptic ulcer disease in infected individuals are amount of gastric acid production, gastric metaplasia in the duodenal bulb, smoking, and genetic factors (e.g., blood group O and lack of the secretor gene) [42]. Testing for *H. pylori* is recommended in all patients with peptic ulcer bleeding [43]; eradication therapy for those who are *H. pylori*-positive and then evaluation of the effect of this therapy. Retreatment with subsequent regimen should also be considered in the patients who had eradication failure. The effectiveness of eradication treatment and maintenance antisecretory therapy for the prevention of rebleeding has been evaluated in several studies. A meta-analysis showed that *H. pylori* eradication group had significantly decreased risk of rebleeding; even when only patients with successful *H. pylori* eradication were evaluated, the rebleeding rate was found significantly lower [44]. Thus, confirmation of eradication should be tested. Diagnostic tests for *H. pylori* have a low negative predictive value in case of active bleeding [45]. Thus, initial negative results on biopsies obtained in the acute setting should be judged with caution and repetition of the test during follow-up is recommended [43].

Gastric carcinoma is also one of the important causes of gastrointestinal bleeding accounting for nearly 4–8% of all cases [46]. The most common histopathological features of gastric malignancies are adenocarcinoma and lymphoma of mucosa- associated lymphoid tissue (MALT). Approximately 90% of gastric tumors are adenocarcinoma, whereas gastric MALT lymphomas are considerably less common (approximately 3% of all gastric tumors) [47]. *H. pylori* infection plays an important carcinogenic role in both gastric carcinoma and MALT lymphoma [48]. It has been calculated that the risk for gastric adenocarcinoma and MALT lymphoma is three- to sixfold higher in *H. pylori*-infected individuals than those who are noninfected [47]. Because of the strong association between gastric cancer and *H. pylori* infection, the World Health Organization (WHO) classified *H. pylori* as a class I carcinogen in 1994 [49]. In gastric carcinogenesis, host-related genetic elements such as a pro-inflammatory cytokine profile and/or a positive family history as well as bacterial virulence factors play important roles. Furthermore, environmental factors, like nutrition, and socioeconomic factors are suggested to be also important. After the initiation by *H. pylori* and the influence of variable environmental and host factors, chronic active gastritis may progressively evolve to atrophic gastritis and intestinal metaplasia. In some individuals, the metaplastic epithelium will undergo further genomic and phenotypic changes, resulting in gastric dysplasia and eventual adenocarcinoma [50]. The "test and treat" strategy for *H. pylori* infection should be considered effective for prevention of gastric carcinoma only in communities with a high incidence of gastric carcinoma [51].

H. pylori has been identified as causative agent for chronic erosive gastritis, erosive esophagitis, and erosive duodenitis [52-54]. These lesions are also among the important causes of occult gastrointestinal bleeding [3].

4.2. Decreased iron absorption secondary to hypo- or achlorhydria

Iron malabsorption is one of the most important causes of IDA. Decreased iron absorption may result from intestinal mucosal disorders (most frequently, celiac disease), impaired gastric acid secretion (including use of proton pump inhibitors), and gastric/intestinal bypass procedures [3].

As mentioned above, nonheme ferric iron is required to be reduced to a ferrous form before its absorption in the duodenum and first jejunum. Gastric acid has an important role in reducing and solubilizing the inorganic form of the iron [30]. Ferric iron has been demonstrated to be insoluble and precipitates at pH above 3 [55]. Thus, IDA can develop in patients with hypochlorhydria because of gastric surgery or atrophic body gastritis [56, 57].

Atrophic body gastritis is characterized by atrophy of the gastric body mucosa, hypergastrinemia, and hypo-achlorhydria [58]. Atrophy is a time-related phenomenon and *H. pylori* infection is considered an etiologic factor in the development of atrophic body gastritis [59]. This can eventually lead to loss of gastric glands and development of multifocal atrophic gastritis, which is often accompanied by intestinal metaplasia. A steady increase in the prevalence of atrophy and metaplasia is seen with advancing age [60]. As with peptic ulcer disease, the chance for development of atrophic body gastritis depends on the severity of gastritis and the characteristics of the bacterial strain [59]. Another interesting factor that can influence the development of atrophic body gastritis is *H. pylori* lipopolysaccharide mimicking Lewis x and y antigens. The presence of cross-reacting antibodies against the antigens and the gastric mucosa may have a great chance to develop atrophy [61]. Atrophic body gastritis may improve on long-term follow-up after *H. pylori* eradication, which is thus strongly recommended in atrophic gastritis [62].

It is well known that *H. pylori* infection induces gastric acid hyposecretion irrespective of presence of fundus atrophy when affecting the gastric body [63]. Also, *H. pylori* gastritis has been demonstrated to be associated with a reversible reduction in the ascorbic acid levels of gastric juice [64]. Therefore, a diffuse *H. pylori*-gastritis could decrease iron absorption by altering the physiological gastric secretion, even if it is mild [65].

4.3. Increased iron uptake and utilization by bacteria

H. pylori has been shown as a causative agent in IDA that is not attributable to usual reasons such as intestinal losses or poor intake, malabsorption or diversion of iron in the reticuloendothelial system, and unresponsive to iron therapy. The possible mechanism may be explained via bacterial competition for dietary iron.

Iron is an essential trace element in all organisms, even for pathogenic bacteria. Acquisition of iron by *H. pylori* from the host is necessary for colonization and infection [66]. Intracellular bacterial iron is exactly regulated and kept at an optimal level. Mostly, the free iron in the host is found to be complexes with proteins such as Tf and lactoferrin on mucosal surfaces. Thus, the available extracellular host iron is at a very low level. Therefore, bacterial pathogens such as *H. pylori* have to develop some mechanisms to compete for the restricted extracellular iron in the host to survive and maintain disease [67, 68].

In the gastric mucosa, iron is available as lactoferrin, heme compounds arising from damaged tissues, and iron based on pepsin-degraded food. Iron represents increased solubility in the acidic fluid, and iron-complexing proteins of eukaryotic organisms exhibit lower binding capacity under the acidic conditions in gastric juice.

H. pylori produce several iron transport proteins and iron storage proteins [69-72,Table 3]. Fe^{2+} is the main form of free iron in the gastric medium, and *H. pylori* keeps this ferrous ion through the FeoB protein [73]. FeoB-mediated iron acquisition has great importance for *H. pylori*. It has been shown that isogenic FeoB mutant mice could not colonize the gastric mucosa [73]. Ferric reductase activity for conversion of Fe^{3+} to Fe^{2+} is transported by the FeoB system of *H. pylori* [74].

Function	Protein
Enzyme	Ferri-reductase
	Hemeoxygenase-1 (HugZ)
Transport	FeoB
	FecA (ferric citrate outer membrane receptor)
	FecD (inner membrane permease)
	FecE (ATP-binding protein)
	FrpB (outer membrane receptor)
	CeuE (periplasmic-binding protein)
	Iron repressible outer membrane proteins (IROMPs)
	Lactoferrin-binding protein
	Siderophore
Storage	Pfr-ferritin
	Helicobacter pylori-neutrophil-activating protein-(HP-NAP)-
	Bacterioferritin

Table 3. Proteins Involved in Iron Acquision System of *Helicobacter pylori*

Additionally, *H. pylori* also has various transport systems for ferric iron [72, 75]. Since the ferric iron is insoluble, its transport needs an outer membrane receptor to transport the iron over the outer membrane. *H. pylori* has three copies of the ferric citrate outer membrane receptor FecA and three copies of the FrpB outer membrane receptor [69-72]. There are two copies of the periplasmic-binding protein CeuE and finally a single inner membrane permease (FecD) and an ATP-binding protein (FecE). ABC transporter system transports the iron from the periplasm to the cytoplasm [73].

Subsequently, specific outer membrane receptor proteins bind the iron. It has been suggested that heme-iron-repressible outer membrane proteins (IROMPs) are involved in heme binding and/or uptake by *H. pylori* [39]. When the heme is located in the cytoplasm, it can be used by a heme oxygenase protein. Heme oxygenase catalyzes the NADPH-reductase-dependent degradation of heme to biliverdin, which is the rate-limiting step leading to the release of iron

and carbon monoxide. Some researchers have identified a heme oxygenase protein called HugZ that is responsible for heme iron utilization in *H. pylori* [76].

A common iron acquisition system present in many pathogens is the secretion of low-molecular-mass, high-affinity iron chelators, which are called siderophores. These chelators are able to remove iron from Tf or lactoferrin [77-78].

Two iron storage proteins in *H. pylori* have been characterized, the Pfr ferritin and *H. pylori* neutrophil-activating protein (HP-NAP) bacterioferritin. The 19-kDa Pfr ferritin serves as an intracellular iron deposit and protects *H. pylori* against iron toxicity and free iron-mediated oxidative stress [79-83]. Iron-binding Pfr ferritin can be delivered and reused to maintain growing up in the iron-limited states [83]. HP-NAP was isolated from neutrophilic granulocytes as an immuno-dominant protein in vitro [84]. It was demonstrated to mediate adhesion of *H. pylori* to mucin [85]. The HP-NAP protein is similar to bacterioferritins [86, 87]. Although it is suggested, a role of HP-NAP in *H. pylori* iron storage is yet to be demonstrated [87].

In addition, lactoferrin-binding protein has been suggested to be highly specific for human lactoferrin in *H. pylori* infection [40].

All these mechanisms suggest that *H. pylori* utilize the iron from host and use or store for colonization and growth.

4.4. Changing molecular mechanisms in iron metabolism

H. pylori may act in changing molecular mechanisms that play a role in iron metabolism.

The best evaluated molecule in the association between *H. pylori* and ID is hepcidin. Hepcidin is a protein that is secreted into the blood and interacts with villous enterocytes to regulate the rate of iron absorption by controlling the expression of ferroportin-1. When hepcidin is increased, iron release from enterocytes is reduced. The anemia of chronic inflammation is mediated, in part, by the stimulation of hepcidin by cytokines [35]. Hepcidin has been reported to be elevated in patients infected with *H. pylori*, acting as an acute-phase reactant in response to the inflammation produced in the gastric mucosa and resulting in a pathology known as "anemia of inflammation or chronic disease" [88-90]. Prohepcidin, hepcidin's precursor, was also shown to increase in *H. pylori* infection and is decreased after eradication of *H. pylori* infection [91].

HO-1 is an enzyme that is responsible in heme degradation in host enterocytes. *H. pylori* may affect levels of HO-1. A significant increase in Keap1 gene expression was found in transfected AGS cells with *H. pylori* HspB. The increase in Keap1 was associated to decreased antioxidant enzymes including HO-1, and phase II detoxifying enzyme NAD(P)H:quinone oxidoreductase-1 [92]. CagA status is suggested to be important in this action of *H. pylori*. HO-1 is also found to be down-regulated in gastric epithelial cells of patients infected with cagA-positive *H. pylori* but not in gastric epithelial cells of patients infected with cagA-negative *H. pylori* [93].

TfR1 and TfR2 on cell surface mediate the cellular uptake of Tf-bound iron from plasma [28]. *H. pylori* is known to affect host cell polarity and intracellular trafficking [94]. In *H. pylori*-infected cell lines, it has been shown that Tfr was mislocalized to sites of *H. pylori* microcolony

growth at the apical cell surface. *H. pylori* colonization of the polarized epithelium has been shown to lead to increased apical release of Tf [95].

5. Factors that affect iron deficiency development in *H. pylori* infection

Although *H. pylori* gastric infection has been shown to be strongly associated with IDA, it is only a small portion of patients with *H. pylori* gastritis that develop IDA. The main question is why only a small portion of patients with *H. pylori* gastritis develop IDA, and what differentiates these patients.

The pattern of *H. pylori*-related gastritis is a significant predictor of the results of infection, and it determines the different effects of the bacteria on gastric functions. The panelists of the updated Sydney system suggested that most individuals infected with *H. pylori* develop a more evident inflammation in the antrum (nearly double) compared to the corpus in the absence of atrophy [96].

The relationship between chronic gastritis and gastric acid secretion is strictly dependent on the topography of gastric inflammation [97]. It has been demonstrated that gastritis in the corporal mucosa leads to decreased acid secretion with a consequent increase in intragastric pH [98]. Severity of inflammation is also important in terms of clinical outcomes.

Additionally, *H. pylori* strains owning the cagA or the vacuolating cytotoxin A (vacA), which are highly virulent, display potent mechanisms to produce or magnify ID in patients comparing less virulent strains [99, 100]. For example, Baysoy et al. have reported that cagA-positive strains was associated with a greater decrease in gastric juice ascorbic acid compared to cagA-negative strains [101]. Tan et al. reported that cagA and vacA contribute to iron uptake from gastric epithelial cells in a cooperative manner. VacA induces apical mislocalization of TfR. CagA alters internalization and intracellular transport of TfR. These pathogenic factors take away iron from holo-transferrin of host and maintain colonization on the gastric epithelial cell surface [95]. Moreover, Cardenas et al. found that patients infected with the cagA-positive strains did not improve their ferritin levels after eradication treatment as much as those who were cagA-negative [102].

6. Management of iron deficiency in *H. pylori* infection

Like other hematological conditions such as MALT lymphoma, vitamin B12 deficiency, and idiopathic thrombocytopenic purpura, IDA is also included in the international consensus and guidelines as an indication for "test and treat" of *H. pylori* [51, 62, 103,Table 4]. Whereas, it should not substitute the other workup for IDA. The endoscopic evaluations for upper and lower gastrointestinal tracts in men and postmenaposal women, celiac serology should be performed in cases of IDA.

Hematological Condition	Level of Evidence
MALT lymphoma	Evidence level: 1a Grade of recommendation: A
IDA	Evidence level: 1a
	Grade of recommendation: A
Idiopathic thrombocytopenic purpura	Evidence level: 1b
	Grade of recommendation: A
Vitamin B12 deficiency	Evidence level: 3b
	Grade of recommendation: B

Abbreviations: Grades of recommendations and evidence levels in support of recommendations
Grade of recommendation: A; Evidence level: 1a: Systematic review of randomized controlled trial (RCT) of goog methodological quality and with homogeneity
Grade of recommendation: A; Evidence level: 1b: Individual RCT with narrow CI
Grade of recommendation: B; Evidence level: 3b: Individual case-control study

Table 4. Evidence Based Relationship between *H. pylori* and the Etiology of other Hematological Conditions (in these disorders, *H. pylori* should be sought and eradicated)

It is possible to rescue hematological and ferro-kinetic parameters after *H. pylori* eradication. Its implication as an unexplained origin of ID was revealed in the international consensus and management guidelines of *H. pylori* infection. It should be tested and eradicated in both adults and children with unexplained origin of ID [104,105].

There has not been any concensus on the treatment of IDA in *H. pylori*-infected patients yet. Three meta-analyses evaluated the effect of *H. pylori* eradication on IDA. Qu et al. reported that eradication of *H. pylori* improved hemoglobin and serum ferritin levels but not significantly [27]. Whereas, Huang et al. reported another meta-analysis of 8 randomized controlled trials (RCTs) in which five RCTs had used PPI-based triple therapy and three RCTs had used bismuth-based triple therapy as eradication regimens. They found that anti-*H. pylori* treatment combined with iron supplement was more effective than iron administration alone in the treatment of IDA in *H. pylori*-infected patients. They also showed that bismuth-based triple therapy had an advantage over PPI-based triple therapy [26]. However, this finding needs to be confirmed. In another meta-analysis involving 956 patients and 16 RCTs in which 13 RCT had used PPI-based triple treatment and 3 RCT used bismuth-based triple treatment, it was shown that the increase in Hb, serum iron, and serum ferritin levels were significantly higher with anti-*H. pylori* treatment plus oral iron compared with oral iron alone in patients with documented *H. pylori* infection and IDA [24]. Recently in a study by Habib et al., sequential and standard therapies were compared in children. It was shown that there was no significant difference in *H. pylori* eradication success between two groups and there was no significant relationship between eradication treatment and serum ferritin levels [106].

In conclusion, refractoriness to oral iron treatment and unexplained IDA may justify a "test-and-treat" approach of *H. pylori* eradication as recommended by the Maastricht IV European Consensus Conference [62], Second Asia–Pacific Consensus Guideline [51], and the III Working Group Consensus Report 2015 [103]. Standard treatment regimens that are recommended in dyspeptic patients by current guidelines combined with iron supplement are effective in IDA in patients with *H. pylori* infection. These eradication regimens are listed in Table 5 based on current guidelines [Table 5,51, 62, 103].

First-line therapy	Duration	Drugs and doses
Standard PPI-based triple therapy	7-14 days	PPI 2x1
		+ Amoxicillin 1g 2x1
		+ Clarithromycin 500 mg 2x1
		or
		(in the presence of penicillin allergy)
		PPI 2x1
		+ Metronidazole 500 mg 2x1
		+Clarithromycin 500 mg 2x1
		or
		(in areas of low clarithromycin resistance)
		PPI 2x1
		+ Amoxicillin 1 g 2x1
		+ Metronidazole 400 mg 2x1
Sequential therapy	First 5 days	PPI 2x1 + Amoxicillin 1 g 2x1
	Followed by 5 days	PPI 2x1
		+ Metronidazole or tinidazole 500 mg 2x1
		+ Clarithromycin 500 mg 2x1
Concomitant therapy (non-bismuth quadruple)	10 days	PPI 2x1
		+ Amoxicillin 1g 2x1
		+ Metronidazole or tinidazole 500mg 2x1
		+ Clarithromycin 500 mg 2x1
Second-line therapy	**Duration**	**Drugs and doses**
*Bismuth-containing quadruple therapy (when bismuth is available)	7–14 days	PPI 2x1
		+ Bismuth salts 4x1 or 2x2
		+ Tetracycline, 500mg 3x1
		+ Metronidazole, 500mg 3x1
Levofloxacin-containing triple therapy	10 days	PPI 2x1
		+ Amoxicillin 1g 2x1
		+ Levofloxacin, 500mg 1x1 or 250mg 2x1
		or
		(in the presence of penicillin allergy)
		PPI 2x1
		+ Clarithromycin 500 mg 2x1
		+ Levofloxacin, 500mg 1x1 or 250mg 2x1
Rifabutin-based triple therapy:	7–10 days	PPI 2x1
		+Rifabutin 150 mg 2x1
		+Amoxicillin 1 g 2x1
Third-line therapy		
After failure of second-line therapy, treatment should be guided by antimicrobial susceptibility testing, whenever possible		

*In areas of high clarithromycin resistance, bismuth-containing quadruple therapy is recommended for first-line empirical treatment.
Abbrevations: PPI: Proton pump inhibitor

Table 5. Treatment regimens recommended for first- and second-line therapy of *Helicobacter pylori* infection

7. Summary

Iron is an essential element for all living organisms. Iron metabolism is controlled mainly by absorption. ID is the most common nutritional deficiency and causes clinically important outcomes. One of the most common results of ID is IDA. ID results from increased physiological needs, blood losses, inadequate intake, and diminished absorption. *H. pylori* infection is one of the important causes of IDA especially in undetermined and refractory cases.

In the literature case series, sero-epidemiological studies and meta-analysis showed strong evidence regarding the relationship between IDA and *H. pylori*. Several mechanisms have been proposed for IDA in *H. pylori* infection. First, blood loss from gastrointestinal lesions related with *H. pylori*; second, malabsorption due to hypo- or achlorhydria resulting from gastric body inflammation and atrophy; third, bacterial competition for dietary iron with several mechanisms; and last, changing regulatory pathways especially hepcidin levels in iron metabolism by the bacteria.

Although *H. pylori* infection is more prevalent, frequency of IDA related with *H. pylori* is low. Influencing factors for developing IDA in *H. pylori* infection include topographic distribution of gastric inflammation, severity of inflammation, virulence factor of the bacteria.

Once IDA is diagnosed in *H. pylori*-infected patient, other most common causes of IDA should be evaluated carefully. Depending on "test and treat" strategy, the *H. pylori* infection should be eradicated based on recommendations by the current guidelines.

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