

Iron-Deficiency Anemia and *Helicobacter pylori* Infection: A Review of the Evidence

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INTRODUCTION

Iron deficiency is the most common cause of anemia in the world, affecting an estimated 500–600 million persons (1). It is also estimated to be the most common nutritional deficiency in both underdeveloped and developed nations, the most common cause of anemia, and possibly the most common organic disorder in clinical practice (2). The prevalence of iron-deficiency anemia (IDA) was evaluated in a large cross-sectional survey of the United States and found to affect 2.7–4.4% of adult males, with a progressive increase in frequency with increasing age (3). Established causes of iron deficiency include inadequate iron intake, chronic blood loss, malabsorption, hemolysis, or a combination of these factors. IDA is often an indication to evaluate the upper and lower gastrointestinal tract to exclude chronic blood loss secondary to cancers, ulcerations, angiodysplasias, or malabsorption from celiac disease. However, endoscopic studies are frequently unrevealing and the cause of iron deficiency remains unexplained in a significant proportion of cases. In a prospective study of 100 patients with IDA, endoscopy failed to discover a culprit lesion in 48% of subjects (4). In another study of adults who underwent endoscopic evaluation for IDA, a cause of anemia was found in only 55% of outpatients (5). The failure to identify a cause of iron deficiency in a substantial subset of patients with low iron stores raises the question of whether there are additional as of yet unexplained causes of iron depletion. Recently, there has been a growing body of evidence to suggest a relationship between *Helicobacter pylori* gastritis and IDA in the absence of peptic ulcer disease.

METHODS

A MEDLINE search was performed for the years 1966 through June 2004 using the keywords *H. pylori* and anemia, iron-deficiency. We identified clinical studies that addressed the association of *H. pylori* infection and iron deficiency. Additional references were retrieved from the published reviews of this topic.

CLINICAL DATA

Prevalence of Gastritis in IDA and H. pylori Infection

The association between chronic gastritis, achlorhydria, and IDA has long been reported in the literature. Davidson and Markson in 1955 compared gastric histology in 42 patients with IDA and 31 age-matched controls (6). Histamine-fast achlorhydria was found in 48% of IDA patients compared with 13% of controls. The prevalence of histologic abnormalities of the gastric mucosa was significantly higher in the IDA group than controls, as only 26% of patients with IDA had normal mucosa compared with 71% of controls. Furthermore, mucosal abnormalities were more severe and frequent in the presence of achlorhydria. Only one of the IDA patients with achlorhydria was found to have normal gastric histology. No relationship was found between degree of anemia and mucosal changes. In 1964, Ikkala and Siurala evaluated gastric histology and iron studies in 100 consecutive patients with IDA (7). They found that 75% of patients had histologic evidence of gastritis; no control group was assessed. Patients with more severe gastritis were more likely to have abnormal peak acid secretion by the Histalog test. The authors also noted no difference in serum iron or hemoglobin (Hb) according to gastritis severity. These studies predate the *H. pylori* literature. More recently, Dickey *et al.* studied patients with IDA and no identifiable source of gastrointestinal blood loss, and identified a group of subjects (8 of 41 patients) in whom atrophic body gastritis was the only abnormality (8). Six of the eight subjects identified had antiintrinsic factor or antiparietal cell antibodies, suggesting an autoimmune basis. Another recent prospective study in subjects with unexplained microcytic anemia revealed that approximately 20% had atrophic body gastritis, with significantly more microcytic subjects infected with *H. pylori* as compared to macrocytic controls (61% vs 5%; $p < 0.01$) (9). Kuipers *et al.* found *H. pylori* infection to be a significant risk factor in the development of atrophic gastritis in a prospective study (10). Infection with the bacteria was accompanied by chronic gastritis in all 58 subjects, with 24% having moderate-to-severe atrophy. Atrophic gastritis and intestinal metaplasia developed in 4%

Table 1. *H. Pylori* and Iron-Deficiency Anemia: Case Reports/Series

Author	Year	Country	Study Type	Population	Cases (n)	Results
Blecker	1991	Belgium	Case report	Adolescent	1	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Dufour	1993	Italy	Case report	Child	1	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Bruel	1993	France	Case report	Child	1	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Marignani	1997	Italy	Case report	Adolescent	1	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Carnicer	1997	Spain	Case report	Child	1	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Barabino	1999	Italy	Case series	Children	4	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Choe	1999	Korea	Randomized controlled trial	Adolescents	43	<i>H. pylori</i> + IDA patients after eradication had increased Hb compared with placebo
Konno	2000	Japan	Case series	Adolescents	6	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Ashorn	2001	Finland	Case series	Children	7	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Choe	2001	Korea	Subset: Controlled trial in IDA/ <i>H.pylori</i> seropositives	Adolescents	12 athletes, 10 controls	Significant increases in Hb, iron, and ferritin after <i>H. pylori</i> eradication c/w controls given iron therapy
Sugiyama	2002	Japan	Case series	Adult females	2	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Kostaki	2003	Greece	Case series	Children	3	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis
Yoshimura	2003	Japan	Case series	Adults	2	Resolution of IDA after eradication of <i>H. pylori</i> -associated gastritis. One case had Menetrier's disease.
Hacihanefioglu	2004	Turkey	Case series	Adult females	14	Increase in Hb, iron, transferrin saturation, no change in ferritin

IDA = Iron deficiency anemia; Hb = hemoglobin.

of *H. pylori*-uninfected as compared to 28% of *H. pylori*-infected subjects.

Case Series

In 1993, Dufour *et al.* reported a case of a 7-yr-old male who presented with IDA refractory to oral iron therapy, *i.e.*, Hb parameters did not normalize despite adequate iron supplementation (11). There was no evidence of poor diet, gastrointestinal symptoms, or occult blood in the stool. A thorough evaluation was negative for etiology, except for upper endoscopy that revealed chronic superficial pangastritis, with histological evidence of *H. pylori* infection. The child was given *H. pylori* eradication therapy without concomitant iron supplementation and subsequently had resolution of his anemia and iron deficiency. Following this case report, several others have presented similar results of iron-deficient, anemic patients with no apparent cause other than chronic *H. pylori*-associated gastritis. The majority of case reports describe standard evaluation of IDA including laboratory work, upper endoscopy with gastric and small bowel biopsies, imaging such as Meckel's scanning and ultrasound as appropriate, stool studies for infectious pathogens, colonoscopy as appropriate, and urinalysis. Subjects normalized Hb and iron parameters after *H. pylori* bacterial eradication without iron supplementation (12–24) (Table 1).

Annibale *et al.* conducted the largest prospective case series to date, involving 30 adult patients with IDA and *H. pylori*-gastritis as the only pathologic finding (13). Patients with fecal occult blood positivity, an obvious cause of blood loss (including heavy menses), severe comorbid conditions, and those using nonsteroidal antiinflammatory drugs were excluded. Patients underwent dietary evaluation, as well as double-contrast barium enema or colonoscopy, small bowel radiographic evaluation, or Meckel scintigraphy, if indicated. Upper endoscopy was performed with gastric biopsies for rapid urease test and histologic evaluation, and duodenal biopsies were performed to exclude celiac disease. Patients found to be positive for *H. pylori* on urease test and/or histology were treated with 2 wk of amoxicillin, metronidazole, and omeprazole without iron replacement. All had a previous suboptimal response to oral iron therapy. In a follow-up period of 12–24 months, all patients successfully treated for *H. pylori* resolved their anemia and iron deficiency without further iron supplementation. The three patients in whom *H. pylori* infection was not successfully treated had no change or a slight decrease in iron parameters at 6-month follow-up.

A retrospective study of 105 patients with unexplained IDA also showed an association with *H. pylori* infection (25). Patients had undergone evaluation with upper endoscopy with gastric biopsies, colonoscopy with terminal ileum intubation

(in the majority), small bowel biopsies, and enterocytosis. Patients with nonsteroidal antiinflammatory use, abnormal menses, or iron-poor diet were excluded. Patients with IDA were compared to an age- and sex-matched control group comprised of patients undergoing upper endoscopy for symptoms of dyspepsia. Significantly more patients with unexplained anemia had *H. pylori*-associated chronic gastritis compared with controls ($p < 0.01$).

In the only randomized, controlled trial in the published literature, Choe *et al.* studied 43 adolescents with IDA, the majority of whom were females (14). All had negative specimens for fecal occult blood and underwent upper endoscopy with no evidence of obvious bleeding lesions. Twenty-two subjects found to be infected with *H. pylori* by rapid urease test and histology were randomly assigned to one of three treatment groups: oral iron plus a 2-wk course of eradication triple therapy; placebo for iron plus eradication therapy; or iron plus a 2-wk course of placebo. The authors found that the groups that underwent *H. pylori* treatment, with or without iron, showed a significant increase in Hb level at 8 wk after therapy as compared with those that received only iron ($p < 0.01$).

Epidemiologic Studies

Several seroepidemiologic studies support an association between *H. pylori* infection and decreased iron stores (26–30). In an analysis of a cross-sectional national health survey conducted in Germany, Berg *et al.* found that *H. pylori* infection was associated with a 17% decrease (95% CI: 9.8–23.6) in serum ferritin concentration, after adjustment for age and sex. The association of decreased ferritin and *H. pylori* infection was similar regardless of infection with CagA positive or negative strains, age, sex, or iron intake (22). In a Danish population-based study ($n = 2,794$), persons seropositive for *H. pylori* infection had a 40% increased risk of having a reduced serum ferritin level ($<30 \mu\text{g/L}$) as compared to seronegative individuals, after adjustment for age, gender, menopausal status, socioeconomic status, blood donation, and alcohol consumption (23). In a large study of Alaskan natives ($n = 2,080$), the relative risk for low serum ferritin among persons seropositive for *H. pylori* was 1.13 ($p = 0.013$), after adjustment for age and sex. Low levels of ferritin were most common among persons less than 20 yr of age and among women of childbearing age (24). In a study of Korean children aged 6–12 yr ($n = 753$), *H. pylori* seropositivity correlated with lower serum ferritin levels (24 ng/ml vs 39 ng/ml; $p < 0.001$) (26). The prevalence of iron deficiency (serum ferritin $< 15 \text{ ng/ml}$) was also significantly higher in seropositive (13.9%) as compared to seronegative children (2.8%). In another study of Korean adolescents ($n = 937$), it was found that *H. pylori* seropositivity rates for anemia, hypoferritinemia, and iron deficiency were 34.2%, 29.5%, and 35.3%, respectively, compared with 19.6% for nonanemic persons ($p = 0.003$), 19.2% for persons with a normal ferritin ($p = 0.005$), and 19.4% for persons without iron deficiency ($p = 0.001$) (31). The authors found that the asso-

ciation between decreased iron stores was more pronounced in girls as compared to boys (31). Peach *et al.* also found significantly lower ferritin levels among Australian women with *H. pylori* infection as compared to noninfected controls despite similar dietary iron intake (29). The latter studies reflect the possibility of *H. pylori* infection acts as an iron stressor in susceptible individuals, such as females, secondary to losses from menstruation, and the requirements of pregnancy, or children, who have increased iron requirements for growth. Another study has shown that persons with celiac disease are more likely to have IDA if infected with *H. pylori* (32).

However, a few epidemiologic studies do not support an association between *H. pylori* infection and IDA. Collett *et al.* found no significant differences in serum ferritin levels between *H. pylori* seropositive or seronegative males or females in a study of 1,060 adult subjects in Christchurch, New Zealand (33). Of note, seropositive male subjects did have lower serum iron levels compared with seronegative males. In Korea, a study of 693 children ages 9–12 yr showed no significant differences in the seroprevalence of *H. pylori* infection between subjects with IDA and nonanemic controls (34). Furthermore, nutritional indices including serum iron and ferritin were not found to be different between *H. pylori* seropositive compared with seronegative asymptomatic, elderly subjects (35).

POSSIBLE PATHOGENIC MECHANISMS

Occult Blood Loss Secondary to Chronic Erosive Gastritis

Several theoretic mechanisms have been proposed to explain the possible relationship between *H. pylori* infection and decreased iron stores. One potential mechanism is that the bacteria exerts a negative effect on body iron balance by chronic blood loss from the gastrointestinal tract. Most published cases and case series have found no bleeding lesions at the time of endoscopy and have reported negative testing for fecal occult blood among study subjects; these facts argue against chronic blood loss as an etiology of iron deficiency (11–13, 15, 16, 19, 20). However, there have been reports of *H. pylori*-associated hemorrhagic gastritis associated with iron deficiency. Blecker *et al.* reported a case of a young girl who presented with syncope and was found to have IDA related to *H. pylori* infection and hemorrhagic gastritis (36). Furthermore, Yip *et al.* in a descriptive study of Alaskan natives showed a dramatically high prevalence of IDA associated with an atypical, grossly hemorrhagic gastritis related to *H. pylori* infection (37). However, all subjects that underwent endoscopy in the study had evidence of elevated fecal Hb levels. The study did not comment on treatment of *H. pylori* or outcomes thereafter.

Decreased Iron Absorption Secondary to Chronic Gastritis and Hypo- or Achlorhydria

Another explanation for a relationship between *H. pylori* infection and IDA involves the possible effect of *H. pylori* gastritis on gastric acid secretion and iron absorption. The

regulatory and metabolic pathways of iron in the body are complex and not yet completely understood. However, a basic understanding of iron absorption is essential in considering the pathogenesis of IDA in *H. pylori*-infected persons. In humans, the level of iron is controlled mainly by the regulation of iron absorption from the duodenum and jejunum (38). Dietary iron must be made available for absorption, taken up by epithelial cells, and finally transferred to plasma. However, only a limited proportion of the iron in the diet can be absorbed due to the restricted bioavailability of certain dietary forms (39). Dietary iron is available as heme iron (primarily from meat), which is readily absorbed, or nonheme iron (vegetables, cereals, rice), in which bioavailability is dependent on a variety of factors. Nonheme iron accounts for 80% of dietary iron in industrialized countries, and even a greater proportion worldwide (38).

Crucial to the effective solubility and absorption of nonheme iron is hydrochloric acid in gastric secretions. Reduction of the ferric to ferrous form is dependent upon the pH of gastric juice; reduction to the ferrous form facilitates membrane transport (38). An important promoter of iron absorption is ascorbic acid, which appears to act in two ways: by promoting reduction to the ferrous form, and by forming an absorbable molecular complex with ferric iron, which is insoluble at pH values above 5 (39). Substances such as ascorbic acid, sugars, and amino acids form ligands with iron that are soluble at the neutral or alkaline pH range encountered in the small intestine, thereby facilitating iron absorption (40). The reaction of ferric iron with these substances must be initiated at an acid pH, thus normal gastric acidity is required (41).

Ascorbic acid is actively secreted into gastric juice, and it has been shown that gastric pathology affects this secretion and may result in reduced levels of gastric ascorbic acid (42). Zhang *et al.* studied 115 patients with dyspepsia, and found that gastric juice ascorbic acid was significantly lower in *H. pylori*-infected patients compared with uninfected persons (43). Ascorbic acid concentrations decreased as gastritis progressed in severity as well as extent, *i.e.*, with involvement of the gastric body. Furthermore, gastric juice pH values were inversely associated with gastric juice ascorbic acid concentrations, underscoring the importance of gastric acid in determining ascorbic acid level. Gastric juice concentrations of ascorbic acid have been shown to improve with eradication of *H. pylori* infection (44, 45).

Gastric acid hyposecretion results from the atrophy of the gastric glands and fundic mucosa, which has been associated with chronic *H. pylori* infection. It has been shown that patients with IDA and *H. pylori* infection are more likely to have a pattern of gastritis involving the gastric corpus, with related increases in intragastric pH (46). Capurso *et al.* evaluated the pattern of gastritis in 51 patients with iron deficiency and compared the findings to 103 *H. pylori*-infected nonanemic controls. They found that gastritis involved the gastric corpus in 90% of IDA patients as compared to 43% of controls ($p < 0.0001$). Annibale *et al.* also showed a high frequency of corpus gastritis in a series of patients with refractory iron

deficiency and *H. pylori* infection. They found that 24 (80%) of 30 of their patients had involvement of the gastric corpus as well as the antrum (pangastritis) (13). In patients with *H. pylori*-associated gastritis of the corpus, an inverse relationship has been reported between the severity of gastritis and acid secretion, with return of acid secretion to the normal range after eradication of *H. pylori* (47). It has been shown that the number of parietal cells in the secretory phase is lower in *H. pylori*-infected individuals compared with controls, which may account for the higher gastric pH in these patients (48).

Annibale *et al.* specifically addressed the question of whether gastric pH or ascorbic acid concentrations differ among patients with *H. pylori* infection with or without associated IDA, as well as compared with *H. pylori*-negative IDA patients (49). They studied patients with unexplained IDA with upper endoscopy and colonoscopy and excluded those with apparent causes for anemia. The remaining 43 patients were separated into groups according to whether they had *H. pylori*-associated gastritis ($n = 30$) or normal gastric histology ($n = 13$); the latter group served as controls. Included as a separate control group were 11 nonanemic patients evaluated with upper endoscopy for dyspepsia who were found to have *H. pylori*-associated gastritis as the only abnormality on exam. At endoscopy all patients and controls underwent biopsies of the stomach and duodenum for histologic evaluation and Giemsa staining, as well as gastric pH and ascorbic acid determination. The investigators found that mean intragastric pH values were significantly higher in patients with *H. pylori*-associated IDA compared with either of the control groups ($p < 0.0001$), whereas no difference was found between control groups. Similarly, gastric juice ascorbic acid concentrations were significantly lower in *H. pylori*-positive IDA patients compared with uninfected IDA patients ($p = 0.0033$), and nonanemic *H. pylori*-positive patients ($p = 0.002$). In histologic evaluation of the extent of gastritis among the *H. pylori*-infected individuals, it was found that 94% of patients in the IDA group had pangastritis, whereas the majority of those without IDA had antrum-predominant gastritis ($p = 0.0069$). There was an inverse correlation between intragastric pH and ascorbic acid levels, as well as lower ascorbic acid levels in patients with more severe damage in the gastric body. The effect on gastric acid secretion and ascorbic acid levels was determined in only a subgroup of patients after *H. pylori* eradication. In patients with chronic superficial gastritis, there was a decrease in pH and increase in ascorbic acid concentration following treatment for *H. pylori*. However, in patients with atrophic body gastritis, there were no changes in these parameters. This study, though small and limited by the poor reliability of gastric pH measurements, provides evidence for physiologic abnormalities that occur in the setting of *H. pylori* infection that could plausibly affect iron absorption and provide a mechanism for the development of anemia. A recent study from Italy confirmed decreased oral absorption in *H. pylori*-positive ($n = 33$) versus -negative persons ($n = 22$) and showed improvement in iron absorption 2 months following successful *H. pylori* treatment for infected subjects

(50). In addition, *H. pylori*-positive subjects had lower serum ferritin levels as compared to negative subjects. In a subgroup analysis, women with IDA and *H. pylori* infection were found to have decreased iron absorption as compared to *H. pylori*-negative women with IDA, supporting the hypothesis that *H. pylori* infection may cause IDA in populations at increased risk for iron depletion. There was no difference in iron absorption in women without IDA irrespective of *H. pylori* status (50). Of note, 80% of *H. pylori*-infected anemic persons had pangastritis or atrophic gastritis. Another smaller study examined iron absorption and gastric acid output in Bangladeshi children with ($n = 12$) and without ($n = 12$) *H. pylori* infection (51). These investigators found that basal acid output and stimulated acid output were significantly lower in *H. pylori*-infected children as compared to uninfected children, and that Hb levels improved significantly in *H. pylori*-infected children after *H. pylori* treatment (51). However, no significant improvement in absorption of ferrous sulfate and ferrous fumarate was observed after *H. pylori* eradication despite improvement in acid secretion following successful *H. pylori* treatment, suggesting that *H. pylori* treatment did not affect iron absorption (51). However, the authors note that the increase in acid output after *H. pylori* treatment could have increased the absorption of native food iron, which was not measured in the study.

Increased Iron Uptake and Utilization by Bacteria

It has been hypothesized that *H. pylori* may lead to IDA by sequestering and utilizing iron, thus competing with the human host. The results of the ferrokinetic studies of Barabino *et al.* suggested the diversion of iron to some extramedullary focus, hypothesized but not proven to be *H. pylori*-associated gastric infection (12). Similar to many bacteria, *H. pylori* requires iron as a growth factor. Pathogenic bacteria need to develop specific and effective iron uptake systems in order to thrive in the host environment. There has been much recent investigation into the potential mechanisms involved in iron uptake and metabolism by *H. pylori*, which is only beginning to be appreciated.

H. pylori has been found to possess a 19 kDa iron-binding protein resembling ferritin (Pfr) morphologically and biochemically (52). This ferritin-like protein has been considered to play a role in storage of excess iron sequestered by the bacteria, as well in protection against toxicity in conditions of iron excess. Choe *et al.* studied the mutations in the *PFR* gene in the gastric biopsy specimens of 26 *H. pylori*-infected patients with and without IDA, but did not find significant differences in *PFR* gene mutations between groups in this small study (53). In *H. pylori*, both acquisition and storage of iron are governed by the ferric uptake regulator gene product (Fur), which has been shown to regulate transcription of iron uptake genes and Pfr-mediated iron storage (54). In contrast to other bacteria, *H. pylori* expresses iron uptake proteins in iron-replete conditions, and when exposed to iron restricted conditions it expresses additional iron transporters. A Fur mutant has been described that results in increased *H. pylori*

whole cell iron content (54). Further mechanisms of iron uptake and metabolism by *H. pylori* and their interactions are yet to be characterized. Additional studies are needed to assess the impact of strain differences in iron regulatory genes on clinical phenotype (*e.g.*, IDA).

Another possible mechanism for iron deficiency in *H. pylori*-infected subjects involves sequestration of iron in lactoferrin in the gastric mucosa and uptake of iron by the *H. pylori* organism. Although many pathogenic bacteria utilize the secretion of chelators (siderophores) that can remove iron from transferrin or lactoferrin, this has not been characterized in *H. pylori* microbiology. Rather, studies indicate that *H. pylori* iron uptake occurs through a receptor-mediated lactoferrin acquisition method, which has been shown to be specific for human lactoferrin (55). Lactoferrin is an iron-binding glycoprotein found in body fluids including milk, lacrimal secretions, saliva, and urine, and its secretion in the gastric mucosa seems to be influenced by some signal from *H. pylori* (56). It appears that *H. pylori* then absorbs the iron from lactoferrin via a specific lactoferrin-binding protein expressed by *H. pylori*. In 1997, Dhaenens *et al.* identified a 70-kDa lactoferrin-binding protein from outer membrane proteins of *H. pylori* (57). The protein was only expressed when *H. pylori* was grown in an iron-restricted environment, suggesting a role in iron uptake. Furthermore, lactoferrin concentration is increased in gastric specimens of patients with *H. pylori*-associated gastritis, supporting the importance of the lactoferrin receptor in the virulence of the organism (56, 58). In addition, Choe *et al.* provided evidence that lactoferrin may play a role in the pathogenesis of IDA by demonstrating that lactoferrin levels in the gastric mucosa are significantly elevated in *H. pylori*-positive persons with IDA as compared to nonanemic *H. pylori*-negative persons, nonanemic *H. pylori*-positive persons, and *H. pylori*-negative persons with IDA (56). Worst *et al.* discovered three heme-binding iron-repressible outer membrane proteins that may be involved in the uptake of heme from the host by *H. pylori*, which could contribute greatly to the virulence of the organism (59). Furthermore, Velayudhan *et al.* has shown a major role for FeoB, a ferrous iron transporter in *H. pylori* iron acquisition (60). The neutrophil-activating protein (NapA) of *H. pylori* is a major antigen of the immune response in infected individuals and has also been shown to act as an iron-binding protein (61).

CONCLUSION

Unexplained IDA is a frequent indication for endoscopic evaluation of the gastrointestinal tract. However, a specific etiology cannot be identified in a significant proportion of patients. Epidemiologic studies support an association between *H. pylori* infection and lower iron stores, and small, uncontrolled case series (and a single, small, randomized trial) have shown improvement in anemia following *H. pylori* treatment. *H. pylori* infection is widespread, and it is unclear why only a small proportion of individuals develop

clinical complications, including iron deficiency. The available evidence suggests that person at increased risk of iron deficiency, such as premenopausal women and children, are more likely to develop iron deficiency associated with *H. pylori* infection. Further study, including larger randomized trials, is needed to clarify whether patients with unexplained iron deficiency benefit from *H. pylori* treatment. However, the evidence that currently exists supports an association between *H. pylori* infection and IDA, and testing and treatment of persons with unexplained IDA for *H. pylori* infection is a reasonable practice, and is recommended by the authors. Further studies are required to confirm a causal relationship and explore mechanisms of disease.

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