

## TOPIC HIGHLIGHT

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# A short review of malabsorption and anemia

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**Author contributions:** All authors contributed equally to reviewing the literature and writing the paper; all authors revised the final version of the paper.

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Received: July 23, 2009 Revised: September 4, 2009

Accepted: September 11, 2009

Published online: October 7, 2009

## Abstract

Anemia is a frequent finding in most diseases which cause malabsorption. The most frequent etiology is the combination of iron and vitamin B12 deficiency. Celiac disease is frequently diagnosed in patients referred for evaluation of iron deficiency anemia (IDA), being reported in 1.8%-14.6% of patients. Therefore, duodenal biopsies should be taken during endoscopy if no obvious cause of iron deficiency (ID) can be found. Cobalamin deficiency occurs frequently among elderly patients, but it is often unrecognized because the clinical manifestations are subtle; it is caused primarily by food-cobalamin malabsorption and pernicious anemia. The classic treatment of cobalamin deficiency has been parenteral administration of the vitamin. Recent data suggest that alternative routes of cobalamin administration (oral and nasal) may be useful in some cases. Anemia is a frequent complication of gastrectomy, and has been often described after bariatric surgery. It has been shown that banding procedures which maintain digestive continuity with the antrum and duodenum are associated with low rates of ID. *Helicobacter pylori* (*H pylori*) infection may be considered as a risk factor for IDA, mainly in groups with high demands for iron, such as some children and adolescents. Further controlled trials are needed before making solid recommendations about *H pylori* eradication in these cases.

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**Key words:** Anemia; Celiac disease; *Helicobacter pylori*; Cobalamin deficiency; Gastrectomy

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Fernández-Bañares F, Monzón H, Forné M. A short review of malabsorption and anemia. *World J Gastroenterol* 2009; 15(37): 4644-4652 Available from: URL: <http://www.wjgnet.com/1007-9327/15/4644.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.4644>

## INTRODUCTION

Anemia is a frequent finding in most digestive diseases which cause malabsorption. In this review we will focus on some frequent entities producing anemia and malabsorption, which are of current interest because of recent advances regarding each of them. Celiac disease (CD) may be considered as an archetypal malabsorption syndrome, and it is a frequent cause of anemia without associated intestinal symptoms. Anemia due to isolated cobalamin deficiency is a frequent finding in the elderly, and its etiology goes beyond the classical pernicious anemia concept. On the other hand, physicians should be aware that anemia often follows gastric surgery procedures, mainly after bariatric surgery, in order to implement prevention strategies. *Helicobacter pylori* (*H pylori*) infection is being recognized as a frequent cause of iron deficiency (ID), both in developed and developing countries. In these cases eradication of the infection could be a successful therapy of the anemia.

## ANEMIA IN CD

CD is an immunologically-mediated enteropathy, triggered in genetically susceptible subjects, by the intake of certain proteins of wheat, barley and rye, and resulting in small-bowel mucosal villous atrophy with crypt hyperplasia<sup>[1]</sup>.

Anemia has frequently been reported as the only manifestation or the most frequent extra-intestinal symptom of CD<sup>[2-4]</sup>. Although folate and cobalamin deficiency are known complications of CD, the most common nutritional anemia associated with CD is ID. ID anemia (IDA) was reported in up to 46% of patients with subclinical CD in one study, and its prevalence was higher in adults than in children<sup>[4]</sup>. In a recent case-control study, only anemia (OR: 26.3; 95% CI: 6-120) and diarrhea

Table 1 Prevalence of CD in patients presenting with IDA

Study, yr	n	Positive serology (%)	Positive biopsy (%)	Comments
Corazza <i>et al</i> <sup>[16]</sup> , 1995	200	8	5	IDA. 8.5% if only obscure IDA considered. All patients with positive serology were biopsied
Carroccio <i>et al</i> <sup>[17]</sup> , 1998	85	5.8	5.8	IDA. 20% if only refractory obscure IDA considered. All patients with positive serology were biopsied. 80% of CD cases were women
Unsworth <i>et al</i> <sup>[18]</sup> , 2000	483	6.6	4.6	Blood donors with anemia, most with IDA. Not all seropositive patients were biopsied. 95% of CD cases were women
Haslam <i>et al</i> <sup>[19]</sup> , 2001	216	2.3	n/a	Pregnant women with anemia. Four of five anemic women with positive serology have IDA. Only serology was performed
Annibale <i>et al</i> <sup>[20]</sup> , 2001	190	n/a	13.7	Obscure IDA. All patients were biopsied. 85% of CD cases were women
Howard <i>et al</i> <sup>[21]</sup> , 2002	258	10.9	4.7	Majority of patients with previously not studied IDA (4% folate deficiency). Not all seropositive patients were biopsied. 83% of CD cases were women
Ransford <i>et al</i> <sup>[22]</sup> , 2002	484	3.5	2.3	Previously not studied IDA. Not all seropositive patients were biopsied. 73% of CD cases were women
Grisolano <i>et al</i> <sup>[23]</sup> , 2004	103	n/a	8.7	Previously not studied IDA. All patients were biopsied. 100% of CD cases were women
Mandal <i>et al</i> <sup>[24]</sup> , 2004	504	n/a	1.8	IDA with normal upper gastroscopy. Not all patients were biopsied
Hershko <i>et al</i> <sup>[25]</sup> , 2005	150	5.3	5.3	Previously not studied IDA. All seropositive patients were biopsied
Kalayci <i>et al</i> <sup>[26]</sup> , 2005	135	4.4	4.4	Previously not studied children with IDA. All seropositive patients were biopsied
Zamani <i>et al</i> <sup>[27]</sup> , 2008	206	15	14.6	Obscure IDA. All patients were biopsied
Carter <i>et al</i> <sup>[28]</sup> , 2008	116	n/a	6.5	Previously not studied premenopausal women with IDA. All patients were biopsied

n/a: Not available data; IDA: Iron deficiency anemia; CD: Celiac disease.

(OR: 4.5; 95% CI: 2-10) were identified as independent predictors of an eventual diagnosis with CD among the different clinical presentations in general practice during the 5 years prior to the diagnosis of CD<sup>[5]</sup>. Similarly, among patients identified by population screening, 50% were anemic as the primary presentation<sup>[6]</sup>.

Iron is absorbed in the proximal small intestine and the absorption is dependent upon several factors, including an intact mucosal surface and intestinal acidity<sup>[7,8]</sup>. ID in CD primarily results from its impaired absorption as a result of the villous atrophy of the intestinal mucosa. Consequently, IDA develops. The concept of abnormal iron absorption is supported by the failure to increase serum iron following oral iron supplementation.

Occult gastrointestinal bleeding has been described in CD in correlation with the severity of villous atrophy<sup>[9]</sup>. More recent studies have found, however, that the rate of positive occult blood tests in CD is low and does not exceed that of the general population<sup>[10,11]</sup>.

Anemia of chronic disease has also been described in CD<sup>[12,13]</sup>. It is well known that pro-inflammatory cytokines play an essential role in the pathogenesis of CD<sup>[14]</sup>. In this regard, both interferon- $\gamma$  and interleukin-6 are powerful mediators of hypoferrremia in inflammation, leading to the abnormalities in iron homeostasis associated with the anemia of chronic disease<sup>[15]</sup>. Accordingly, Harper *et al*<sup>[12]</sup> described that in the majority of CD patients with anemia, low serum ferritin levels were an indicator of ID. However, in 13% of patients with anemia, serum ferritin levels were increased, such abnormalities reverting to normal after a gluten-free diet. In a recent study, refined precision laboratory methods to identify anemia of inflammation were used<sup>[13]</sup>. Among 65 anemic CD patients, 45 had IDA, two had cobalamin or folate deficiency, and 11 had anemia of chronic disease alone or in combination with ID, which implies

a prevalence of 17%. After 12-mo on a gluten-free diet, the response was equally favorable in the patients with either IDA or anemia of chronic disease, indicating that the suppression of inflammatory intestinal changes by the diet improves anemia both by correcting iron absorption and by blunting the inflammatory response.

CD is frequently diagnosed in patients referred for evaluation of anemia, and subclinical CD appears to be a relatively common cause of IDA. Studies using serologic tests and small-bowel biopsies in patients referred for evaluation of IDA have reported CD in 1.8%-14.6% of patients (Table 1)<sup>[16-28]</sup>. These studies are heterogeneous in design, as some included only patients with IDA whereas others included both folate and iron deficient patients, and used different methods for diagnosis of CD, often in selected referral populations. Highest frequencies of CD were observed in patients with obscure IDA, and frequency may be as high as 20% in patients with refractory obscure IDA<sup>[17]</sup>. The frequency of CD in women with IDA is higher than in other risk groups of CD, with a female:male ratio of 2:1<sup>[4,29]</sup>, and several studies have reported that 73%-100% of IDA patients diagnosed with CD were adult pre-menopausal women<sup>[17,18,20-23]</sup>. The higher iron demand in adult pre-menopausal women as a result of menstrual loss in a condition of chronic iron malabsorption attributable to CD probably explains this higher prevalence of CD in this group of patients.

Clinicians should consider CD as a possible cause of anemia in all subjects with IDA of unknown origin, even in menstruating women. Recent guidelines from the British Society of Gastroenterology recommend that duodenal biopsies should be taken during endoscopy if no obvious case of ID can be found<sup>[30]</sup>. The treatment of IDA associated with CD is primarily a gluten-free diet with iron supplementation until the iron stores have been restored.

Table 2 Stages of cobalamin metabolism and corresponding causes of cobalamin deficiency

Stage of cobalamin metabolism	Causes of cobalamin deficiency
Intake solely through food	Strict vegetarianism without vitamin supplementation
Digestion brings into play haptocorrin, gastric secretions (hydrochloric acid and pepsin), pancreatic and biliary secretions, enterohepatic cycle	Gastrectomy; pernicious anemia (Biermer's disease); food-cobalamin malabsorption
Absorption brings into play intrinsic factor and cubilin	Ileal resection; malabsorption; pernicious anemia; Imerslund syndrome
Transport by transcobalamins	Congenital deficiency of transcobalamin II
Intracellular metabolism based on various intracellular enzymes	Congenital deficiency of various intracellular enzymes

Several studies have shown that many untreated patients with CD are folate deficient<sup>[7]</sup>. Deficiency of vitamin B12 is also common in CD and frequently results in anemia<sup>[7]</sup>. The main site of vitamin B12 absorption is the distal ileum; a small proportion is also absorbed passively along the entire small bowel. The causes of vitamin B12 deficiency in CD may include associated autoimmune gastritis, bacterial overgrowth, decreased gastric acid or decreased efficiency of mixing with transfer factors in the intestine.

## ANEMIA AND COBALAMIN DEFICIENCY

Literature of the last 10 years has provided several definitions of cobalamin (vitamin B12) deficiency, depending mainly on the population studied and on the particular assay kits used. Cobalamin deficiency is defined in terms of the serum values of cobalamin and of homocysteine and methylmalonic acid, two components of the cobalamin metabolic pathway. High homocysteine levels (hyperhomocystinemia) may also be caused by folate or vitamin B6 deficiencies, and these should be excluded before a diagnosis of cobalamin deficiency is made<sup>[31]</sup>. Accordingly, definitions of cobalamin deficiency are<sup>[32]</sup>: (1) Serum cobalamin levels < 150 pmol/L (< 200 pg/mL) with clinical features and/or hematological anomalies related to cobalamin deficiency; (2) Serum cobalamin levels < 150 pmol/L on two separate occasions; (3) Serum cobalamin 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 deficiencies); (4) Low serum holotranscobalamin levels < 35 pmol/L.

Epidemiological studies show that in the general population of industrialized countries, cobalamin deficiency has a prevalence of around 20%, ranging from 5% to 60% depending on the definition of cobalamin deficiency used<sup>[31,32]</sup>.

### Cobalamin metabolism and corresponding causes of deficiency

The metabolic pathway starts when dietary cobalamin, obtained through animal foods, enters the stomach bound to animal proteins. A typical Western diet contributes 3-30 μg of cobalamin per day towards the recommended dietary allowance of 2.4 μg/d for adults<sup>[33]</sup>. Pepsin and hydrochloric acid in the stomach split the animal protein, releasing free cobalamin. Most

of the free cobalamin is then bound to R-protein which is released from the parietal and salivary cells. Intrinsic factor is also secreted in the stomach, but its binding to cobalamin is weak in the presence of gastric and salivary R-protein. In the duodenum, dietary cobalamin bound to R-protein is joined by cobalamin-R-protein complexes that have been secreted in the bile. Pancreatic enzymes degrade both biliary and dietary cobalamin-R-protein complexes, releasing free cobalamin. The cobalamin then binds with intrinsic factor. The cobalamin-intrinsic factor complex remains undisturbed until the distal 80 cm of the ileum, where it attaches to mucosal cell receptors (cubilin) and the cobalamin is bound to transport proteins designated transcobalamin I, II and III. Transcobalamin II, although it represents only a small fraction (about 10%) of the transcobalamins, is the most important because it is able to deliver cobalamin to all cells in the body. The cobalamin is subsequently transported systemically *via* the portal system. Within each cell, the transcobalamin II-cobalamin complex is taken up by means of endocytosis and the cobalamin is liberated and then converted enzymatically into its two coenzyme forms, methylcobalamin and adenosylcobalamin. The causes of cobalamin deficiency according to the stage of cobalamin metabolism are described in Table 2<sup>[31,32]</sup>.

### Cobalamin deficiency in the elderly: clinical entities

Vitamin B12 or cobalamin deficiency occurs frequently among elderly patients, but it is often unrecognized or not investigated because the clinical manifestations are subtle<sup>[33]</sup>. However, the potential seriousness of the complications (particularly neuropsychiatric and hematological) requires investigation of all patients who present with vitamin or nutritional deficiency. In elderly patients, cobalamin deficiency is caused primarily by food-cobalamin malabsorption and pernicious anemia<sup>[31]</sup>. Food-cobalamin malabsorption accounts for about 60%-70% of the cases among elderly patients, and pernicious anemia accounts for 15%-20% of the cases. Other causes included dietary deficiencies (< 5%), malabsorption (< 5%) and hereditary cobalamin metabolism diseases (< 1%).

Intrinsic factor, which is released by parietal cells in the stomach, binds to vitamin B12 in the duodenum. This vitamin B12-intrinsic factor complex subsequently plays a role in the absorption of vitamin B12 in the terminal ileum. This mechanism is responsible for 60% of the absorption of cobalamin. In addition, an alternate system exists that is independent of intrinsic factor or

even an intact terminal ileum: cobalamin is absorbed by simple diffusion or mass action independent of intrinsic factor if 300-1000 µg/d cobalamin is administered orally or intramuscularly to patients with pernicious anemia. Approximately 1%-5% of free cobalamin (or crystalline cobalamin) is absorbed along the entire intestine by passive diffusion<sup>[33,34]</sup>.

**Food-cobalamin malabsorption:** Food-cobalamin malabsorption syndrome is characterized by the inability to release cobalamin from food or from intestinal transport proteins, particularly in the presence of hypochlorhydria, where the absorption of “unbound” cobalamin remains normal. This syndrome is defined by cobalamin deficiency in the presence of sufficient food-cobalamin intake and a negative Schilling test, where the latter rules out malabsorption or pernicious anemia. Thus in this syndrome, patients can absorb “unbound” cobalamin through intrinsic factor or passive diffusion mechanisms. The recognition of the syndrome permits new developments of oral cobalamin therapy<sup>[31-33,35]</sup>. Researchers have supported the existence of this syndrome by using a modified Schilling test, which employs radioactive cobalamin bound to animal proteins and reveals malabsorption when the results of a standard Schilling test are normal.

Food-cobalamin malabsorption is caused primarily by gastric atrophy. Over 40% of patients older than 80 years have gastric atrophy that may or may not be related to *H pylori* infection<sup>[31]</sup>. Other factors that contribute to food-cobalamin malabsorption in elderly people include: intestinal microbial proliferation; long term ingestion of biguanides (metformin) and antacids, including H<sub>2</sub>-receptor antagonists and proton pump inhibitors; chronic alcoholism; surgery or gastric reconstruction; partial pancreatic exocrine failure; and Sjögren's syndrome<sup>[31,32]</sup>.

The partial nature of this form of malabsorption may produce a more slowly progressive depletion of cobalamin than does the more complete malabsorption engendered by disruption of the intrinsic factor-mediated absorption. The slower progression of cobalamin depletion probably explains why mild, preclinical deficiency is more frequently associated with food-cobalamin malabsorption than with pernicious anemia<sup>[32,33,35]</sup>. When associated with *H pylori* infection, eradication of the infection alone may correct cobalamin levels<sup>[36]</sup>.

**Pernicious anemia:** This is the classic cause of cobalamin deficiency and one of the most frequent among elderly patients. Pernicious anemia is an autoimmune disease characterized by the destruction of the gastric mucosa, especially fundal mucosa, by a primarily cell-mediated process<sup>[31,37]</sup>. Gastric secretions are neutral to slightly acidic even in the presence of gastrin and contain little or no intrinsic factor. The disease is also characterized by the presence of two antibodies, particularly in plasma and gastric secretions: few people who do not have the disease have antibodies

(specificity 98%), but only about 50% of patients will have anti-intrinsic factor antibodies (IFA) (sensitivity 50%). Anti-gastric parietal cell (GPC) antibodies can also be measured in the serum (sensitivity > 90% but specificity 50%). Moderate hypergastrinemia, and sometimes major hypergastrinemia, have also been associated with pernicious anemia, but this is not a pathognomonic finding. A positive Schilling test with the addition of a test for IFA virtually confirms the diagnosis (specificity > 99%)<sup>[31]</sup>.

The optimal testing strategy remains unclear and considerable controversy still exists as to whether both indirect immunofluorescence testing for GPC and enzyme linked immunosorbent assay for IFA need to be performed as screening tests for pernicious anemia. It has been suggested that both autoantibodies do not need to be tested simultaneously, as the finding of IFA alone is very rare. GPC testing is therefore the most appropriate means of screening for pernicious anemia, with IFA testing as a more specific, but less sensitive test, being reserved for confirmatory testing<sup>[38]</sup>.

### Treatment

The classic treatment of cobalamin deficiency has been parenteral administration, usually by intramuscular injection, of the vitamin (in the form of cyanocobalamin and, more rarely, hydroxocobalamin or methylcobalamin). The recommended practice involves administration of 1000 µg of cyanocobalamin per day for 1 wk, followed by 1000 µg/wk for 1 mo, and then the dose is reduced to 1000 µg/mo, normally for the rest of the patient's life<sup>[31,33]</sup>.

Alternative routes of cobalamin administration have been used: oral<sup>[32-35]</sup> and nasal<sup>[32,33]</sup>. These other routes of administration have been proposed as a way of avoiding the discomfort, inconvenience and cost of monthly injections. An evidence-based analysis supports the efficacy of oral cobalamin therapy<sup>[32,33,35,39]</sup>. Sublingual therapy (2000 µg/d for 7-12 d) is another treatment modality for cobalamin deficiency, applicable in patients who refuse parenteral treatment and present either diarrhea or vomiting, and/or are unable to take oral medication<sup>[34]</sup>.

The procedure for oral cobalamin therapy has, however, not been completely validated yet in clinical practice, most notably the long-term efficacy. The current literature does not suggest a strategy in terms of the optimal form (hydroxy- or cyanocobalamin), frequency or duration of treatment. The therapeutic schema for use of oral cyanocobalamin would be<sup>[33]</sup>: (1) Intensification treatment: cyanocobalamin 1000 µg/d for 1 mo; (2) Maintenance treatment: cyanocobalamin 125-500 µg/d for intake deficiency and food-cobalamin malabsorption, and cyanocobalamin 1000 µg/d for pernicious anemia.

### ANEMIA AND GASTRIC SURGERY

Gastrectomy, previously used for peptic ulcer and its complications, is the preferred operation for palliation of gastric cancer either as total or partial gastrectomy.



Anemia is a frequent complication of gastrectomy. There are many reports addressing iron, vitamin B12 or folate deficiencies either alone or in combination after gastric surgery. The most frequent is the combination of iron and vitamin B12 deficiency<sup>[40]</sup>. Impaired absorption of iron following gastrectomy is probably due to operative bypass of the duodenum and to rapid intestinal transit. Reduction in gastric acid (necessary for the absorption of food iron), a common consequence of subtotal gastrectomy, has also been incriminated. Vitamin B12 deficiency develops as a consequence of the decreased production of intrinsic factor which is essential for vitamin B12 absorption in the lower small bowel, and also because of a defect in the separation of vitamin B12 from its transporter protein. It is a frequent deficiency which will appear 2-4 years or even longer after gastrectomy, when the vitamin stores are exhausted. Thus, gastrectomized patients should be followed carefully to avoid iron and vitamin B12 deficiencies and anemia.

Over the last few decades, bariatric surgery has been suggested as an effective treatment for obesity. There are several different procedures, including gastric bypass, laparoscopic adjustable gastric banding, vertical banded gastroplasty, biliopancreatic diversion, and biliopancreatic diversion with duodenal switch<sup>[41]</sup>. All of these procedures may be associated with long-term sequelae including iron, vitamin B12 and folate deficiencies<sup>[41,42]</sup>. ID and anemia can have a strong impact on quality of life, especially in menstruating women who make up the majority of bariatric surgery patients. Most studies report ID, ranging from 6% to 50% within months to years of follow-up<sup>[43-45]</sup>. Vitamin B12 deficiency may appear 1-9 years after gastric bypass, and its prevalence has been estimated to be 12%-33%<sup>[42]</sup>.

The main causes of ID after bariatric surgery are similar to those described after gastrectomy; diminished gastric acid secretion and exclusion of the duodenum. In gastric bypass, patients experience decreased gastric acid production in their proximal pouch and, in addition, the duodenum is excluded from digestive continuity. Thus, banding procedures which maintain digestive continuity with the antrum and duodenum are associated with low rates of ID and other nutritional deficiencies<sup>[41]</sup>. Conversely, the biliopancreatic diversion with duodenal switch, a gastric bypass procedure that may preserve some function of the proximal duodenum, may offer protection from ID, as compared with biliopancreatic diversion (which excludes the duodenum)<sup>[46,47]</sup>.

Physicians should be aware that folate, vitamin B12, and iron deficiencies occur after gastric bypass, though the time to development is variable. In an attempt to prevent nutritional deficiencies, multivitamin preparations are in general prescribed to all patients. Systematic prescription of such supplements may prevent most nutritional deficits. However, vitamin B12 and iron deficits require specific supplementation. In spite of a multivitamin, ID still develops postoperatively in some patients. Adherence to oral iron supplements is often low because of digestive intolerance, and unresponsive IDA

can be an important problem in these patients. Parenteral iron treatment is recommended in those patients refractory to oral iron supplementation. Intramuscular vitamin B12 supplementation is recommended only when a deficiency becomes clinically apparent.

## ANEMIA AND *H PYLORI* INFECTION

The current evidence regarding the association between *H pylori* infection and either ID or IDA is mainly based on case reports<sup>[48-53]</sup>, observational epidemiologic studies<sup>[54]</sup>, and a very limited number of intervention trials<sup>[55-64]</sup>. The mechanisms of *H pylori*-related anemia have not been well defined and it is not known why only a small population develops IDA despite a significant worldwide *H pylori* infection rate<sup>[65]</sup>. Individuals with increased demands of iron needed for growth and tissue building such as children, pregnant, postpartum or premenopausal women, or those with chronic inflammatory disorders such as CD, are thought to be more likely to develop IDA associated with *H pylori* infection.

*H pylori* infection has been shown to be associated with ID in asymptomatic *H pylori*-infected subjects in several cross-sectional studies. However, a great variability was found across the studies and most of these have been conducted in countries with high prevalence of *H pylori* infection. Recently, Muhsen *et al*<sup>[54]</sup> performed two different meta-analyses of observational epidemiologic studies aimed at examining the association between *H pylori* infection and either ID or IDA. These analyses yielded a 2.8-fold increased risk for IDA (95% CI: 1.9-4.2), and an 1.38-fold increased risk for ID (95% CI: 1.16-1.65) in *H pylori*-infected subjects as compared with non-infected subjects.

In clinical and interventional trials, the participants were mostly children and adolescents, and only three trials were conducted among ill people (those presenting with symptoms for investigation in clinical settings)<sup>[58,59,62]</sup>. Small sample sizes<sup>[56-59,62]</sup>, lack of control groups, and other methodological issues, including the use of validated tests to confirm active *H pylori* infection, are among factors that limit the interpretation and ability to generalize the relevance of the results of these studies<sup>[54]</sup>. Several studies reported resolution of IDA with eradication of *H pylori* infection, regardless of the absence of iron supplementation. The study of Kurekci *et al*<sup>[59]</sup>, in which all participants received *H pylori* eradication therapy without a control group, emphasized that resolution of both ID and IDA associated with *H pylori* infection may be achieved by *H pylori* eradication treatment alone. The antagonistic effect of asymptomatic *H pylori* infection on the response to iron supplementation was investigated in India among participants of a randomized, controlled trial of iron supplementation ( $n = 169$ , age 1-10 years). It was found that asymptomatic *H pylori* infection was not associated with higher rates of anemia or ID, but had a significant adverse effect on response to iron supplementation among children<sup>[53]</sup>.

Sarker *et al*<sup>[61]</sup> completed a population-based,

randomized, double-blind, and placebo-controlled trial to evaluate the response of iron *plus* anti-*H pylori* therapy in children with IDA ( $n = 200$ ). This trial was performed in Bangladesh, an area highly endemic for ID and *H pylori* infection. Results failed to observe any additional impact of combined anti-*H pylori plus* iron therapy over the iron therapy alone. These findings support those obtained by an Alaskan trial<sup>[60]</sup>, in another highly prevalent *H pylori* infection area, where a large therapeutic, randomized, controlled, unblinded trial in children ( $n = 219$ ) was performed. There were no significant differences between the intervention and the control groups in the rates of ID and anemia, during 14 mo follow-up period. The authors hypothesized that 14 mo was too early to resolve *H pylori*-induced gastric damage. Consequently, in a follow-up study performed at 40 mo, 176 children were reevaluated. Re-infection occurred among 52% of children who had initially cleared their infection. However, *H pylori*-negative children had lower prevalence of ID (RR: 0.62; 95% CI: 0.38-1.01) and IDA (RR: 0.22; 95% CI: 0.03-1.50), compared with *H pylori*-positive children. It was concluded that the resolution of *H pylori* infection for > 14 mo modestly reduced the prevalence of ID and substantially reduced the prevalence of ID and IDA<sup>[64]</sup>.

In the light of the above mentioned studies, *H pylori* infection may be considered as a risk factor for IDA, mainly in groups with high demands for iron, such as some children and adolescents. However, the relationship between *H pylori* and ID may be stronger than that described, since most of the above mentioned studies have been performed in geographical areas where both ID and *H pylori* infection are highly prevalent, and where the etiology of ID is possibly multifactorial (malnutrition, vitamin deficits, chronic parasitic infections, malaria)<sup>[66]</sup>. In this setting, poor response to *H pylori* eradication should be viewed with caution. Thus, further large and well-controlled trials will be of value. Both the impact of anti-*H pylori* therapy on the improvement of iron stores and the role the infection plays in interfering with iron supplementation in patients with IDA require further evaluation before making solid recommendations.

### The biologic mechanism

The relationship between refractory IDA and *H pylori* infection may be explained by several hypotheses. One of the possible explanations is the gastrointestinal blood loss that may range from chronic occult bleeding from discrete gastric erosions<sup>[67]</sup> to massive bleeding from peptic ulcers<sup>[68]</sup> and gastric carcinomas. However, most patients with *H pylori*-associated IDA have no evidence of gastrointestinal bleeding. Data obtained through case series and case reports mostly described patients with IDA after a comprehensive investigation including laboratory tests, imaging, and endoscopic studies, and *H pylori* gastritis was the only pathologic finding<sup>[55,61-63]</sup>.

Intragastric acidic pH plays an important role in the reduction of the ferric to the ferrous form. This reaction is enhanced by ascorbic acid. Gastric juice and mucosal ascorbic acid concentrations were significantly lowered

in *H pylori*-infected subjects as compared to those non-infected; the lower concentrations were associated with more severe gastritis<sup>[69]</sup>. This negative influence of *H pylori* on gastric ascorbic acid was reversed after eradication of the infection<sup>[70]</sup>.

The results of some studies support the hypothesis that the infection by *H pylori* influences iron absorption directly, and that iron absorption improves significantly after clearance of the infection<sup>[71,72]</sup>. It has been suggested that there is a competition for iron between the bacteria and the host. Iron is an essential nutrient for bacterial growth. Therefore, an efficient iron uptake system is an important factor for the maintenance of virulence<sup>[73]</sup>. Many pathogens use the siderophore-mediated iron acquisition system that removes iron from lactoferrin or transferrin. The regulation of iron uptake systems in *H pylori* are different from other bacteria since they are constitutively expressed, most probably as a part of the germ adaptation to the conditions in the human stomach, where iron starvation and iron overload can be encountered frequently<sup>[74]</sup>. The siderophore of *H pylori* has not yet been identified. Several studies support this hypothesis<sup>[75-78]</sup>.

Bacterial genetic factors related to *H pylori*-associated IDA pathogenesis have been studied. Non-IDA and IDA strains can be distinguished by their protein expression profiles, suggesting that polymorphisms in *H pylori* strains may be one of the factors determining the occurrence of *H pylori*-associated IDA<sup>[79]</sup>. A mutation in the *H pylori pfr* gene causing overproduction of *H pylori* ferritin protein (Pfr) has been proposed as playing a role in the imbalance of body iron<sup>[80]</sup>. However, an analysis of the complete coding region of the *pfr* gene revealed three sites of mutation with no differences in the mutation among *H pylori*-positive patients with or without IDA<sup>[80]</sup>. On the other hand, three heme-binding iron-repressible outer membrane proteins that may be involved in the uptake of heme from the host by *H pylori* were described in the presence of poor iron environment<sup>[81]</sup>. Recently, *feoB* gene product, which was regarded as a high-affinity ferrous iron transporter, was proposed as a possible pathway related to the bacterium itself; however, its relation to IDA remains unclear<sup>[82]</sup>. Although *H pylori* CagA strains were proposed to be involved in alteration of the host's iron stores in some studies, more recent work does not support this hypothesis<sup>[72,83,84]</sup>. However, seropositivity to *H pylori* CagA antibodies was inversely associated with gastric ascorbic acid concentrations<sup>[84]</sup>.

### CONCLUSION

CD should be considered as a possible cause of anemia in all subjects with IDA of unknown origin, even in menstruating women. Duodenal biopsies should be taken during endoscopy if no obvious case of IDA can be found. Vitamin B12 or cobalamin deficiency occurs frequently among elderly patients, but it is often unrecognized or not investigated because the clinical manifestations are subtle. In this age group, cobalamin

deficiency is caused primarily by food-cobalamin malabsorption (60%-70% of cases) and pernicious anemia (15%-20% of cases). The classic treatment of cobalamin deficiency has been parenteral administration of the vitamin. However, recent data support the efficacy of oral cobalamin therapy. Folate, vitamin B12, and iron deficiencies occur after gastric bypass, with an incidence ranging from 6% to 50% within months to years of follow-up. *H pylori* infection may be considered as a risk factor for IDA, mainly in groups with high demands for iron, such as some children and adolescents. However, further large and well-controlled trials will be required before making solid recommendations about *H pylori* eradication in these cases.

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