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## **Helicobacter pylori and Iron Deficiency Anemia: Guilty as Charged?** [Editorials]

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### Outline

- [REFERENCES](#)

Under normal physiologic conditions, iron homeostasis is tightly regulated. Dietary intake of heme and nonheme iron must balance daily iron losses, which are approximately 1 to 2 mg per day (1). Iron deficiency develops when iron intake is insufficient or iron absorption is inadequate, or when daily iron losses exceed the capacity of the small bowel to absorb iron. If iron balance cannot be maintained, iron stores are eventually depleted, and iron deficiency anemia develops.

Iron deficiency is the most common cause of anemia in the United States. Data from the third National Health and Nutrition Examination Survey (NHANES III) indicate that 5% to 11% of women and 1% to 4% of men in the United States are iron deficient, with 2% to 5% of women and 1% to 2% of men having iron deficiency anemia (2). In men and postmenopausal women, iron deficiency anemia may be due to chronic gastrointestinal blood loss. In contrast, iron deficiency anemia in premenopausal women is usually attributed to menstrual and pregnancy-associated iron losses. However, chronic gastrointestinal blood loss must also be considered in the differential diagnosis of iron deficiency anemia in premenopausal women (3).

Recent guidelines recommend that the upper and lower gastrointestinal tract be evaluated in patients with confirmed iron deficiency anemia, unless there is a history of significant nongastrointestinal blood loss (4). Upper endoscopy and colonoscopy should be performed to exclude lesions—such as carcinoma, large adenomas, severe mucosal erosions, ulcer disease, and vascular lesions and other sources of occult bleeding—that can cause chronic gastrointestinal blood loss. In this patient group, lesions causing chronic bleeding are more commonly found in

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the upper gastrointestinal tract than in the colon (5).

Despite a thorough endoscopic evaluation, approximately 35% of patients with iron deficiency anemia do not have a source of chronic gastrointestinal blood loss identified (5). Because iron deficiency anemia is often considered synonymous with occult gastrointestinal blood loss, nonbleeding lesions are often not considered in the differential diagnosis of iron deficiency anemia. In this issue of *The American Journal of Medicine*, Annibale et al. (6) prospectively evaluated the bleeding and non-bleeding gastrointestinal causes of refractory iron deficiency anemia. Among 668 patients referred to a university hematology department, 71 patients without gastrointestinal symptoms underwent esophagogastroduodenoscopy, with gastric (antrum and body) and duodenal biopsies as well as colonoscopy. A potential cause of iron deficiency anemia was detected in 85% of patients, including 37% of patients with bleeding lesions and 51% with nonbleeding sources. The bleeding lesions identified in this study are well-known causes of occult gastrointestinal bleeding and iron deficiency anemia (5). The non-bleeding lesions, which are often overlooked in patients with iron deficiency anemia, included atrophic gastritis in 27% of patients, *Helicobacter pylori*-associated chronic gastritis (in the absence of mucosal erosions, ulcers, or other potential sources of gastrointestinal blood loss) in 18%, and celiac disease in 6%. The cross-sectional design of this study posed inherent limitations in establishing a causal relation between *H. pylori* and iron deficiency anemia. Although these findings are very interesting, the study design would have been strengthened by the inclusion of an appropriate age- and sex-matched control group without iron deficiency anemia.

Celiac disease results in malabsorption of iron and is a well-described cause of iron deficiency anemia, especially among persons from Northern Europe. The British Society of Gastroenterology recommends that small bowel biopsies be obtained during endoscopy because 2% to 3% of patients with iron deficiency anemia have celiac disease (4). Although this is the standard of care in Europe, routine performance of small bowel biopsy in patients with iron deficiency anemia in the United States may not be cost effective because of the much lower prevalence of celiac disease in this country (3).

Chronic atrophic gastritis can be classified as body predominant (type A, or autoimmune) and antrum predominant (type B, or nonautoimmune). Body-predominant atrophic gastritis involves the fundus and body of the stomach, spares the antrum, and is associated with pernicious anemia and hypochlorhydria or achlorhydria (7). In contrast, antrum-predominant atrophic gastritis involves the body and fundus of the stomach in addition to the antrum, and is associated with hypogastrinemia because of destruction of gastrin-producing cells in the antrum (7). Because gastric acid is critical for the absorption of iron, both types of atrophic gastritis can cause malabsorption of iron and iron deficiency anemia. Therefore, some investigators recommend that gastric biopsies be taken to exclude chronic atrophic gastritis in patients with no other explanation for iron deficiency anemia (8).

*Helicobacter pylori* are gram-negative, urease-producing organisms that are common throughout the world. Infection with *H. pylori* causes chronic gastritis. Although chronic infection is usually asymptomatic, it may predispose infected persons to gastric and duodenal ulcers, gastric cancers, and mucosal-associated lymphoid tissue lymphomas. These lesions can cause chronic gastrointestinal bleeding, resulting in iron deficiency anemia. In addition, *H. pylori* infection may be associated with iron deficiency anemia and hemorrhagic gastritis in Alaskan Yupik Eskimos (9). However, Annibale et al. (6) report that *H. pylori*-associated chronic gastritis is a cause of refractory iron deficiency anemia in the absence of bleeding lesions in 18% of their patients.

These findings raise several important questions. First, does *H. pylori* infection really cause anemia in the absence of bleeding? Second, if *H. pylori* is associated with iron deficiency anemia, why does anemia develop in only a small percentage of *H. pylori*-infected persons? Third, how does *H. pylori* infection cause iron deficiency anemia? Finally, does eradicating *H. pylori* resolve iron deficiency anemia?

Several cross-sectional serologic surveys have been performed to determine whether there was an association between *H. pylori* infection and iron deficiency anemia. In a study of 2794 Danish adults, Milman et al. (10) reported that ferritin levels were significantly lower in patients with immunoglobulin G antibodies to *H. pylori* than in noninfected patients; there was no difference in hemoglobin levels between the two groups. In a recent study of 1806 adults in Germany, Berg et al. (11) noted that *H. pylori* infection was associated with a 17% decrease in serum ferritin levels. Collett et al. (12), however, found no substantial differences in serum ferritin levels between *H. pylori*-infected and noninfected patients. Although two of these studies showed a statistically significant association between *H. pylori* infection and decreased serum ferritin concentrations, they did not adjust for confounding factors. Furthermore, none of these studies used endoscopy to exclude other gastrointestinal causes of iron deficiency, making it difficult to determine whether *H. pylori* caused the decrease in serum ferritin levels or whether this organism was just an "innocent bystander."

Although *H. pylori* infection is common, iron deficiency anemia does not develop in all infected patients. The ability to cause iron deficiency anemia does not appear to be related to the virulence of the organism because ferritin levels did not differ between patients infected with cytotoxin-associated gene A (CagA)-positive and CagA-negative strains of *H. pylori* (11). It may be possible that other bacterial virulence factors or host factors are responsible for the development of iron deficiency anemia. Children and premenopausal women have smaller iron stores and are therefore at increased risk of iron deficiency. For this reason, they may also be more vulnerable to *H. pylori*-induced iron losses. Interestingly, the majority of patients with *H. pylori*-associated chronic gastritis and iron deficiency anemia in the present study by Annibale et al. (6) were premenopausal women.

Although the mechanisms by which *H. pylori* infection can cause iron deficiency anemia are still unclear, several possibilities have been suggested. For example, *H. pylori* may be an etiologic factor in the development of atrophic body gastritis (13). Patients with atrophic body gastritis may have hypochlorhydria or achlorhydria, resulting in decreased iron absorption. *H. pylori* may cause iron deficiency anemia by competing with the host for iron absorption. Iron is an essential growth factor for all bacteria, including *H. pylori*, which contains a system of iron-repressible outer membrane proteins that may be involved in iron uptake as well as a system for intracellular storage of iron that consists of the ferritin-like molecules Pfr and NapA (14). *Helicobacter pylori*-associated gastritis has also been associated with decreased levels of ascorbic acid—a potent enhancer of nonheme iron absorption—in gastric juice that are reversible after the infection is eradicated (15).

If *H. pylori* infection is associated with iron deficiency anemia, then eradicating the organism should increase iron stores and resolve the anemia. In an earlier study, Annibale et al. (16) tested this hypothesis in 30 asymptomatic patients with iron deficiency anemia. Twelve months after treatment of *H. pylori* and discontinuation of oral iron therapy, 92% of patients recovered from anemia. *Helicobacter pylori* eradication was unsuccessful in 3 patients; all 3 had a further decline in serum ferritin levels, and 1 had slightly lower hemoglobin levels (16). In a randomized, placebo-controlled trial of *H. pylori* eradication in 43 children, Choe et al. (17) showed that eradication was associated with a substantial increase in hemoglobin levels. Although the results

of this study are promising, the sample size was very small, and the applicability of these findings to adults with iron deficiency anemia requires further investigation. It will be interesting to see whether the incidence of iron deficiency anemia decreases as the number of patients treated for *H. pylori* infection increases.

Although these studies further support a possible causative role of *H. pylori* in iron deficiency anemia, they do not prove that the organism is a cause of the anemia. Demonstrating a temporal relation between acquiring *H. pylori* infection and developing iron deficiency anemia will be critical to establishing causality. Prospective cohort studies to determine the incidence of iron deficiency anemia among *H. pylori*-infected patients compared with noninfected patients would strengthen the association between the infection and the anemia. These trials would be difficult and costly to perform, however. In addition, well-designed, randomized, double-blind, placebo-controlled trials with a sufficient number of subjects and long-term follow-up are needed to test the hypothesis that eradicating *H. pylori* resolves iron deficiency anemia. Until such evidence is available, the jury finds the defendant, *H. pylori*, not guilty.

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