

Iron-deficiency Anemia

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One of the most common causes of iron-deficiency anemia (IDA) in men and postmenopausal women in the United States is gastrointestinal blood loss, and therefore IDA is a frequent reason for referral to a gastroenterologist. It is important to begin the workup with confirmation of the diagnosis of IDA and to exclude other causes of anemia, including nongastrointestinal sources of blood loss. We review the mechanisms and regulation of iron absorption, storage, and iron loss, an understanding of which can be particularly useful in evaluating patients with concomitant chronic inflammatory diseases, end-stage renal disease, and patients receiving erythropoietin during chemotherapy. A major component of the evaluation of IDA is gastrointestinal investigation, usually beginning with bidirectional endoscopy, including colonoscopy and esophagogastroduodenoscopy. If patients have a negative lower and upper gastrointestinal evaluation, examination of the small bowel with enteroscopy and/or capsule endoscopy must be considered. The standard treatment of IDA requires correction of the underlying abnormality and oral iron replacement therapy, but in certain cases will require parenteral iron replacement. We will review the physiology, differential diagnosis, and evaluation of IDA, including the appropriate gastrointestinal evaluation of this disease process, along with a concise review of iron replacement therapy.

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The diagnosis of iron-deficiency anemia (IDA) requires the laboratory diagnosis of concomitant anemia and iron deficiency. Anemia is defined by the World Health Organization (WHO) as a hemoglobin concentration of less than 13 mg/dL in men and less than 12 mg/dL in women.¹ This definition can be inadequate in particular clinical situations. For example, severely volume-depleted anemic patients can have normal hemoglobin concentrations. Pregnant patients expand their plasma volume by 50%, and their red blood cell volume by 25%, resulting in (fictitious) dilutional anemia. Patients living at high altitudes or with chronic lung disease can have high baseline hemoglobin concentrations and can have significant blood loss before becoming anemic as defined by the WHO.

The gold standard for the diagnosis of iron deficiency is the absence of iron staining (Prussian blue stain) on bone marrow biopsy. In clinical practice, this invasive test is often replaced by

evaluation with several more readily available laboratory parameters. The classic hallmarks are a low serum ferritin (<20 ng/L), a low serum iron (<33 µg/dL), and a high serum total iron-binding capacity (>400 µg/dL), often with a low mean corpuscular volume (MCV < 80 fL). The best laboratory test to make the diagnosis of IDA is the serum ferritin, which, when less than 15 ng/L, has a specificity of 99% for the disease. However, a low serum ferritin is not the most sensitive marker of IDA (59% at this cutoff value),² and IDA is often present at borderline-low ferritin levels in the 20 to 45 ng/L range.

Iron deficiency is less common in the United States than it is worldwide, but it is remarkably frequent despite the iron-rich diet available to Americans. Iron deficiency without anemia occurs in 11% of women and 4% of men, and full-blown IDA was present in 1% to 2% of adults in the National Health and Nutrition Examination Survey (1988 to 1994).³ The most common cause of IDA in the United States is menstrual and/or pregnancy associated blood loss. Iron deficiency without anemia is also prevalent in premenopausal women, who frequently have difficulty maintaining their iron stores in the face of chronic monthly bleeding.

Physiology of Iron Deficiency Anemia

Iron is a critical element in human metabolism that is not excreted. Under normal circumstances, iron absorption and iron loss are tightly coupled (Fig 1). Iron losses in the absence of bleeding, which occur through sweat, shedding of skin cells, and sloughing of gastrointestinal epithelial cells, amount to approximately 1 to 2 mg/d from a body store of approximately 4,000 mg. Menstrual losses can add another 30 mg/mo,⁴ and fetal needs during pregnancy can require an additional total of 1,000 mg, leading to more frequent iron deficiency in women. Patients on hemodialysis can also lose excessive amounts of iron, averaging 2,000 mg/yr,⁵ invariably leading to IDA in the absence of replacement therapy.

Humans are very efficient at salvaging iron from aging red blood cells (RBCs) because the bone marrow needs 20 mg of iron each day to replace the approximately 1% of RBCs turned over each day. This efficient conservation can lead to iron overload and multisystem disease in individuals who have excessive iron uptake, as in hereditary hemochromatosis or excessive blood transfusion.

Total body iron stores are distributed into several compartments. In iron-depleted individuals, the circulating red blood cell compartment contains 1,800 mg in hemoglobin, the liver stores approximately 1,000 mg as ferritin, and macrophages contain another 600 mg. Muscle myoglobin accounts for approximately 300 mg, whereas the bone marrow stores another 300 mg. Only approximately 3 mg exists in the transport form, transferrin, in the circulation (Fig 1).

Iron deficiency can occur as a result of either inadequate absorption or excessive loss of iron, although gastrointestinal

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Supported by the Burroughs Wellcome Fund (DCR is the recipient of a BWF Translational Scientist Award).

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1096-2883/03/0503-0007\$30.00/0

doi:10.1053/j.tgie.2003.08.002

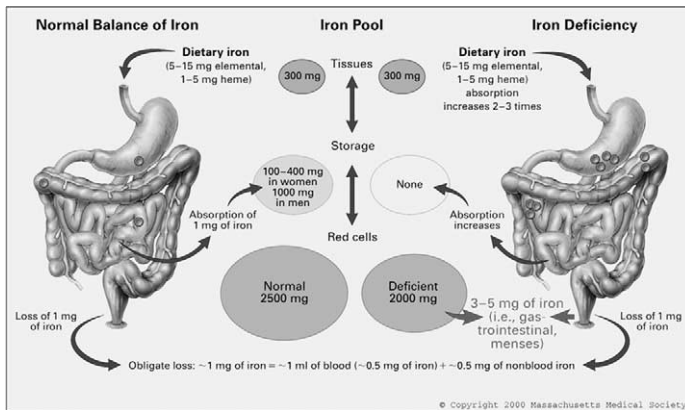


Fig 1. Gastrointestinal blood loss and iron balance. Normal obligate daily iron loss is from the following: (1) blood loss (presumably from gastrointestinal mucosal microerosions or microulcerations) and (2) iron in sloughed gut epithelial cells. Total daily iron loss is thus approximately 1 mg. The usual Western diet contains mostly elemental iron of which about 10% is absorbed. Heme-iron, derived primarily from myoglobin in meats, is preferentially absorbed and accounts for 60% to 80% of the iron absorbed per day. Under normal circumstances, iron homeostasis is tightly regulated and daily iron loss is precisely balanced by iron absorption. Iron deficiency results only when the dynamic but limited absorptive capacity of the small intestine is exceeded by iron loss. The time required to develop iron deficiency depends on the size of initial iron stores, the rate of bleeding, and intestinal iron absorption. Iron deficiency generally occurs only with continued loss of over 5 mL of blood daily. Importantly, anemia is a late manifestation of the iron-depleted state. (Reprinted with permission from Rockey DC: Primary care: Occult gastrointestinal bleeding. *N Engl J Med* 341:38-46, 1999. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

blood loss is the most common cause of iron deficiency anemia in men and postmenopausal women.⁶ Iron is absorbed primarily in the duodenum and proximal jejunum, although the process is relatively inefficient. Heme iron, typically found in meat, is absorbed at a rate of about 30% of intake (typically 1-2 mg in the United States), whereas inorganic iron is absorbed at only a 10% rate of intake (10-15 mg in the United States), producing a net absorption of 1 to 2 mg/d.⁷

However, the inorganic absorption of iron can be up- or downregulated in the duodenal wall through regulation of a number of iron transport proteins. On the luminal side, ferric (3+) iron is converted to ferrous (2+) iron by duodenal cytochrome b; subsequently, the divalent metal transporter 1 (DMT1) transports ferrous iron from the duodenal lumen into the intestinal epithelial cell. On the basolateral side, ferroportin 1 (FP1) transports ferrous iron out of the cell, and Hephaestin (Hph) converts ferrous (2+) iron back to the ferric (3+) form when it enters the circulation and is bound by transferrin for transport (Fig 2).

This transport mechanism can be regulated by 5 variables. First, duodenal epithelial cells themselves decrease absorption shortly after ingestion of large amounts of dietary iron (the dietary regulator). This is thought to be because of high concentrations of intracellular iron in the epithelial cell and returns to normal after a few days.^{8,9} Second, the “iron stores regulator” senses total body iron through unclear mechanisms and drives increased expression of DMT1. This leads to an increase in iron absorption by approximately 3-fold in iron deficiency or when

there is inappropriate regulation of iron absorption such as in hereditary hemochromatosis.¹⁰ Third, an erythropoietic regulator increases iron absorption in response to rapid erythropoiesis and can increase iron absorption approximately 5-fold through mechanisms that have not yet been defined.¹¹

Acute hypoxia is a fourth factor that can acutely increase iron absorption,^{8,12,13} a fifth factor, chronic inflammation, appears to decrease the absorption of iron in the duodenum via DMT1 and FP1 downregulation.¹⁴⁻¹⁶ This appears to be mediated through the iron regulatory hormone hepcidin,¹⁷ which is induced during systemic infection, and is associated with decreases in DMT1 and FP1. Recent evidence suggests that hepcidin may also play a signaling role in regulating iron absorption in response to changes in iron stores.¹⁸

However, even with maximal upregulation and adequate dietary supplementation, the duodenum can absorb a maximum of 5 to 7 mg/d, less than 0.2% of the total body iron stores.^{19,20} Thus, even small amounts of blood loss can create an iron-deficiency state. Iron losses initially deplete the storage pool in the liver and macrophages, without causing an anemia. Continued iron losses produce a normocytic anemia without reticulocytosis. Further iron losses will produce classic hypochromic, microcytic anemia.

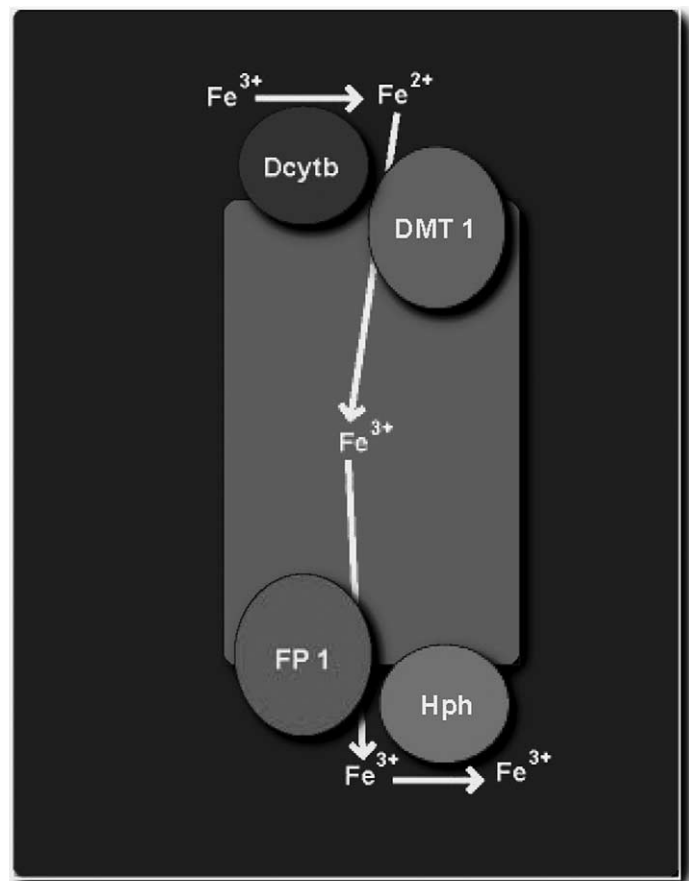


Fig 2. Duodenal iron transport. On the luminal side, ferric (3+) iron is converted to ferrous (2+) iron by duodenal cytochrome b (Dcytb). DMT1 then transports ferrous iron from the duodenal lumen into the intestinal epithelial cell. On the basolateral side, FP1 transports ferrous iron out of the cell, and Hephaestin (Hph) converts ferrous (2+) iron back to the ferric (3+) form when it enters the circulation and is bound by transferrin for transport.

TABLE 1. Common Gastrointestinal Lesions in IDA

Lesion	Rate per 100
Colon polyps	18.6
Esophagitis	18.3
Gastritis	13.0
Colon cancer	12.7
Angiodysplasia	12.3
Gastric Ulcer	9.6
Duodenal Ulcer	9.3
Gastric Cancer	3.1
Colitis	1.9
Celiac sprue	1.2

NOTE. These rates represent a weighted average of 5 prospective studies of IDA with bidirectional endoscopy.^{28,41-44} Of note, the first 3 studies did not routinely biopsy for celiac sprue, and Rockey's 1998 study included patients with + FOBT alone.

Differential Diagnosis of Iron Deficiency Anemia

When a patient is referred for evaluation of IDA, it is essential that the diagnosis be confirmed. Both anemia (hemoglobin < 13 for men, < 12 for women) and iron deficiency (ferritin < 45 ng/L) should be present. In the absence of iron deficiency, other causes of anemia, including the anemia of chronic disease, thalassemia, hemolysis, and causes of erythropoietic failure should be considered. When iron deficiency without anemia is found, the patient may merely be at an early stage of iron deficiency, and both blood loss and chronic iron malabsorption because of celiac sprue should be considered.²¹ It is also helpful to assess the chronicity of IDA if records are available. It is not uncommon in menstruating women for chronic IDA to have been present for many years before evaluation.

The presence of IDA that is new or of indeterminate duration should not eliminate the consideration of additional causes of anemia. Many elderly patients have multiple reasons for anemia, and IDA may overlap with anemia of chronic disease, thalassemia, sickle cell anemia, hemolysis, or any other cause of anemia. An assessment of blood loss from sources other than the gastrointestinal tract must be performed. Patients can frequently have significant blood losses from menstruation, surgery (losses are frequently underestimated), retroperitoneal or other obscure bleeds, and occasionally from gross hematuria.

Evaluation of IDA

If IDA is present and there is no other obvious source of blood loss, the current standard of care mandates that the gastrointestinal tract be investigated. Common gastrointestinal lesions found in 5 prospective studies of bidirectional (upper and lower) endoscopy are listed in Table 1 by weighted average. Large colon adenomas (18.6%) and esophagitis (18.3%) were the most common lesions found. Examples of endoscopic views of lesions typically associated with IDA are presented in Figure 3A through E. Although not all studies have identified significant lesions in both the upper and lower GI tract, the aggregate data suggest that dual lesions were found in 10.8% of the patients evaluated with bidirectional endoscopy. A critical aspect of managing patients with IDA is to appropriately judge whether blood loss can be ascribed to specific lesions. Indeed, many gastrointestinal tract lesions have been shown to lead to significant amounts of blood loss²²; however, it is clear that other lesions, especially trivial lesions, do not bleed significantly.

The evaluation should begin with a careful history and physical examination. Important history includes that of bleeding from the gastrointestinal (GI) tract, the nasopharynx, the urinary tract, from surgery, into atypical areas (ie, thigh, soft tissues), menstrual bleeding, and frequent repeated phlebotomy. Unfortunately, menstrual bleeding histories are often unreliable,²³ but occasionally non-GI sources of bleeding can be identified. Personal history of nonsteroidal anti-inflammatory drug use, liver disease (gastropathy, gastric antral vascular ectasia [GAVE], varices), and kidney disease (platelet dysfunction, angiodysplasia) can be useful in focusing the differential. A family history of bleeding diathesis or vascular malformations can be helpful.

Symptoms of IDA can include fatigue, dyspnea, weakness, headache, and exercise intolerance. An unusual symptom that requires direct questioning to elicit is pica, an appetite for nonfood substances, often including ice or clay, which has often been described in patients with iron deficiency, affecting greater than half of the patients with IDA in 1 study.²⁴

Physical signs specific for IDA are uncommon but can include paleness with significant anemia, angular cheilitis, koilonychia (spoon nails), esophageal webs, and atrophic glossitis with dysphagia and dry mouth (Plummer-Vinson syndrome). Laboratory evaluation, if not already performed, should include a complete blood count with MCV and mean corpuscular hemoglobin (MCH), ferritin, iron and total iron-binding capacity, reticulocyte count (for bone marrow response), lactate dehydrogenase (LDH), and haptoglobin (for hemolysis).

In interpreting the laboratory results, ferritin is the most appropriate starting point. A ferritin of less than 15 ng/mL is 99% specific but is only 59% sensitive for the diagnosis of IDA.² A cutoff of less than 31 ng/mL provided 92% sensitivity and 98% specificity in an American population,²⁵ although others have suggested that the cutoff for iron deficiency anemia be less than 45 ng/mL in the elderly.²⁶ Ferritin is an acute-phase reactant that will be elevated in patients with inflammatory disease, and such a potential elevation should be considered in evaluating patients with inflammatory diseases. If an MCV less than 80 fL is found in patients of Mediterranean or African descent, thalassemia should be considered and hemoglobin electrophoresis performed. The most definitive diagnostic tool for diagnosis of IDA is replacement therapy. In patients with IDA, adequate iron replacement should result in an increase in the hemoglobin concentration by 0.1 mg/dL/d.

In the absence of obvious sources of blood loss, the most common cause of IDA in men and in postmenopausal women is GI tract blood loss. The majority of causes of blood loss within reach of an gastroscope or colonoscope can be effectively treated,²⁷ and these can include early-stage, treatable malignancies that should not be missed. In deciding how best to pursue the workup of gastrointestinal tract causes of IDA, prospective series have provided us with valuable information. Upper gastrointestinal tract lesions are found within reach of an esophagogastroduodenoscopy (EGD) scope in 29% to 56%, and colonic lesions are found in 22% to 30%. Importantly, lesions in both upper and lower gastrointestinal tract have been found in 1% to 17%, and no bleeding source was found in 29% to 52%.^{28,29}

GI symptoms that are suggestive of either an upper or lower gastrointestinal source are somewhat helpful in directing the endoscopist where to start the evaluation but are not sufficiently specific to rule out a lesion elsewhere in the GI tract.^{28,30}

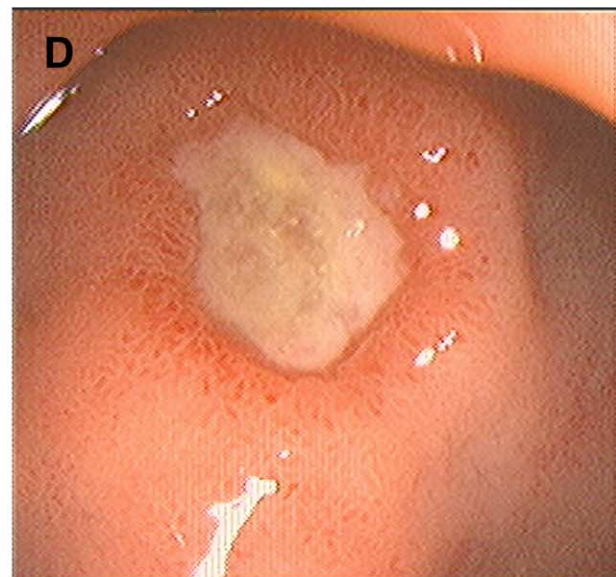
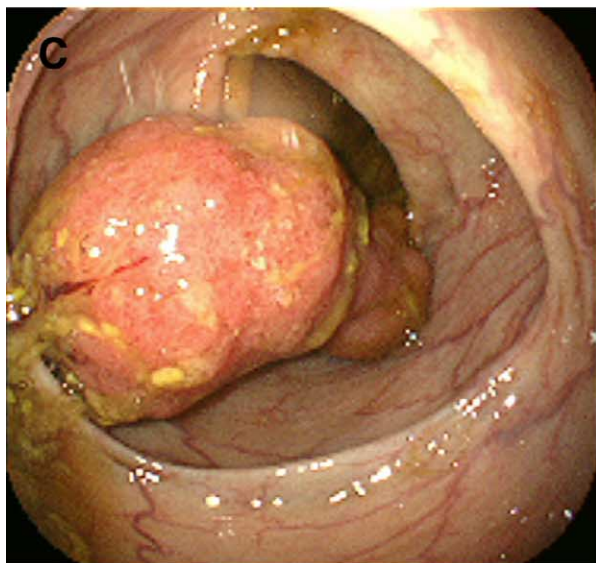
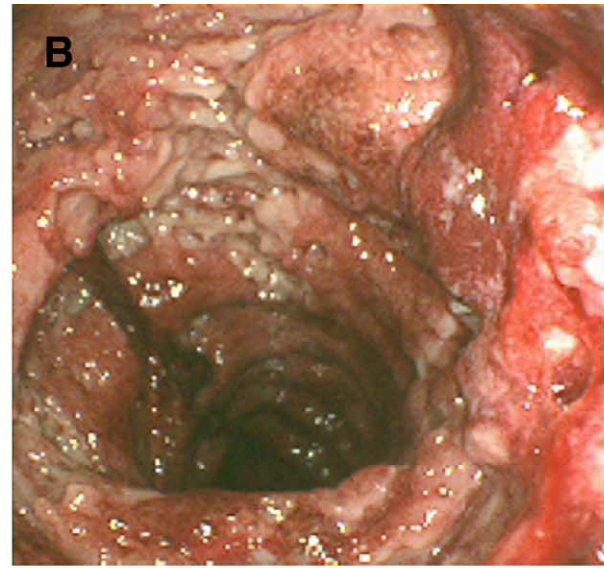
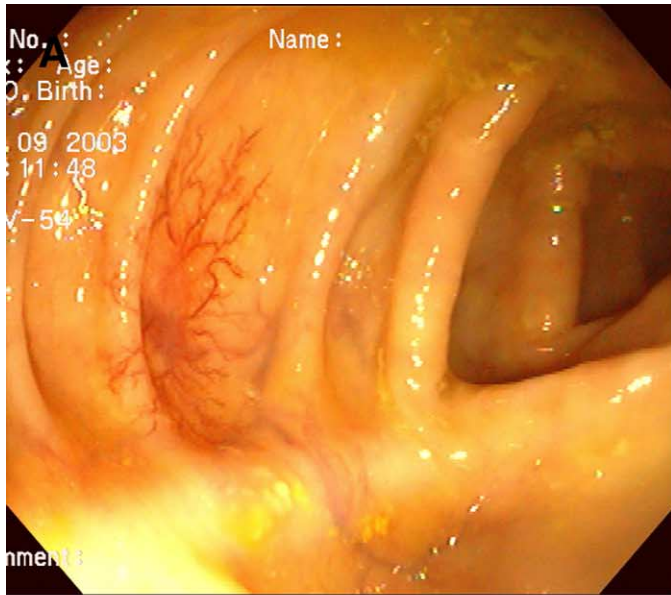
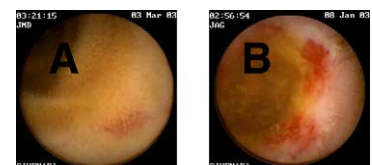


Fig 3. Common gastrointestinal tract lesions that cause IDA. A number of lesions can be associated with chronic bleeding from the GI tract. Several representative examples are shown. (A) An arteriovenous malformation in the colon. (B) Colitis is shown. (C) A colon mass is shown. (D) A large duodenal ulcer is evident. (E) Erosive gastritis is shown. All of these lesions are potentially consistent with chronic blood loss.

Fig 6. Capsule endoscopy views of small bowel lesions potentially responsible for IDA. Representative examples are shown. (A) An arteriovenous malformation of the jejunum is shown, and in (B) an example of ileal Crohn's disease is shown. As in Figure 3, these lesions are potentially consistent with IDA.



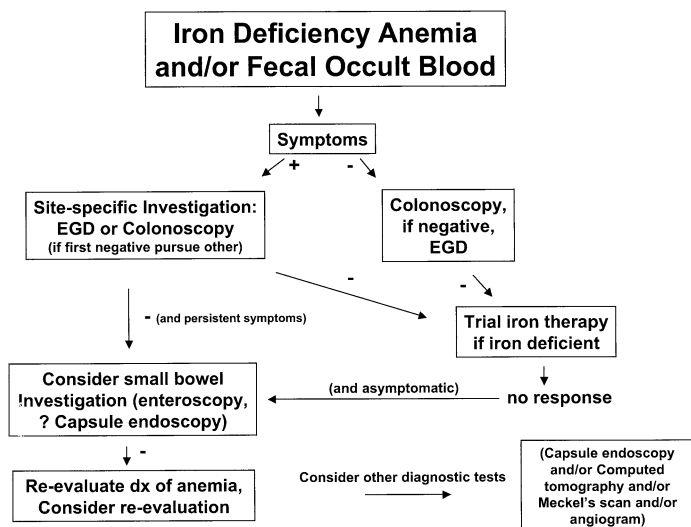


Fig 4. A proposed algorithm for evaluation of IDA in men and postmenopausal women. The evaluation should begin with a careful history and physical examination. Symptoms can be used to help triage the evaluations. The role of wireless capsule endoscopy has not been fully determined.

In recent prospective studies of bidirectional endoscopy for IDA in asymptomatic patients, 44% to 85% had a causative lesion found, 8% to 29% had lesions on both upper and lower examinations, and in 1 study 23% had cancer of the GI tract.^{27,31,32}

These data lead us to recommend that in patients with IDA, upper and lower gastrointestinal evaluation should be scheduled to take place at the same sitting. Furthermore, the initial examination can be tailored to the presence of specific clinical symptoms and signs. If a major lesion (ie, colorectal cancer or gastric cancer) is identified on the first examination, and the endoscopist is certain that it is consistent with the clinical presentation, the second procedure can be reasonably avoided. An algorithm for the evaluation of IDA in men and postmenopausal women is presented in Figure 4.

Controversies: Evaluation of IDA in Premenopausal Women

In women who have not yet reached menopause, the most common cause of IDA is chronic menstrual losses and the iron deficits caused by pregnancies. It is estimated that 11% of the premenopausal women in the United States have IDA.³ Many of these patients will be young and asymptomatic and are unlikely to have GI lesions, and the need for endoscopy is controversial. On one hand, the likelihood of identifying a lesion is small; however, the available data suggest that even young asymptomatic women with IDA may harbor significant GI tract lesions.

A retrospective study of 111 premenopausal women who underwent endoscopy for IDA²³ found significant lesions in 20% and found an increased rate of significant lesions in patients with gastrointestinal symptoms, positive fecal occult blood testing, or weight loss. Of note, 18 patients had barium studies of the small bowel after negative endoscopy, and no lesions were found. A similar study by Bini et al³³ retrospectively evaluated 186 premenopausal women with IDA who had bidirectional endoscopy, and upper GI lesions were found in 6% and lower GI lesions were found in 6%, with no synchronous lesions. The presence of a positive fecal occult blood test

(OR = 10), a hemoglobin of less than 10 g/dL (OR = 6.1), or abdominal symptoms (OR = 3.1) were the best predictors of the presence of a GI lesion in a premenopausal woman with IDA. Long-term follow-up (mean 33.1 months) was available on 96% of the patients without an identified bleeding source. IDA resolved with oral iron supplementation in 92% of these patients.

Another retrospective study of 241 women with IDA included postmenopausal women and found GI lesions in 49%.³⁴ Risk factors associated with GI lesions were abdominal symptoms (OR 8.3), age greater than 50 (OR 4.4), and hemoglobin less than 9 g/dL (OR 3.0). The negative predictive value of the absence of these factors was 93.5%.

From these studies, it is clear that the majority of premenopausal women with IDA do not have gastrointestinal lesions. However, we recommend selective use of bidirectional endoscopy in this population based on the following clinical and laboratory "red flags": abdominal or gastrointestinal symptoms, positive FOBT, age greater than 50, hemoglobin less than 9 g/dL, overt bleeding, family history of GI malignancy, or weight loss.

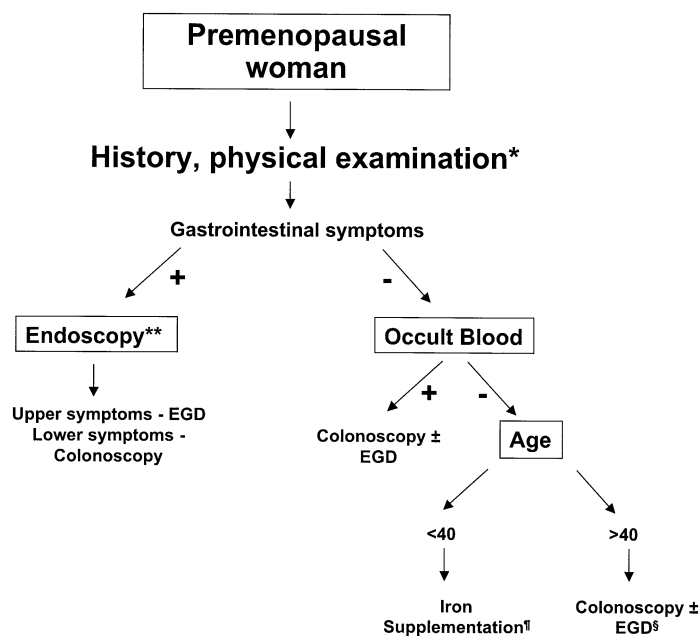


Fig 5. A proposed algorithm for evaluation of IDA in premenopausal women. A careful history and physical examination is essential for all women with IDA. Fecal occult blood testing should be considered in all patients with IDA. Patients with gastrointestinal symptoms or fecal occult blood should undergo evaluation. Young women without symptoms or occult blood can probably be followed carefully on iron replacement therapy. Small bowel barium studies should be reserved for patients with a high clinical suspicion of small bowel disease. The role of capsule endoscopy in this patient population is currently unknown. *Serologic tests for sprue should be considered in patients not of Asian or African-American descent. **Endoscopy should be pursued regardless of the presence or absence of FOB. In patients in whom a finding can not be identified after upper or lower endoscopy, examination of the other portion (ie, upper or lower) of the GI tract should be considered. †A defined trial of iron therapy is recommended, if there is no response to iron or if fecal occult blood or symptoms develop, endoscopy should be pursued. §In patients over 40, colonoscopy should be considered mandatory, whereas EGD is optional because of the relatively low prevalence of gastric malignancy in this group.

For the remaining majority of patients, a 4-week therapeutic trial of oral iron supplementation should be sufficient to raise the hemoglobin by 2 g/dL. If the expected rise in hemoglobin does not occur, bidirectional endoscopy should be pursued. (An algorithm specifically for premenopausal women is presented in Figure 5.) A prospective study of the sensitivity and specificity of these red flags for significant GI lesions, and long-term outcomes of this approach would be a valuable addition to the field.

Controversies: Evaluation of IDA in the Elderly

In the elderly, iron deficiency can be an early sentinel of gastrointestinal malignancy. A colonoscopic evaluation is important to rule out colon cancer, but upper gastrointestinal tract evaluation will identify lesions in up to 54% of iron-deficient elderly patients.³⁰ In this study of 151 elderly (>70 years old) patients with iron deficiency, 22% had a lower gastrointestinal lesion, and 9.5% of those with a benign upper gastrointestinal lesion had a synchronous colon cancer. The presence of anemia made a lower gastrointestinal lesion twice as likely (32% v 16%) but did not increase the rate of upper gastrointestinal lesions (49% v 56%). Neither nonsteroidal anti-inflammatory drug use, GI symptoms, or FOBT predicted lesions in this elderly population with iron deficiency. The available data suggest that evaluation of iron deficiency anemia in the elderly should start with bidirectional endoscopy, just as in younger patients, and that, in the elderly, synchronous lesions in upper and lower tracts may be more common.

Controversies: Whether (and How) to Explore the Small Bowel?

If examination of the upper and lower gastrointestinal tracts is negative, how far should small bowel evaluation go? Options include push enteroscopy, sonde enteroscopy, capsule endoscopy, and intraoperative endoscopy. Studies that have followed up patients for long periods of time after negative complete upper and lower endoscopic evaluation for IDA indicate that most are cured by empiric oral iron supplementation and, moreover, that their long-term prognosis is good.^{31,33,35,36} The importance of searching for small bowel lesions in patients with IDA but without a readily identifiable lesion at the time of upper and lower endoscopy is extremely controversial because in the majority of patients with negative upper and lower gastrointestinal tract evaluation, oral iron therapy leads to correction of IDA. In addition, it has been shown that patients with lesions found in the small bowel had no improvement in rebleeding rate compared with those without lesions found on enteroscopy.³⁷ At 2-year follow-up, 28% of patients with no lesions on enteroscopy rebled, 24% of those with nonangiodysplasia lesions rebled, and 56% of those with angiodysplasia rebled. This may be because in part of the inability to survey the entire small bowel and in part because of the difficulty in permanently treating small bowel lesions, particularly angiodysplasia. Additionally, in 42% of patients with IDA undergoing small bowel enteroscopy after negative upper and lower tract evaluation, a cause for bleeding was identified, but whether identification of these lesions is clinically meaningful (ie, it allows interventions that change the clinical outcome) remains unproven.

The newest tool in the evaluation of the small bowel is the wireless capsule,³⁸ which has been compared with push en-

teroscopy in a pilot study, and a statistically significant diagnostic improvement was not found.³⁹ Wireless capsule endoscopy (WCE) is an intriguing new option in the evaluation of iron deficiency anemia because it can visualize extensive portions of the small bowel beyond the view of standard endoscopes (it is more likely to be of benefit for patients with overt bleeding, for whom surgery can be a reasonable therapy). Examples of capsule endoscopy findings are presented in Figure 6A and B. At this point, data supporting the use of WCE in IDA are limited, without any prospective data on the effect on outcomes. On one hand, it seems likely that making a diagnosis such as a neoplasm or Crohn's disease with WCE would change outcomes. On the other hand, making a diagnosis of angiodysplasia with WCE would be unlikely to change outcomes because effective therapy for angiodysplastic lesions beyond the reach of a therapeutic endoscope is not readily available. Indeed, in our experience, capsule evaluations of patients with obscure occult IDA are low yield and previous data suggest that most of these patients will improve with iron supplementation; furthermore, the push enteroscopy literature suggests that diagnosing a small bowel cause of bleeding does not necessarily improve outcomes. Prospective trials of WCE in obscure-occult IDA that examine whether this diagnostic strategy changes important clinical endpoints (mortality, hospitalization, transfusion requirements) are needed.

Treatment of IDA

The first element in the management process is to identify and treat any lesions found on EGD and colonoscopy to stop blood loss. Once this is accomplished (or no lesion is identified), iron repletion should be undertaken. It is helpful to calculate the iron deficit to appreciate the length of time required to replete a significant iron deficiency by mouth. An example is presented in Table 2. A patient with significant blood loss can require almost a year to replete both the lost RBC mass and the iron stores in liver and macrophages. It is important to note that transfusion of 1 unit of packed red blood cells contains 250 mg of iron, nearly all of which will be salvaged. However, repletion by transfusion without a clinical indication is unwise because the risks of transfusion reactions and infections far outweigh the risks of oral iron therapy.

Oral iron replacement is generally performed with ferrous sulfate, 300 mg tablets containing 60 mg elemental iron, taken 1 to 3 times per day. This formulation can cause a high rate of nausea and GI distress and should be titrated to tolerable levels. It should be emphasized that no more than 5 mg elemental

TABLE 2. Calculating Iron Deficit and Replacement in IDA

1. Assume a 70 kilogram patient with hemoglobin of 9.0.
2. Their blood volume is 65 ml/kg, or (65 × 70) 4550 mL.
3. Their hemoglobin deficit is 5 g/dL (14 - 9), so the Hgb deficit in grams is (5 × 45.5) 227.5 g.
4. There are 3.3 mg of iron in each gram of Hgb, so the iron deficit is (3.3 × 227.5) 750.75 mg
5. At a rate of 5 mg/day, it will take (750.75/5) 150 days to replace the RBC mass deficit in a compliant patient, and
6. An additional 200 days (5 mg × 200 = 1,000 mg) is required after the Hgb is normalized to replete the liver and macrophage stores. In this example, 350 days, or approximately one year of oral iron, is required.

$$\text{Days} = \frac{65 \text{ mL/kg} \times \text{weight}(\text{kg}) \times (14 - \text{Hgb}) \times 3.3}{5 \text{ mg/d} \times 100} + 200$$

iron/d (usually no greater than 10% of inorganic iron intake) will be absorbed. Other, reputedly more tolerable forms of iron, generally have significantly less elemental iron and are more expensive at a higher price. If patients are compliant, a mild reticulocytosis should be expected after 1 week and a rise in the hemoglobin by 2 g/dL by 4 weeks.

In certain clinical situations, including rapid dialysis losses and failure to absorb oral iron (duodenal failure, inflammation), parenteral iron can be required. Iron dextran is available in 100-mg vials. Intramuscular use is painful, and absorption is not significantly faster than oral administration. Anaphylactic reactions can occur in 1% of patients; thus, a 0.5-mL test dose is recommended before administration. Intravenous administration at a rate of 100 mg/d can be performed in patients with ongoing blood loss (ie, on hemodialysis) or in those in whom iron absorption may be problematic. A ferric gluconate intravenous form is available that causes approximately two thirds fewer anaphylactic reactions⁴⁰ and is recommended if there is any history of adverse reaction to iron dextran.

Summary

Iron deficiency anemia is common in the United States and is an appropriately common reason for referral to gastroenterology clinics because it frequently is a marker of occult gastrointestinal blood loss. Iron is abundant in the Western diet, is not excreted by the human body, and is usually lost through bleeding. The diagnostic evaluation should begin with confirmation of iron deficiency and of anemia and an assessment of any history of blood loss.

Patients who do not have an obvious cause for large non-GI blood losses and who are not premenopausal women should be evaluated with bidirectional endoscopy, beginning with the portion of the GI tract affected by symptoms. Premenopausal females with "red flags" (gastrointestinal symptoms, age > 50, weight loss, hemoglobin < 9, positive FOBT, overt GI blood loss, family history of GI malignancy) and elderly patients should also be evaluated with bidirectional endoscopy.

Premenopausal women without warning symptoms or signs can usually be empirically treated with oral iron replacement therapy for 4 weeks. If their hemoglobin rises by 2 g/dL in that time, they can safely be continued on oral iron therapy to repletion. If they fail to increase their hemoglobin appropriately in response to oral iron, they should also be evaluated with bidirectional endoscopy. Endoscopists can reasonably cancel the second procedure in a bidirectional endoscopic evaluation if a malignancy is found on the first procedure, although a complete bidirectional evaluation may be more justifiable in the elderly, who more frequently have synchronous upper and lower GI tract lesions.

In patients with negative upper and lower endoscopic evaluation without overt blood loss, oral iron supplementation will lead to the resolution of IDA in more than 90% of patients, and further endoscopic or radiologic evaluation does not appear to affect prognosis or outcomes. Identification of small bowel lesions by small bowel enteroscopy or wireless capsule endoscopy is appealing, but currently available prospective data do not show that these diagnostic tests lead to effective therapies nor do they change important clinical outcomes.

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