

The Evidence-Based Evaluation of Iron Deficiency Anemia



Eliana V. Hempel, MD, Edward R. Bollard, MD, DDS*

KEYWORDS

• Iron deficiency anemia • Microcytic anemia • Occult gastrointestinal bleed

KEY POINTS

- The identification of iron deficiency anemia and any underlying contributing comorbidities is necessary to initiate the appropriate treatment.
- In the United States, iron deficiency anemia is most prevalent in young women due to menorrhagia. In this population, a focused history, a complete blood count and a ferritin level are sufficient to confirm the diagnosis of iron deficiency anemia.
- Profoundly low mean corpuscular volume in the setting of mild anemia and a normal red cell distribution width are more suggestive of thalassemia than iron deficiency anemia and necessitate hemoglobin electrophoresis for confirmation.
- In many chronic disease states, it can be difficult to distinguish between iron deficiency anemia and anemia of chronic disease. Transferrin receptor assays and the transferrin receptor-ferritin index will help to distinguish between the two.
- Iron deficiency anemia in the elderly, even in the absence of overt gastrointestinal bleeding, necessitates endoscopic evaluation for underlying gastrointestinal malignancy.

INTRODUCTION

Anemia is of interest to the general internist, as it results in significant morbidity and mortality in a variety of patient populations. It is associated with impaired cognitive function and development in young women,¹ perinatal complications in pregnancy,² an increased risk of falls in the elderly^{3,4} and a variety of other symptoms that affect patients' daily lives. Iron deficiency anemia (IDA) is a common cause of anemia and accounts for 50% of all cases of anemia worldwide. In the United States, IDA affects 1% to 2% of the population and is most prevalent in reproductive-aged women, affecting up to 12% of women aged 20 to 49.⁵ Sufficient iron stores are required for multiple processes, including oxygen transport as part of the hemoglobin molecule, enzymatic reactions as part of the cytochrome system, and electron transport and

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Department of Medicine, Hershey, PA, USA

* Corresponding author. 500 University Drive, PO Box 850, Hershey, PA 17033.

E-mail address: ebollard@hmc.psu.edu

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energy metabolism throughout the body.⁶ Early diagnosis of IDA can prevent multiple complications and improve quality of life. However, despite the multiple complications associated with IDA, routine screening for anemia in the asymptomatic, nonpregnant population is not recommended by the US Preventive Services Task Force.^{7,8}

Although iron deficiency is a common cause of anemia, there are additional potential etiologies for a reduction in the number of red blood cells or quantity of hemoglobin. Thus, on initial diagnosis of anemia, an internist must perform the appropriate evaluation to identify the cause of the anemia and subsequently select the appropriate treatment regimen. However, the process of evaluation can result in significant cost. In a nation suffering from rising health care expenditures, it is the responsibility of all physicians to do their part in decreasing this burden. Therefore, whereas identifying the underlying etiology of anemia is important, it is equally critical that we perform the evaluation in a cost-conscious manner. The purpose of this review is to suggest the most cost-effective, evidence-based assessment of IDA.

To fully understand the evaluation of IDA, we must first review the physiology of iron storage. Iron is absorbed from the diet, mainly in the small intestine, and released from stores when necessary. Free iron can be toxic to cells; therefore, it is bound to transferrin while in circulation. The transferrin-iron complex is taken up by erythroid marrow or liver parenchymal cells that express transferrin receptors. Once released from the transferrin receptor complex, iron becomes available for heme synthesis and other processes. Excess iron is bound to ferritin for storage. Hepcidin, another protein produced by the liver, is also integral in the regulation of iron stores. The physiology of hepcidin and its function in iron regulation is discussed later in this article, but it is important to note that hepcidin is increased in the setting of inflammation or iron overload and decreased in the setting of IDA.⁹ It also should be noted that given the multiple mechanisms for maintenance of physiologic iron stores, true iron depletion develops over time.¹⁰

Case 1 Presentation

A young, otherwise healthy woman presents to the clinic with complaints of fatigue. If you were concerned for anemia as the underlying cause of her fatigue, what further information would you obtain from the patient?

As discussed previously, women of reproductive age are most commonly affected by IDA. In these and all the cases detailed later in this article, the first and most cost-conscious tool in a physician's diagnostic arsenal is the history and physical examination.

The first step in obtaining the history from this patient is to identify any other symptoms potentially attributable to IDA. A list of symptoms that occur in IDA can be seen in **Box 1**.^{10,11} Next, further inquiry regarding possible etiologies of iron deficiency is warranted. These causes of IDA can be categorized into insufficient intake, malabsorption, and blood loss.

Chronic blood loss is commonly associated with menstruation and conditions involving the gastrointestinal tract. Therefore, a detailed gynecologic history as well as questions directed at symptoms of dyspepsia, melena, or hematochezia are essential. In consideration of an underlying malabsorptive state, the patient must be questioned specifically regarding symptoms related to or a personal history of inflammatory bowel disease, celiac disease, and gastrointestinal surgery.¹²

Insufficient intake of iron is rare in the United States; however, it can still occur in a variety of patients, including those with eating disorders or in individuals who follow a restricted diet, as in vegetarians and vegans. Therefore, a careful diet history can also prove useful.

Box 1**Symptoms associated with iron deficiency anemia**

- Fatigue
- Dyspnea on exertion
- Dysphagia
- Pallor
- Koilonychia
- Angular stomatosis
- Cheilosis
- Glossitis
- Esophageal and pharyngeal webs
- Palpitations
- Headaches
- Tinnitus
- Taste disturbance
- Pica

Data from Clark SF. Iron deficiency anemia. *Nutr Clin Pract* 2008;23:128–41; and Frewin R, Henson A, Provan D. ABC of clinical haematology. Iron deficiency anemia. *BMJ* 1997;314:360–3.

Multiple medications, including over-the-counter preparations, can contribute both to malabsorption of iron and increased risk of bleeding. Therefore, a comprehensive medication history with particular focus on over-the-counter medications and supplements is also necessary. Specific medications that can contribute to IDA are listed in **Box 2**.

IDA itself can be a presenting symptom of other previously undiagnosed conditions. Therefore, a family history of hereditary disorders, such as inflammatory bowel disease, colorectal cancer, thalassemia, Plummer-Vinson syndrome, and bleeding disorders is necessary.

Once the history has been obtained, a thorough physical examination must be performed. Findings suggestive of IDA are listed in **Box 3**.

During your comprehensive history and physical examination, you discover that the patient described previously has been having heavy and prolonged uterine bleeding during her menstrual cycle. Due to continued suspicion for IDA, you decide to perform a laboratory evaluation. What studies would you obtain in this patient?

Box 2**Medications that may contribute to iron deficiency anemia**

- Antacids
- H₂ blockers
- Proton pump inhibitors
- Nonsteroidal anti-inflammatory drugs
- Aspirin
- Zinc and manganese supplements

Box 3**Physical examination findings in iron deficiency anemia***General:*

- Fatigued appearing

HEENT:

- Conjunctival or lingual pallor
- Angular stomatitis
- Glossitis

Cardiovascular:

- Tachycardia
- Systolic murmur (flow murmur)

Pulmonary:

- Pulmonary edema

Abdomen:

- Hepatomegaly
- Splenomegaly

Extremities:

- Koilonychia

Skin:

- Pallor
- Poor capillary refill

Once anemia is suspected due to history and/or the physical examination, the diagnosis must be confirmed with laboratory analysis. A complete blood count (CBC) can provide not only confirmatory data but also information about the degree of the anemia and the possible etiology. Also included in a CBC are several red blood cell indices. The mean corpuscular volume (MCV) can be particularly useful with a sensitivity of 97.6% for IDA.^{13,14} In IDA, the MCV is typically low with values below 80 μm^3 .¹⁵ If a microcytic, hypochromic anemia is noted on CBC, further evaluation can be limited to those conditions that result in microcytosis. However, it is important to keep in mind that although the sensitivity of MCV is high, IDA can also present with a normocytic anemia up to 40% of the time. Therefore, in the appropriate clinical context, the following evaluation may still be necessary even in the setting of normocytosis.¹⁶ The CBC also offers the red cell distribution width (RDW). This can further help characterize microcytic anemia, as attempts at replenishing the red blood cell store in IDA would result in an increased RDW but would remain normal in thalassemia, another common cause of microcytic anemia.

Although the red blood cell indices are very useful, a peripheral smear may still be indicated in the evaluation of IDA. A peripheral smear is particularly useful in identifying features characteristic of hemolytic anemia and macrocytic anemia, such as hypersegmented neutrophils, keratocytes, and so forth. It is less useful in the evaluation of a microcytic anemia, however, and may be avoided if microcytosis is clearly identified on the CBC.¹⁷

In addition to a CBC, a reticulocyte count may also prove to be useful in determining the cause of the patient's anemia. The reticulocyte count is a measure of the immature red blood cells present in circulation and reflects red cell production from the bone marrow. Due to decreased availability of substrate, the marrow cannot maintain production of reticulocytes. Therefore, the reticulocyte count is typically low in IDA.^{6,18}

In this otherwise healthy young woman, the most likely etiology of microcytic anemia is IDA secondary to menstrual blood loss. The studies described later in this article may be required in the process of evaluation for IDA in this patient or others in whom you may suspect IDA. Remembering the physiology of iron transport and storage will aid in the interpretation of these values. **Table 1** includes the normal values for the studies outlined later in this article, although individual laboratory reference ranges may differ.

Serum iron levels reflect the amount of transferrin-bound iron in circulation. Total iron binding capacity (TIBC) is an indirect measure of the amount of circulating unbound transferrin. An elevated TIBC is consistent with IDA. Transferrin saturation is calculated using the following formula and is expressed as a percentage: $(\text{Iron} \times 100) / \text{TIBC}$. With low amounts of iron available for binding to transferrin, the transferrin saturation is low in IDA, typically less than 10%.¹⁹

Ferritin is a reflection of the total amount of stored iron in the body. In IDA, the ferritin is typically low, with values less than 15 $\mu\text{g/L}$ being highly suggestive of a diagnosis of IDA. A ferritin level of less than 45 $\mu\text{g/L}$ is 85% sensitive and 92% specific for IDA. The sensitivity and specificity of ferritin once the level rises above 45 (45–100 ng/mL) decreases significantly to 9.4% and 80.0% respectively.^{13,14}

Other less commonly ordered but also useful studies include protoporphyrin levels and transferrin receptor assays. Protoporphyrin functions in the pathway of heme synthesis and is a reflection of the rate of synthesis. If heme synthesis is impaired by a lack of iron, protoporphyrin builds up in the cell, resulting in elevated levels in IDA.¹⁰

A transferrin receptor assay reflects the amount of available transferrin receptors and is performed using enzyme-linked immunosorbent assay testing. In IDA, transferrin receptors are upregulated, resulting in elevated transferrin receptor levels. Transferrin receptor levels have been studied and shown to be an accurate marker of IDA, even in the setting of inflammation.²⁰ It is, therefore, especially useful in distinguishing between IDA and anemia of chronic disease (ACD), where the transferrin receptor level would be normal.²⁰

Table 1
Normal values for laboratory studies

Laboratory Study	Normal Values
Hemoglobin	♂ >13 g/dL, ♀ >12 g/dL
Reticulocyte count	1%–2%
Iron	50–150 $\mu\text{g/dL}$
Ferritin	♂ 100 $\mu\text{g/dL}$, ♀ 30 $\mu\text{g/dL}$
TIBC	300–360 $\mu\text{g/dL}$
Transferrin saturation	25%–50%
Protoporphyrin	<30 $\mu\text{g/dL}$
Transferrin receptor assay	4–9 $\mu\text{g/L}$

Data from Adamson J. Iron deficiency anemia and other hypoproliferative anemias. In: Kasper D, Fauci A, Hauser S, et al, editors. *Harrisons*. 19th edition. New York: McGraw-Hill; 2015. p. 626–8.

Although ferritin can be a very worthwhile study in the evaluation of IDA, it also can be misleading. As an acute phase reactant, it can be elevated in the setting of infection and other chronic diseases. This may lead the interpreter away from a true diagnosis of IDA, especially in elderly patients with multiple comorbidities. In instances in which the clinical picture and the ferritin do not correlate with each other, another alternative diagnostic tool is the transferrin receptor-ferritin index. It has been studied in comparison with transferrin receptor levels alone and was found to be highly sensitive and 93% specific for the diagnosis of IDA.²¹ It is calculated using the ratio of the serum transferrin receptor to the log ferritin level.¹⁴ Ratios less than 1 are more consistent with ACD, whereas ratios greater than 2 are more suggestive of IDA.²²

The gold standard for diagnosis of IDA is iron staining of a bone marrow aspirate. In IDA, staining would be absent or decreased. Bone marrow staining is more expensive and more invasive than the other studies previously described and is typically unnecessary.

Although the testing outlined previously is available, all of these tests may not be necessary. In an otherwise healthy woman of reproductive age, a detailed history and physical examination, CBC, and ferritin are likely sufficient to diagnose IDA.¹⁹ If ferritin levels are nondiagnostic, serum iron, TIBC, and transferrin saturation are appropriate next steps.

Conclusion: You refer the patient for laboratory studies and confirm a diagnosis of anemia with a CBC that reveals a moderate normocytic anemia with an expanded RDW. In conjunction with the CBC, you also ordered a ferritin which returned significantly depressed. The patient is counseled on initiation of iron supplementation. Consideration is also given to the addition of oral contraceptive agents to control the source of her IDA, her menorrhagia.

Case 2 Presentation

A 25-year-old, healthy woman of Indian descent presents to the clinic after evaluation in the emergency department for right lower quadrant pain. In the process of her evaluation, she had a CBC performed that revealed a mild microcytic anemia. She was instructed to follow up with her primary care physician. She reports minimal fatigue but otherwise has no associated symptoms. You suspect thalassemia. What evaluation would you perform to distinguish between thalassemia and IDA?

Thalassemia is an autosomal recessive hemoglobinopathy that results in microcytic anemia. Beta chains are affected in beta thalassemia and those who are heterozygous for this condition are said to have beta thalassemia minor (thalassemia trait). Beta thalassemia minor can be difficult to distinguish from IDA, as they both present with mild to moderate microcytic anemias. Patients with beta thalassemia minor are typically asymptomatic and diagnosed incidentally. However, misdiagnosis of IDA in a patient with beta thalassemia minor will result in futile treatment with supplemental iron. Additionally, patients with beta thalassemia need preconception counseling to be educated on the hereditary nature of their disease. Thus, it is important to identify the correct cause of the microcytic anemia in these patients.

Findings that can aid in this distinction are the degree of microcytosis and the red cell indices. Thalassemia typically presents with profound microcytosis despite having relatively mild anemia. The MCV in a patient with thalassemia is typically less than $75 \mu\text{m}^3$, whereas MCVs are typically depressed, but often above $80 \mu\text{m}^3$ in IDA. Additionally, as the red blood cells are fairly uniform in thalassemia, the RDW is normal. An elevated RDW would be expected in IDA.^{23,24} The red blood cell (RBC) count has been found to be most helpful in differentiating between IDA and beta thalassemia, with a

sensitivity and specificity above 80%. An RBC count less than $5 \times 10^{12}/L$ is consistent with IDA.^{25,26} If the red cell indices support a diagnosis of thalassemia trait, the next best diagnostic test is hemoglobin electrophoresis.

Conclusion: A hemoglobin electrophoresis reveals beta thalassemia minor. She is counseled on the possibility of worsening of her anemia during pregnancy and the chances of her condition being passed on to her children.

Case 3 Presentation

A 30-year-old gentleman with a history of known Crohn disease that is well controlled presents with a longstanding history of progressive fatigue and depression. Recent blood work revealed anemia. What possible etiologies would you consider for his anemia and how might you begin his evaluation?

In the absence of obvious blood loss as a source of IDA, other diagnoses must be considered. Although this patient presents with known Crohn disease, his symptoms have been well controlled. Due to the high degree of variability in severity and presenting symptoms, other similar patients may not yet carry the diagnosis of inflammatory bowel disease (IBD) and can go untreated for prolonged periods of time. Anemia has been identified as an exceedingly common extraintestinal manifestation of IBD. IDA is the most common subtype of anemia in this population with a prevalence of 30% to 90%.²⁷ The high prevalence of anemia in IBD is likely secondary to 2 contributing mechanisms of iron deficiency. The intestinal inflammation likely leads to decreased absorption of iron, and the chronic bleeding associated with IBD leads to persistent losses. However, malabsorption can also lead to B12 and folate deficiency and chronic inflammatory processes can lead to ACD.

Distinguishing IDA from other causes of anemia in IBD can be challenging. Identification of the underlying etiology is nonetheless an important task, as treatment decisions depend on the type(s) of anemia involved.

ACD is another common cause of anemia. It is important to understand the suspected underlying physiology to be able to distinguish between ACD and IDA. In addition to inflammatory diseases, such as IBD, ACD also can be caused by chronic infections and malignancy. The pathophysiology of ACD is still not well understood and is likely multifactorial. One of the main culprit proteins identified in ACD is hepcidin. Hepatocytes produce hepcidin and it functions in iron metabolism. Hepcidin binds to and blocks ferroportin. Ferroportin is required to access stored iron. Interleukin (IL)-6, an inflammatory cytokine, is increased in the setting of inflammation. IL-6 leads to the increased production of hepcidin, thus resulting in inhibited access to iron stores. In contrast, it is suspected that hepcidin is downregulated in IDA, allowing for release of stored iron and increased iron absorption.⁹

Additionally, there is some evidence to suggest that iron absorption is also affected by chronic inflammation. The increase in inflammatory cytokines has been implicated in suppression of RBC production in the bone marrow. RBC longevity is also affected by ACD, again likely due to inflammatory cytokine-mediated activation of macrophages.^{9,22,28}

Unfortunately, the laboratory evaluation detailed previously may not be useful in distinguishing IDA from ACD. Nutritional deficiencies associated with chronic malabsorption can decrease albumin levels. Hypoalbuminemia is associated with low transferrin levels. Therefore, transferrin levels may not be accurate in IDA associated with IBD. Additionally, ferritin, as an acute phase reactant, is often elevated in chronic inflammation and is also unreliable. In this setting, soluble transferrin receptor assays and transferrin receptor-ferritin indices will be most useful.²⁷

Impaired absorption and inflammatory states are not limited to IBD alone. Other gastrointestinal conditions that can result in malabsorption include celiac disease and post resection or post gastric bypass states.¹⁶ As noted previously, proper identification of the underlying etiology is important, as it dictates treatment. In celiac disease, for example, untreated disease can lead to persistent alterations of the duodenal mucosa that persistently impair iron absorption. Therefore, even if IDA is correctly diagnosed, lack of treatment of the underlying condition can lead to refractory anemia.

Conclusion: In the process of evaluation of this gentleman's anemia, a ferritin was obtained and was nondiagnostic. Subsequently, a transferrin receptor assay was performed and was found to be elevated. The transferrin receptor-ferritin index was greater than 2, confirming a diagnosis of IBD-associated IDA. Due to concern for intolerance and poor absorption of oral iron in the setting of IBD, iron supplementation intravenously was initiated and the patient's symptoms gradually improved.

Case 4 Presentation

A 62-year-old otherwise healthy gentleman presents to the clinic with complaints of dyspnea on exertion and palpitations. He does not disclose any additional symptoms. With the exception of mild pallor, his physical examination is normal. A CBC is obtained due to concern for anemia and reveals mild anemia. What additional workup would you consider in this case?

In men and postmenopausal women, IDA is associated with gastrointestinal lesions 50% to 70% of the time.^{14,29} In a prospective study performed with the goal of assessing a guideline-based approach to the evaluation of anemia, the findings revealed a significant rise in the number of serious gastrointestinal lesions identified once a diagnosis of IDA was established. In this study, of the 100 patients evaluated with upper and lower endoscopy, 62 patients were found to have a likely culprit lesion. Because IDA can be the presenting symptom of underlying gastrointestinal malignancy in patients older than 50, further evaluation with endoscopy is indicated. If there are no signs of overt bleeding, such as melena or hematochezia, it is reasonable to initiate evaluation with a fecal occult blood test, although a negative fecal occult blood test does not preclude the need for further endoscopic evaluation. Positive fecal occult blood tests in combination with localized gastrointestinal symptoms have been found to correlate strongly with bleeding lesions at the predicted site.

Signs and symptoms associated with identification of a suspect lesion include age older than 50 years, male gender, recent nonsteroidal anti-inflammatory drug use and more significant anemia (hemoglobin <9 g/dL).^{30,31} This suggests that we may be able to direct our initial endoscopic evaluation to the location of symptoms.³² If an upper endoscopy is indicated by the clinical presentation and a suspect lesion is identified, the patient likely does not require further evaluation with a colonoscopy, assuming the patient is up to date on current recommendations for colorectal cancer screening. This would result in not only decrease in unnecessary resource utilization but also limit the risks associated with avoidable procedures.

In an otherwise asymptomatic patient with IDA, especially elderly patients in whom the risk of malignancy is high, it is reasonable to initiate workup with a colonoscopy. In the setting of a negative colonoscopy, subsequent upper endoscopy is necessary.³²

If endoscopic evaluation is unrevealing and anemia is not severe, oral iron supplementation and monitoring are acceptable. However, 5% of tumors resulting in IDA are missed due to improper bowel preparation, operator variability, and other factors affecting reliability of colonoscopy. Therefore, if anemia and symptoms are persistent despite a negative endoscopic evaluation, repeat upper endoscopy and colonoscopy are indicated.

If, despite multiple endoscopic evaluations, a lesion is still not identified and the patient has persistent anemia, the lesion is likely located in the small bowel. Evaluation of the small bowel can be challenging. The options for investigation include video capsule endoscopy (VCE) and single or double balloon enteroscopy (SBE). VCE is less invasive but is limited in that it can still fail to identify the lesion, and if a lesion is identified and treatment is necessary, enteroscopy is still required. In a meta-analysis that reviewed VCE versus other forms of small bowel evaluation, the yield of VCE for a culprit lesion was higher than that of SBE and small bowel barium radiography. This particular meta-analysis did not find a statistically significant difference in the identification of malignant lesions compared with SBE. Nevertheless, VCE information is valuable, as vascular or inflammatory lesions can still be major contributors in the development of IDA and may require treatment.³³

Another randomized study investigated VCE versus push enteroscopy as first-line evaluation of obscure gastrointestinal bleeding identified by either overt bleeding or chronic IDA with a negative workup. This study reported that VCE did not fail to identify the bleeding lesion in any cases, whereas SBE failed to identify a lesion that was subsequently identified with VCE in 26% of patients.³⁴

SBE affords the ability to both identify and treat the lesion simultaneously and has previously been shown to successfully locate the likely bleeding lesions in 53% of cases of obscure gastrointestinal bleeding.³² However, in addition to the higher rate of missed lesions, it is significantly more invasive, can be technically difficult, and can result in postprocedural complications. Although the yield of VCE has been variable in the multiple studies performed to compare it with other modalities, the risk/benefit ratio is in favor of initiating evaluation with VCE.^{35–42}

Conclusion: Despite his lack of overt gastrointestinal bleeding, due to his age and subsequent laboratory findings suggestive of IDA, this patient was referred for colonoscopy. He was found to have two, 2-cm adenomatous polyps that were successfully removed. He was scheduled for follow-up colonoscopy.

In summary, IDA is a common disease that the internist will encounter regularly. It can take many forms and has multiple possible etiologies. A detailed history and thorough physical examination are both cost-effective and valuable. Based on diagnostic information obtained in the history and physical, further laboratory evaluation can be limited to the studies with the highest yield, depending on the clinical scenario. Appropriate identification of IDA and any underlying contributing pathologies is critical in the management of this condition.

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