

# Iron deficiency anemia: diagnosis and management

Susan F. Clark

Department of Human Nutrition, Foods and Exercise,  
Virginia Polytechnic Institute and State University,  
Blacksburg, Virginia, USA

Correspondence to Susan F. Clark, RD, PhD,  
Department of Human Nutrition, Foods and Exercise,  
Virginia Polytechnic Institute and State University, 223  
Wallace (0430), Blacksburg, VA 24061, USA  
Tel: +1 540 231 8768; fax: +1 540 231 3916;  
e-mail: sfclark@vt.edu

**Current Opinion in Gastroenterology** 2009,  
25:122–128

## Purpose of review

Iron deficiency anemia (IDA) still remains universally problematic worldwide. The primary focus of this review is to critique articles published over the past 18 months that describe strategies for the diagnosis and management of this prevalent condition.

## Recent findings

The medical community continues to lack consensus when identifying the optimal approach for the diagnosis and management of IDA. Current diagnostic recommendations revolve around the validity and practicality of current biomarkers such as soluble transferrin-receptor concentrations and others, and cause-based diagnostics that potentially include endoscopy. Management of IDA is based on supplementation combined with effective etiological treatment. Advances in oral and parenteral low-molecular-weight iron preparations has expanded and improved treatment modalities for IDA. Since the introduction of low versus high-molecular-weight intravenous iron administration, there have been fewer serious adverse events associated with parenteral iron preparations.

## Summary

Best practice guidelines for diagnosing and managing IDA should include the design of an algorithm that is inclusive of multiple biomarkers and cause-based diagnostics, which will provide direction in managing IDA, and distinguish between IDA from the anemia of chronic disease.

## Keywords

iron deficiency anemia, transferrin-receptor/ferritin ratio, zinc protoporphyrin/heme

Curr Opin Gastroenterol 25:122–128  
© 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins  
0267-1379

---

## Introduction

The primary focus of this article will be to evaluate specific diagnostic criteria for iron deficiency anemia (IDA) and describe management strategies to correct IDA. Approaches for differentiating IDA from the anemia of chronic disease (ACD) will only be discussed within the context of identifying IDA. Nevertheless, a working consensus on a pragmatic approach to diagnosis and treatment despite the prevalence of this condition remains paramount.

---

## Background

IDA is the most common nutritional deficiency around the globe, yet universal standards of practice guidelines for diagnostic and treatment modalities are riddled with inconsistencies and disagreements among practitioners. A recent review article [1••] presents evidence-based data on the incidence of IDA associated with a myriad of diseases and medical conditions that complicate the diagnosis of true IDA. It also describes the diverse causes of IDA, diagnostic parameters and management strategies. Table 1 summarizes the physiologic and pathologic causes of IDA, and Table 2 delineates diagnostic tests.

There is no sole, reliable biochemical indicator that is consistently diagnostic of iron deficiency except the ‘gold standard’, bone marrow iron aspirates. As iron status changes are sequential, we need to move beyond the current philosophy using a single assay to diagnose IDA but rather take an intentional approach that involves the systematic assessment of the underlying cause and use of multiple parameters.

## Diagnostic indicators of iron deficiency anemia

Intuitively, combining several iron status indicators provides the best assessment of iron status. Evaluation of multiple indicators such as soluble transferrin receptors (sTfRs), sTfR–ferritin index (sTfR–F), zinc protoporphyrin/heme ratio (ZPP/H), reticulocyte hemoglobin (Hb) content (CHR) and selective endoscopy will provide better diagnosis and treatment iron status to prevent IDA.

## Serum transferrin receptor and serum transferrin receptor log/ferritin index

sTfR reflects erythropoiesis and inversely the amount of iron available for erythropoiesis. Values of sTfR are elevated in IDA due to the upregulation of synthesis of transferrin receptors on the erythrocytes so the cells can

**Table 1 Physiologic and pathologic conditions associated with iron deficiency anemia**

Physiologic conditions (growth and development)	Pathologic conditions
Increased iron demands	Chronic inflammatory states
Pregnancy	Chronic renal disease
Lactation	Congestive heart failure
Infants	Obesity
Children and adolescents	Blood loss
Increased dietary demands	Inflammatory bowel disease <sup>a</sup>
Pregnancy	Blood donations
Lactation	Excessive blood sampling
Infants	Excessive surgical blood loss without replacement
Children and adolescents	Excessive menstrual losses
Menstrual losses	Medications <sup>b</sup>
Inadequate dietary intake	Aspirin
	NSAIDS
	Antacids
	H <sub>2</sub> antagonist
	Proton-pump inhibitors
	Gastrointestinal conditions <sup>c</sup>
	Upper gastrointestinal conditions
	Gastric ulcer
	Duodenal ulcer
	Carcinoma
	Esophagitis
	Erosive gastritis
	Celiac disease
	Peptic ulcer disease
	<i>H. pylori</i> gastritis
	Crohn's disease
	Malabsorptive states (surgical or medical)
	Gastrectomy
	Chronic atrophic gastritis
	Lower gastrointestinal conditions
	Colonic adenoma
	Carcinoma
	Ulcerative colitis
	Malabsorptive states
	Other
	Restless leg syndrome

<sup>a</sup> Active Crohn's disease and ulcerative colitis.  
<sup>b</sup> Defective iron absorption.  
<sup>c</sup> Defective iron absorption or iron loss secondary to blood loss.

compete for iron more efficiently. Unlike serum ferritin, sTfR concentrations are not affected by the presence of inflammation [2]. The ratio between sTfR and serum ferritin concentrations, or sTfR-F index, is also considered a good indicator for evaluation of iron deficiency.

sTfRs can contribute significantly to the detection of IDA; however, some claim it to be not any better than serum ferritin [3–7]. Yang *et al.* [8<sup>•</sup>] compared the plasma ferritin concentrations alone with the sTfR-F ratio in infants, school-aged children and pregnant women measuring plasma ferritin, sTfR and C-reactive protein (CRP). They concluded that iron status can be effectively measured using plasma ferritin concentrations alone, provided a biomarker such as CRP is also measured to avoid falsely elevated plasma ferritin secondary to concurrent inflammation.

Chang *et al.* [9<sup>•</sup>] compared the utility of serum sTfR levels to bone marrow iron stores in identifying IDA. Bone marrow aspirates were performed in adult patients and hematologic assays: sTfR, serum ferritin, Hb, mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). Cutoff values consistent with previous studies [10,11] that were used to exclude iron deficiency included ferritin values of at least 100 mcg/l and an sTfR/log ferritin ratio of more than 2.5. Elevated sTfR levels were found to be the most sensitive marker for the detection of absent bone marrow iron (100%), whereas the sTfR-F ratio of more than 2.5 had a lower sensitivity (50%). sTfR-F did have better sensitivity and specificity compared with the serum sTfR value alone when differentiating between IDA from ACD, which has been previously reported [2,10–13].

Goyal *et al.* [14<sup>•</sup>] evaluated sTfR-F indices to determine the prevalence of ACD, and ACD with coexistent IDA in rheumatoid arthritis (RA) patients. The sTfR-F index was found to be a useful measure in classifying patients with ACD and coexistent IDA (80%) versus patients with

**Table 2 Diagnostic test related to sequential changes in iron status**

Measure	Normal	Early negative-iron balance	Iron depletion	Iron-deficient erythropoiesis	IDA
Bone marrow iron <sup>a</sup>	2–3 <sup>+</sup>	1 <sup>+</sup>	0–1 <sup>+</sup>	0	0
TIBC <sup>b</sup> (μg/dl)	330 ± 30	330–360	360	390	410
Ferritin (μg/l)	100 ± 60	<25	20	10	<10
Iron absorption (%)	5–10	10–15	10–15	10–20	10–20
Plasma iron (μg/dl)	115 ± 50	<120	115	<60	<40
Transferrin saturation (%)	35 ± 15	30	30	<15	<15
Erythrocyte protoporphyrin (μg/dl)	30	30	30	100	200
Erythrocytes	Normal	Normal	Normal	Normal	Microcytic hypochromic
Serum transferrin receptors	Normal	Normal–high	High	Very high	Very High

IDA, iron deficiency anemia.  
<sup>a</sup> Estimates of iron stored in bone marrow according to a six-point scale: 0 = iron absent, 1 = iron decreased, 2–3 = normal amount of iron, 4 = iron markedly increased and 5 = iron massively increased.  
<sup>b</sup> Transferrin iron-binding capacity. Adapted with permission [1<sup>••</sup>].

pure ACD (20%). They also determined that sTfR-F index values of less than 2.2 mg/l excludes IDA, whereas values of more than 2.9 mg/l confirmed IDA. A similar study [15<sup>\*</sup>] compared the utility of serum ferritin, serum iron and bone marrow iron stores in diagnosing iron deficiency in RA outpatients. On the basis of the bone marrow iron stores, 36% of patients had IDA and 64% exhibited ACD. Correlation between the serum ferritin and the bone marrow iron stores was poor in the IDA group yet significant in the ACD group. Negative predictive values were highest when cutoff values for serum ferritin were less than 82 mcg/l in contrast to other studies' cutoff values of 30–70 µg/l [16,17].

### Zinc protoporphyrin/heme ratio

Evaluation of iron status using the ZPP/H is another diagnostic indicator of IDA diagnostic of early iron depletion [18]. The ZPP/H ratio reflects iron status in the bone marrow during the formation of Hb [19]. When iron supply is diminished, Zn utilization increases resulting in a high ZPP/H ratio. Das and Philip [20<sup>\*</sup>] compared the utility of ZPP/H ratio as a diagnostic measure of IDA with bone marrow iron store aspirates. In tandem with Hb and red blood cell indices, ZPP was reliable in reflecting the bone marrow iron status except in the prelatent phase of iron deficiency; however, it lacked the ability to distinguish between ACD and IDA. Using ZPP/H ratio to determine iron stores is preferential over the invasiveness of bone marrow aspiration. Others have reported that the ZPP/H ratio increase also compares favorably with serum ferritin concentration decrease, MCV and Hb levels in diagnosing IDA and preanemic iron depletion [19,21]. As zinc is also influenced by inflammation, ZPP interpretation can be challenging [22,23].

### Reticulocyte hemoglobin content

CHr assesses the amount of Hb in reticulocytes [24–27]. Measurement of CHr provides a snapshot of iron immediately available for erythropoiesis over the previous 3–4 days, making it functional as an early indicator of iron stores. Blood CHr has been found to be comparable to the traditional parameters for iron deficiency (serum iron, serum ferritin and Hb) for confirming the diagnosis of iron-deficient states [25–27,28<sup>\*</sup>]. Blood CHr has also been identified as an early indicator of the response to parenteral iron therapy, increasing within 2–4 days if sequential measurements are observed [28<sup>\*</sup>].

### Diagnostic endoscopic procedures

Current recommendations for adults with unexplained IDA include endoscopy. Capruso *et al.* [29] identified risk factors that would predict the presence of abnormalities in patients with IDA that would indicate whether colonoscopy or esophagogastroduodenoscopy (EGD) should be performed first. Serum ferritin, routine blood counts

and fecal occult blood test (FOBT) were measured. Endoscopic findings revealed at least one likely cause for unexplained IDA in 86.7% of patients; causes included: bleeding, colon cancer, peptic ulcer, nonbleeding related, atrophic gastritis, *Helicobacter pylori* and celiac disease. Significant risk factors identified were older age (>50 years), lower MCV and male sex. They concluded that a diagnostic endoscopy in patients with IDA should be based on age with colonoscopy performed first in older patients (>50 years of age) with low MCV and Hb below 12 g/dl, and EGD with biopsy should be done first in younger patients with unexplained IDA. However, the disproportion of women (76%) to men calls into question the conclusions drawn.

Vannella *et al.* [30<sup>\*</sup>] also evaluated the cause of unexplained IDA in premenopausal women between the ages of 20 and 56 years using endoscopy. IDA was defined as Hb below 12 g/dl with serum ferritin less than 30 µg/dl, and iron deficiency as serum ferritin less than 30 µg/dl. All patients underwent a gastroscopy including biopsies and FOBTs. Patients (≥50 years of age), with positive FOBT or positive family history for colonic cancer were invited to undergo a colonoscopy. Endoscopic evaluation revealed a likely cause of IDA in 68.5% of patients. The cause was due to iron malabsorption in 65.2% of patients, secondary to *H. pylori* pangastritis, celiac disease and atrophic gastritis. Only 3.7% of iron deficiency anemic patients exhibited bleeding lesions, whereas 67.4% were diagnosed with menorrhagia. This study produced a high diagnostic yield for the cause of IDA.

Another study by Ioannou *et al.* [31<sup>\*</sup>] identified diagnostic tests and clinical features that were predictive for endoscopic evaluation in patients with anemia (<13 g/dl women, <12 g/dl men) using serum ferritin (<45 ng/dl) and transferrin saturation (<15%) as outcome measures. Anemia was found in 35.4% of the 1798 hospitalized patients; 74% were men, 26% women, mean age is equal to 62 years, 51% white and 49% nonwhite. Those diagnosed with IDA, 39% had either low serum ferritin or low transferrin saturation and underwent endoscopic evaluation. The only significant predictor for endoscopic evaluation was a positive FOBT.

### Newer diagnostic biomarkers: hepcidin

Hepcidin is considered a key regulator of iron metabolism; it regulates iron concentrations and tissue iron distribution via inhibition of intestinal iron absorption, iron reclamation by macrophages and iron mobilization from hepatic stores [32]. Its production is decreased in IDA and increased during inflammation and iron overloading. The overproduction of hepcidin during an acute phase response results in reduced iron absorption, mobilization, or both, contributing to the disease of anemia.

Kemna *et al.* [33\*\*] developed the algorithm [transferrin saturation (%) – sTfR (mg/l) + CRP (mg/l) = hepcidin] to predict hepcidin levels. A strong correlation between the predicted hepcidin values and the actual measured hepcidin levels was found. Despite the selected parameters used in this algorithm, each has shortcomings; the lab indices are readily available and less expensive than serum hepcidin. Hepcidin levels have the potential to improve accuracy when differentiating between IDA and ACD.

### Management of iron deficiency anemia

The treatment modalities for managing IDA will depend on the underlying cause. Once the cause of IDA has been ascertained, either oral or parenteral iron therapy is commonly prescribed to correct the deficiency.

### Oral iron therapy

Oral iron therapy is usually adequate for most patients; it is an efficient, well tolerated and cost-effective way to replace iron stores. Four common preparations are found in Table 3. Historically, ferrous sulfate has been used to treat IDA because it is better absorbed by the gastrointestinal tract and causes fewer side effects (heartburn, abdominal pain, nausea, diarrhea and constipation). When complexes or chelated forms of iron are used the gastrointestinal symptoms are minimal.

### Oral iron therapy using iron complexes-chelates

Pitarresi *et al.* [34\*] described the utility of an inulin–iron complex. Inulin is a naturally occurring fructose polymer with fermentation products that enhance iron absorption within the colon. Two derivatives were used, a carboxylated inulin–iron complex formed with succinic anhydride and a thiolated inulin–iron complex formed using a reaction with cysteine. The iron source was ferric chloride, a more bioavailable iron form. Iron release studies were conducted with both complexes simulating intestinal condition; iron was released from the complexes at a rate of 60–70%. They concluded that the delivery of iron into the intestinal tract using an inulin–ferric chloride iron complex might be superior to the commonly used ferrous form.

**Table 3 Common oral iron preparations**

Iron salt	Elemental iron (%)	Typical dosage (mg)	Elemental iron/dose (mg)
Ferrous sulfate	20	325, t.i.d.	65
Ferrous sulfate exsiccated	30	200, t.i.d.	65
Ferrous gluconate	12	325, t.i.d.	36
Ferrous fumarate	33	325, b.i.d.	106

b.i.d., twice daily; t.i.d., three times daily.

Mimura *et al.* [35\*\*] compared the use of another iron complex, ferrous glycinate chelate to ferrous sulfate for the treatment of IDA in postgastrectomized patients. Standard indices were determined (Hb, MCH, MCHC, serum iron, serum ferritin, transferrin and transferrin saturation) and an EGD. Patients received either 400 mg/day ferrous sulfate or 250 mg/day ferrous glycinate chelate. After 2 months, transferrin levels were significantly decreased in patients receiving ferrous sulfate. Results favored ferrous sulfate as more effective in improving iron status over ferrous glycinate chelate, contrary to previous studies [36–38]. Some of the unfavorable results observed were attributed to decreased iron absorption in patients with alkaline gastritis. Another contributing factor could have been presence of *H. pylori* infection. *H. pylori* infection is a common comorbidity found in the gastric remnant of gastrectomized patients, which is known to decrease iron absorption [1\*\*,39]. Identifying the presence of *H. pylori* or alkaline gastritis was not verified in this current study.

### Response to oral iron therapy

The treatment of IDA should include a strategy for measuring response to iron therapy. Historically, a 2 g/dl improvement in Hb levels has been considered an appropriate response to iron supplementation; yet, other parameters may be more reliable. Lin *et al.* [40\*\*] measured sTfR levels to assess the response and efficacy of 12 weeks of oral ferrous L-threonate in patients with IDA or iron deficiency erythropoiesis (IDE). Iron status was assessed in women (18–45 years) using the serum ferritin, ZPP and Hb levels at weeks 0, 3, 6 and 12. The IDE and IDA group received ferrous L-threonate supplements for 12 weeks (14 and 28 mg/day, respectively). Significant changes occurred in sTfR levels at all measurement intervals in both groups; sTfR levels were normal at week 12. A correlation between sTfR concentrations was found with other iron-related indices sampled, but ZPP was the best indicator. Another beneficial finding regarding the response to iron supplementation was that the sTfR–F ratios decreased more significantly during iron therapy.

When refractory IDA is nonresponsive to oral iron therapy, *H. pylori* infection and chronic gastritis are often to blame [41–45]. Chen and Luo [46\*] evaluated the effects of *H. pylori* therapy on erythrocytic and iron parameters in *H. pylori* gastritis patients with IDA. Patients received ferrous succinate and treatment for *H. pylori* or only the iron supplement. Changes in Hb, MCH, serum iron and serum ferritin were compared between groups. Ferrous succinate (200 mg) and ascorbic acid (100 mg) was administered three times per day. Treatment for *H. pylori* included three medications: deuteron–bismuth citrate, amoxicillin and metronidazole

for 2 weeks. After *H. pylori* was eradicated, Hb, serum iron and serum ferritin values significantly increased to normal. The eradication of *H. pylori* is warranted to maximize oral iron therapy in the recovery from IDA.

### Parenteral iron therapy

Parenteral iron therapy is necessary for patients intolerant or unresponsive to oral iron supplementation [1<sup>••</sup>]. Historically, parenteral iron therapy has been used with caution because of its anaphylactic potential. Despite the introduction of newer intravenous (i.v.) iron preparations with improved safety profiles, practitioners seem hesitant to administer i.v. iron [47<sup>•</sup>]. Four parenteral iron preparations are available (Table 4). Two are iron dextrans that differ in molecular weight and the other two preparations are iron salt preparations, ferric gluconate and iron sucrose. An investigational i.v. iron preparation, ferric carboxymaltose complex (i.v.-FeCarb), is a nondextran-containing i.v. iron only approved for use outside the USA.

### Parenteral iron versus oral iron therapy

Van Wyck *et al.* [48<sup>••</sup>] compared the use of i.v.-FeCarb with oral iron in the treatment of anemic postpartum women. Patients were stratified by Hb levels, need for cesarean section, transferrin saturation more than 20% and serum ferritin values at least 50 ng/ml and randomized to receive i.v.-FeCarb, 1000 mg or less over 15 min, weekly until iron replacement was complete, or oral ferrous sulfate, 325 mg (65 mg elemental iron) three times a day, 1 h prior to meals for 42 days. The efficacy endpoint was the proportion of patients that achieved an Hb increase of at least 2 g/dl after treatment. Adherence to prescribed therapy was greatest among the i.v.-FeCarb group, and the median time to achieve the endpoint was shorter than the oral iron group (7 vs. 14 days). The proportion of patients who experienced correction of anemia was higher in the i.v. iron group. Serum ferritin and transferrin saturation increased significantly in the i.v.-FeCarb compared with the oral iron group after 1 week. No serious adverse events occurred, yet gastrointestinal complaints were reported in 20% of patients receiving oral iron. Early intervention with iron therapy was well tolerated, and regardless of the administration route improved the health-related quality of life (QoL) in women with postpartum anemia.

Breymann *et al.* [49<sup>••</sup>] also compared i.v.-FeCarb to oral ferrous sulfate in the treatment of postpartum IDA by

assessing the effects of this iron preparation on Hb increase, iron status and its safety and tolerability in mothers and breast-fed infants. Patients received either i.v.-FeCarb (maximum dose of 1000 mg over 15 min) or oral ferrous sulfate (100 mg twice a day for 12 weeks). The primary endpoint to assess efficacy was evaluating the change in Hb, serum ferritin and transferrin saturation levels from baseline to week 12. The Hb values in both groups increased over the 12 weeks. The mean increase in the i.v.-FeCarb patients was 13.04 g/dl compared with 12.89 g/dl in the ferrous sulfate group, although not statistically significant. In contrast, the change from baseline for serum ferritin levels was significant in the i.v.-FeCarb compared with the ferrous sulfate group. Transferrin saturation increased in both groups with maximum mean values reached at week 4, yet response rates (RR) for serum ferritin and transferrin saturation were significantly higher in the i.v.-FeCarb group. Both treatment courses were well tolerated and treatment was not associated with any safety concerns. Breast milk iron content was significantly higher in mothers receiving the FeCarb at 48 h. Both parenteral FeCarb and oral ferrous sulfate treatment were effective in treating postpartum anemia; the increases in Hb, serum ferritin and transferrin saturation were significantly higher in the i.v.-FeCarb group at all time points. The rapid replacement in iron stores after i.v.-FeCarb was an advantage as the oral iron therapy did not replenish iron stores. Although these findings are promising, we are reminded that i.v.-FeCarb US Food and Drug Administration (FDA) approval is pending in the USA.

### Parenteral iron sucrose

Intravenous iron sucrose is approved to treat anemia related to chronic kidney failure (CKF). However, minimal data exist on using i.v. iron sucrose infusions in patients without CKF. Wall and Pauly [50<sup>•</sup>] attempted to determine the efficacy and safety of an i.v. iron sucrose protocol for patients with IDA not related to erythropoietin therapy, blood product usage, oral iron supplementation or CKF. Iron necessary for repletion was calculated and the dose was divided into portions (250 mg, maximum of 500 mg) and administered every other day until total dose was given. They measured Hb levels as the efficacy outcome on days 1, 10, 21 and after last infusion; and collected transferrin saturation and serum ferritin between days 10 and 14. Day 13 mean Hb levels after last infusion increased ( $11 \pm 1.2$  mg/dl) compared with

**Table 4 Parenteral iron preparations**

	Low-molecular-weight iron dextran	Iron sucrose	Ferric gluconate	High-molecular-weight iron dextran
Test dose required	Yes	No	No	Yes
Iron per vial (mg/ml)	50	20	12.5	50
Molecular weight (Da)	165 000	34–60 000	289–440 000	265 000

baseline Hb levels ( $9.45 \pm 0.8$  mg/dl). Mean transferrin saturation levels improved from less than 11% to more than 20% but data existed for only three patients. Although no adverse events were reported after infusion, definitive efficacy outcomes were lacking in the majority of patients.

### Management strategies: a simple or sophisticated algorithm

The ultimate goal in anemia management is to maintain safety, correct anemia, maintain iron status parameters or all within recommended limits and improve patient QoL and survival. To help achieve these goals, practitioners must move beyond the current treatment philosophy and implement a strategy with a more balanced, systematic approach that is applicable in diverse settings. Concrete clinical practice guidelines for diagnosis and treatment of IDA in at risk populations still lack uniformity partly because of the increasing prevalence of multiple comorbidities among anemic patients. Updated practice standards need to include specific recommendations for diagnosis that also includes management strategies based on the known risks or causes of IDA.

Gasche *et al.* [51\*\*] used a systematic approach to develop such guidelines for diagnosis and management of iron deficiency and IDA in patients with inflammatory bowel disease (IBD). A panel of gastroenterologists evaluated the literature and addressed: anemia evaluation (definition of anemia, screening parameters, anemia workup, iron deficiency and ACD), triggers for treatment of anemia (initiation of therapy, initiation of iron supplementation, initiation of erythropoietic therapy, initiation of vitamin supplementation and blood transfusions), targets of iron therapy (treatment goals, response to treatment and treatment evaluation), and treatment of anemia (iron supplementation, erythropoietic agents and adjustment of IBD therapy). This article describes recommendations regarding diagnostic tools to screen for IDA; it identifies the triggers for medical intervention, treatment goals and treatment modalities. It could serve as a model for a universal practice guideline in which updated diagnostic and management algorithms are presented [52]. Establishing the cause as the first step in an algorithm would be pivotal to the remaining components of the algorithm such as key parameters with quantified reference limits, follow-up assays such as sTfR, sTfR-/F index, ZPP/H, testing for *H. pylori*, recommendations for endoscopy and intervention modalities inclusive of expected response rates [30\*,53–55]. A more definitive algorithm would also include assessment of chronic inflammation measuring CRP, hepcidin or the possibility of using the predictive formula for hepcidin. Incorporating more diagnostic components into existing algorithms that evaluate early iron depletion will ultimately prevent progression to IDA.

### Conclusion

In 2008, the prevalence of IDA still remains the most common nutritional deficiency throughout the world that negatively impacts on health and development. We must move beyond current ideology, and learn how to better assess those populations at risk for the development of iron deficiency regardless of concurrent medical conditions. Evidence-based practice guidelines need to include diagnostic measures that identify changes in iron status early to avoid progression to IDA, and specific management goals that include treatment strategies including what constitutes a favorable response to iron therapy along with timelines for treatment.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 168–169).

- 1 Clark SF. Iron deficiency anemia. *Nutr Clin Pract* 2008; 23:128–141.
- comprehensive review of iron deficiency inclusive of prevalence, causes, diagnosis and treatment.
- 2 Mast AE, Blinder MA, Gronowaki AM, *et al.* Clinical utility of soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem* 1998; 44:45–51.
- 3 Suominen P, Punnonen K, Rajamaki A, *et al.* Serum transferrin receptor and transferrin receptor-ferritin index identify healthy subjects with subclinical iron deficits. *Blood* 1998; 92:2934–2939.
- 4 Skikne BS, Flowers CH, Cook JD. Serum transferrin receptor: a quantitative measure of tissue iron deficiency. *Blood* 1990; 75:1870–1876.
- 5 Gimferrer E, Ubeda J, Royo MT, *et al.* Serum transferrin receptor levels in different stages of iron deficiency. *Blood* 1997; 90:1332b–1333b.
- 6 Choi JW. Sensitivity, specificity, and predictive value of serum soluble transferrin receptor at different stages of iron deficiency. *Ann Clin Lab Sci* 2005; 35:435–439.
- 7 Punnonen K, Ijala K, Rajamäki A. Serum transferrin receptor, ferritin and TfR-F index in identification of latent iron deficiency. *Eur J Haematol* 1998; 60:135–137.
- 8 Yang Z, Dewey KG, Lönnerdal B, *et al.* Comparison of plasma ferritin concentration with the ratio of plasma transferrin receptor to ferritin in estimating body iron stores: results of 4 intervention trials. *Am J Clin Nutr* 2008; 87:1892–1898.
- A large, well designed study validating serum ferritin use in healthy populations to assess IDA, but not necessarily in inflammatory conditions.
- 9 Chang J, Bird R, Glague A, *et al.* Clinical utility of serum soluble transferrin receptor levels and comparison with bone marrow iron stores as an index for iron-deficient erythropoiesis in a heterogeneous group of patients. *Pathology* 2007; 39:349–353.
- A retrospective study supports that sTfR can be a valuable marker of iron deficient erythropoiesis.
- 10 Margetic S, Topic E, Ruzic DF, *et al.* Soluble transferrin receptor and transferrin receptor-ferritin index in iron deficiency anemia and anemia of rheumatoid arthritis. *Clin Chem Lab Med* 2005; 43:326–331.
- 11 Malope BI, MacPhail AP, Alberts M, *et al.* The ratio of serum transferrin receptor and serum ferritin in the diagnosis of iron status. *Br J Haematol* 2001; 115:84–89.
- 12 Rimon E, Levy S, Sapir A, *et al.* Diagnosis of iron deficiency anemia in the elderly by transferrin receptor-ferritin index. *Arch Intern Med* 2002; 162:445–449.
- 13 Das Gupta A, Abbi A. High serum transferrin receptor level in anemia of chronic disorders indicate coexistent iron deficiency anemia. *Am J Hematol* 2003; 72:158–161.
- 14 Goyal R, Das R, Bamberg P, *et al.* Serum transferrin receptor-ferritin index shows concomitant iron deficiency anemia and anemia of chronic disease is common in patients with rheumatoid arthritis in north India. *Indian J Pathol Microbiol* 2008; 51:102–104.
- This study validates that TfR-ferritin index is useful when distinguishing prevalence of iron deficiency in ACD.

- 15 Ravindran V, Jain S, Mathur DS. The differentiation of anaemia in rheumatoid arthritis: parameters of iron-deficiency in an Indian rheumatoid arthritis population. *Rheumatol Int* 2008; 28:507–511.  
Serum ferritin correlation with bone marrow iron stores is a poor indicator of IDA.
- 16 Bultink IE, Lems WF, van de Stadt RJ, *et al.* Ferritin and serum transferrin receptor predict iron deficiency in anemic patients with rheumatoid arthritis. *Arthritis Rheum* 2001; 44:979–981.
- 17 Ganti AK, Moazzam N, Laroia S, *et al.* Predictive value of absent bone marrow iron stores in the clinical diagnosis of iron deficiency anemia. *In Vivo* 2003; 17:389–392.
- 18 Rettmer RL, Carlson TH, Origenes ML, *et al.* Zinc protoporphyrin/heme ratio for diagnosis of preanemic iron deficiency. *Pediatrics* 1999; 104:e37.
- 19 Labbé RF, Dewanji A. Iron assessment tests: transferrin receptor vis-à-vis zinc protoporphyrin. *Clin Biochem* 2004; 37:165–174.
- 20 Das S, Philip KJ. Evaluation of iron status: Zinc protoporphyrin vis-a-vis bone marrow iron stores. *Indian J Pathol Microbiol* 2008; 51:105–107.  
ZPP is reliable in reflecting bone marrow iron stores during prelatent iron deficiency. ZPP/H increase compares favorably with serum ferritin.
- 21 Koulaouzidis A, Bhat S. Investigating iron status in microcytic anaemia, zincprotoporphyrin and soluble transferrin receptor has a role. *BMJ* 2006; 222:972. [letter].
- 22 Hastka J, Lasserre JJ, Schwarzbeck A, *et al.* Zinc protoporphyrin in anaemia of chronic disorder. *Blood* 1993; 81:1200–1204.
- 23 Hastka J, Lasserre JJ, Schwarzbeck A, *et al.* Laboratory tests of iron status: correlation or common sense? *Clin Chem* 1996; 42:718–724.
- 24 Brugnara C. Iron deficiency and erythropoiesis: new diagnostic approaches. *Clin Chem* 2003; 49:1573–1578.
- 25 Brugnara C, Schiller B, Moran J. Reticulocyte hemoglobin equivalent (Ret He) and assessment of iron-deficient states. *Clin Lab Haematol* 2006; 28:303–308.
- 26 Kotisaari S, Romppanen J, Penttila I, *et al.* The Advia 120 red blood cell and reticulocyte indices are useful in diagnosis of iron-deficiency. *Eur J Haematol* 2002; 68:150–156.
- 27 Kotisaari S, Romppanen J, Agren U, *et al.* Reticulocyte indices rapidly reflect an increase in iron availability for erythropoiesis. *Haematologica* 2003; 88:1422–1423.
- 28 Mast AE, Blinder MA, Dietzen DJ. Reticulocyte haemoglobin content. *Am J Hematol* 2008; 83:307–310.  
CHR is a functional early indicator of iron store status that is underused. Good indicator of response to parenteral iron therapy.
- 29 Capruso G, Baccini F, Osborn J, *et al.* Can patient characteristics predict the outcome of endoscopic evaluation of iron deficiency anemia: a multiple logistic regression analysis? *Gastrointest Endosc* 2004; 59:766–771.
- 30 Vannella L, Aloe Spiriti MA, Cozza G, *et al.* Benefit of concomitant gastrointestinal and gynaecological evaluation in premenopausal women with iron deficiency anaemia. *Aliment Pharmacol Ther* 2008; 28:422–430.  
Endoscopic evaluation was beneficial and produced a high diagnostic yield for IDA.
- 31 Ioannou GN, Spector J, Rockey DC. Predictors of endoscopic and laboratory evaluation of iron deficiency anemia in hospitalized patients. *South Med J* 2007; 100:976–984.  
Endoscopy can be done safely to improve the evaluation of IDA.
- 32 Kemna EH, Tjalsma H, Willems HL, *et al.* Hepcidin: from discovery to differential diagnosis. *Haematologica* 2008; 93:90–97.
- 33 Kemna EH, Kartikasari AER, Lambertus JH, *et al.* Regulation of hepcidin: insights from biochemical analyses on human serum samples. *Blood Cells Mol Dis* 2008; 40:339–346.  
This study highlights new advances in iron regulation.
- 34 Pitarresi G, Tripodo G, Cavallaro G, *et al.* Inulin-iron complexes: a potential treatment of iron deficiency anemia. *Eur J Pharm Biopharm* 2008; 68:267–276.  
An insight into the efficacy and safety of new parenteral iron therapy; FDA approval pending.
- 35 Mimura EC, Bregano JW, Dichi JB, *et al.* Comparison of ferrous sulphate and ferrous glycinate chelate for the treatment of iron deficiency anemia in gastrectomized patients. *Nutrition* 2008; 24:663–668.  
The first study to compare the use of ferrous sulfate with oral iron chelates in the gastrectomized population. Ferrous sulfate was more effective in improving iron status; however, the presence of *H. pylori* infection was not determined and may have influences on the results.
- 36 Pineda O, Ashmead HD, Perez JM, *et al.* Effectiveness of iron amino acid chelate on the treatment of iron deficiency anemia in adolescents. *J Appl Nutr* 1994; 46:2–13.
- 37 Pizarro F, Olivares M, Hertrampf E, *et al.* Iron bis-glycine chelate competes for the nonheme iron absorption pathway. *Am J Clin Nutr* 2002; 76:577–581.
- 38 Melamed N, Ben-Haroush A, Kaplan B, *et al.* Iron supplementation in pregnancy: does the preparation matter? *Arch Gynecol Obstet* 2007; 276:601–604.
- 39 Katsube T, Ogawa K, Hamaguchi K, *et al.* Prevalence of *Helicobacter pylori* in the residual stomach after gastrectomy after gastric cancer. *Hepatogastroenterology* 2002; 49:128–132.
- 40 Lin X, Tian W, Ma L, *et al.* The responses of serum transferrin receptors to iron supplements in subjects with iron-deficiency erythropoiesis and iron-deficiency anaemia. *Br J Nutr* 2008; 99:416–420.  
Both ZPP and sTfR concentrations are an effective sensitive index for assessing efficacy of iron therapy.
- 41 Franceschi F, Gasbarrini A. *Helicobacter pylori* and extragastric diseases. *Best Pract Res Clin Gastroenterol* 2007; 21:325–334.
- 42 Nahon S, Lahmek P, Massard J, *et al.* *Helicobacter pylori*-associated chronic gastritis and unexplained iron deficiency anemia: a reliable association? *Helicobacter* 2003; 8:573–577.
- 43 Annibale B, Capurso G, Lahner E, *et al.* Concomitant alterations in intragastric pH and ascorbic acid concentration in patients with *Helicobacter pylori* gastritis and associated iron deficiency anaemia. *Gut* 2003; 52:496–501.
- 44 DuBois S, Kearney D. Iron-deficiency anemia and *Helicobacter pylori* infection: a review of the evidence. *Am Coll Gastroenterol* 2005; 100:453–459.
- 45 Hacinanefioglu A, Edebali F, Celebi A, *et al.* Improvement of complete blood count in patients with iron deficiency anemia and *Helicobacter pylori* infection after the eradication of *Helicobacter pylori*. *Hepatogastroenterology* 2004; 51:313–315.
- 46 Chen L, Luo H. Effects of *H. pylori* therapy on erythrocytic and iron parameters in iron deficiency anemia patients with *H. pylori*-positive chronic gastritis. *World J Gastroenterol* 2007; 13:5380–5383.  
This study supports the testing and eradication of *H. pylori* infection prior to iron therapy in IDA.
- 47 Auerbach M, Goodnough LT, Picard D, *et al.* The role of intravenous iron in anemia management and transfusion avoidance. *Transfusion* 2008; 48:988–1000.  
This study provides insights into the history of parenteral iron therapy; highlights new low molecular weight i.v. iron.
- 48 Van Wyck DB, Martens MG, Seid MH, *et al.* Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. *Obstet Gynecol* 2007; 110:267–278.  
A randomized controlled clinical trial provides new insight on efficacy of i.v. FeCarb compared with oral iron therapy in managing postpartum anemia inclusive of the response to therapy in correcting anemia, adherence to treatment, potential adverse effects and improved health-related QoL.
- 49 Breyman C, Gliga F, Bejenariu C, *et al.* Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. *Int J Gynecol Obstet* 2008; 101:67–73.  
This study points out the efficacy and safety of i.v. FeCarb in the treatment of IDA; lacks FDA approval to date.
- 50 Wall G, Pauly RA. Evaluation of total-dose iron sucrose infusions in patients with iron deficiency anemia. *Am J Health Syst Pharm* 2008; 65:150–153.  
The relative safety of i.v. iron sucrose was shown but definitive efficacy outcomes were lacking.
- 51 Gasche C, Berstad A, Befrits R, *et al.* Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007; 13:1545–1553.  
This study provides an excellent model on how to design a universal standard of care for the diagnosis and treatment of IDA.
- 52 Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. *Am Fam Physician* 2007; 75:671–678.
- 53 Rockey DC, Cello JP. Evaluation of the gastro-intestinal tract in patients with iron deficiency anemia. *N Engl J Med* 1993; 329:1691–1695.
- 54 Annibale B, Lahner E, Chistolini A, *et al.* Endoscopic evaluation of upper gastrointestinal tract is worthwhile in premenopausal women with iron-deficiency anaemia irrespective of menstrual flow. *Scand J Gastroenterol* 2003; 38:239–245.
- 55 Harris JK, Froehlich F, Gonvers JJ, *et al.* The appropriateness of colonoscopy: a multicenter, international, observational study. *Int J Qual Healthcare* 2007; 19:150–157.