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Individualized treatment for iron deficiency anemia in adults

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Abstract

Iron deficiency is one of the most common disorders affecting mankind, and iron deficiency anemia continues to represent a major public health problem worldwide. It is especially common among women of childbearing age due to pregnancy and menstrual blood loss. Additional patient groups include those with other sources of blood loss, malnutrition or gut malabsorption. Iron deficiency anemia remains quite prevalent despite the widespread ability to diagnose the disease and availability of medicinal iron preparations. Therefore, new approaches are needed to effectively manage these patient populations. In this review, the diagnosis and treatment of iron deficiency anemia are discussed with emphasis placed upon consideration of patient specific features. It is proposed that all patients participate in their own care by helping their physician to identify a tolerable daily iron dose, formulation, and schedule. Dosing cycles are recommended for iron replacement based upon the tolerated daily dose and the total iron deficit. Each cycle consists of 5000mg of oral elemental iron ingested over at least one month with appropriate follow-up. This approach should assist physicians and their patients with the implementation of individualized treatment strategies for patients with iron deficiency anemia.

Keywords

iron; anemia; hepcidin; dosing cycles

Introduction

Iron is critical for the growth of all cells. Not surprisingly, therefore, iron deficiency anemia independently increases morbidity and mortality.¹ There are an estimated 3.5 billion iron deficient people worldwide, the vast majority in developing countries.² Remarkably, iron deficiency is also the most common cause of anemia in the United States.³ A history of chronic fatigue or blood loss should alert the clinician to consider the diagnosis of iron deficiency. Occasionally, more subtle histories of hair loss or pica (appetite for substances not appropriate as a food source like ice, clay, soil or paper products) provide the initial suspicion for iron

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deficiency anemia. The classical textbook findings of Plummer-Vinson syndrome (dysphagia, esophageal web, and atrophic glossitis with iron deficiency anemia) and koilonychia (spoon nails) are rarely present in developed countries. Even in the absence of overt signs and symptoms, a likely diagnosis of iron deficiency anemia may be revealed to the clinician by routine blood testing.

Once the diagnosis of iron deficiency anemia is made, the physician must identify the cause and devise a treatment plan. As shown in Table 1, iron deficiency anemia results from a variety of causes that fall in to four general categories related to the intake or loss of iron. In the vast majority of cases, the cause of iron deficiency anemia results in an anemia that is both avoidable and reversible by increasing iron supplementation or reducing iron loss. However, the fact that over three million females in this country continue to manifest iron deficiency anemia⁴ suggests that generic therapeutic approaches remain suboptimal. It may be necessary to rethink general treatment approaches in order to reduce the incidence of iron deficiency anemia. In this review, concepts of iron storage and kinetics are combined with an overview of oral iron supplements to provide clinicians with individualized treatment strategies for iron deficiency anemia.

Iron kinetics and the development of anemia

Most adults have at least 3000mg (45mg/Kg) elemental iron in their bodies. Females generally have lower levels than males because of the iron loss during menses, pregnancies and lactation. Within that pool of total body iron, approximately two-thirds is contained in heme (mostly incorporated in erythrocyte hemoglobin) and one-third in the storage forms of ferritin or hemosiderin. To maintain adequate supplies of iron for heme synthesis, 20mg of iron is recycled daily, from senescent red cells that are removed from the circulation, to new cells in the bone marrow.⁵ Iron from those older cells is loaded by macrophages onto transferrin for delivery to the bone marrow. Around 1-2mg/day of additional dietary iron is needed to balance losses in urine, sweat, and stool. The hormone hepcidin regulates iron homeostasis by regulating ferroportin-mediated release of iron from enterocytes and macrophages.⁶ If dietary intake is inadequate to replace the 1-2 mg/d of obligate iron loss or to replace additional loss from bleeding, iron deficiency will develop.

Of fundamental importance is the realization that iron stores are depleted before iron deficient erythropoiesis occurs. Hence, laboratory parameters associated with the depletion of iron stores usually precede the onset of anemia (Table 2). Three years of a severely iron deficient diet (less than 1-2 mg/d dietary iron X 1000 days) or more acute hemorrhage of two liters (0.4 mg elemental iron per ml whole blood) will both cause a complete loss of iron stores (normally about 1 gram of iron in the form of ferritin and hemosiderin). The loss of iron stores is reflected in the blood by a reduction in ferritin and reduced levels of iron bound to transferrin. As the iron stores become more severely depleted, availability of transferrin-bound iron to the erythroid precursor causes reduced heme and hemoglobin production. This is reflected in a drop in the red blood cell count and mean corpuscular volume. The red cell count usually becomes abnormal before the mean corpuscular volume, which remains within the normal range until the hemoglobin reaches about 10 g/dl. Additionally, the red cell distribution width increases because the smaller, iron deficient cells are being mixed with normocytic cells. In the absence of therapy, erythrocyte production remains inadequate and anemia develops. Importantly, many patients with iron deficiency anemia have normal red cell indices because the red cell count becomes abnormal before there is much change in red cell morphology.⁷ In those cases, more specialized testing of iron status may be required to confirm the diagnosis of iron deficiency anemia.⁸

Dietary iron supplementation

Once iron deficiency has been diagnosed and its underlying cause addressed, the next challenge is restoration of the iron supply. Assuming an average absorption of 10% of the iron in a medicinal form, the daily elemental iron requirement is 10 mg in children, adult males and post menopausal women (to provide 1 mg to the body), 20 mg in young non-pregnant women and 30 mg in pregnant women.⁹ Of course, patients who malabsorb iron, such as those who have undergone gastric bypass, require more.¹⁰

If dietary history suggests a deficiency, patients should be encouraged to augment their diet with foods rich in heme iron such as red meat (full of hemoglobin and myoglobin) or liver. Non-heme iron, which is prevalent in cereals, egg yolk and green leafy vegetables, is not efficiently absorbed. Vitamin C is known to increase iron absorption and can be increased in the diet by addition of citrus fruits. In contrast, tea inhibits iron absorption so iron deficient patients should wait 1-2 hours after the meal before drinking tea or alternatively, remove tea from their diet. Optimum management may require referral to a registered dietitian or nutritionist for more intensive nutrition assessment and counseling. While dietary review and counseling are important, diet alone is usually inadequate as a source of replacement iron in most patients who have iron deficiency anemia.¹¹

Medicinal iron supplementation

Iron preparations generally contain one of three iron salts: iron sulphate, iron gluconate, and iron fumarate. It is important to realize, however, that a tablet of the sulfate salt contains twice the amount of iron as a tablet of the other two salts, although the differing molecular weights of the compounds obscure this fact (Table 3). Therefore, twice as many ferrous gluconate or ferrous fumarate tablets are required to provide the amount of elemental iron in ferrous sulfate tablets.

The choice of delivery formulation is another source of confusion. Oral iron may be given as tablets or elixirs. Among the tablet preparations, there are non-enteric coated pills and enteric-coated and prolonged-release formulations. Non-enteric coated iron tablets are most commonly used as initial treatment due to their lower cost. Delayed release and enteric-coated iron preparations have been advocated since they are better tolerated than the non-enteric coated tablets. However, they are less effective since they may contain less iron and their iron may not be released in the duodenum, where iron is absorbed. In fact, patients who have been treated unsuccessfully with enteric-coated and prolonged-release iron preparations may respond well to the administration of nonenteric-coated ferrous salts.¹²

There are multiple variables that may enhance or inhibit the absorption of medicinal iron (Table 4A). Differences in absorption are most likely due to the requirement of acidity in the duodenum and upper jejunum for iron solubility. For iron released beyond these sites, the alkaline environment reduces absorption.¹³ Ideally, patients should not take iron supplements within 1-2 hours of antacids. The inhibition of iron absorption by other medications that reduce stomach acid like H2 blockers may be even more prolonged. Absorption is also delayed with tetracyclines, milk, and phosphate-containing, carbonated beverages such as soft drinks. Even the calcium, phosphorus and magnesium salts contained in iron-containing multivitamin pills impair absorption of elemental iron.¹⁴ For this reason, multivitamin preparations should never be recommended as a sole therapy for iron deficient anemia. Iron tablets are recommended between meals or at bedtime to avoid the alkalinizing effect of food and to take advantage of the peak gastric acid production late at night.

A common generic approach for iron deficiency in adults consists of a daily dose of 150-200 mg of elemental iron. This approach entails prescribing one ferrous sulfate tablet 3 times daily

since each tablet contains approximately 60 mg of elemental iron. Assuming that 10% of the iron is absorbed, the hemoglobin concentration may fully correct after 4 weeks in patients with moderate, uncomplicated iron deficiency (about 500–800 mg of iron, enough for 500 to 800 mL of packed red blood cells, or enough to raise the whole blood hemoglobin 2–3 g/dL).¹⁵ To further replenish iron stores, some recommend continuation of this regimen for several additional months.¹⁶ Unfortunately, this approach often fails. Up to 20 percent of patients experience some type of gastrointestinal discomfort while taking 180 mg of elemental iron per day using this regimen¹⁷, and 30 per cent of some patient groups may self discontinue the medication.¹⁸ Major stumbling blocks toward successful oral iron therapy are dose-related, upper gastrointestinal side effects such as nausea and epigastric discomfort which occur approximately one hour after ingestion. Lower gastrointestinal side effects such as constipation and diarrhea are less dose-related and are managed by symptom specific remedies (e.g. magnesium citrate for constipation).¹⁹ If a patient quickly becomes constipated or nauseated from commonly recommended dose of 150–200mg of daily elemental iron, dose reductions are applied. Changes in iron salts (and hence elemental iron per tablet) and formulations are commonly tried, and most involve dose reductions by lengthening the dose interval.¹⁹ These dose-lowering maneuvers may permit iron-intolerant patients to continue oral therapy, and avoid parenteral therapy.

In some centers, an outpatient measurement of oral iron absorption is performed for suspected malabsorption among iron deficient patients. A fasting serum iron level is compared to the level measured 1–2 hours after oral ingestion of 324 mg ferrous sulphate (66mg elemental iron). If the serum iron increases over 100 µg/dl from the baseline, iron absorption is likely adequate (Table 4B).⁸ Despite the simplicity of iron absorption testing, the utility of this approach has been challenged.^{12,20} Along with consideration parenteral iron therapy, diagnosis and therapy for potentially reversible gastrointestinal diseases including autoimmune gastritis, *Helicobacter pylori* and celiac disease must be considered for those patients with demonstrable malabsorption.²¹

Consideration of dosing cycles for oral iron replacement

When adjusting daily iron supplementation regimens, the physician must remember that lowering the daily iron dose requires a longer duration of therapy. For example, a switch from iron sulphate to iron gluconate will double the duration of treatment. If this important relationship between the dose and duration of iron replacement is not fully considered, evaluation after four weeks may be inappropriate or even mislead further care.

Instead of a principal focus upon the duration of therapy, the estimated total-dose for elemental iron may be used to guide therapy, and replacement may be provided in cycles. According to this approach, the patients should participate in their own care by determining the iron formulation and dose schedule that they are able to tolerate. The amount of elemental iron that is absorbed in the gut is not constant, and can vary significantly depending on several factors, including hemoglobin level and body iron stores. The amount of absorbed iron decreases as the iron deficiency is corrected. Hence, it is not possible to predict the exact percentage of iron that will be absorbed for individual patients, but it is suggested that approximately 10%–20% of an oral iron dose will be absorbed upon initiation of therapy.²² As such, an estimated average of 10% of the oral dose of iron will be used in this review for estimating the total dose needed for iron replacement therapy.

Based upon this estimate of 10% absorption, at least 5000 mg of oral elemental iron (defined here as 1 cycle of therapy) should be prescribed for absorption of 500 mg. Estimates of the number of tablets needed to achieve this cycled dose of elemental iron are shown in Table 3. For ferrous sulphate, one cycle consists of 75 pills or three pills daily for 25 days. Among

patients with moderate levels of anemia, a single cycle of 5000 mg should be adequate for correction of anemia and partial replacement of iron stores as evidenced by serum ferritin levels.²³ If the anemia is not severe and there is no complicating feature such as ongoing blood loss or enteropathies, additional iron supplementation cycles may not be required for correction of the anemia. Re-evaluation of the anemia after completion of first 5000 mg dosing cycle should be performed to determine if additional iron supplementation is necessary. Among patients with more severe anemia, alternative dose estimates may be generated based upon the hemoglobin level (Table 5). If a patient is predicted to have ongoing iron deficits (e.g. menorrhagia), maintenance dosing of iron supplements can easily be devised. The key feature of the cycled dosing strategy proposed here is that several factors including the cause of iron deficiency anemia, the total iron deficit, replacement iron formulations, and the predicted duration of replacement therapy are integrated for implementation of an individualized therapeutic plan.

Failure of oral iron therapy

On occasion, the treatment of oral iron therapy does not result in the expected increase in hemoglobin. In general, patients with iron deficient anemia should manifest a response to iron with reticulocytosis in three to seven days, followed by an increase in hemoglobin in 2-4 weeks. Theoretically, 500 mg of absorbed iron should produce 500 cc of packed cells, the amount in about 2 units of blood, or enough to raise the hemoglobin by about 2 g/dL. Unless the patient's anemia is severe, completion of a 5000 mg dosing cycle of ingested elemental iron over one or more months (500 mg absorbed elemental iron) should therefore be sufficient to correct the patient's hemoglobin to the normal range. Patients may be assessed earlier in the iron replacement course to confirm an appropriate reticulocyte response. Considerations for an insufficient response include ongoing blood loss, malabsorption, which could be anatomical or inhibiting factors e.g. antacids or tea, incorrect diagnosis, or noncompliance.¹⁹ Patient noncompliance should be investigated by history, but other causes should be ruled out in cases of uncertainty. In general, compliant patients who fail to respond to iron therapy may be referred to a hematologist for further evaluation of the anemia or a gastroenterologist for possible malabsorption or occult blood loss.

Summary

Despite the well-recognized pathology, the prevalence of the iron deficient anemia remains enormous even in the developed world. Diagnosis is usually made in primary practice, but successful therapy is frequently hampered by the high frequency of side effects as well as patient noncompliance. In this review, we proposed that dosing of replacement iron should be achieved in 5000 mg cycles according to the formulation and schedule that is best tolerated by individual patients. A simplified treatment algorithm for this approach is shown in Figure 1. Patients that fail to manifest an appropriate erythroid response should be referred for additional evaluation. It is predicted that better understanding of hepcidin or other iron regulating molecules should help clinicians to further tailor medicinal iron therapy in the future. In any case, individualized or patient-specific strategies for patients with iron deficiency anemia should be sought to achieve greater success in the treatment of this common and important disease.

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References

1. Nissenson AR, Goodnough LT, Dubois RW. Anemia: or just an innocent bystander? *Arch Intern Med* 2003;163:1400–1404. [PubMed: 12824088]
2. United Nations Sub-Committee on Nutrition (ACC/SCN). Fourth report on the world nutrition situation. United Nations; 2000.
3. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Morb Mortal Wkly Rep* 1998;47(RR3):1–29. [PubMed: 9450721]
4. Looker AC, Dallman PR, Carroll MD, et al. Prevalence of iron deficiency in the United States. *JAMA* 1997;277:973–976. [PubMed: 9091669]
5. Heeney MM, Andrews NC. Iron homeostasis and inherited iron overload disorders: an overview. *Hematol Oncol Clin North Am* 2004;18:1379–1403. [PubMed: 15511621]
6. Kemna EH, Tjalsma H, Willems HL, Swinkels DW. Hepsidin: from discovery to differential diagnosis. *Haematologica* 2008;93:90–97. [PubMed: 18166790]
7. Farley PC, Foland J. Iron deficiency anemia. How to diagnose and correct. *Post grad Med* 1990;87:89–101.
8. Cook JD. Diagnosis and management of iron-deficiency anaemia. *Best Pract Res Clin Haematol* 2005;18:319–332. [PubMed: 15737893]
9. Institute of Medicine. Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington, DC: National Academy Press; 2001.
10. Love AL, Billett HH. Obesity, bariatric surgery, and iron deficiency: True, true, true and related. *Am J Hematol* 2008;83:403–409. [PubMed: 18061940]
11. Crosby WH. The rationale for treating iron deficiency anemia. *Arch Intern Med* 1984;144:471–472. [PubMed: 6703813]
12. Beutler, E. Williams Hematology. Seventh. Chpt 40. USA: McGraw-Hill; Disorders of iron metabolism; p. 511–553.
13. Provan D. Mechanisms and management of iron deficiency anemia. *Br J Haematol* 1999;105(Suppl 1):19–26. [PubMed: 10330929]
14. Stang, J.; Story, M., editors. Guidelines for Adolescent Nutrition Services. 2005.
15. Cook JD. Iron-deficiency anemia. *Baillieres Clin Haematol* 1994;7:787–804. [PubMed: 7881154]
16. Massey A. Microcytic Anemia. Differential diagnosis and management of iron deficiency anemia. *The Medical Clinics of North America* 1992;76:549–565. [PubMed: 1578956]
17. Rimón E, Kagansky N, Kagansky M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005;118:1142–1147. [PubMed: 16194646]
18. Bonnar J, Goldberg A, Smith JA. Do pregnant women take their iron? *Lancet* 1969;1:457–458. [PubMed: 4179514]
19. Beutler E, Hoffbrand AV, Cook JD. Iron deficiency and overload. *Hematology Am Soc Hematol Educ Program* 2003:40–61. [PubMed: 14633776]
20. Wiltink WF, Ybema HJ, Leijnse B, Gerbrandy J. The iron tolerance test. Measurement of absorption and utilization of a therapeutic dose of iron. *Clin Chim Acta* 1966;13:701–707. [PubMed: 5962598]
21. Hershko C, Hoffbrand AV, Keret D, et al. A Role of autoimmune gastritis, *Helicobacter pylori* and celiac disease in refractory or unexplained iron deficiency anemia. *Haematologica* 2005;90:585–595. [PubMed: 15921373]
22. Goroll AH, Mulley AG. Office evaluation and management of the adult patient. *Primary Care Medicine Chpt* 82:607–608.
23. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. *Blood* 2003;101:3359–3364. [PubMed: 12521995]

Figure 1.

Table 1

Causes of iron deficiency in adults.

Causes	Examples
Increased iron loss	<p>Acute hemorrhage</p> <ul style="list-style-type: none"> • Alimentary • Respiratory • Urinogenital • Dermal <p>Chronic or occult hemorrhage</p> <ul style="list-style-type: none"> • Menstruation • Inflammatory • Cancer • Vascular malformation • Hemolysis <p>Blood donation</p> <ul style="list-style-type: none"> • ≥ 2 units per year in women • ≥ 3 units per year in men <p>Iatrogenic</p>
Decreased Iron in Diet	<p>Vegetarian diet</p> <p>Malnutrition</p> <p>Dementia, psychiatric illness</p>
Decreased Iron Absorption	<p>Antacid therapy or high gastric pH</p> <p>Celiac disease</p> <p>Inflammatory bowel disease</p> <p>Partial gastrectomy</p>
Increased iron requirements	<p>Pregnancy</p> <p>Lactation</p>

Table 2

Laboratory abnormalities in iron deficiency.

	Lab test	Lab Finding
Ferritin	< 40 µg/l
	Serum iron	< 50 µg/dl
	Transferrin saturation	< 15 %
	Total iron binding capac.	> 450 µg/dl
	Red cell count	< $4 \times 10^6 / \text{mm}^3$
	Red cell distribution width	> 14.5 %
	Mean corpuscular volume	< 80 fl
	Hemoglobin	< 13 g/dl males
		< 12g/dl menstruating females

Table 3

Common oral iron preparations.

Preparation	Dose (mg)	Elemental iron content (mg)	5000mg dose cycle (tablets)
Ferrous sulphate	324	65	75
Ferrous gluconate	300	36	140
Ferrous fumarate	100	33	150

Table 4

Oral iron absorption.

A. Effectors of iron absorption.	
Inhibiting iron absorption	Facilitating iron absorption
<ul style="list-style-type: none"> • Coffee, tea, milk, cereals, dietary fiber, phosphate-containing carbonated beverages • Multivitamin or dietary supplements containing calcium, zinc, manganese or copper • Antacids, H2 blockers and proton pump inhibitors. • Quinolones and tetracycline antibiotics 	<ul style="list-style-type: none"> • Vitamin C • Acidic foods e.g. tomato sauce • Non enteric coated iron tablets • Fasting ingestion of iron supplements
B. Oral iron absorption test. ⁸	
Step 1: Measure morning serum iron level (fasting).	
Step 2: Ingest approximately 60mg elemental iron (324 mg ferrous sulphate) with water.	
Step 3: After 1-2 hours, measure the serum iron level.	
Step 4: Compare the serum iron levels.	
Interpretation: An increase in serum iron of >100 µg/dL suggests gut absorption is generally adequate.	

Table 5

Iron replacement dose estimates.

A. Estimated total oral dose of elemental iron for anemia correction. Additional dosing cycle(s) of 5000mg may be required to replenish iron stores.	
Hemoglobin (g/dl)	Elemental Iron Total dose (mg) *
> 11	5000
9-11	10,000
< 9	15,000
B. Calculation based upon total blood volume and hematocrit (Hct)	
Total iron deficit = Iron stores deficit + Hemoglobin iron deficit	
Iron stores deficit = 500-1000 mg	
Hemoglobin iron deficit = body wt (lb) × (target Hb - actual Hb)	
Target Hb 14 g/dl.	
Oral elemental iron replacement estimate (mg) = 10 × total iron deficit	

* assuming 10% absorption, 60 kg patient.