REVIEW PAPER

Current Practice of Iron doses for Treatment of Iron Deficiency Anaemia - A Review

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1. Background

Although functional impairment begins with iron deficiency in the absence of anaemia, the development of anaemia heralds a homeostatic dysfunction that impairs daily activity. Iron deficiency anaemia is often the reason for poor physical performance, maternal and child morbidity and referral to a healthcare professional. (1) Women in their reproductive years, pregnant women and children are most vulnerable to develop iron deficiency anaemia (IDA) and will be the focus of this review.

Patients with iron deficiency present with symptoms attributable to anaemia resulting from decreased oxygen delivery to tissues and decreased oxidative capacity at the cellular level. These include fatigue, exertional dyspnea and/or palpitations, vertigo and syncope with the physical finding of pallor; none of which are specific to iron deficiency. Features that may occur more often in iron depleted states than in anaemia due to other causes are pica (craving for objects not considered appropriate as food, e.g., clay, soil, ice), restless leg syndrome, koilonychia, alopecia and the very rare Plummer Vinson syndrome (triad of esophageal webs, dysphagia and iron deficiency). Irrespective of the degree of anaemia, decreased productivity, defective immune function with susceptibility to infections and, in the elderly, a greater risk of developing neurocognitive decline and dementia are noted.1 Iron deficiency during pregnancy is associated with various adverse outcomes for both mother and infant, including increased risk of sepsis, preterm labour and maternal mortality. Sequelae for the fetus are influenced by intrauterine growth retardation, prematurity and low birth weight. Perinatal iron deficiency can predispose to delayed neurological development and psychiatric illness. (2)

The aim of treatment is to supply enough iron to normalize haemoglobin (Hb) concentrations and replenish iron stores thereby improving the quality of life. This document reviews evidence on treatment of anaemia for different population groups. The cut-off for the definition of anaemia is given below.

WHO DEFINITION OF ANAEMIA (3)

Age or sex group	Haemoglobin (g/dL)	Hematocrit %
Children 6 months to 5 years	11.0	33
Children 5-11 years	11.5	34
Children 12-13 years	12	36
Non-pregnant women	12	36
Pregnant women	11	33
Men	13	39

2. Tests for iron deficiency

A detailed history and physical examination preclude unnecessary testing for other causes of anaemia, since IDA is the most common cause. The presence of jaundice, hepatosplenomegaly, family history of haemoglobinopathy, associated symptoms of gum bleeds, bruises or epistaxis should alert the caregiver to a possibility that the cause of anaemia is unlikely to be iron deficiency alone.

Mean corpuscular volume (MCV) that estimates red cell size is a basic indicator of iron status. While microcytosis is not exclusive to IDA, the presence of low MCV (MCV < 80 fL) without the contributory history delineated above should be considered as indicative of IDA, that accounts for 80% of microcytic anaemia. (4) However, in up to 40 % of patients with IDA, the erythrocytes may still be normocytic. Hence, a mean corpuscular volume (MCV) less than 95 fL is taken as cutoff value below which iron deficiency is considered, as this threshold has a sensitivity of 97.6 percent for diagnosing IDA. (5) A peripheral smear examination for accurate diagnosis requires the skill of a haematopathologist or laboratory scientist and where available, should be performed. In chronic iron deficiency, the RBCs appear microcytic and hypochromic.

The most accurate test for iron deficiency is serum ferritin level; a measure of stored iron. Levels below 15 ng/L are diagnostic of iron deficiency anaemia. A higher threshold of 30 ng/L improves sensitivity from 25 to 92%, while specificity remains high at 98%.5Where there is underlying chronic inflammation, the threshold may be even higher. Additional contributory tests include Serum iron <30 mcg/dl, Total iron binding capacity > 450 mcg/dL, Transferrin saturation <16%.

The presence of a reticulocyte count > 2% and RBC count >5x106 cells/L is an important indicator of a close differential, Thalassemia trait, in endemic areas. (4) The absence of target cells and more marked anisopoikilocytosis (reflected by Red cell Distribution Width or RDW >14) are features that favour IDA over thalassemia.

A bone marrow sample for iron stores has been considered the gold standard for assessment of iron deficiency; however, this test is clearly too invasive and not practical for any but the most complicated cases. In patients with severe anaemia (Hb< 7g/dL), blood films for malarial parasites and stool examination for ova, cyst and occult blood are recommended by National guidelines. (6)

3. Existing guidelines for treatment of iron deficiency anaemia (IDA)

While there is disparity in the approach to treatment of anaemia across the globe, most recommendations suggest that:

- All patients with iron deficiency should have iron supplementation to correct anaemia *and* replete body stores.
- Dietary sources are resorted to for secondary prevention and are unlikely to provide adequate iron for correcting negative iron balance. (7)
- Oral iron therapy is considered effective and, by far the safest route of correction making it the standard first choice. (8)

Iron therapy can be administered at the primary health care level. Patients at risk for developing complications who may need to be treated in a hospital setting include those with severe anaemia (Hb< 7g/dL) and/or any of the following (9):

- cardiac compromise resulting from anaemia, identified by breathlessness at rest/ lower limb swelling
- those with pre-existing heart disease
- pregnancy beyond 36 weeks of gestation.

3a. IDA in infants and children<12 years

The dose of elemental iron advocated for treatment of IDA in children varies from 3-6 mg/kg/day depending on the severity of anemia. (10) A randomized clinical trial in infants and children up to the age of 48 months suggested a unifying recommendation of 3mg/kg as a single daily dose of ferrous sulfate in the pediatric population. (11) The risk of developing iron deficiency falls after 24 months owing to diversification in food intake and reduced rate of growth implying less need for iron compared to infancy. The results from the RCT could thus probably be extrapolated to children in general. The Centre for Disease Control (CDC) also endorses the 3 mg/kg dose throughout childhood.

3b. IDA in Adolescents

Prepubertal growth spurts impose great demand on iron requirement making this population subset a target for developing iron deficiency. In addition, adolescent girls enter menarche and begin to lose iron in menstrual blood. (12) Standard dosing of iron therapy in adolescents with IDA varies widely. Proposed doses of elemental iron range from 65-300 mg in one to three divided doses. (12) Lower doses are preferred owing to their better tolerability as demonstrated in adults.

3c. IDA in women of reproductive age

Women in their reproductive years seldom develop severe iron deficiency anemia due to nutritional inadequacy alone. Menstrual losses are often not compensated for entirely, especially in developing countries with low dietary iron. Mild anemia may be treated with oral iron tablets amounting to 120 mg elemental iron per day. (13) Severe anemia should be evaluated for contributory causes in the absence of obvious excessive blood loss (menorrhagia). (13)

3d. IDA in Pregnant Women

Owing to the large quantity of iron required by the growing fetus and placenta, mild iron deficiency anaemia is common in pregnancy. Oral iron supplementation should be commenced as soon as the diagnosis is made. (14) In women with co-existing Haemoglobinopathies, serum ferritin < 30 µg/L should have oral iron supplementation. (15)

Single total dose iron infusions have shown better improvements in the blood indices compared to oral iron supplementation during pregnancy. However, the safety profile and cost-effectiveness with the advantage of home therapy, makes oral iron the preparation of choice. (14)

In general, parenteral iron therapy in pregnancy is indicated when there is absolute noncompliance with, or intolerance to, oral iron therapy or proven malabsorption. There are some recommendations for multi-dose intramuscular iron for pregnant women with Hb< 8 g/dL. (16) A randomized control study that compared oral and IV iron sucrose in pregnant women with iron deficiency anaemia enrolled 100 women with singleton pregnancy between 24 and 34 weeks; 180 mg of elemental iron was administered in 3 divided doses for 4 weeks. The other arm received 200 mg of iron sucrose on alternate days to achieve the total calculated dose requirement. Mean rise in Hb at day 14 and 28 were higher in the IV group. (0.23g/dL; 0.58 g/dL at day 14 and 1.3 g/dL vs 1.9 g/dL at day 28; $p<0.05$). 36% subjects reported gastrointestinal side effects in the oral group while no significant adverse events were noted in the IV group. This study indicates that intravenous iron replacement may be more beneficial than oral therapy in pregnant women presenting in the latter half of pregnancy with moderate anaemia. (17) A few other studies have indicated that intravenous iron therapy in pregnant women with iron sucrose and iron carboxymaltose have had restoration of iron stores faster than oral iron, with no serious adverse reactions. Until further data is available, however, ferric carboxymaltose use should be restricted to the second and third trimesters. (18)

Transfusion is recommended in pregnant women with Hb levels of less than 6 g/dL because of potentially abnormal fetal oxygenation resulting in non-reassuring fetal heart tracings, low amniotic fluid volumes, fetal cerebral vasodilation, and fetal death. (19)

3e. IDA in Lactating women

Lactating mothers would be considered to require less iron than that required for nonpregnant, non-lactating women provided they are iron replete during pregnancy. This assumption is based on lactational amenorrhea and iron conservation that results. (20) However, many women enter or conclude pregnancy with iron insufficiency. Additionally, blood loss occurring at delivery makes them susceptible to further iron depletion. (21) Breast milk is the primary source of nutrition in infants, the quality and quantity of which relies on the mother's nutritional status. The Guidelines by the Swiss Society for Gynecology and Obstetrics recommend that if the woman's hemoglobin is 95-120 g/L, first-line treatment is to increase the oral iron to 80-200 mg/day. (22)

4. Iron Therapy for IDA

4a. Oral Iron Therapy

Most recommendations favour an oral dose of 100–200 mg of elemental iron daily, in 2 to 3 divided doses. In general, ferrous iron is better absorbed than ferric salts. (23) Of the several iron formulations available to choose from, ferrous sulphate is preferred, since, apart from being inexpensive, it contains twice the iron content of gluconate or fumarate salts necessitating the use of fewer tablets to reach the same dosage range. A study by Zariwala et al showed that ferrous sulfate has better absorbability compared with other oral iron formulations. (24) The Table below gives the different recommendations:

ORAL IRON THERAPY RECOMMENDATIONS

SOURCE OF RECOMMENDATION	AGE	DOSE	DURATION
National Iron + Initiative (NIPI) (6)	6 months – 10 years	3mg/kg/day	2 months
	10-19 yr	60 mg of elemental iron daily	2 months
	Pregnancy and lactation	2 IFA tablets (1 in the morning and 1 in the evening) per day	At least 100 days
WHO (9)	Children < 2 yr	25 mg	3 months
	Children 2-12 yr	60 mg	3 months
	Adolescents, adults including pregnant women	120 mg/day	3 months
CDC (23)		150-180 mg/day in divided doses	

Patients should be instructed to take oral iron preferably on an empty stomach (1 hour before meals) with a source of vitamin C like orange juice to maximize absorption. (15) When there is GI intolerance to iron at standard doses, lower doses must be tried. (7) Enteric coated iron, though likely to be better tolerated in terms of gastrointestinal side effects, contains less iron and the available iron may not be released in the duodenum for absorption. (7)

COMMON ORAL IRON PREPARATIONS ARE GIVEN IN THE TABLE BELOW:

Preparation	Dose (mg)	Elemental Iron Content (mg)
Iron polymaltose drops	-	50 mg/ml
Ferrous sulphate	324	65
Ferrous gluconate	330	36
Ferrous fumarate	100	33

Oral iron should be continued for 3 months after anaemia has been corrected to replenish stores. While ascorbic acid is known to augment iron absorption there are insufficient data to co-prescribe it with iron. (14)

Inadequate response to oral iron therapy can be due to a number of factors, such as poor intake or absorption, ongoing losses, coexisting conditions, incorrect diagnosis or true refractoriness with more than one factor often being involved. (7) Non-compliance is estimated at 10-32% among those on oral iron supplements contributing to curtailed therapeutic responses. (8) Though daily oral iron replacement has been the norm for treatment of iron deficiency anaemia thus far, there has been a suggestion that the current practice might paradoxically interfere with iron absorption. This hypothesis is supported by the study by Moretti et al who demonstrated that daily or twice daily doses of oral iron increased hepcidin levels which in turn suppressed iron absorption for up to 48 hours. (25)

This finding is likely to play an important role from a public health perspective where alternate day therapy could reduce costs, increase compliance and absorption; thereby possibly translating to better treatment success rates.

Follow up after oral iron

Secondary analysis of data from five randomized clinical trials (RCTs) of oral iron *versus* intravenous (IV) ferric carboxymaltose was carried out to characterize response to oral iron therapy. The major conclusion from this pooled analysis was that day-14 Hb response to oral iron was an accurate predictor of longer-term and sustained treatment response to continued oral iron supplementation. Hb level on day 14 should

be considered a useful tool for clinicians in determining whether to transition patients from oral to IV iron or evaluate for other contributory causes of anaemia. (8)

The Table below shows the selected trials:

SUMMARY OF INCLUDED RCTS (REPRODUCED FROM 8)

Study	Population	Intervention	Comparator	Outcome measures
Van Wyck N=361	Postpartum IDA Mean age 26 Mean Hb<9.1 in 80%	FCM (a,b)	Ferrous sulfate 325 mg TID day 0-42 Compliance: 83.9%	Proportion of patients with Hb increase ≥2.0 g/dl at day 42
Seid N=91	Postpartum IDA Mean age 26 Mean Hb 8.9	FCM (a,b)	Ferrous sulfate 325 mg TID day 0-42 Compliance: 96.2%	Percentage of patients achieving Hb>12.0 g/dl between day 0 and 42
Van Wyck N=477	Heavy uterine bleeding Mean age 39 Mean Hb 9.4	FCM (a,b)	Ferrous sulfate 325 mg TID day 0-42 Compliance: 90.3%	Proportion of patients with Hb increased ≥2.0 g/dl at day 42
Barish N=1446 Multi Dose Trial (708) FCM= 343, SMC= 360	IDA of various etiologies FCM multi dose trial Mean age 49/48 Mean age 49/48	FCM (a,c)	Standard Medical Care Oral iron, IV iron, or no iron replacement Compliance not calculated for oral iron patients	Primary outcome: Safety from day 0 to day 42 Secondary outcome: Various efficacy measures
Kulnigg N= 200	IBD with IDA Mean age 40/45 Mean Hb 8.8	FCM (a,d)	Ferrous sulfate (100 mg elemental iron) BID for 12 weeks Compliance 98.5%	Non-inferiority in improving Hb to week 12

Legend:

BID: twice a day; FCM: ferric carboxymaltose; Hb: hemoglobin; IBD- inflammatory bowel disease; IDA: iron deficiency anemia; IV: intravenous; SMC: standard medical care; TID: three times a day.

a) Based on a modified Ganzoni formula Milligrams of iron administered pre-pregnancy wt in (kg) × (15 – Baseline Hb) × 2.4 + [500 if transferrin is <20% and ferritin <50 ng/ml]
b) Maximum weekly dose 15 mg/kg not to exceed 1000 mg/dose administered intravenously over 15 min or less
c) FCM given as 15 mg/kg up to 750 mg weekly until calculated iron deficit reached
d) A maximum dose of 1000 mg or patients with body weight <66 kg, 15 mg/kg body weight. The total dose administered was split across visits so that a maximal weekly dose of 1000 mg or if bodyweight <66 kg, 15 mg/kg body weight was not exceeded; a maximum of 3 injections was permitted per cycle. A second treatment cycle was permitted if iron parameters indicated IDA between the end of first cycle and week 9 of the study.

4b. Parenteral iron therapy

Though the initial rise in Hb is more rapid with parenteral iron, the increase at 12 weeks is not different from that observed with oral therapy. (14) Indications for parenteral iron include (26):

1. Contraindications / GI intolerance to oral iron
2. Pregnancy (beyond the first trimester) and postpartum if oral iron not suitable (GI intolerance) or ineffective.
3. Diseases which may affect oral iron absorption (e.g. intestinal mucosal disorders).
4. Chronic renal impairment receiving erythropoiesis-stimulating agent therapy.
5. Ongoing iron losses that exceed absorptive capacity.
6. Requirement for rapid iron repletion (e.g. pre-operatively for non-deferrable surgery)

The cumulative dose for IV iron is calculated based on the patient's Hb and body weight. The Ganzoni formula is popularly used and is as follows:

Total body iron deficit (mg) = body weight* (kg) x (target Hb – actual Hb in g/L) x 0.24** + 500 (mg) *** *Use ideal body weight in overweight patients.

**The factor 0.24= 0.0034 x 0.07 x 1,000: For this calculation the iron content of haemoglobin = 0.34%, blood volume = 7% of the bodyweight, and 1,000 is the conversion from g to mg

***Iron depot

Since the Ganzoni-calculated dosing is perceived to be cumbersome, with a potential to underestimate the iron dose, a simpler dosing scheme was developed in the FERGIcor (FERinject in GI Disorders to Correct Iron Deficiency) trial.[27] This is likely to be more useful while considering blanket therapy. The Table below shows a simple scheme for estimating total iron need.

Simple Scheme for the Estimation of Total Iron Need

Degree of Iron Deficiency	Haemoglobin Level, g/dL	Dose for Body Weight <70 kg, mg	Dose for Body Weight ≥70 kg, mg
No anaemia	Normal	500	1000
Moderate	10-12 (women) 10-13 (men)	1000	1500
Severe	7-10	1500	2000
Critical	<7	2000	2500

When large amounts of iron are required, ferric carboxymaltose and low-molecular-weight iron dextran are advantageous because higher doses can be administered per infusion. (8) The advantage of ferric carboxymaltose (FCM) is the abbreviated infusion rate, single infusion requirement and that it does not necessitate a test dose. Though anaphylaxis has not been reported with FCM, intravenous iron should be administered only at a centre where resuscitation facilities are available. (16) While intramuscular and intravenous formulations are comparable, intramuscular injections are painful and can lead to permanent skin discoloration. It follows that their use is least preferred and often discouraged. (4)

COMPARISON OF IV IRON PREPARATIONS

Iron preparation	Maximum single dose	Duration of infusion
Iron dextran*(Cosmofer)	20 mg/kg	6 h
Iron sucrose (Venofer)	200 mg 500 mg	10 min 4h
Ferric carboxymaltose (Ferinject)	1000 mg	15 min

*can also be given intramuscularly.

4c. Transfusion for IDA

The decision to transfuse must be individualized, with risk-benefit ratio being weighed before recommending that a patient gets transfused. Review of literature found insufficient evidence to justify the use of a single Hb concentration as a threshold for the transfusion of patients with acute or chronic anaemia. (9) Blood transfusion should be highly restricted in chronic iron deficiency anaemia. It should be considered for patients with active bleeding who are hemodynamically unstable, or for patients with critical anaemia (Hb level <7 g/dL), acute myocardial ischemia, or if all other treatments fail to correct the anaemia. In patients over 65 years of age or with significant cardiovascular disease who may tolerate anaemia poorly, higher threshold values (Hb<8 g/dL) may apply. (23) The National Iron Plus Initiative (NIPI) in addition recommends transfusion for

- All children with Hb ≤4 gm/dl
- Children with Hb 4–6 gm/dl with any of the following:

Dehydration, Shock (blood loss >10% of blood volume) or Impaired consciousness.[6]

4d. Indications for referral to a higher center

The National Iron Plus Initiative (NIPI) suggests that the following patients be referred to First Referral Units (FRU)/ District Health Centers:

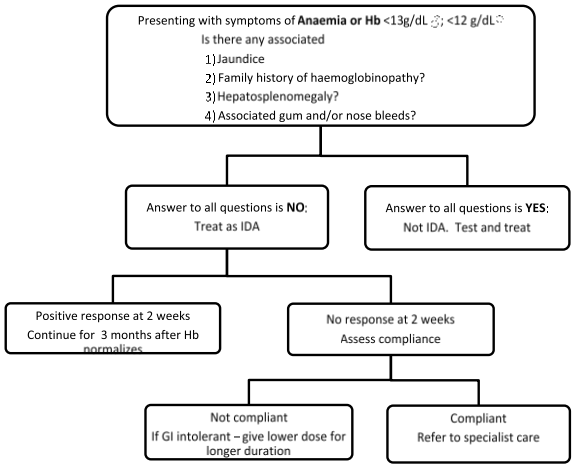
- Patients with hepatosplenomegaly /splenomegaly or lymphadenopathy where malaria is not the cause.
- Patients with a family history of similar illness.
- Patients with history suggestive of other cytopenia, e.g., bleeding manifestations.
- Bicytopenia, pancytopenia or leucocytosis where blood counts are available, and presence of abnormal cells on the peripheral smear examination.
- Severe anaemia (Hb< 7g/dL)
- Patients not responding to oral iron in the time frame as outlined below:
    1. Children < 10 years – at 2 weeks
    2. Adolescents and adults – at 3 months

- Women during pregnancy identified with Hb<8 g/dL in the third trimester.

4e. Dietary advice

All patients with iron deficiency anemia should be encouraged to consume a diet rich in iron in addition to medicational iron therapy. The richest source of heme iron is lean meat, fish, poultry and seafood. Non heme iron is available primarily in vegetarian diets - nuts, beans, cereals, pulses and vegetables. (28) While heme iron has higher bioavailability, Vitamin C enhances the absorption of non heme iron. It is therefore advisable to consume supplemental iron tablets with water or orange juice rather than with milk. Coffee and tea have tannins which inhibit iron absorption and thus must be avoided with meals.

5. Proposed algorithm for treatment of IDA



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