Review Article

Iron Deficiency Anemia: An Overview

Udayashankar D*, Sarah P**, Indrani N**, Nagajothi**

Associate Professor*, Assistant Professor**, Department of Internal Medicine, Chettinad Hospital & Research Institute, Chettinad Academy of Research and Education, Chennai, India.

Dr.Udayashankar completed his MBBS in 1972 and MD General Medicine in 1982. He has over 30 years of experience in tertiary care institutions, both in India and abroad. He has keen interest in the fields of Nephrology and Intensive care.

Corresponding author - Udayashankar (ushankar1995@gmail.com)

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Abstract

Iron deficiency anemia (IDA) is the leading cause of anemia worldwide, which causes significant morbidity. In this evidence based review, the etiology of IDA, guidelines on screening, most useful diagnostic tests, and the role of various modalities of treatment have been elaborated. Timely diagnosis and appropriate management of IDA are crucial especially in developing countries.

Key Words: Anemia, Iron Deficiency, Screening, Intravenous Iron, Oral Iron, Blood Transfusion

Introduction

Anemia affects almost a quarter of the world's population and iron deficiency is the commonest cause[1]. Other causes include megaloblastic anemia due to Vitamin B12 and folate deficiency. This review summarizes the etiology, screening, diagnosis of nutritional anemia with special importance to the management of anemia related to the deficiency of iron. Evidence based guidelines have been discussed and the levels of evidence with grades of recommendation are shown in Table 1.

Grades of Recommendation	
A	Supported by, at least, two level I investigations
B	Supported only by one level I investigation
C	Supported only by level II investigations
D	Supported by, at least, one level III investigation
E	Supported by level IV or V Evidence
Evidence Levels	
Level I	Randomized trials; great sample size; clear results; low risk of alpha (false-positive) or beta(false-negative) errors
Level II	Randomized trials; small sample size; uncertain results; moderate to high risk of alpha (false-positive) or beta(false-negative) errors
Level III	Nonrandomized, contemporaneous controls
Level IV	Nonrandomized, historical control and experts opinion
Level V	Case series; without control subjects and experts opinion

Table 1 - Grades of recommendation and levels of evidence[2]

Iron deficiency anemia (IDA)[3,4]

Iron deficiency affects both men and women and prevalence of anemia increases with age[3]. Anemia decreases the increases costs of health care by retarding the capacity to work[4]. Iron deficiency is known to be associated with fatigue, cognitive dysfunction, infertility, restless leg syndrome (RCS) and overall reduced quality of life, all of which can be easily reversed with early and appropriate iron therapy[5-11]. Conditions of the gastrointestinal tract such as hook worm infestation, inflammatory bowel disease, malignancy and celiac disease are notorious for causing IDA. Comorbidities such as chronic kidney disease (CKD) and chronic heart failure (CHF) also increase the risk of anemia and iron deficiency. In turn, iron deficiency in CHF is associated with increased risk of death, irrespective of the level of hemoglobin. It is also associated with increase in platelet count, with consequent risk of thrombosis and embolism.

Etiology

The commonest cause of iron deficiency anemia in India is worm infestation. Iron deficiency anemia also occurs in premenstrual women due to normal uterine bleeding with inadequate nutrition or abnormal uterine bleeding. In developing countries, anemia is due to diminished RBC production due to low iron stores, decreased iron intake, impaired absorption, increased iron demand and excessive loss. The causes are represented in Table 2.

There are 4 stages of iron deficiency anemia[3]:

Stage I : Moderate depletion of iron stores

Stage II: Severe depletion of iron stores

Stage III: Iron deficiency

Stage IV: Iron deficiency/dysfunction and anemia

In premenstrual women	In men and post-menopausal women
Normal uterine bleeding with inadequate nutrition	Long term aspirin and NSAID use
Abnormal uterine bleeding	Peptic ulcer disease
Thyroid disorders	H.pylori infection
Polycystic ovary syndrome	Esophageal and colonic cancer
Uterine fibroids	Celiac disease
Hyperprolactinemia	Gastric antral ectasia
Endometrial hyperplasia	Bacterial overgrowth
Drugs such as anti-psychotics and anti-epileptics	Gastrectomy, intestinal resection
	Angio dysplasias

Table 2 - Causes of Iron Deficiency Anemia[4,5]

Screening of patients for iron deficiency[6-8]

1. Screening during pregnancy (C)
2. Children at one year of age (C)
3. Men and post menopausal women need not be screened but may be evaluated when iron deficiency anemia is present (C)
4. Screening for celiac disease in adults with IDA (C)
5. CDC recommends screening of children from low income families at 9 and 12 months of age.
6. CDD recommends screening of preterm and low birth weight babies before six months of age
7. A meta analysis has shown that in neonates in whom cord clamping was delayed for up to two minutes after birth, there was a diminished risk of low iron stores in these infants up to six months.
8. Babies breastfed exclusively for beyond four months and weaning without iron fortified formulas need to be screened.

Diagnosis

WHO criteria[3]

Anemia is defined as a hemoglobin concentration below 13g/dl in men over 15 years; below 12 g/dl for non pregnant women over 15 years, and below 11g/dl in pregnant women. In pregnancy hemoglobin level less than 11g/dl in first or third trimester, or less than 10.5 g/dl in second trimester is considered as anemia. A maternal hemoglobin less than 6g/dl has been associated with poor fetal outcome including death.

Hemoglobin levels may vary according to age, race, smoking status, people living in higher altitudes and participants in endurance sports. The age related variation in hemoglobin and mean corpuscular volume (MCV) is represented in Table 3.

Diagnosis of iron deficiency anemia[7]

One of the simple and informative tests in the diagnosis of anemia is the complete blood count. It can be used to determine the Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCV), and mean corpuscular

Age	Hemoglobin level		Mean corpuscular volume (MCV)	
	Mean (g/dl)	Diagnosis of anemia	Mean	Diagnosis of microcytosis
3-6 months	11.5	9.5	91	74
6-24 months	12	10.5	78	70
2-6 years	12.5	11.5	81	75
6-12 years	13.5	11.5	86	77
12-20 years female	14.0	12	90	78
12-20 years male	14.5	13	88	78
20-59 years		13.7	90	80
60 years and above		13.2	90	80

Table 3 - Age related variation in hemoglobin and MCV[9]

hemoglobin concentration (MCHC) all of which are reduced in IDA (microcytic, hypochromic RBCs). However, it should be noted that normocytic erythrocytes may be seen in upto 40% of patients with IDA. Hence iron deficiency should still be considered in all cases of anemia unless the MCV is more than 95fl, since at this level MCV has a sensitivity of 97.6%. It is not uncommon to find dual deficiency anemia (combination of IDA and macrocytosis) resulting from deficiency of multiple nutrients or use of some medications. In this condition, although MCV may normal,peripheral smear will reveal both micro and macrocytic RBCs. A wide red cell distribution width (RDW) should arouse a suspicion of IDA combined with macrocytic anemia.

The most accurate test for the diagnosis of iron deficiency anemia is serum ferritin level since it effectively reflects iron stores. Serum ferritin below 15ng/ml is diagnostic of IDA. Nevertheless, if the cut-off is increased to 30ng/ml the sensitivity increases from 25 to 92% while retaining a specificity of 98%. At this juncture, it should be mentioned that ferritin is also an acute phase reactant which can be elevated in chronic inflammatory states as well in certain

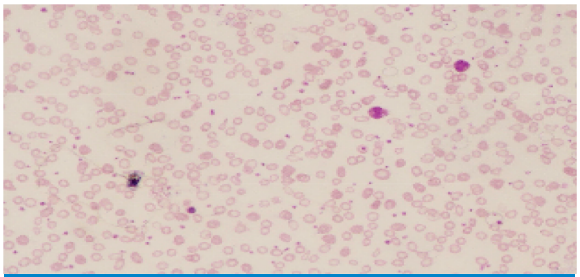

Fig 1 : Peripheral smear showing microcytic hypochromic RBCs

infections.Patients with chronic inflammation should be suspected of having iron deficiency anemia if their ferritin level is less than 50ng/ml, and in such patients ferritin level equal to or greater than 100ng/ml virtually excludes iron deficiency. Additionally, C-reactive protein measurements serve to confirm that raised ferritin level may be due to inflammation.

For patients with no inflammatory states and in whom ferritin level is indeterminate 31-99 ng/ml, further tests is warranted to determine the iron status. In iron deficiency, seum iron will be low, with increased TIBC (total iron binding capacity). Other tests of value include transferrin level,soluble transferrin receptor, erythrocyte protoporphyrin testing or bone marrow biopsy with iron staining.

Soluble transferrin receptor (sTfR) level is elevated only in IDA and is unaltered in inflammatory states, thereby identifying concomittant IDA in patients with chronic disease. sTfR and sTfR/log ferritin index (<1) can also be used.

The heme precursor RBC protoporphyrin accumulates in the absence of adequate iron stores. The gold standard in the diagnosis of IDA is the absence of stainable iron in bone marrow biopsy specimens.

Transferrin saturation (TfS) signifies the amount of iron available for erythropoeisis. A TfS below 20% and ferritin level below 30ng/ml are indicative of IDA. For example, in patients with inflammatory bowel disease, ferritin level less than 100ng/ml with TfS<30%; In chronic kidney disease, ferritin level less than 500ng/ml with TfS<30% and in congestive heart failure, ferritin level less than 100ng/ml with TfS<20% are indicative of iron deficiency.

	Key recommendations	Grade of recommendation
1	Anemia should be defined according to the lower limit of normal range of the concerned laboratory	B
2	Presence of iron deficiency should prompt investigation irrespective of the level of anemia.	B
3	A lower the hemoglobin level increases the likelihood of a serious undelrying pathology	B
4	In the absence of chronic inflammation, infection or hemoglobinopathy RBC indices are reliable indicators of iron deficiency	A
5	Serum ferritin is the most useful test for IDA	A

Table 4 - Summary of key recommendations for iron deficiency anemia

Management[10]

Aim

After discovering any underlying cause, the aim of treatment should be to restore the hemoglobin concentration and RBC indices to normal, and replenish iron stores.

Iron therapy

Intestinal iron absorption is limited. Maximal absorption of oral iron is between 20 to 25% and is reached in the late stages of iron deficiency. Latent iron deficiency and iron deficiency anemia correspond to absorption rates of nearly 10% and 13% respectively. Healthy males and females absorb iron at the rate of 5% and 5-6% respectively.

Calculation of iron deficit

In iron deficiency, dose of iron required is calculated by certain formulae:

Ganzoni formula[11]:

Total iron deficit in mg =

[Body weight in kg x (target Hb - actual Hb in g/dl)] x 0.24]+ 500mg for body iron stores.

Patients with more severe anemia of Hb<7g/dl may need additional 500mg of elemental iron. Treatment of iron deficiency without anemia can be undertaken with 500-1000 mg of elemental iron. Iron deficit may be corrected either in the form of oral or intravenous iron therapy.

Poor compliance and non adherence to oral iron therapy are due to unpleasant dose dependent gastrointestinal side effects in nearly 50% of patients. Normal range of oral iron administration is between 100 to 200 mg of elemental iron per day, however IDA can be treated even with lower doses of 15-20 mg of elemental iron per day by oral administration, which may improve compliance. The GI effects of oral iron may be minimized by giving iron during meals, but the rate of absorption falls below 40%. Proton Pump inhibitors, chronic atrophic gastritis, vagotomy or recent gastrectomy reduce oral absorption. The different forms of oral iron, their formulations, content of

Form of Oral iron	**Formulation**	**Elemental iron**	**Adult dose/day**
Ferrous sulphate	325 mg tablet	65 mg	1 tablet thrice daily
Ferrous fumarate	324 mg tablet	106 mg	1 tablet twice daily
Ferrous gluconate	300 mg tablet	38 mg	2-3 tablets, 2-3 times a day
Dose in children: 3mg/kg/day up to 60mg/ day			

Table 5 - Oral iron therapy

elemental iron and dose in adults and children are summarized in Table 5.

Intravenous iron[12,13]

When uptake through the gut is impaired in conditions such as celiac disease, autoimmune gastritis, past gastric or duodenal resection, the efficacy of oral iron may be poor.Further, oral iron therapy may not be able to keep up with ongoing blood loss as in menorrhagia/ gastrointestinal bleeding, or in non-compliance with oral iron medication. Under these circumstances, intravenous iron is very effective. The main disadvantage of IV iron is its cost. Although safety of IV iron preparations has been a concern, a review by the US food and drug administration database from 1998-2000 showed that the cumulative risk of adverse reactions by all IV formulations (except high molecular weight iron dextran) is quite low (1 in 200,000). Intravenous formulations are solutions for infusion, and dose is based on the patient's weight and expected change in hemoglobin level. The various preparations of IV iron available are shown in Table 5.

IV iron formulation	Iron concentration
Sodium ferric gluconate	12.5 mg/ml
Iron dextran	50 mg/ml
Iron sucrose	20 mg/ml
Ferumoxytol	30mg/ml
Ferric carboxy maltose	50 mg/ml

Table 6 - Intravenous iron formulations

Blood transfusion in IDA[14-16]

1. Patient's clinical condition and symptoms should determine whether there is a need for blood transfusion, since there are no established guidelines on the level of hemoglobin below which transfusion is beneficial.

2. In pregnancy a hemoglobin less than 6g/dl warrants transfusion as there may be resultant abnormal fetal oxygenation with fetal distress, reduced amniotic fluid volume, fetal cerebral vasodilation and consequent fetal death.

3. In the event of transfusion, 2 units of packed RBCs should be given initially and later clinical scenario should be assessed for further management.

4. Transfusion may be considered for patients have cardiovascular compromise due to active bleeding or myocardial injury, and as a last resort when other treatment modalities have failed.

5. In the presence of significant underlying cardiovascular disease, transfusionmay have to be done at higher levels of Hb(<8g/dl).

6. Intravenous iron should be supplemented whenever transfusions are given in order to prevent the need for subsequent transfusions.

Follow up and monitoring

The hemoglobin level raises by 2g/dl within 4-8 weeks of therapy., and depending on the severity of deficiency, normalization of hemoglobin may take up to 3 months, and further longer to replenish body iron stores. Therefore, another hemoglobin value should be obtained at 12 months. The first marker to increase in the first few weeks of transfusion is serum ferritin. However, it does not correlate with body iron stores and estimation of ferritin may be beneficial only 8-12 weeks after the end of treatment. On the other hand, iron overload should also be avoided in patient requiring recurrent transfusions, and this may be reflected by a TfS exceeding 50%. Patients who do not respond to IV iron therapy should be given Erythropoeitin stimulating agents in addition, and the target Hb should not exceed 12g/dl.

Conclusion

Iron deficiency anemia is one of the easily treatable causes of anemia. Early detection, evaluation for the underlying etiology, screening in the appropriate population at risk is essential. Initiation and continuation of treatment through various modalities including oral and intravenous iron as well as blood transfusions should be the mainstay of management.

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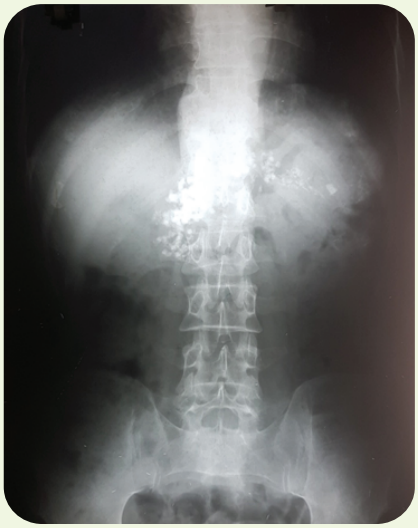
Image Challenge - 3



Clue: 27 year old lady with diabetes whose sugars were highly fluctuant

- Answer in page : 94