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Different forms of iron therapy in the treatment of iron deficiency anemia in children

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Abstract
In pediatrics: IDA remains a challenging health problem. It's the commonest nutritional deficiency worldwide, specifically in developing nations. The causes of ID in children are insufficient Fe intake along with increased requirements because of fast growth. Children who have mild IDA are often asymptomatic. Yet, children with marked Fe deficiency anemia, increased HR and HF might occur. Treatment of IDA is based on the cause of the disorder. Oral administration of Fe+2 salts offers cheap yet efficient improvement in correcting anemia due to its high bioavailability. The commonest Fe salt utilized for oral administration is Fe+2 sulfate, yet it's proved to cause intestinal adverse influences (including nausea, vomiting abdominal pain, constipation, diarrhea) in a lot of users. Ferrous fumarate has less GIT adverse influences and is actually absorbed better than Fe sulfate. The iron polymaltose complex is absorbed and exchanged to transport proteins gradually, avoiding fast increase in Fe in serum and Fe distribution to various tissues. Lactoferrin is an Fe binding, non-heme protein that's structurally and chemically resembles serum transferrin. The transporter of Fe in the serum. It's produced by mucosal epithelium, detected in secretions like salivary, nasal, bronchial secretions and highly produced in milk.

Keywords: Iron deficiency, iron therapy, anemia in children

Introduction
Iron deficiency (ID) is the commonest nutritional deficiency in pediatrics. Iron deficiency is specifically a great challenge because of the resource-limited nations in Asia and Africa. In the USA and other resource-rich nations, rate of ID are substantially less, however ID remains common and might cause pivotal consequences to health and development [1].
Anaemia typically refers to a Hb level that's ≥2 standard deviations (SD) less than the mean for healthy individual of the same gender and age. The WHO used the following Hb thresholds to define anaemia [2].

Iron deficiency anemia (IDA): It is defined in children as [3].

Children 6 months to <5 years
- Ferritin level is less than 15 ng/ml.
- The hemoglobin level is less than 11 gm/dL.

Children 5 to <12 years
- Ferritin level is less than 15 ng/ml.
- Hemoglobin level is less than 11.5 gm/dL.

These definitions are commonly utilized yet not internationally used; some experts depend on the use of slightly increased Hb and ferritin cutoffs as threshold for starting an assessment and defining IDA, respectively. The degree of the assessment required is based upon the possibility of IDA in individual and on the clinical history of each case [4].

Causes of iron deficiency anemia
1. Dietary factors
Inadequate Fe intake.

- Ineffective absorption because of factors related to the dietary sources of Fe with reduced bioavailability.
- Introduction of unmodified co milk (non-formula cow milk) in children aged <12 months.
- Occult blood loss due to cow milk protein-induced colitis.
- Obese children.

Clinical manifestations of iron deficiency anemia

Stages of iron deficiency

With ID, stored Fe is depleted, yet there's enough Fe in the "labile" Fe pool from the daily turnover of RBCs for normal Hb synthesis, unless further Fe loss happens. Anaemia occurs only in the last stage of ID. On the contrary, when Fe repletion begins, the anaemia is the 1st to recover and normal level of stored Fe the last thing to be corrected completely [5].

Clinical findings

The commonest presentation of IDA is asymptomatic in well-nourished infants or children who have mild to moderate microcytic, hypochromic anaemia. Much less common are cases with marked anaemia, they suffer from lethargy, pallor, being irritable, tachycardia, enlarged heart, poor feeding, and increased respiratory rate [6]. Pica might happen as well in children aged of 2-3 y in addition to developmental disability such as autism and intellectual disability [7].

Nutritional IDA typically presented by (all of the following) [8]

1. Age 9 months to 3 y.
2. One or more risk factors for nutritional IDA.
3. Lack of Fe supplementations in breastfed babies (start from the 4th-6th month in full-term babies or by 2 weeks of age for preterm babies), feeding of low-Fe formula or unmodified (non-formula) cow milk, and inadequate Fe-rich complementary foods at the age 4-6 months.
4. In toddlers and young children (≥12 months), dietary risk factors like excess intake of cow milk (more than 20 oz [600 mL] / day) and inadequate consumption of Fe-rich diet.

Atypical presentation of nutritional IDA (any of the following) [8]

1. Age 3 - 12 y.
2. No dietary risk factors for ID.

Features that suggest non-nutritional aetiology of IDA (caused by blood loss or malabsorption)

- Severe loss of blood e.g., frequent epistaxis, gross loss of blood in stool, or menorrhagia in menstruating girls.
- Disorders accompanied by Fe malabsorption e.g., celiac disease or IBD.

Features that suggest other etiologies of anaemia, include

- Other systemic diseases accompanied by anaemia e.g., systemic inflammatory diseases or tumors.
- Acute or recurrent infection consistent with anemia of inflammation.
- Family history of anaemia or hemoglobinopathy like thalassemia trait.

Associated disorders and effect of therapy

IDA is accompanied by various deficits such as impairment of neurodevelopmental parameters, and impaired growth& immunity [9].

1. **Neurodevelopment:** The determined associations give the rationale for routine supplementation to breastfed babies and subsequently carrying out screening of all individuals during infancy and early childhood in the USA and universal Fe supplements for children in individuals with elevated rate of IDA [10]. The majority of such clinical evidence were obtained from longitudinal cohort studies in low- & middle-income countries with elevated rate of IDA that revealed a correlation between IDA and neurodevelopmental deficits, in particulate for children with markedly serious and chronic IDA [11].
2. **Febrile seizures:** In fact, there is No causal relationship between ID and development of febrile convulsions. Nevertheless, serum ferritin level is notably reduced in children experienced febrile seizures in comparison with children with fever alone. Thus, screening for ID in young children having a history of febrile convulsions is warranted [12].
3. **Immunity and infection:** On one hand, ID seems to be accompanied by mild to moderate defect in WBCs and lymphocytes functions such as defective IL-2 & IL-6 synthesis [13]. On the other hand, Fe supplementation might cause paradoxical elevation the risk for particular types of infections. Specifically, Fe supplementation might elevate the risk for bacterial infections due to the fact that Fe-binding proteins transferrin and lactoferrin have bacteriostatic impacts that are lost if they're saturated with Fe [14].
4. **Exercise capacity:** Reduced Fe stores, without the evidence of anemia, is accompanied by reduced exercise performance in laboratory animals. The same finding was documented in children, in particular adolescent athletes [15].

Diagnosis of IDA

Diagnosis of IDA depends upon clinical history of the patient, examination, laboratory investigations and differential diagnosis with the similar clinical conditions [16].

Hematological markers

Hemoglobin

Age along with other conditions are considered in the WHO guidelines, leading to different Hb thresholds denoting anaemia. These thresholds are:

- 11g/dl in age 6 m to 5y,
- 11.5 g/dl in 5-12 y.
- 12 g/dl in 12-15 y.
- 13g/dl in >15y [17].

Common laboratory findings in iron deficiency

Complete blood count

- **Hb, Hct:** Decreased relative to age and gender.
- **RBCs:** Low.
- **MCV:** Decreased relative to age and gender (microcytosis).
- MCH less than 27 pg (hypochromia).
- MCHC less than 30 percent.
- **Thrombocytosis, rarely:** thrombocytopenia and leucopenia

- **Peripheral smear:** Anisochromia, anisocytosis and pencil cells, rarely: basophilic stippling, target cells, hypersegmented neutrophils.
- Serum ferritin is less than 15 ng/ml
- Serum iron is less than 30 mcg/dl.
- TIBC is more than 480 mcg/dl.
- Transferrin saturation (Iron/TBCx100) less than 16 percent
- Metzner index (MCV/RBC) is more than 13.

Hepcidin

Hepcidin synthesis is reduced in Fe deficiency anemia yet, it's elevated in inflammatory conditions. Hepcidin might potentially be utilized to discriminate IDA and anemia of chronic illnesses [18]. In addition, plasma hepcidin has an obvious diagnostic role in IRIDA when low blood ferritin levels are associated with elevated serum hepcidin. Thus, serum hepcidin might help prediction of the treatment response, it might help identifying cases in whom the response to oral Fe is probable (cases having decreased hepcidin level) and cases in whom it isn't probable (cases having normal or increased hepcidin level) [19].

Contributing factors for IDA

Despite IDA is actually result from inefficient dietary Fe, it sometimes occurs due to underlying medical conditions as GIT bleeding, malabsorption diseases, or irregularities of menstruation following the menarche, each of which have to be evaluated on history. For instance, refractory IDA might be the symptom of celiac disease, *H. pylori* infection, or IBD [20, 21].

Treatment of IDA

Nutritional counseling

Iron rich food should be used and facilitators of Fe absorption like Vit C-rich food. On the other hand, inhibitors of Fe absorption as tea, phosphate and phytates should be avoided. Avoid cow milk in the 1st year of life due to the poor bioavailability of Fe in cow milk along with the possibility of occult gastrointestinal bleeding induced by the cow milk protein. Start weaning as early as 6 months of age and use Fe-fortified cereals starting six months to one year [22].

Oral iron therapy

For adequate Fe absorption, administration 30–45 min prior meals or 2 h following meals is potentially recommended and with Vit C in the form of juice as opposed to milk. The dosage of essential Fe stays the exact same, yet the amount of essential Fe differs in different salts. Ascorbic acid in combination with Fe enhances Fe absorption, yet this advantage is absent due to the high occurrence of negative impacts [23].

To achieve successful therapy of IDA in infancy and childhood, it's crucial to detect the proper dosage and schedule of oral Fe treatment, applying dietary modification in addition to Fe supplementation, and follow-up the response to therapy [24].

Available iron formulations

Ferrous iron salts

Ferric (Fe+3) is 3–4 times less bio-available in comparison with Fe+2, as Fe+3 has poor solubility in alkaline medium so for its absorption, it has to be converted to Fe+2 iron *in vivo* [25]. Ferrous salts aren't expensive in comparison with other available formulas. But they develop many side effects including poor taste and gastrointestinal intolerance.

1. **Ferrous fumarate:** Fe (II) fumarate, Fe+2 fumarate, is the Fe (II) salt of fumarate, utilized to supplement Fe intake. Its chemical formula is C4H2FeO4. Pure Fe+2 fumarate has an Fe content of 32.87 percent, thus 1 tablet (300 mg) Fe fumarate will contain 98.6 mg of Fe (548 percent of the Daily Value according to 18 mg RDI) [26].
2. **Ferrous sulfate:** iron (Fe+2) sulphate is an iron salt known as green vitriol. It's the commonest Fe salt utilized for oral intake, yet it's proved to cause intestinal adverse influences (such as nausea, vomiting, abdominal cramps, constipation, diarrhea) in a lot of users [27].
3. **Ferrous gluconate:** Iron (Fe+2) gluconate, or Fe+3 gluconate, is a black component usually utilized as Fe supplement. It is the Fe (Fe+2) salts of gluconic acid. It has the chemical formula C12H24FeO14. Ferrous gluconate has 12 percent elemental Fe; thus one 300 mg tablet of Fe gluconate has 36 mg of elemental Fe [28].

Ferric salts

The bioavailability of Fe from ferric salts is 3 -4times < that of F+2 sulphate. While 100 mg of F+2 sulfate iron daily is enough for the appropriate oral compensation Fe treatment in adults and to yield initial Hb regeneration rate of ~ 0.26 gm/100 mL daily, 400 - 1000 mg of Fe+3 /daily are required for the same treatment effects due to the poor bioavailability of Fe+3 iron [29].

Iron polymaltose

Iron (Fe+3)-hydroxide polymaltose complex is a medical preparation utilized for treating ID / IDA and belongs to the group of oral iron preparations. It's a macromolecular complex, composed of iron (Fe+3) hydroxide (trivalent iron, Fe3+, Fe OH) 3·H2O) in addition to the carrier polymaltose that's present in solid form. It's used in treating ID without anaemia (latent ID) or with anemia (apparent ID). Before administration, the ID should be diagnosed and confirmed by laboratory investigations (including decreased ferritin concentrations, decreased transferrin saturation) [30].

The preparation is present in diverse galenic formulas: syrup, drops, drinkable solution, film-coated tablet, as well as chewable tablet. The syrup, drops, or drinkable solution are preferable for children [31].

- Premature babies: 2.5–5 mg/kg.
- Children aged ~ 1 y o: 25–50 mg.
- Children aged 1–12 y: 50–100 mg.

Carbonyl Iron

Given the small particle size (less than 5 mm) the gastric acid can solubilize this Fe. In the process of this solubilization, hydrogen ions are consumed thus the pH increases. In addition, due to the slowly absorbed Fe (allowing for continuous release for 1 - 2 days) and self-limited by the rate of acid synthesis by the gastric mucosa [29].

Iron protein succinylate (IPS)

In general, IPS is formed of a ferric iron bound to succinylated casein. The Fe in IPS is kept bound to the protein matrix in the acidic gastric medium. The Fe is thereafter released in the less acidic medium in the

duodenum as well as the proximal part of jejunum. Different formula of IPS are available [32].

Iron amino acid chelates

Absorption of chelated Fe occurs in the same way as other non-heme Fe preparations; nevertheless, chelated Fe might be less influenced by promoters or inhibitors of Fe absorption in comparison with ferrous salts. Chelated Fe pass via the acidic gastric content without interaction with dietary phosphate, phytate and fibers, and are thereafter direct absorption occurs in the duodenum [33].

Sucrosomial iron (SI)

It's a novel oral formula that's composed of ferric pyrophosphate protected by a phospholipid bilayer along with a sucrester matrix (called sucrosome). Absorption of SI occurs via para-cellular & trans-cellular routes (M cells) [34]. Various studies have recommended it as an efficient alternate to IV iron particularly for cases suffering severe anaemia and inflammatory conditions [35].

Lactoferrin

It has postulated to have 300 times more affinity to Fe in comparison with serum transferrin and can retain Fe over a broader PH range. In addition, it has been demonstrated that it can affect Fe homeostasis via enhancing Fe export from GIT and inducing Fe storage in ferritin. [36]. Lactoferrin poses several physiological functions that include Fe absorption & promotion, has antiviral, antibacterial, antifungal, anti-inflammatory, antiparasitic effects, as well as immunomodulation role. The vast majority of Lf found in human milk is in the Fe-depleted form (apo-Lf). When it binds Fe forming holo-Lf, the open conformation of apo-Lf closes, that elevates the resistance to proteolytic effect during digestion [37]. A promising method for treatment of IDA with Lf as an alternative to Fe supplementation is of great importance. Both bLf and IPC were utilized for years in pediatrics [38].

Parenteral iron therapy

This form is indicated only in some situations as poor tolerance to Fe orally due to appearance of gastrointestinal adverse impacts, malabsorption diseases, chronic hemorrhagic disease to which the rate of blood loss is highly rapid for oral iron intake to compensate the loss, acute diarrhea, marked Fe deficiency necessitating fast substitution of stores, hereditary IDA and in iron deficiency in a patient with heart failure. Iron dextran is a parenteral form of Fe given IM and present in complexes that provide 50 mg elemental iron/ml and it is the only FDA approved parenteral form for pediatric use [39].

Blood transfusion

It's rarely needed in cases with IDA. Transfusions aren't considered mandatory even with Hb levels 4–5 gm/dl, if the child has good health. It is administered only if there's an emergent necessity to restore O2-carrying ability, i.e., in severely decompensated anaemia [40].

Response assessment

If Hb has been elevated ≥ 1 gm/dl following four weeks of oral Fe supplementation, treatment should be continued, and Hb re-evaluation is carried out / 2‑3 months till Hb level becomes normal. It's recommended to continue Fe treatment for another 2‑3 months to replace Fe storage pools. If the treatment is discontinued, IDA recurrence is possible [41].

If the proper response isn't achieved following 4 weeks of therapy, additional assessment of anaemia should be done. Probable causes of persistence or recurrence of IDA include inefficient therapy, blood loss, malabsorption, or faulty diagnosis. Asking the parents about Fe preparation administered, as well as the dose used to know if it's proper or not. Also, asking about following the dietary modification recommended to their child have been followed or not. In addition, if there was intercurrent illnesses that might cause temporary reduction in Hb levels should be consider [42].

If the child hadn't any intercurrent illness and the Fe supplement was utilized appropriately regarding the dose and timing, the following assessment should be done [20, 43].

- **Assessment for the type of anaemia:** Measurement of serum ferritin levels, Hb electrophoresis, Vit B12, and folic acid might exclude thalassemia trait, chronic disease anaemia as well as mixed nutritional deficiency.
- **Assessment of GIT blood loss:** Stool is tested for the presence of occult blood in a few separate samples. If the result is positive, further assessment is done through investigations for frequent causes of GIT bleeding, such as cow milk protein-induced colitis, celiac disease, and IBD.

Conclusion

Lactoferrin is better than iron polymaltose complex and ferrous fumarate when used with iron replacement therapy in children with IDA.

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