
به نام خدا

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Iron Absorption

- Iron absorption occurs predominantly in the proximal duodenum.
- At neutral pH, ferrous iron is rapidly converted to the insoluble ferric form.
- Normally, only about 10% of dietary nonheme iron entering the duodenum is absorbed.
- Acid produced by the stomach serves to lower the pH in the duodenum and enhance the solubility and uptake of iron .
- Heme is absorbed separately from and more efficiently than inorganic iron, independent of duodenal pH. Consequently, meat is an excellent nutritive source of iron.
- Ascorbate and citrate increase iron uptake.
- plant phytates, bran, and tannins inhibit iron absorption.

Iron Absorption

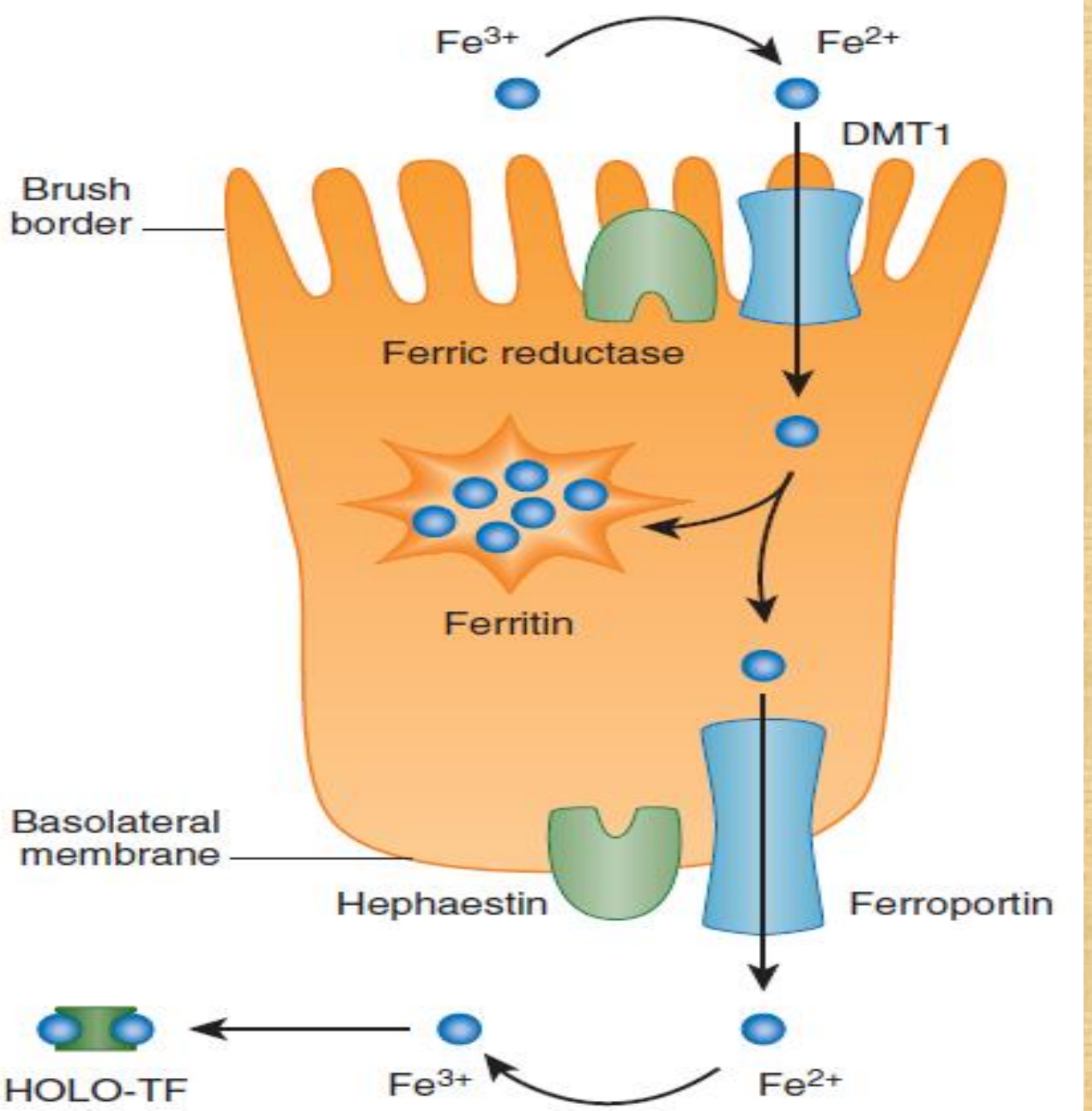
- Nonheme iron arrives at the apical surface of the absorptive duodenal enterocyte in its ferric (Fe3+) form. It is reduced through the action of a brush border ferric reductase. This enzyme may be duodenal cytochrome b.

- cytochrome b is significantly greater in the proximal duodenum than elsewhere and increases in iron deficiency.
- Ferrous (Fe2+) iron is then taken up by the enterocyte through the action of divalent metal transporter 1 (DMT1, also known as Nramp2, DCT1, and SLC11A2).

- DMT1 is widely expressed, but duodenal levels increase dramatically in iron deficiency.

Iron Absorption

- DMT1 can also transport other divalent metal ions, including Cd^{2+}, Co^{2+}, Cu^{2+}, Mn^{2+}, Pb^{2+}, and Zn^{2+}.
- Increased iron absorption induced by iron deficiency also enhances the uptake of these elements.
- After iron enters the absorptive enterocyte through the action of DMT1, it has at least two possible fates.
- 1-retained by the cell and subsequently be lost when the enterocyte dies is used for cellular metabolism or incorporated into ferritin.
- 2-Exported iron leaves the cell by way of a unique basolateral transmembrane iron transporter, ferroportin
- Basolateral iron transfer also requires hephaestin and ceruloplasmin, which are membrane associated and present in the plasma, respectively.


Fe3+
Fe2+
DMT1
Brush border
Ferric reductase
Ferritin
Basolateral membrane
Hephaestin
Ferroportin
HOLO-TF
Fe3+
Fe2+

Iron Absorption

- Both iron deficiency anemia and forms of anemia associated with ineffective erythropoiesis induce a marked increase in iron absorption.
- Hypoxia also increases iron absorption, independent of anemia.
- Hepcidin, an iron-regulated peptide hormone, It circulates in the plasma and binds to the iron exporter ferroportin on the basolateral surface of absorptive enterocytes.
- Hepcidin thus regulates iron absorption at the level of the intestinal epithelium in that any iron unable to leave the enterocytes is lost when these cells turn over.
- Expression of hepcidin is induced in response to iron overload42,43 and inflammation and is repressed in response to increased erythropoietic activity and hypoxia.

Intercellular Iron Transport

- intercellular iron transport is quantitatively more important than intestinal absorption.
- To accommodate ongoing erythropoietic needs, the reticuloendothelial system recycles approximately 20 to 25 mg of iron from effete red cells each day.
- A small fraction, 0.1% or 4 mg, of total body iron circulates in plasma in an exchangeable pool.
- all of the circulating plasma iron is bound to transferrin.
- The liver is the major site of synthesis and secretion of transferrin.

Intercellular Iron Transport

- Transferrin serves three purposes:
- 1-it renders iron soluble under physiologic conditions.
- 2-it prevents iron-mediated free radical toxicity.
- 3-it facilitates transport into cells.

Intercellular Iron Transport

- In the setting of iron deficiency, serum transferrin levels rise substantially as a result of enhanced synthesis of transferrin mRNA by the liver.
- Inflammation depresses levels of both serum transferrin and serum iron, through the action of the iron regulatory hormone hepcidin.
- The sum of all iron-binding sites on transferrin constitutes the total iron-binding capacity (TIBC) of plasma.
- About a third of transferrin iron-binding sites are filled.
- IN iron overload, transferrin-binding sites are occupied.
- Non–transferrin-bound iron (NTBI) in the circulation is present at very low concentrations.

ROLE OF IRON IN CELL PROLIFERATION

- Iron is indispensable for DNA synthesis and a host of metabolic processes. Iron starvation arrests cell proliferation, presumably because ribonucleotide reductase and other enzymes require the metal.

- The transferrin receptor also appears to have a role in early lymphocyte development.

Epidemiology of Iron Deficiency

- Iron deficiency is the most frequent and widespread nutritional deficiency .
- it is common in developing and developed countries alike.
- toddlers and women of childbearing age .
- participating in strenuous training .
- Socioeconomic factors are associated with iron deficiency anemia in children.
- bottle-feeding patterns.
- The iron status of young children correlates closely with the iron status of their mothers.

Epidemiology of Iron Deficiency

- Increasing rates of breast-feeding .
- iron-fortified formula .
- Promotion of formula in place of cow’s milk .
- Iron deficiency without anemia exists in 7% of toddlers aged 1 to 2 years, 9% of adolescent girls, and 16% of women of childbearing age.
- Between 6 months and 3 years or 11 and 17 years of age because of the rapid growth that occurs during these periods.

Prevalence

- It is estimated that 4050% of children under age 5 years in low- and low middle income countries are iron deficient.
- Due to a combination of rapid growth and insufficient dietary iron.
- Second peak is seen during adolescence with up to 16% of adolescent girls being iron deficient.
- Adolescents also experience rapid growth and occasionally suboptimal iron intake.

Phases of Development of Iron Deficiency

- 1. **Prelatent iron deficiency:**
- occurs when tissue stores are depleted, without a change in hematocrit or serum iron levels. This stage of iron deficiency may be detected by low serum ferritin measurements.
- **2. Latent iron deficiency:**
- occurs when reticuloendothelial macrophage iron stores are depleted. The serum iron level drops and TIBC increases without a change in hematocrit.
- **detected by a routine check of fasting, early-morning transferrin saturation.**
- **sTfR levels increase.**
- The reticulocyte hemoglobin content (CHr) decreases because newly produced erythrocytes are iron deficient.
- **The bulk of the erythrocyte population appears normal.**

Phases of Development of Iron Deficiency

- 3. Frank iron deficiency anemia is associated with erythrocyte microcytosis and hypochromia. It is detected when iron deficiency has persisted long enough that a large proportion of the circulating erythrocytes were produced after iron became limiting.

Etiology of Iron Deficiency

- The development of iron deficiency is a result of the interaction between iron intake, physiologic iron requirements, and the potential for blood loss.

Etiology of Iron Deficiency
INADEQUATE ABSORPTION

- Poor bioavailability (absorption of heme Fe > Fe2+ > Fe3+)
- Antacid therapy/high gastric pH
- Bran, tannins, phytates, starch
- Other metals (e.g., cobalt, lead)
- Loss or dysfunction of absorptive enterocytes (e.g., glutensensitive enteropathy, gastric bypass, Crohn disease)

Insufficient or inaccessible Iron stores

- Physiologically Increased Requirements
- Pregnancy, particularly repeated
- Rapid growth (e.g., infancy)
- Gastrointestinal Blood Loss
- Epistaxis
- Gastritis
- Ulcer
- Meckel diverticulum
- Milk-induced enteropathy
- Parasitosis
- Varices
- Tumor or polyps
- Inflammatory bowel disease
- Arteriovenous malformation
- Colonic diverticula
- Hemorrhoids

Insufficient or inaccessible iron stores

- Vaginal Blood Loss
- Increased menstrual blood loss
- Tumor
- Urinary Blood Loss

Chronic intravascular hemolysis (e.g., paroxysmal nocturnal hemoglobinuria)

- Chronic glomerulonephritis
- Chronic infection
- Tumor
- Pulmonary Blood Loss
- Pulmonary hemosiderosis
- Tuberculosis
- Bronchiectasis
- Inflammation or Infection
- Defects in intestinal iron uptake (e.g., TMPRSS6 mutations)

Inadequate presentation to erythroid precursors

- Atransferrinemia
- Anti-transferrin receptor antibodies

Abnormal Intercellular Transport or Utilization

- Erythroid iron-trafficking defects (e.g., DMT1 mutations)
- Defects in heme biosynthesis

Iron-refractory iron-deficiency anemia

- autosomal recessive
- mutation of TMPRSS6
- inhibits the signaling pathway that activates hepcidin
- microcytosis
- extremely low transferrin saturation
- normal or borderline-low ferritin levels
- high hepcidin levels.

Tissue effects of iron deficiency

- Gastrointestinal tract
- Anorexia: common and an early symptom
- Atrophic glossitis with flattened, atrophic, lingual papillae, which makes the tongue smooth and shiny
- Esophageal webs (KellyPaterson syndrome)
- Exudative enteropathy/leaky gut syndrome
- Beeturia
- Decreased cytochrome oxidase activity, succinic dehydrogenase
- Decreased disaccharidases
- Increased absorption of cadmium and lead
- Increased intestinal permeability index
- Generalized malabsorption
- Dysphagia

Central nervous system

- Irritability
- Fatigue and decreased activity
- Reduced cognitive performance; lower mental/motor developmental test scores
- Decreased attentiveness, shorter attention span
- Breath-holding spells
- Papilledema

Cardiovascular system

- Increase in exercise and recovery heart rate and cardiac output
- Cardiac hypertrophy
- Increase in plasma volume
- Increased minute ventilation values
- Increased tolerance to digitalis

Musculoskeletal system

- Deficiency of myoglobin and cytochrome C
- Decreased physical performance in both brief, intense exercise and prolonged endurance work
- Rapid development of tissue lactic acidosis on exercise

Immunologic system

- Impaired rate of recovery from illness; increased frequency of respiratory infections
- Impaired leukocyte transformation; impaired granulocyte killing
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- Decreased myeloperoxidase in leukocytes and small intestine
- Transferrin inhibition of bacterial growth by binding iron so that no free iron is available for growth of microorganisms

Red cells

- Increased auto-hemolysis
- increased red cell rigidity
- decreased globin and α-chain synthesis
- susceptibility to H2O2 hemolysis
- Increase in free erythrocyte protoporphyrin
- Impairment of DNA and RNA synthesis in bone marrow cells

Clinical features

- Pallor(hemoglobin falls to 7-8 g/dL)
- irritability,
- anorexia,
- listlessness
- fatigue
- pica
- Tachycardia
- splenomegaly
- systolic murmur

Laboratory parameters

- ١.Hemoglobin: below the acceptable level for age
- 2. Red cell indices: lower than normal MCV; widened RDW.
- 3. Reticulocyte count: usually normal.
- 4. Reticulocyte hemoglobin content/equivalent (Ret-He, CHr): low, occurs prior to a drop in hemoglobin
- 5. Platelet count: varies from thrombocytopenia to thrombocytosis; thrombocytopenia more common in severe
- IDA.
- 6.Blood smear: red cells are hypochromic and microcytic with anisocytosis and poikilocytosis; thrombocytosis
- 7. Bone marrow: not indicated to diagnose iron deficiency.
- 8. FEP:high FEP levels.
- a. Normal FEP level is 15.568.3 mg/dL (upper limit 40 mg/dL).
- b. Elevated in both iron deficiency and lead poisoning but much higher in lead poisoning; normal in thalassemia trait.
- c. Elevated FEP level, an indication for iron therapy even when anemia and microcytosis have not yet developed.

Laboratory parameters

- 9. Red blood cell (RBC) zinc protoporphyrin/heme ratio: increased when there is disruption of normal heme production. Nonspecific—raised in iron deficiency, lead poisoning; markedly raised in protoporphyria, congenital erythropoietic porphyria

- 10. Serum ferritin:≤5 yr <12
- Children >5 yr <15
- In all age groups in the presence of infection <30

- 11.Serum iron and iron saturation percentage.
- 12.Soluble transferrin receptor (STfR) levels:increased in instances of hyperplasia of erythroid precursors such as IDA and thalassemia. It is unaffected by infection and inflammation, unlike serum ferritin.
- 13. STfR/log ferritin ratio:highest sensitivity and specificity in the presence of chronic inflammation or infection. less than2.2 mg/L exclude iron deficiency and values of more than 2.9 mg/L confirm iron deficiency.

Laboratory parameters

- 14. Serum hepcidin:

usually ≤10 ng/mL

Extremely elevated in anemia of inflammation and suppressed in iron deficiency anemia

15. Transferrin saturation:

<16%

limited by diurnal variation in serum iron and

by many clinical disorders that affect transferrin concentrations including in

inflammatory conditions.

Differentiating the Most Common Microcytic Anemias

STUDY	IRON-DEFICIENCY ANEMIA	α- OR β-THALASSEMIA	ANEMIA OF CHRONIC DISEASE
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
RDW	Increased	Normal or minimally increased	Normal-increased
RBC	Decreased	Normal-increased	Normal-decreased
Serum ferritin	Decreased	Normal	Increased
Total Fe binding capacity	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
FEP	Increased	Normal	Increased
Transferrin receptor	Increased	Normal	Increased
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal-decreased

PREVENTION

- Promote breastfeeding for at least 6 months, if possible.
- Infants who are not breastfed should only receive iron-fortified formula (12 mg of iron per liter) for the first year.
- Avoid cow's milk until after the first year of age because of the poor bioavailability of iron in cow's milk and because the protein in cow's milk can cause occult GI bleeding.
- Routine screening using hemoglobin or hematocrit is done at 12 mo of age, or earlier if at 4 mo of age the child is assessed to be at high risk for iron deficiency.
- Iron-rich foods should be provided to children in all age-groups.
- acilitators of iron absorption such as vitamin Crich foods (citrus, tomatoes, and potatoes), meat, fish, and poultry should be included in the diet.
- Inhibitors of iron absorption such as tea, phosphate, and phytates common in vegetarian diets should be minimized

Treatment

- A daily total dose of 3-6 mg/kg of elemental iron in 3 divided doses is adequate, with the higher dose used in more severe cases.
- The maximum dose would be 150-200 mg of elemental iron daily.
- Ferrous sulfate is 20% elemental iron by weight and is ideally given between meals with juice.
- 3 mg/kg/day divided into three-times-a-day.
- Administration of iron on an empty stomach at night will lessen the gastrointestinal difficulties.
- The decreased gastrointestinal motility of sleep will also enhance absorption.

Amount of elemental iron:

Salt	% elemental
Ferrous sulfate	20-30% but can vary by manufacturer 325 mg tablet (contains 65 mg elemental iron per tablet)
Ferrous fumarate	33% (324 mg tablet contains 106 mg elemental iron per tablet)
Ferrous gluconate	10-14% (240 mg tablet contains 27 mg elemental iron per tablet)
Polysaccharide-iron complex (PIC)	100% (NovaFerrum 50 contains 50 mg elemental iron per tablet) variable
Heme iron polypeptide	100%
Ferric ammonium citrate	
Ferric diphosphate complex	
Iron pyrophosphate	
Ferrous bisglycinate	20%
Ferrous glycine sulphate	23%
Sucrosomial iron	100%

Percent of absorption of elemental IRON (Bioavailability)

Salt	% absorption
Ferrous sulfate	10-15%, 40%
Ferrous fumarate	10-15%, 40%
Ferrous gluconate	10-15%, 40%
Polysaccharide-iron complex (PIC)	
Heme iron polypeptide	
Ferric ammonium citrate	
Ferric diphosphate complex	
Iron pyrophosphate	
Ferrous glycine sulphate	40%
Ferrous bisglycinate	80%
Sucrosomial iron	100%

نمک	اسامی تجاری موجود (مقدار آهن المنتی به میلی گرم)			
فروس سولفات	Fefol® (۴۷)	فروس سولفات (۵۰)	فولیکوفر® (۶۰)	فولایرون® (۶۰)
فروس فومارات	Ferosis®	هماتینیک (۱۵۰)	Feroglobin® (۲۴)	Flexan® IRON PLUS (۲۵)
	فروس فومارات (۶۰)			
فروس بیس گلیسینات	Ferrodin®	فروشل® (۵۰)	IRON bisglycinate (۳۰) (شرکت هلث اید)	Easy IRON® (۲۸)
فروس گلیسین سولفات	فروفورت گاین® (۸۰)	فروفورت دئودنال® (۱۰۰)		
فروس گلوکونات	Iron (۲۷) (شرکت سنتری)			
آهن لیپوزومال	Irofix® (۲۰)	سیدرال® فورت (۳۰)		
کمپلکس آهن+ پلی ساکارید	feraMAX® (۱۰۰)			
فریک سولفات+ هموگلوبین گاوی	GlobiFer plus® (۱۸)			

Poor Response to Oral Iron

- Noncompliance
- Ongoing blood loss
- Insufficient duration of therapy
- High gastric pH
- Antacids
- Histamine2 blockers
- Gastric proton pump inhibitors
- Inhibitors of iron absorption or utilization
- Lead
- Aluminum intoxication (hemodialysis patients)
- Chronic inflammation
- Neoplasia
- Incorrect diagnosis
- Thalassemia disorder
- Sideroblastic anemia
- Anemia of chronic inflammation
- Genetic disorder of iron absorption or utilization (e.g., iron-refractory,
- iron deficiency anemia [IRIDA])

Response to oral iron

- 12-24 hr Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite.
- 36-48 hr Initial bone marrow response; erythroid hyperplasia.
- 48-72 hr Reticulocytosis, peaking at 5-7 days.
- 4-30 days Increase in hemoglobin level.
- 1-3 mo Repletion of stores.
- The hemoglobin will then begin to increase 0.1-0.4 g/dL per day depending on the severity of the anemia.
- Iron medication should be continued for 2-3 mo after blood values normalize to reestablish iron stores.
- Assessment of a serum ferritin level prior to iron discontinuation can assist with determining whether further iron therapy is indicated.

Parenteral Iron Replacement

- Nonadherence, poor tolerance of oral iron.
- Severe bowel disease (e.g., inflammatory bowel disease) where the use of oral iron might aggravate the underlying disease of the bowel or iron absorption is compromised, after gastrectomy or duodenal bypass surgery, atrophic gastritis, and celiac disease.
- Losing blood at a rate too rapid for oral intake to compensate for the loss.
- Severe iron deficiency requiring rapid replacement of iron stores.
- Concomitant iron deficiency and inflammation, resulting in poor iron absorption.
- Patients anemic after receiving erythropoietin therapy.
- Iron deficiency in heart failure.

Case -1

Case History

- A 12-month-old boy has been in good health except for 1 episode of pharyngitis and 2 episodes of otitis media in the past 2 months. He has been receiving iron-fortified formula since birth. Physical examination shows resolving otitis media.
- The Hgb is 10.4 g/dL, Hct 32%, mcv= 82,mch=27 and reticulocytes 0.9%.

Questions

- What further history or physical findings would you like to know?
- What further studies are needed?
- What is the most probable diagnosis?

Case History

- Serum Fe 40 60 - 130
- TIBC 200 250 - 450
- Ferritin 50 15 - 100

Diagnosis

Anemia of Inflammation

case2

- Male 5 years paleness
- WBC:7000
- RBC:3000000
- Hb:9
- MCV:69
- MCH 24
- RDW:19
- PLT:500000

IRON DEFICIENCY

CASE 3

- Male 9years old paleness
- WBC:5000
- RBC:4500000
- Hb:9
- mcv:58
- MCH:19
- RDW:13
- PLT:300000

Minor thalassemia

CASE 4

- Female 2 years old paleness
- WBC:6000
- RBC:4500000
- Hb:8
- MCV:60
- MCH:19
- PLT:450000
- RDW:19
- HbA:97% HbA2:2% HbF:1%

IRON DEFICIENCY WITH MINOR THALASSEMIA

CASE 5

- Male 7 years old
- WBC:8000
- RBC:4500000
- Hb:9
- MCV:61
- MCH:18
- RDW:17
- PLT:500000
- HbA:94% HbA2:5% HbF:1%

IRON DEFICIENCY AND MINOR BETA THALASSEMIA