

# **Childhood Anemia**

## **A Practical Approach**

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# **Useful facts of childhood anemia**

- 1) In interpretation of laboratory haematological values, age and sex has to be taken into consideration.**
- 2) Reticulocyte count is very often not included in the CBC.**
- 3) Macrocytic anemia is rare in childhood.**

# Useful facts of childhood anemia

- 4) In macrocytosis, it is prudent to determine if the  $\uparrow$ MCV is due to reticulocytosis.
- 5) Many childhood anemias have a hereditary basis.
- 6) Nutritional deficiency is extremely rare in infants who are fed on commercial formula or breastfed by mothers with an adequate diet or taking supplement.

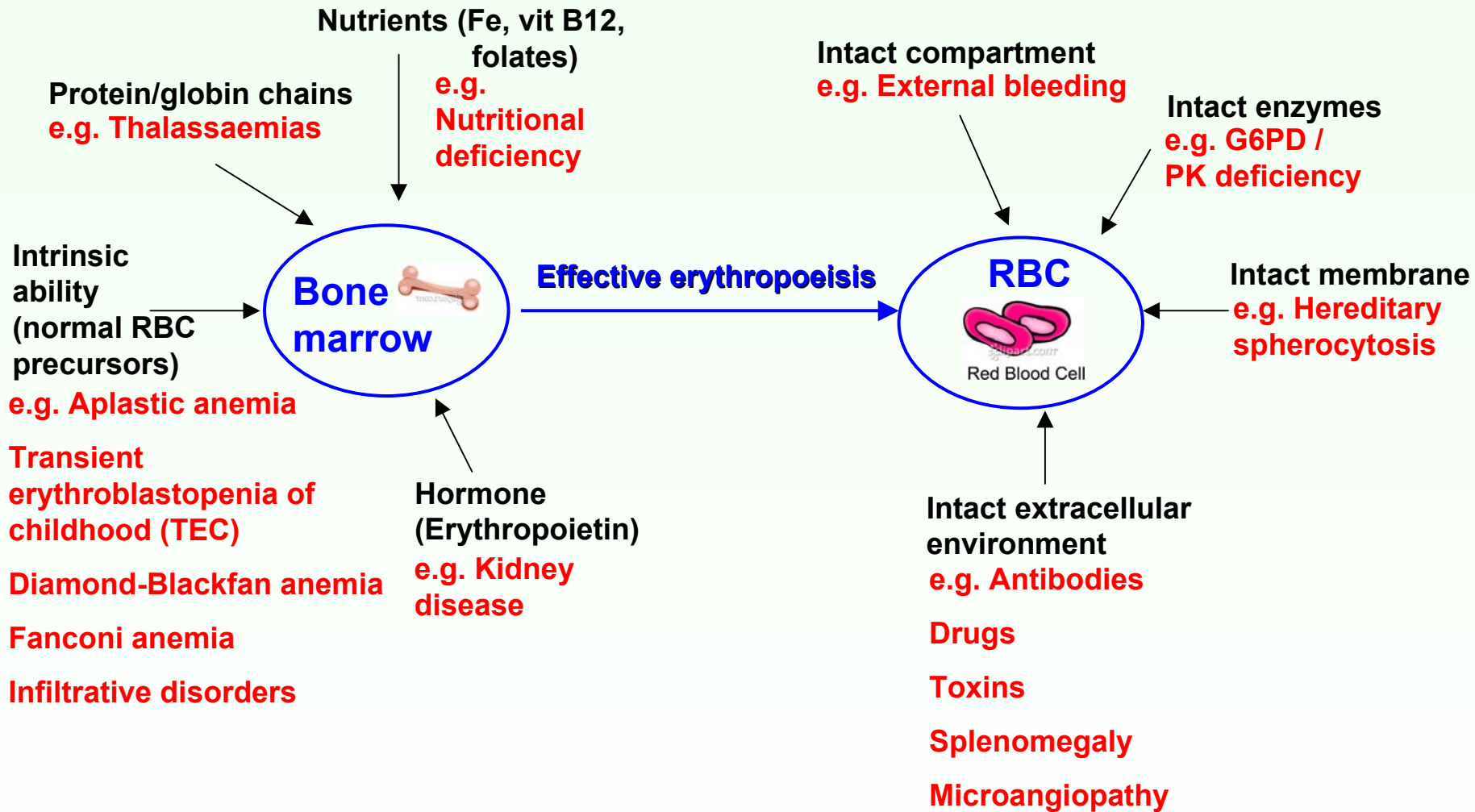
# Useful facts of childhood anemia

- 7) **Worldwide, Fe deficiency is probably the most common cause of isolated anemia especially in children aged 1-5 years.**
- 8) **In a patient with  $\beta$  thalassaemia trait & concomitant Fe deficiency, HbA<sub>2</sub> level can be normal as Fe deficiency depresses  $\delta$  globin synthesis; Hb electrophoresis should be repeated after Fe deficiency is corrected.**
- 9) **A group of anemias unique to childhood is aregenerative anemia and constitutional aplastic anemias.**

# Useful facts of childhood anemia

**10) Parvovirus is unique in its erythrotropic nature & striking affinity for erythroid precursors and produces transient erythroid marrow aplasia. It may cause a dramatic fall in Hb in patients who have chronic haemolysis with a shortened red cell survival – “aplastic crisis”.**

# Pathophysiology of childhood anemia



# Physiologic classification of anemia

## A. Blood loss

## B. Reduced production

### 1. Marrow failure

#### a. Hereditary/constitutional

Fanconi anemia

Diamond-Blackfan anemia

Dyskeratosis congenita

Osteopetrosis.....etc

#### b. Acquired

Idiopathic, infection, drug,  
malignant infiltration,  
myelofibrosis, chronic renal  
disease

### 2. Impaired erythropoietin production

Chronic renal failure,  
Hypothyroidism,  
Hypopituitarism,  
Chronic inflammation,  
Malnutrition

## C. Disorder of maturation & ineffective erythropoiesis

### 1. Abnormal cytoplasmic maturation

Iron deficiency, thalassemia,  
sideroblastic anemia, lead poisoning

### 2. Abnormal nuclear maturation

B12 or folate deficiency, inborn or drug  
induced disorders of DNA synthesis

### 3. Hereditary dyserythropoietic anemia

## D. Hemolytic anemia

### 1. Defects of Hb, RBC membrane or metabolism

Thalassemia, spherocytosis, G6PD or  
pyruvate kinase deficiency

### 2. Antibody mediated

### 3. Mechanical, thermal, oxidant injury

### 4. Infection induced

### 5. Paroxysmal nocturnal hemoglobinuria

# Symptomatology and etiology of anemia in children

- **Non-specific symptoms**
  - Irritability
  - Poor sleep quality
  - Anorexia
  - Poor concentration, school work
  - Failure to thrive
- Dizziness / syncope
- Malaise, easy fatigue, impaired exercise tolerance
- Palpitation

# **Staged algorithm of evaluation of anemia**

- 1) Is the child truly anemic?**
- 2) History**
- 3) Physical examination**
- 4) RBC indices & peripheral blood smear**
- 5) Reticulocyte count**
- 6) Other appropriate investigations**

## Is the child truly anemic?

- **“Pallor” can be due to**
  - True anemia
  - Vasoconstriction
  - Fair color
- **Compare child’s Hb/Hct with normal values for age & sex**
- **Venous blood preferred**
- **Adequate volume of blood**

# Definition of anemia in children

- Anemia is functionally defined as an insufficiency in RBC mass to adequately deliver oxygen to peripheral tissue
- For practical purpose anemia is defined by a laboratory value 2 SD below the mean for normal population in any 1 of the 3 red cell indices:
  - haemoglobin level (Hb), haematocrit (Hct) or red cell count (RBC)

# Physiological changes in red cell indices (Hb,Hct,RBC) with age

- Very high level at birth
  - Relative hypoxemia in fetal life
- Physiological trough at 2 – 3 month of age
  - Dramatic reduction in erythropoiesis after birth
  - Rapid growth in early infancy
- Gradual rise from childhood to adolescent
- Higher level in male vs female in adulthood
  - Effect of androgens vs estrogen, menstruation

# Red Cell Values at Various Ages

Age	Haemoglobin (g/dL)		Haematocrit (%)		Red cell count ( $10^{12}/L$ )		MCV (fl)	
	Mean	$\pm 2$ SD	Mean	$\pm 2$ SD	Mean	$\pm 2$ SD	Mean	$\pm 2$ SD
Birth (cord blood)	16.5	13.5-19.5	51	42-60	4.7	3.9-5.5	108	98-118
<b>1-3 days (capillary)</b>	<b>18.5</b>	<b>14.5-22.5</b>	<b>56</b>	<b>45-67</b>	<b>5.3</b>	<b>4.0-6.6</b>	<b>108</b>	<b>95-121</b>
1 week	17.5	13.5-21.5	54	42-66	5.1	3.9-6.3	107	88-126
2 weeks	16.5	12.5-20.5	51	39-63	4.9	3.6-6.2	105	86-124
1 month	14.0	10.0-18.0	43	31-55	4.2	3.0-5.4	104	85-123
<b>2 months</b>	<b>11.5</b>	<b>9.0-14.0</b>	<b>35</b>	<b>28-42</b>	<b>3.8</b>	<b>2.7-4.9</b>	<b>96</b>	<b>77-115</b>
3-6 months	11.5	9.5-13.5	35	29-41	3.8	3.1-4.5	91	74-108
0.5-2 years	12.0	10.5-13.5	36	33-39	4.5	3.7-5.3	78	70-86
2-6 years	12.5	11.5-13.5	37	34-40	4.6	3.9-5.3	81	75-87
6-12 years	13.5	11.5-15.5	40	35-45	4.6	4.0-5.2	86	77-95
12-18 years								
<b>Female</b>	<b>14.0</b>	<b>12.0-16.0</b>	<b>41</b>	<b>36-46</b>	<b>4.6</b>	<b>4.1-5.1</b>	<b>90</b>	<b>78-102</b>
<b>Male</b>	<b>14.5</b>	<b>13.0-16.0</b>	<b>43</b>	<b>37-49</b>	<b>4.9</b>	<b>4.5-5.3</b>	<b>88</b>	<b>78-98</b>
18-49 years								
<b>Female</b>	<b>14.0</b>	12.0-16.0	41	36-46	4.6	4.0-5.2	90	80-100
<b>Male</b>	<b>15.5</b>	13.5-17.5	47	41-53	5.2	4.5-5.9	90	80-100

Historical factors of importance in  
evaluating anemia in children

# Historical factors of importance in evaluating anemia in children

Age	Anemia manifesting in neonatal period is usually the result of recent blood loss, isoimmunization, congenital hemolytic anemia or congenital infection
	Anemia 1 <sup>st</sup> detected at 3 – 6 months suggests a diagnosis of haemoglobinopathy
	Nutritional iron deficiency is seldom responsible for anemia before 6 months of age in term infants (earlier in preterm infants)
Gender	Consider X-linked disorders in male: G6PD deficiency

Ethnicity	Thalassemia syndrome more common in South East Asians and Mediterraneans Sickle cell disease more common in Africans
Inheritance	Consanguinity, family Hx of anemia, jaundice, gallstone, splenomegaly / splenectomy
Neonatal	Significant jaundice suggest congenital hemolytic anemia (e.g. hereditary spherocytosis, G6PD, pyruvate kinase deficiency) Prematurity predispose to early development of iron deficiency anemia
Diet	Assess for dietary sources of iron, folic acid and vitamin B12 Pica, geophagia, pagophagia suggest iron deficiency

Gastro -intestinal	Chronic diarrhea suggest small bowel disease with malabsorption (folate, B12, iron) or occult blood loss Epigastric pain suggest occult upper GI bleeding
Infection	Hepatitis-induced aplastic anemia, infection induced hemolytic anemia or red cell aplasia Suspect associated WBC abnormalities in recurrent infection
Bleeding	Suspected associated platelet abnormalities
Drugs	Oxidant induced hemolytic anemia, phenytoin induced megaloblastic anemia, drug induced aplastic anemia
MR	Suspect congenital marrow failure or IEM

Physical findings as clues to the  
cause of anemia in children

## Physical Findings as Clues to the Etiology of Anemia

Skin	Hyperpigmentation	Fanconi's aplastic anemia Dyskeratosis congenita
	Petechiae, purpura	Autoimmune hemolytic anemia with thrombocytopenia, hemolytic-uremic syndrome, bone marrow aplasia, bone marrow infiltration
	Keratoderma	Dyskeratosis congenita
	Jaundice	Hemolytic anemia, hepatitis and aplastic anemia
	Large hemangioma	Microangiopathic hemolytic anemia
	Ulcers on lower extremities	Sickle cell disease, thalassemia
Facies	Frontal bossing, prominence of the malar and maxillary bones	Congenital hemolytic anemias, thalassemia major

## Physical Findings as Clues to the Etiology of Anemia

Eyes	Micro-ophthalmia	Fanconi's aplastic anemia
	Cataracts	Galactosemia with hemolytic anemia in newborn period
	Microaneurysms of retinal vessels	Sickle hemoglobinopathies
	Tortuosity of the conjunctival and retinal vessels	Sickle hemoglobinopathies
	Vitreous hemorrhages	Sickle hemoglobinopathies
	Retinal hemorrhages	Chronic, severe anemia
	Edema of the eyelids	Infectious mononucleosis, exudative enteropathy with iron deficiency, renal failure
	Blindness	Osteopetrosis

## Physical Findings as Clues to the Etiology of Anemia

Mouth	Glossitis	Vitamin B12 deficiency, iron deficiency
	Angular cheilosis	Iron deficiency
Chest	Unilateral absence of the pectoral muscles	Poland syndrome (increased incidence of leukemia)
	Shield chest	Diamond-Blackfan anemia
Hands	Triphalangeal thumbs	Diamond-Blackfan anemia
	Hypoplasia of the thenar eminence	Fanconi anemia, Diamond-Blackfan anemia
	Spoon vs dystrophic nail	Iron deficiency vs dyskeratosis
Spleen	Enlargement	Congenital hemolytic anemia, leukemia, lymphoma, acute infection, portal hypertension and esophageal varices

# The red cell indices

- **MCV (mean corpuscular volume)**
  - The only red cell index directly measured by the electronic counter
  - Reflects a quantitative defect in the production of Hb due to ↓ haem or globin synthesis
  - Categorise anemias into microcytic, normocytic and macrocytic types
  - Value must be interpreted with age

- **Rule of thumb:**

- **In children < 10 years age, lower limit of MCV = 70 fl + age in years; if < 72 fl, usually abnormal.**
- **> 6 months of age, upper limit for MCV is 84 + 0.6 fl per year till upper limit of 96 fl; MCV > 98 beyond the immediate neonatal period is very rare.**

- **MCHC & MCH are calculate values & therefore less accurate.**
- **MCHC is a measurement of cellular hydration status; an increase is characteristic of spherocytosis.**

- **RDW (Red cell volume distribution width)**
  - **Reflects the variability in cell size and measures the degree of anisocytosis**
  - **Normal < 14.5%**
  - **↑ in Fe deficiency anemia**
  - **Normal in thalassemia trait**

# Reticulocyte count (RC)

- **Reflects the rate at which new RBC are produced; normal < 1% after 3 months; at birth up to 10%.**

- **RC as percentage =  $\frac{\text{Reticulocytes}}{\text{RBC count}} \times 100\%$**
- **RC as in CBC may not reflect the true marrow response i.e. the raw RC may be misleading in anaemic patients.**
- **In anemic patients, the reticulocyte life span  $\uparrow$  from 1 to 2-2.5 days**

- **Absolute reticulocyte count or reticulocyte index more accurately reflect the rate of erythropoiesis.**
  - **Absolute reticulocyte count**  
= Reported reticulocyte % x RBC count (N: 50-100 x 10<sup>9</sup>/L)
  - **Reticulocyte index (RI)**  
= Reported reticulocyte count x  $\frac{\text{patient's hematocrit}}{\text{normal hematocrit (0.45)}}$
- Normal < 3%

- **Reticulocyte production index (RPI)**
  - To correct the longer life span of prematurely released reticulocytes

<u>Ht (%)</u>	<u>Reticulocyte survival (days)/maturation correction</u>
36-45	1.0
26-35	1.5
16-25	2.0
15 or below	2.5

$$\text{RPI} = \frac{\text{RI}}{\text{Maturation correction}}$$

**Example:**

**Retic count 6%; Hb 7g/dL; Hct 25%**

$$\text{RI} = 6 \times \frac{25}{45} = 3.33\%$$

$$\text{RPI} = 6 \times \frac{25}{45} \times \frac{1}{2.0} = 1.7\%$$

**Normal RPI 1.0 – 2.0**

**< 2 → ↓ production**

**> 2 → ↑ production**

# Differential of anemia (Normal WBC/platelet)

Complete blood count: Hgb, indices, retic count & smear

Appropriate reticulocyte response to anemia (RPI > 2)

Yes

Evidence of haemolysis  
(↑bilirubin, ↑LDH, ↓haptoglobin  
hemoglobinuria)

Yes

Haemolysis

Haemoglobinopathy  
RBC enzymopathy  
RBC membranopathy  
Extrinsic factors

No

Haemorrhage

No

Macrocytic

B12 deficiency  
Folate deficiency  
Medication  
Liver disease

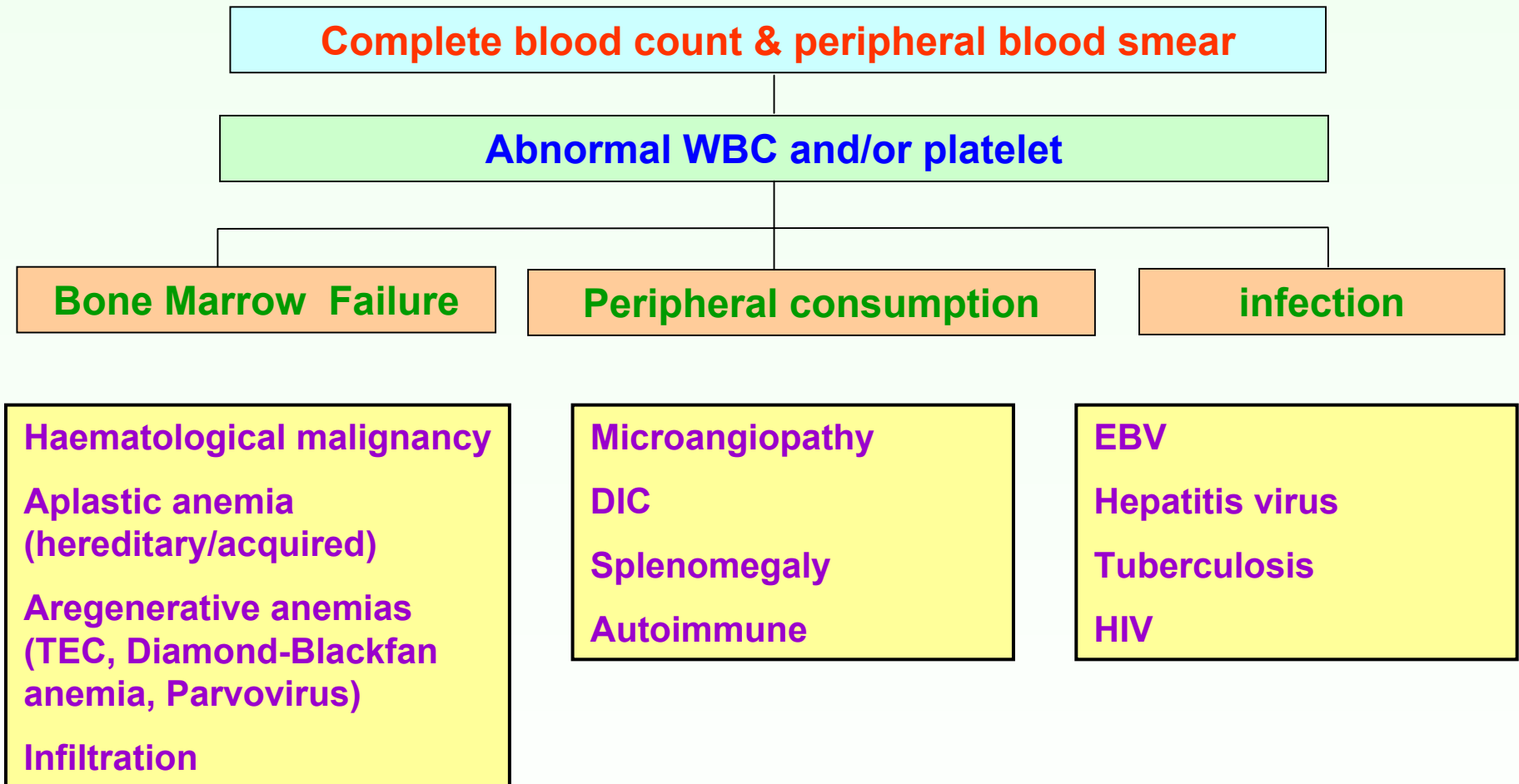
Normocytic

Chronic disease  
Transient erythroblastopenia  
of childhood (TEC)  
Renal disease  
Endocrine disease

Microcytic

Fe deficiency  
β-thalassaemias  
α-thalassaemias  
Lead poisoning

# Differential of anemia (**Abnormal WBC and/or platelet**)



# Microcytic anemia

↓ Serum iron  
↑ TIBC  
↓ Ferritin

Iron  
deficiency

↓ Serum iron  
Normal or ↑ TIBC  
Normal, ↑ or ↓ Ferritin

Anemia of  
chronic disease  
(inflammation)

Normal Serum iron  
Normal TIBC  
Normal Ferritin

Thalassemia trait  
Hemoglobin E  
Hemoglobin C  
Lead poisoning

↑ Serum iron  
Normal TIBC  
↑ Ferritin

Congenital  
sideroblastic  
anemia

# Iron deficiency anemia

- **Most common haematological abnormality of childhood**
- **Total body Fe content 3-5G**
- **2.5G in Hb**

# Causes of Fe deficiency

- **Dietary deficiency**
- **Increased demand (growth)**
- **Defective absorption**
- **Blood loss**

# Who is at risk of Fe deficiency?

- **Infants**
  - **Preterm babies**
  - **Infants after 6 months of age**
    - **Fe store depleted after 6 months**
    - **Rapid growth**
    - **Rapid increase in blood volume**
    - **Especially wholly breast fed**

# Who is at risk of Fe deficiency?

- **Toddlers**

- Too early & too much cow's milk
  - Max 16 oz/day
  - Interferes with food absorption – delay gastric emptying
  - Colitis
  - Decreased appetite – high satiation value
- Picky food

- **Teenagers**

- Increased growth at puberty
- Menstrual loss

# Fe deficiency anemia

## Laboratory findings

### In sequence

- BM haemosiderin
- RDW
- Ferritin
- ↓Fe, ↑TIBC
- ↓ Hb
- PBS – hypochromic, microcytic
- Reticulocyte response - insufficient

# Fe deficiency anemia

## Prevention

- **Preterm – Fe supplement after birth**
- **Breast fed infants – Fe-fortified cereals at 6 months**
- **Formula-fed infants – Fe fortification**
- **No cow's milk until 12 months**
- **Limit cow's milk intake to < 16 oz / day in toddlers**

# Fe deficiency anemia

## Treatment

- **Diet**
  - Decrease cow's milk
  - Fe fortified foods
  - Iron rich food with high bioavailability e.g. fish, poultry, meat
  - Avoid phytates (bran, oats, rye, fiber) and tea
- **Fe therapy**
  - Elemental Fe 4-6 mg/kg/day for at least 3 months

# **Transient erythroblastopenia of childhood (TEC)**

- **Relatively rare**
- **Unknown etiology**
- **Acquired erythroid marrow failure**
- **Often follows viral infection**
- **Age: 18 month to 2 years**
- **Child otherwise normal**

# TEC

- **N<sup>c</sup>N<sup>c</sup> anemia**
- **Hb 5-7 g/dL**
- **Retic count: low**
- **Other cell lines normal**
- **Resolves in weeks to months**
- **Px: Supportive**
  - Transfusion if indicated**

# Constitutional aplastic anemias

- **Inherited bone marrow failure syndromes**
- **Impaired hematopoiesis + congenital anomalies  
+ cancer predisposition**
- **Genomic instability or ribosomal dysfunction**
- **Fanconi's anemia (FA)**  
**Dyskeratosis congenita (DC)**  
**Diamond-Blackfan anemia (DBA)**  
**Schwachman-Diamond syndrome (SDS)**

<b>Disease</b>	<b>Haematological abnormalities</b>	<b>Age of onset</b>	<b>Congenital anomalies</b>	<b>Cancer predisposition</b>
<b>FA</b>	<b>Aplastic anemia</b>	<b>6-7 years</b>	<b>Short stature Radial &amp; thumb anomalies Pigmentation Microcephaly</b>	<b>Acute leukaemia (AML) Solid tumours - squamous cell CA of head &amp; neck &amp; female genital tract</b>
<b>DC</b>	<b>Aplastic anemia</b>	<b>8-9 years</b>	<b>Dystrophic nails Mucosal leukoplakia Reticular rash Short stature</b>	<b>Acute leukaemia Solid tumours - squamous cell CA</b>
<b>DBA</b>	<b>Reticulocytopenic anemia</b>	<b>Infancy</b>	<b>Craniofacial anomaly Radial ray abnormality Cardiac defect</b>	<b>AML Osteosarcoma</b>
<b>SDS</b>	<b>Neutropenia Aplastic anemia</b>	<b>Infancy</b>	<b>Exocrine pancreatic insufficiency</b>	<b>AML</b>

Bring home messages

- Symptoms of anemia in children may be non-specific
- Nutritional history is important, especially in infants and young children for possible iron deficiency
- Family and neonatal history are important for possible inherited causes of anemia (congenital marrow failure, intrinsic RBC defects, inborn error of metabolism)

- Associated physical and developmental abnormalities may provide useful clues for diagnosis (growth parameters, cutaneous or skeletal abnormalities, etc)
- A systemic approach should be adopted in laboratory investigations for the cause of anemia
- Red cell indices and reticulocyte response remain the most useful tools for evaluation of anemia



## Scenario

- **20 month old child, noticed to be a bit pale**
- **Drinks a lot of whole cow's milk since 9 months of age**
- **Hb 7, WBC 7.5, platelet 650**
- **Retic count 0.7%; MCV 60; RDW 21%**
- **PBS: microcytic, hypochromic**
- **Ferritin ↓**

**DX: Fe deficiency anemia**

## Scenario

- **8 year old girl, short, multiple café-au-lait spots and short thumbs**
- **Hb 8.5    MCV 105    WBC 3.5    Platelet 105**
- **Bone marrow: hypoplastic**

**DX: Fanconi's anemia**

## Scenario

- **20 month old girl in good health; suffered from a cold 10 days ago; now pale**
- **Hb 7.0    MCV 82            WBC & Platelet - normal**
- **Retic count 0.2%**

**DX: Transient erythroblastopenia of childhood**

## Scenario

- **6 month old boy with pallor and poor appetite: both parents are China residents.**
- **P/E: pallor +ve; hepatosplenomegaly +ve**
- **Hb 6.0 Retic 10% MCV 55 WBC/Platelet - normal**
- **PBS: target cells +++; hypochromia, microcytosis, polychromasia; basophilic stippling**

**DX:  $\beta$ -thalassaemia major**

## Scenario

- **5 month old boy with fever 39.5°C and lethargy**
- **P/E: pallor +++ & jaundice+; liver° spleen°**
- **Hb 5.5 MCV 83 Retic count 15%**
- **WBC 20 platelet 150**
- **Urine haemstix ++; RBC°**
- **PBS – spherocyte +; blister cells ++; bite cell+**

**DX: G6PD deficiency**

## Scenario

- **4 year old girl has pallor or/and mild jaundice on routine examination**
- **+ve family history of anemia in father who has a splenectomy and cholecystectomy done at 12 years of age**
- **P/E: pallor +ve, Jaundice +ve, spleen 4cm**
- **Hb 9.5 MCV 83 MCHC 39 WBC/Platelet - normal**
- **Retic count 9%**
- **PBS: microspherocytes ++; mild anisocytosis**

**DX: Hereditary spherocytosis**

## Scenario

- **8 year old girl with URTI; otherwise asymptomatic**
- **Routine CBC: Hb 11.5    MCV 68**  
**WBC/Platelet - normal**
- **Retic count 0.9%**
- **Hb pattern: HbA predominant; HbA<sub>2</sub> 4.5%**
- **Fe, TIBC, ferritin: normal**

**DX:  $\beta$ -thalassaemia trait**

## Scenario

- **7 year old boy with fever x 2 days**
- **CBC: Hb 11.5 MCV 66 WBC/Platelet - normal**
- **Retic count 0.8%**
- **Hb pattern: HbA; HbA<sub>2</sub> 2.8%**
- **Fe, TIBC, ferritin: normal**

**DX:  $\alpha$ -thalassaemia trait**

## Scenario

- **3 month old baby with thumb abnormalities seen for progressive pallor for 2 months**
- **Hb 7    MCV 120    WBC/Platelets - normal**
- **Retic count 0.1%**
- **Bone marrow: marked erythroid hypoplasia**

**DX: Pure red cell aplasia (Diamond-Blackfan anaemia)**

## Scenario

- **8 year old boy, known hereditary spherocytosis with baseline Hb of 9.5 & retic count  $\approx$  12%**
- **Fever & mild rash x 2 days with increasing pallor and fatigue**
- **Hb 5, Retic count 2%, MCV 82  
WBC 2.5, Platelet 350**

**DX: Parvovirus infection with transient erythroid marrow aplasia**