APPROACH TO ANEMIA IN CHILDREN

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- **DEFINITION of Anemia**

Anemia is defined as reduction in the blood hemoglobin concentration 2 SD below the mean for the normal population with respect to age and gender

- ***Anemia*** is generally defined as a reduction in the O2 carrying capacity leading to tissue hypoxia.

- However, the 'functional anemia' at the tissue level is more important, as is very well demonstrated in case of congenital cyanotic heart disease.

Table 3.1: Red blood cell values at various ages

	Hb (g/dl)		*PCV (%)*		*RBC count (× 10^3/fl)*		*MCV (fl)*		*MCH (pg)*		*MCHC (g/dl)*	
Age	*Mean*	*–2SD**	*Mean*	*–2SD**	*Mean*	*–2SD*	*Mean*	*–2SD*	*Mean*	*–2SD*	*Mean*	*–2SD*
Birth	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30
1-3 days	18.5	14.5	56	45	5.2	4.0	108	95	34	31	33	29
1 week	17.5	13.5	54	42	3.1	3.9	107	88	34	28	33	28
2 week	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28
1 months	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29
3-6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30
0.5-2 years	12.0	11.0	36	33	4.5	3.7	78	70	27	23	33	30
2-6 years	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31
6-12 years	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31
12-18 years												
M	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31
F	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31

* Values less than 2SD denote anemia

APPROACH TO A CHILD WITH ANEMIA

A. Is the patient anemic for his/her age?

B. How severely is he/she affected?

C. What is the cause and type of anemia?

D. What treatment should he/she be offered?

Causes of Pallor in Children, Based on Etiologic Mechanism

I. Anemia

II. Decreased Tendency of the Skin to Pigment

A. Physiologic (fair-skinned individuals)

III. Alteration of the Consistency of the Subcutaneous Tissue

A. Edematous states

Increased intravascular hydrostatic pressure(e.g., congestive heart failure)

Decreased intravascular oncotic pressure(hypoproteinemia)

Increased vascular permeability (e.g., vasculitis)

B. Hypothyroidism

- ***HOW SEVERE IS THE ANEMIA ?***
- It is important to quickly assess the patient's clinical condition.

- If the patient is severely pale and sick looking, breathless, has tachycardia, raised JVP and tender hepatomegaly, it is suggestive of congestive cardiac failure .

- Such a patient needs immediate attention and prompt treatment including diuretics,restricted fluids, oxygen support and packed cell transfusion.

- One should not waste time for diagnostic tests and do as minimum tests as required. Even removing too much blood for various tests can be hazardous as it can precipitate cardiac failure.

- The clinical condition of the patient depends not only on the severity of anemia but also on the rate of drop of Hb.

- A child with 5 g Hb, when it develops slowly like in iron deficiency, may be comfortable and come by walking whereas, if it develops acutely due to G6PD deficiency, the child may be brought in a collapsed state.

WHAT IS THE TYPE AND CAUSE OF ANEMIA

- Etiological classification, based on the disturbance of erythropoiesis.
- Morphological classification based on findings of red cell size and indices.
- Both these are not mutually exclusive and are often used together to come to a conclusion as to the cause of anemia.

ETIOLOGICAL CLASSIFICATION OF ANEMIA

A. DECREASED EFFECTIVE PRODUCTION

- **Nutritional deficiency-**

  e.g. deficiency of iron, folate, vitamin B12, protien, zinc, copper

- **Bone marrow failure-**

  e.g. aplastic anemia, constitutional hypoplastic anemia, pure red cell aplasia.

- **Bone marrow infiltration-**

  e.g. malignancies like leukemia, lymphoma, osteopetrosis, myelofibrosis.

- **Impaired erythropoietin production**-

  e.g. renal disease, prematurity, hypothyroidism, hypopituitarism, chronic inflammation

- **Ineffective erythropoiesis-**

  e.g. Thalassemia, sideroblastic anemia,lead poisoning, congenital dyserythropoietic anemia, megaloblastic anemia.

B. INCREASED DESTRUCTION (HEMOLYTIC ANEMIA)

- **Extracorpuscular causes**

1. Mechanical- e.g. prosthetic valve, DIC, HUS
2. Immune- e.g. acquired immune hemolytic anemia,
3. Infection
4. Sequestration- e.g. hypersplenism.
5. Complement induced, e.g. paroxysmal nocturnal hemoglobinuria

- **Intracorpuscular causes** (usually congenital)

  1. Membrane defect—spherocytosis, stomatocytosis, elliptocytosis.

  2. Enzyme defect—G6PD deficiency, PK deficiency.

  3. Hemoglobin defect—Sickle cell anemia, thalassemia, HbC, HbD, HbE disease.

- **Blood loss (Hemorrhage):** Acute or chronic, internal or external

1. Internal

   Acute—Massive cephalhematoma, hemothorax

   Chronic—Pulmonary hemosiderosis.

2. External

   Acute—massive GI hemorrhage, trauma, hemoptysis

   Chronic-peptic ulcer, rectal polyp, hookworm infestation

- **Morphological classification of anemia**

A. Microcytic, hypochromic anemia

MCV < 70 , MCH < 28 pg

- Iron deficiency anemia.
- Anemia of chronic infection or inflammation.
- Thalassemia syndromes.
- Sideroblastic anemia.
- Lead poisoning.
- Severe protein deficiency.

B. **Macrocytic anemia**

- Megaloblastic anemia
    1. Folate deficiency
    2. Vitamin B12 deficiency
    3. DNA metabolism defects like orotic aciduria

- **Non-megaloblastic macrocytic anemia**

1. Normal newborn.
2. Reticulocytosis.
3. Aplastic anemia.
4. Liver disorders.
5. Hypothyroidism.
6. Alcoholism.
7. Down’s syndrome.

- **Approach to Establishing Diagnosis**

Approach to an anemic patient includes:

a. Detailed history

b. physical examination

c. Screening laboratory tests

d. Confirmatory laboratory tests.

A. *AGE OF ONSET:*

Nutritional anemia is not seen at birth.

The commonest causes of anemia in a newborn include hemolysis and hemorrhage.

Hemolysis-

- ABO, Rh incompatibility.
- G6PD deficiency or spherocytosis can present at birth.
- Hemolysis is usually associated with icterus besides anemia.

Hemorrhage-

- Huge cephalhematoma, pulmonary hemorrhage,
- Intraventricular hemorrhage
- Umbilical bleeding, fetoplacental or fetomaternal hemorrhage, GI hemorrhage like in vitamin K deficiency, etc.

- Rarely nutritional anemia can start very early, especially in preterms.
- Between 6 months to 2 years nutritional anemia (IDA) and hemoglobinopathies can present as anemia.
- Fanconi anemia usually presents around 4 to 6 years of age.

B. *Sex:*

X-linked diseases will be seen in male

- Includes G6PD deficiency and PK deficiency.

- Hence, there will be similar history in male siblings, maternal male cousins, maternal uncles and maternal grandfather.

- In adolescent age, anemia is more common in females due to nutritional deficiency as a result of menstrual loss of iron

D. *Inheritance:*

- All hemoglobinopathies and thalassemia syndromes are inherited in autosomal recessive manner.

- Spherocytosis is inherited as autosomal dominant condition.

E. *Diet:*

- Exclusive breastfeeding for 6 months, Introduction weaning food thereafter, continuation of breast milk till 18 months, Avoidance of animal milk in first year and balanced diet with occasional non-vegetarian food consumption makes nutritional anemia unlikely diagnosis.

- Iron deficiency develops where there is poor breastfeeding and improper time and quality of weaning food, both of which are exaggerated by bottle-feeding.

- Pica is both an effect and a cause of iron deficiency besides being seen in lead poisoning.

- Eating clay or mud (geophagia), ice (phagophagia), starch (amylophagia), paper, cloth, raw cereals, paint flakes, etc. is commonly seen in iron deficiency.

- Clay or mud can bind whatever little iron is present in food which further precipitates iron deficiency.

- Megaloblastic anemia due to folate deficiency is common in those who consume a lot of goat milk.

- ***Drugs:*** Drugs can induce anemia by many ways.

- ***APLASTIC ANEMIA :*** chloramphenicol, sulpha drugs or analgesics. penicillin, alpha methyldopa or stibophen can lead to immune haemolytic anemia.

- In a patient with G6PD deficiency certain drugs like aspirin, sulpha drugs, primaquine etc can precipitate hemolysis.

- Iron deficiency anemia by chronic GI bleeding following NSAID abuse;

- Megaloblastic anemia as seen with sulpha drugs, phenytoin or folate antagonists.

- *INFECTIONS AND INFESTATIONS:*
- History suggestive of intrauterine infection should be elicited when dealing with neonatal anemia especially when it is associated with hepatosplenomegaly, IUGR, icterus and thrombocytopenia. Hypoplastic anemia can be precipitated by hepatitis virus.

- G6PD deficiency induced hemolysis can be precipitated by many infections and drugs used to treat such infections.

- Hemolysis could also be induced by malaria.

- Marrow suppression can occur following many viral infections, falciparum malaria, kala-azar, fulminant sepsis or drugs used in such cases.

- Nutritional anemia can be precipitated by worms due to malabsorption, nutrient deficiency and micro bleeding especially with hook worm infestations.

- Any acute infection can lead to drop in haemoglobin by 1-1.5 g% over next one week.

- ***Family history:***
- History to be elicited in family members includes history of blood transfusion, unexplained recurrent jaundice, gall stone removal, splenectomy, suggests some hemolytic process.

- Similarly, history of anemia following drugs in other members will suggest G6PD deficiency.

PHYSICAL EXAMINATION

- **A. *Ascertain severity:***
- Pulse, blood pressure and respiratory rate should be recorded.

- Look for puffiness, edema feet, sacral edema, jugulovenous pulse, heptic tenderness, hepatojugular reflux

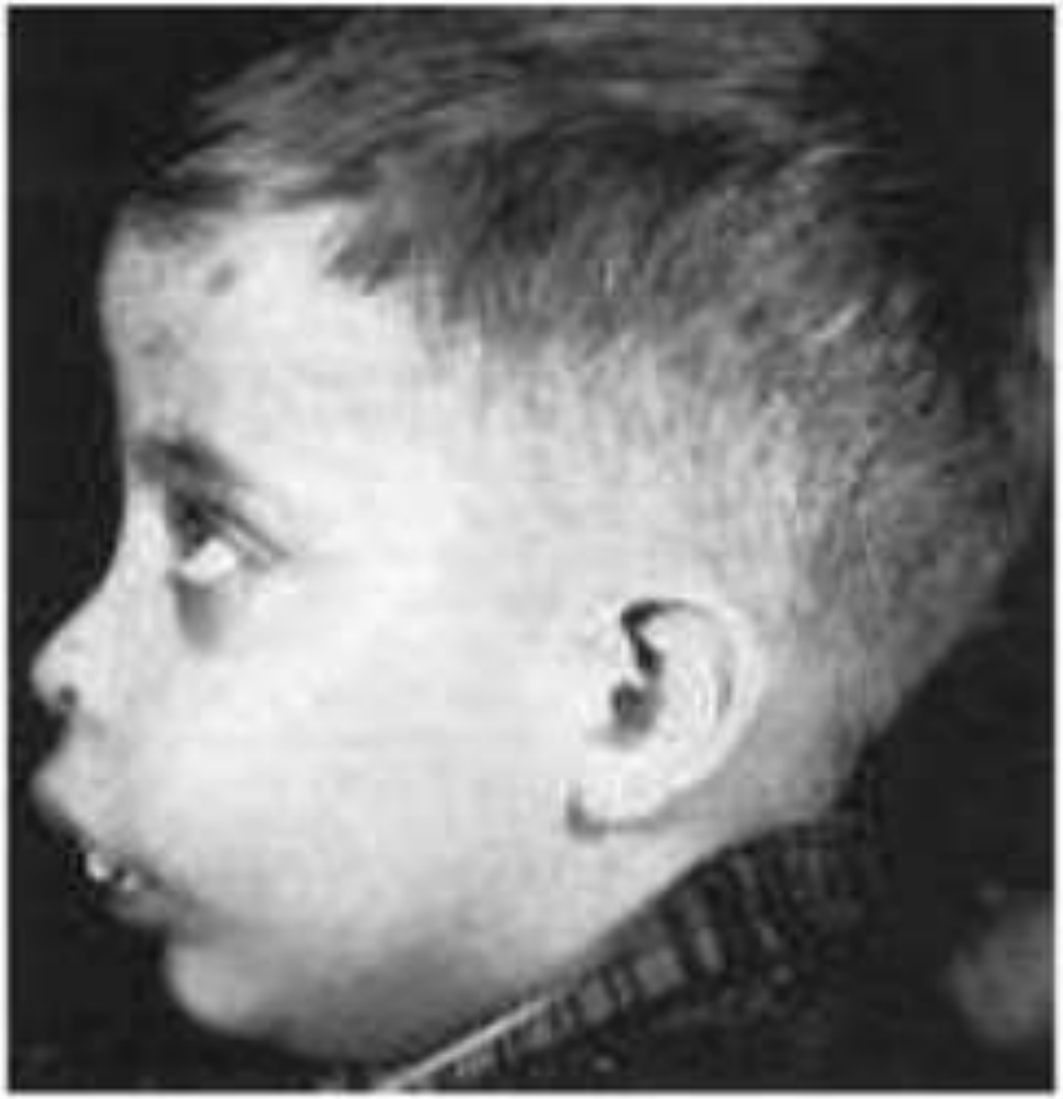
  All these will help to diagnose congestive cardiac failure as such patients need urgent treatment.

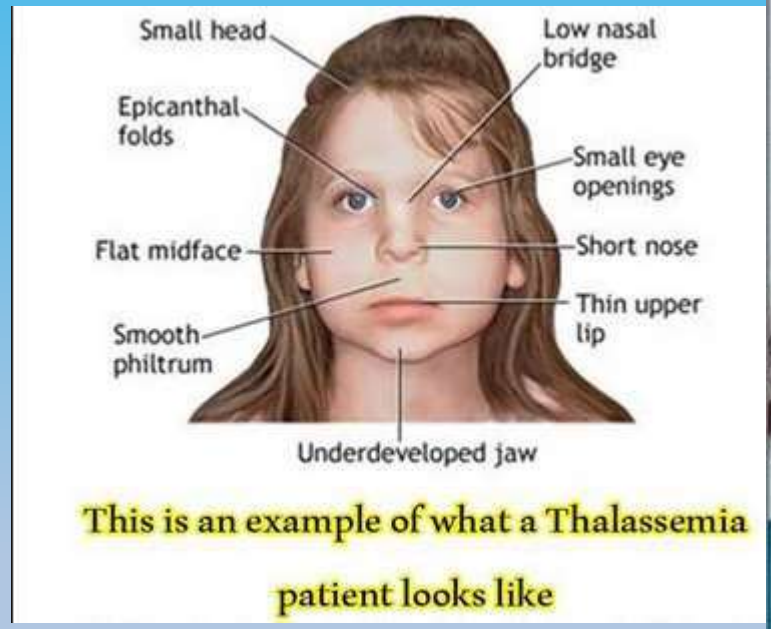
- Hypertension may be seen in anemia due to renal diseases.

B. *Facies:*

- Hemolytic facies will have frontal and parietal bossing, large head, depressed bridge of nose, malar prominance, irregular maxillary teeth.
- Diamond Blackfan syndrome will have box like face and limb anomalies.
- Hypothyroidism will have typical cretin facies and may be missed unless one looks for it carefully.
- Look for periorbital puffiness which can suggest edema due to anemia, CF or myxedema.

HEMOLYTIC FACIES- CHIPMUNK FACIES




Small head
Low nasal bridge
Epicanthal folds
Small eye openings
Flat midface
Short nose
Thin upper lip
Smooth philtrum
Underdeveloped jaw
This is an example of what a Thalassemia patient looks like

- ***Eyes:***
- Fanconi's anemia will have microcornea.

•Conjunctival vessels tortuosity is seen in sickle cell anemia and so is the presence of retinal hemorrhage or microaneurysms.

•Icterus in absence of high colored urine will suggest hemolytic anemia with indirect hyperbilirubinemia.

- Osteopetrosis patients will develop blindness

- ***Oral cavity:*** Look for glossitis, angular stomatitis, bald tongue which will suggest nutritional anemia.
  Look for teeth abnormality for hemolytic anemia.

E. *Nail changes:*

- Platynychia, koilonychia, brittle nails are suggestive of iron deficiency. Less common in children than in adults, but when present are pathognomonic of IDA.
- Dyskeratotic nails will be seen in dyskeratosis congenita.

F. *Lymphadenopathy:*

Significant lymphadenopathy will suggest tuberculosis, HIV, infectious mononucleosis,leukemia, lymphoma as the cause of anemia.


Health Hype
www.healthhype.com
Normal
Health Hype
www.healthhype.com
Koilonychia

- ***Hepatosplenomegaly:*** Palpable tender liver with positive hepatojugular reflux is suggestive of CCF.

- ***Significant hepatosplenomegaly*** will suggest tuberculosis, other viral fever, HIV, leukemia, thalassemia, other hemoglobinopathies, lymphoma, myelodysplastic syndrome, JCML, malaria, kala azar, disorders as a cause of anemia.

- ***Isolated splenomegaly*** will go in favour of enteric fever, malaria, portal hypertension, lymphoma, CML, or hypersplenism,immune hemolytic anemia, congenital spherocytosis as a cause of anemia.

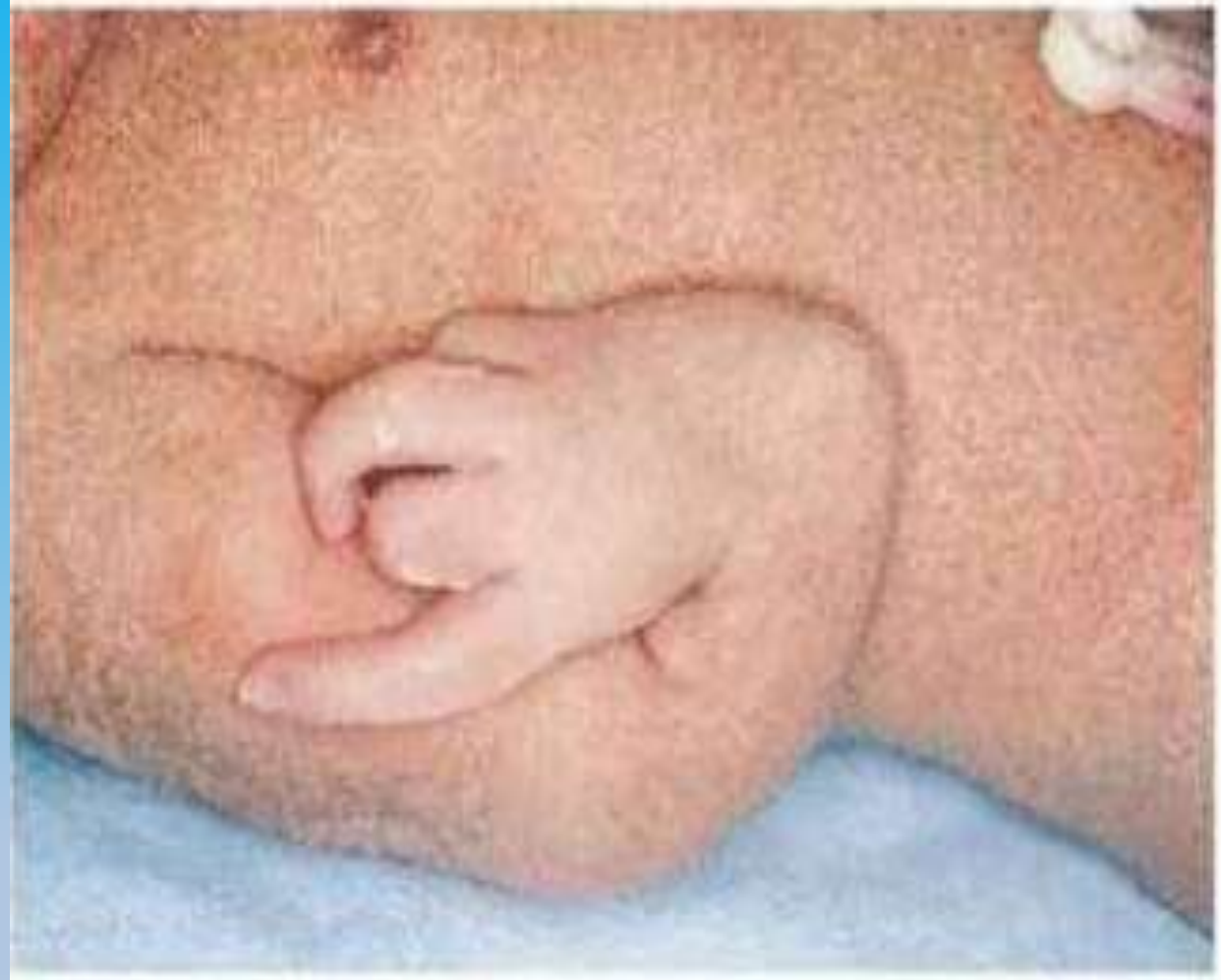
- ***Bleeding manifestation:***
- Presence of bleeding tendencies with petechiae, purpura will suggest thrombocytopenia, which can be seen in benign diseases like ITP.

  Or In serious diseases like aplastic anemia, malignancies or marrow infiltration.

Skeletal changes:

•Patients with Fanconi's anemia, TAR syndrome, etc. have skeletal malformations like absent radius, absent or bifid thumb, triphalangeal thumb, polydactyly, syndactyly, short stature,microcephaly.

•Look for associated anomalies like mental retardation, skin hyperpigmentation,hypogonadism, renal anomalies in such cases.



Skin changes

- Hyperpigmentation is seen in Fanconi's anemia.
- Icterus is seen in liver diseases as well as hemolytic anemia.
- Iron deficiency can be seen in patients with carotenemia.
- Non-healing ulcers over lower limbs are seen in any chronic hemolytic anemia especially in Hb S.
- localized DIC like picture with anemia and thrombocytopenia are present in patients with giant cavernous hemangioma as seen in Kasabach-Merrit syndrome.

SKIN	Hyperpigmentation,	Fanconi aplastic anemia.
	Petechia, purpura thrombocytopenia,	Autoimmune hemolytic anemia with hemolytic-uremic syndrome bone marrow aplasia, bone marrow infiltration.
	Jaundice	Hemolytic anemia, hepatitis, and aplastic anemia
	Cavernous hemangioma	Microangiopathic hemolytic anemia
	Ulcers on lower extremities	S and C hemoglobinopathies,
SKULL	Frontal bossing, prominence of the maxillary bones.	Congenital hemolytic anemias, thalassemia major, severe iron deficiency

EYES	Microcornea	Fanconi's aplastic anemia
	Tortuosity of the conjunctival and retinal vessels Microaneurysms of retinal vessels S and C hemoglobinopathies	S and C hemoglobinopathies S and C hemoglobinopaties
	Cataract	Glucose-6-phosphate dehydrogenase deficiency, galactosemia hemolytic anemia in newborn period
	Vitreous hemorrhages Retinal hemorrhages	S hemoglobinopathy
	Edema of the eyelids	severe anemia Infectious mononucleosis, exudative enteropathy with iron deficiency, renal failure
	Blindness	Osteopetrosis

mouth	Glossitis Angular stomatitis	Vitamin B12 deficiency, iron deficiency Iron deficiency
CHEST	Unilateral absence of the pectoral muscles Shield chest	Poland syndrome (increased incidence of leukemia Diamond-Blackfan syndrome
HAND	Triphalangeal thumbs Hypoplasia of the thenar eminence Spoon nails.	Red cell aplasia Fanconi aplastic anemia Iron deficiency

SPLEEN	**ENLARGEMENT**	Congenital hemolytic anemia, leukemia, lymphoma, acute infection portal hypertension

- **Laboratory studies often helpful in the investigation**
- *Usual initial studies*
    - Hemoglobin and hematocrit determination.
    - Erythrocyte count and red cell indices, including MCV and RDW.
    - Reticulocyte count.
    - Study of stained blood smear.
    - Leukocyte count and differential count.
    - Platelet count.

Suspected iron deficiency-

- Free erythrocyte protoporphyrin.
- Serum ferritin levels.
- Stool for occult blood.
- 99mTc pertechnetate scan for Meckel's diverticulum.
- Endoscopy (upper and lower bowel).

- ***Suspected vitamin B12 or folic acid deficiency***
    - Bone marrow.
    - Serum vitamin B12 level <100pg / ml.
    - Serum folate level < 3pg/ml.
    - Vitamin B12 absorption test (radioactive cobalt) (Schilling test).

- ***Suspected hemolytic anemia-***
    - Evidence of red cell breakdown-
        a. Blood smear.
        b. Serum bilirubin level.
        c. Urinary urobilinogen excretion.
        d. Serum haptoglobin.
    - Evidence of red cell regeneration-
        a. Reticulocyte count.
        b. Blood smear.
        c. Skeleton radiography.

- ***Evidence of type of hemolytic anemia:***

Corpuscular

A. Membrane-

— Blood smear.

— Osmotic fragility test

— Autohemolysis test

B. Enzymes

— Heinz-body preparation

— Enzyme assay

- ***C. Hemoglobin-***
  - — Sickle test.
  - — Hemoglobin electrophoresis.
  - — Hemoglobin F determination.
  - — Kleihauer-Betke smear.

- ***Evidence of type of hemolytic anemia:***

Extracorpuscular

Immune-

— Antiglobulin test

— Donath-Landsteiner antibody

— ANA

Approach to a child with anemia(scenario approach)

Anemia (Hb less than normal level)

- No lymph nodes
- No hepatosplenomegaly
- No petechiae or ecchymosis

----- Nutritional iron deficiency or megaloblastic

----- Pure red cell aplasia

----- Thalassemia trait

----- Lead poisoning

----- Renal disease

Anemia (Hb less than normal level)

- No lymph nodes
- No hepatosplenomegaly
- With petechiae and ecchymosis

----- Aplastic anemia

----- Bleeding disorder

----- Coagulation disorder

----- ITP

----- DIC

Anemia (Hb less than normal level)

With hepatosplenomegaly

----- Thalassemia

----- Liver disorder

Infections

Anemia (Hb less than normal level)

With petechiae, lymphadenopathy and hepatosplenomegaly

--- Leukamia

--- Infections

--- DIC