Anemia

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Definition

Reduction in hemoglobin, hematocrit, or number of red blood cells (two standard deviations below the mean for age and sex for the normal population)

AGE-SPECIFIC BLOOD CELL INDICES

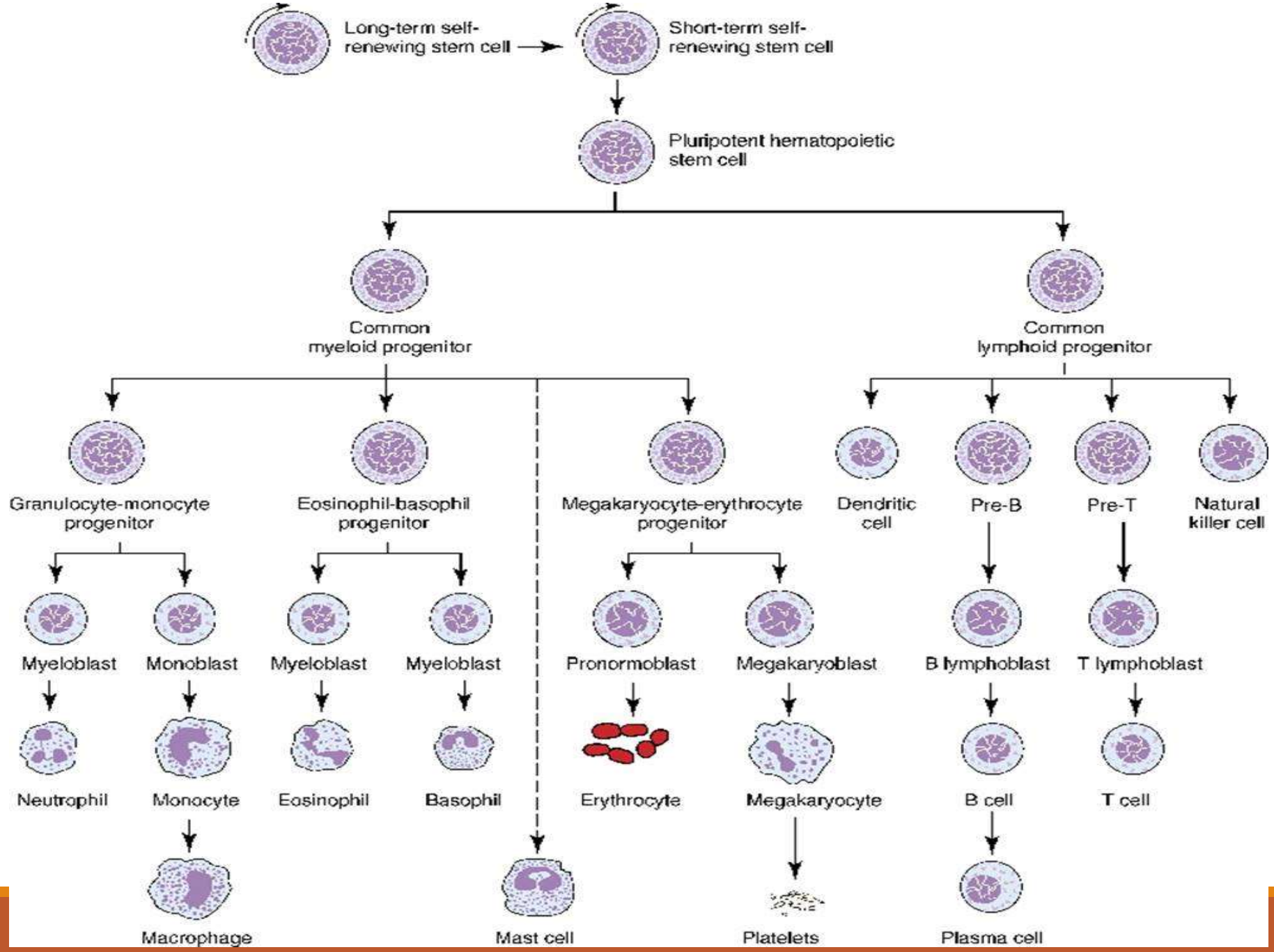
Age	Hb (g/dL)*	HCT (%)*	MCV (fL)*	MCHC (g/dL RBC)*	Reticulocytes	WBCs (×10³/mL)†	Platelets (10³/mL)†
26–30 wk gestation‡	13.4 (11)	41.5 (34.9)	118.2 (106.7)	37.9 (30.6)	—	4.4 (2.7)	254 (180–327)
28 wk	14.5	45	120	31.0	(5–10)	—	275
32 wk	15.0	47	118	32.0	(3–10)	—	290
Term§ (cord)	16.5 (13.5)	51 (42)	108 (98)	33.0 (30.0)	(3–7)	18.1 (9–30)‖	290
1–3 days	18.5 (14.5)	56 (45)	108 (95)	33.0 (29.0)	(1.8–4.6)	18.9 (9.4–34)	192
2 wk	16.6 (13.4)	53 (41)	105 (88)	31.4 (28.1)	—	11.4 (5–20)	252
1 mo	13.9 (10.7)	44 (33)	101 (91)	31.8 (28.1)	(0.1–1.7)	10.8 (4–19.5)	—
2 mo	11.2 (9.4)	35 (28)	95 (84)	31.8 (28.3)	—	—	—
6 mo	12.6 (11.1)	36 (31)	76 (68)	35.0 (32.7)	(0.7–2.3)	11.9 (6–17.5)	—
6 mo–2 yr	12.0 (10.5)	36 (33)	78 (70)	33.0 (30.0)	—	10.6 (6–17)	(150–350)
2–6 yr	12.5 (11.5)	37 (34)	81 (75)	34.0 (31.0)	(0.5–1.0)	8.5 (5–15.5)	(150–350)
6–12 yr	13.5 (11.5)	40 (35)	86 (77)	34.0 (31.0)	(0.5–1.0)	8.1 (4.5–13.5)	(150–350)
12–18 YR							
Male	14.5 (13)	43 (36)	88 (78)	34.0 (31.0)	(0.5–1.0)	7.8 (4.5–13.5)	(150–350)
Female	14.0 (12)	41 (37)	90 (78)	34.0 (31.0)	(0.5–1.0)	7.8 (4.5–13.5)	(150–350)
ADULT							
Male	15.5 (13.5)	47 (41)	90 (80)	34.0 (31.0)	(0.8–2.5)	7.4 (4.5–11)	(150–350)
Female	14.0 (12)	41 (36)	90 (80)	34.0 (31.0)	(0.8–4.1)	7.4 (4.5–11)	(150–350)

Hb, Hemoglobin; HCT, hematocrit; MCHC, mean cell hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell

Physiologic Anemia of infancy

At one week postnatal all RBC indices begin declining to a minimum value reached at about 2 months of age.

- decreased RBC production
- plasma dilution associated with increasing blood volume
- shorter life span on neonatal RBCs (50-70 days)
- more fragile RBCs
- switch from HbF to HbA
  - HbF decreases about 3% per week
  - at 6 mo. HbF represents only 2% of total Hb
  - switch to HbA provides for greater unloading of oxygen to tissues d/t lower oxygen affinit of HbA relative to HbF.
- seldom produces symptoms
- not altered by nutritional supplements


Long-term self-renewing stem cell
Short-term self-renewing stem cell
Pluripotent hematopoietic stem cell
Common myeloid progenitor
Common lymphoid progenitor
Granulocyte-monocyte progenitor
Eosinophil-basophil progenitor
Megakaryocyte-erythrocyte progenitor
Dendritic cell
Pre-B
Pre-T
Natural killer cell
Myeloblast
Monoblast
Myeloblast
Myeloblast
Pronormoblast
Megakaryoblast
B lymphoblast
T lymphoblast
Neutrophil
Monocyte
Eosinophil
Basophil
Erythrocyte
Megakaryocyte
B cell
T cell
Macrophage
Mast cell
Platelets
Plasma cell

Evaluation of anemic patient

Detailed history

Physical examination

Essential laboratory tests

History

- Age: e.g., IDA rare before age of 6 months. Anemia resulting from congenital disorder of hemoglobin usually detected at 3 to 6 months.
- Gender: consider X-linked disorders (G6PD, hemophilia)
- Race and Ethnicity
- Neonatal history: e.g. hyperbilirubinemia, prematurity.

- Diet: Pica, e.g., sources of iron, folic acid, B12, Vit E.
- Drugs: oxidant-induces hemolytic anemia, phenytoin-induced megaloblastic anemia.
- Infections: parvovirus, hemolytic anemia. Infections from recent travels
- Diarrhea and malabsorption

- Family history:
  - hemoglobinopathies, jaundice, gall stones, splenectomy, bleeding disorder.
- History of possible hemolytic crisis or blood loss.
- Menstrual history in all females.

Physical examination

- Pallor (tongue, nail beds, palms, or palmer creases), fatigue, irritability
- Sever acute anemia: compensatory mechanisms; tachycardia, heart murmur, lethargy, or pallor. signs of acute heart failure.
- Sever chronic anemia associated with paucity of symptoms

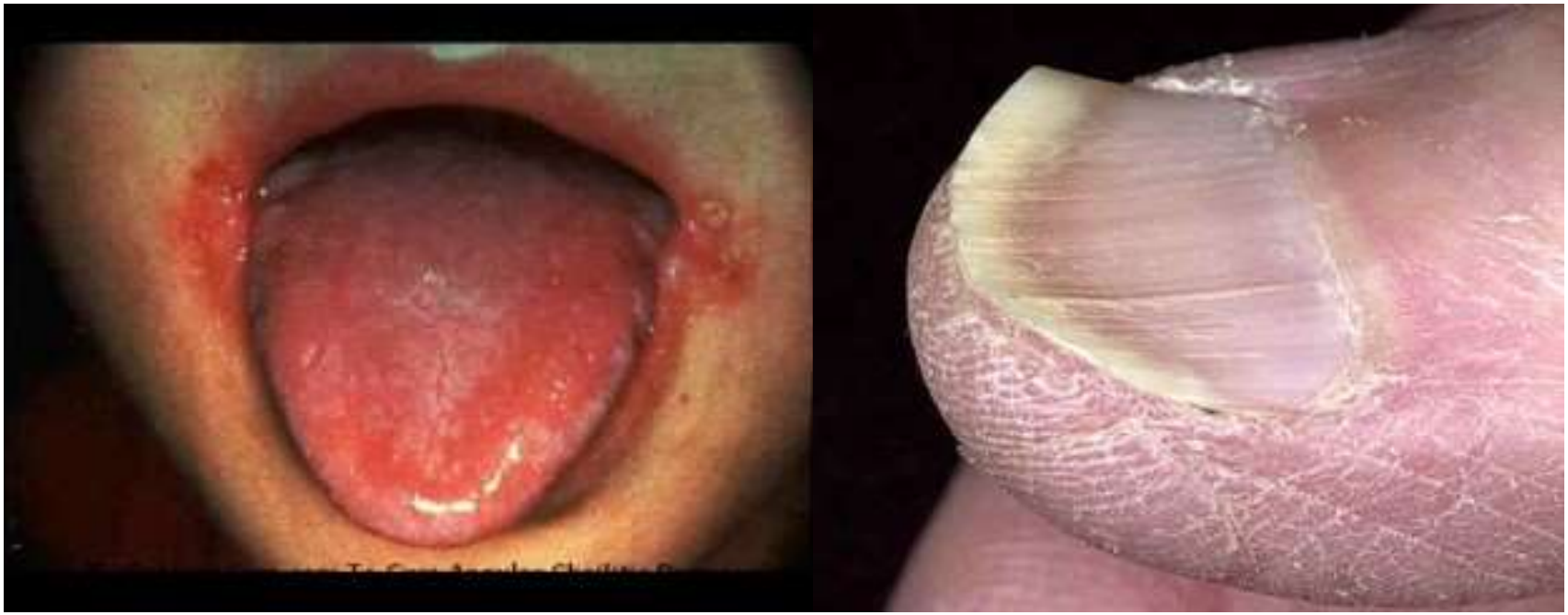
Skin:

- Hyperpigmentation (Fanconi's anemia)
- Jaundice
- Petechiae, purpura
- Cavernous hemangioma

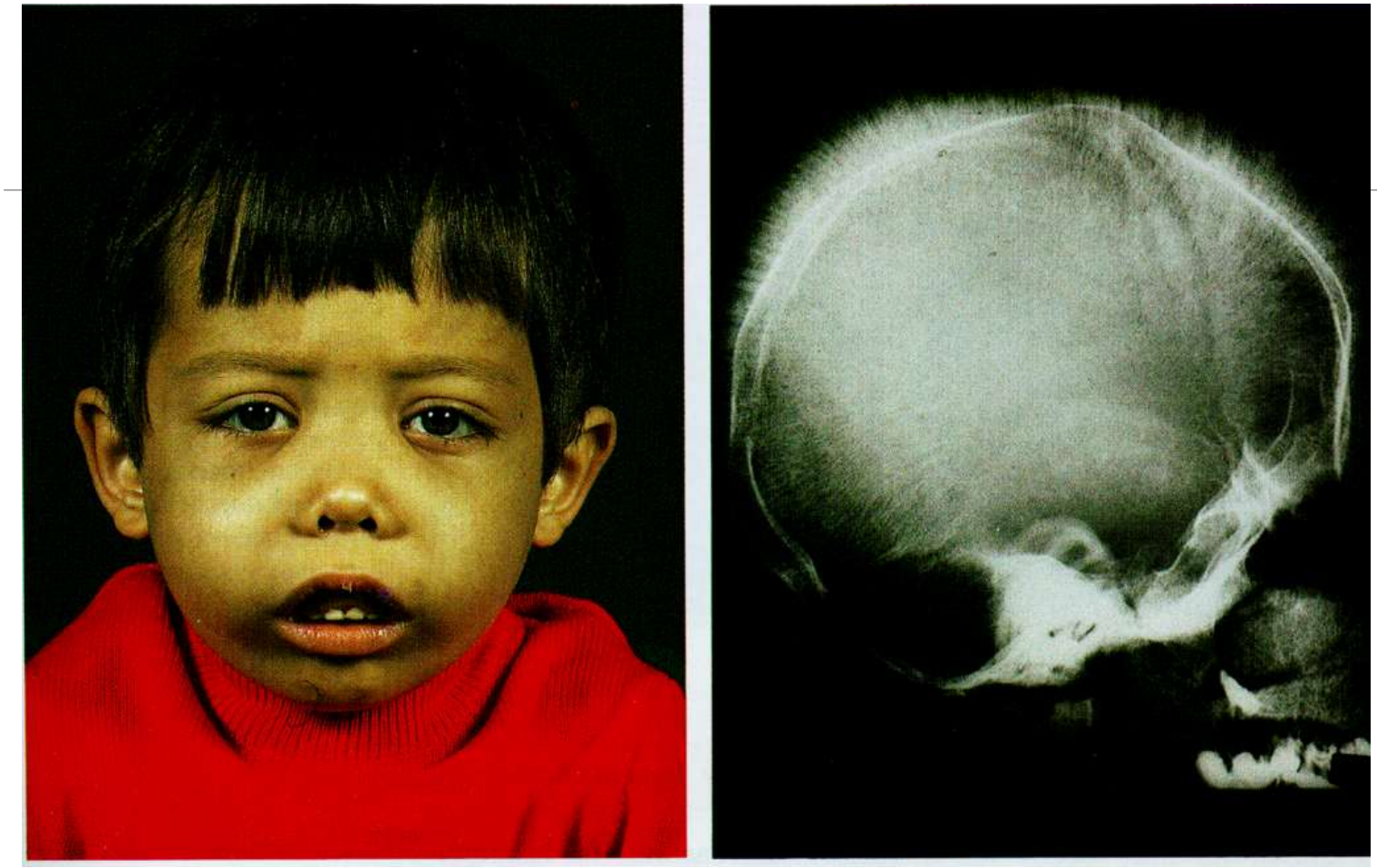
Face and mouth:

- frontal bossing, prominence of maxillary and malar bones
- Glossitis (B12 and iron deficiency), angular stomatitis (IDA)

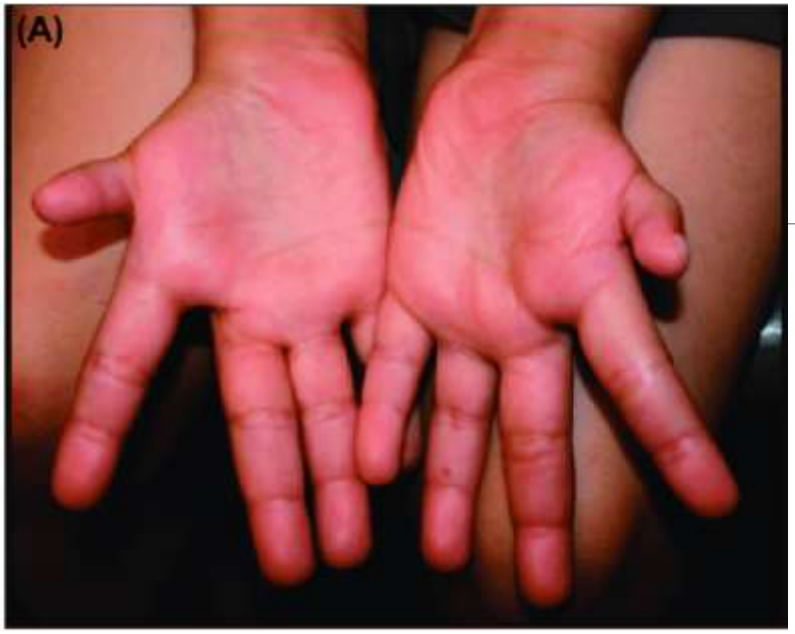
- Skeletal abnormalities:
  - triphalangeal thumb (red cell aplasia), absent thumb/radius (Fanconi's anemia), spoon nails (IDA), short stature.
- Splenomegally: hemolytic anemias, malignancies, infections.

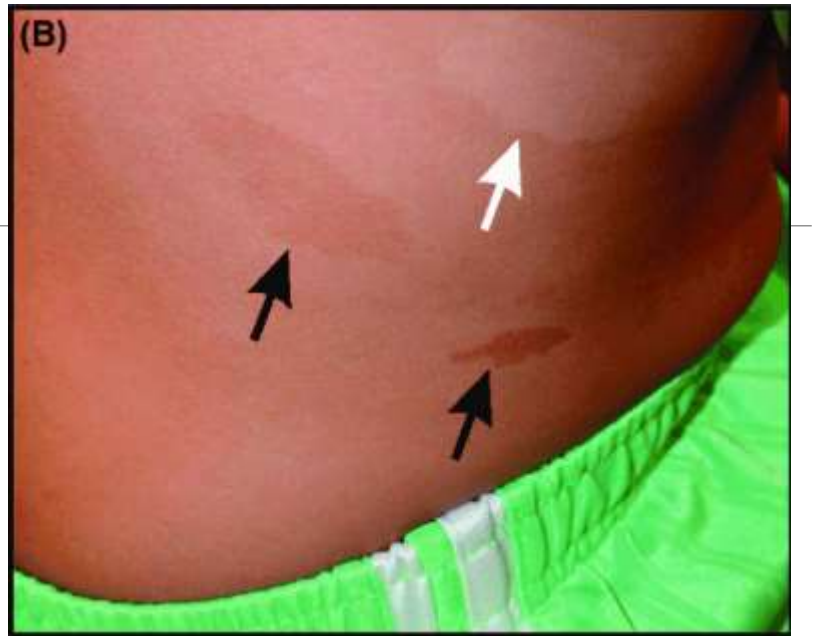


Iron deficiency anemia:
Glossitis, angular stomatitis , spoon nails



Thalassemic facies and ‘hair on end’ Appearance





Fanconi's anemia:
(A) Hypoplastic thumbs in an 11-year-old. (B) Hypopigmented (white arrow) and hyperpigmented (black arrows) skin lesions

Initial laboratory test

1. Complete blood count
2. Reticulocytes count
3. Blood film

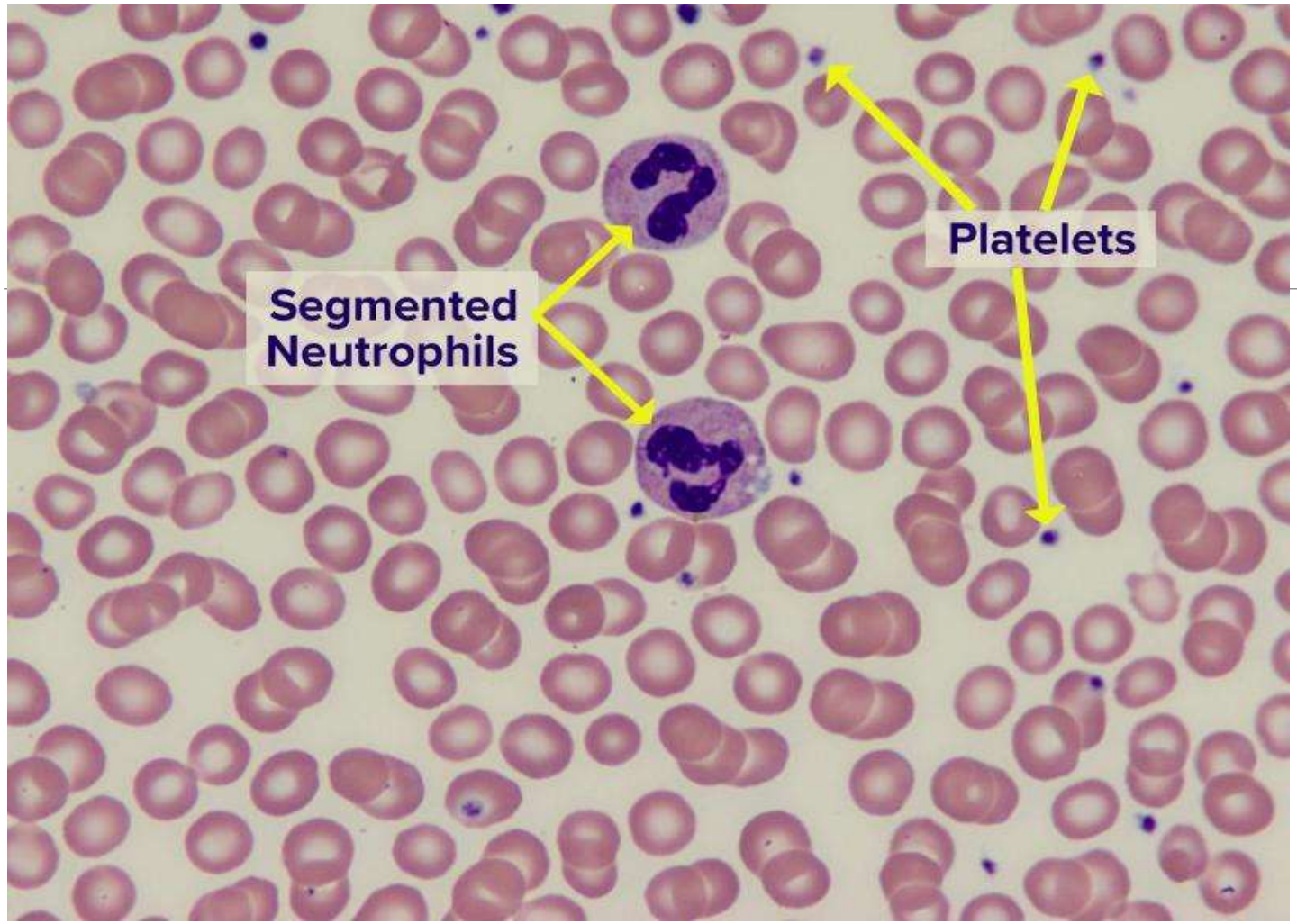
Disease-specific tests based on initial evaluation

Complete Blood count

Haemoglobin	12.2	g/dl	11.5 - 15.5
Haematocrit (PCV)	40.0	%	36 - 45
RBCs Count	4.5	millions/cmm	4.0 - 5.2
MCV	85.0	fl	80 - 100
MCH	30.4	pg	27 - 33
MCHC	35.7	g/dl	31 - 37
RDW-CV	14.4	%	11.5 - 15
Platelet Count	376	thousands/cmm	150 - 450
Total Leucocytic Count	9.3	thousands/cmm	4 - 11

	Percent Values		Absolute Values		
Differential Leucocytic Count					
Neutrophils	70.0	%	6.51	x10^9/L	2 - 7
Staff	2	%	0.19	x10^9	
Segmented	68	%	6.32	x10^9	
Lymphocytes	23.0	%	2.14	x10^9/L	1 - 4.8
Monocytes	5.0	%	0.47	x10^9/L	0.2 - 1
Eosinophils	2.0	%	0.19	x10^9/L	0.1 - 0.45
Basophils	0.0	%	0.00	x10^9/L	0 - 0.1

Other Cells



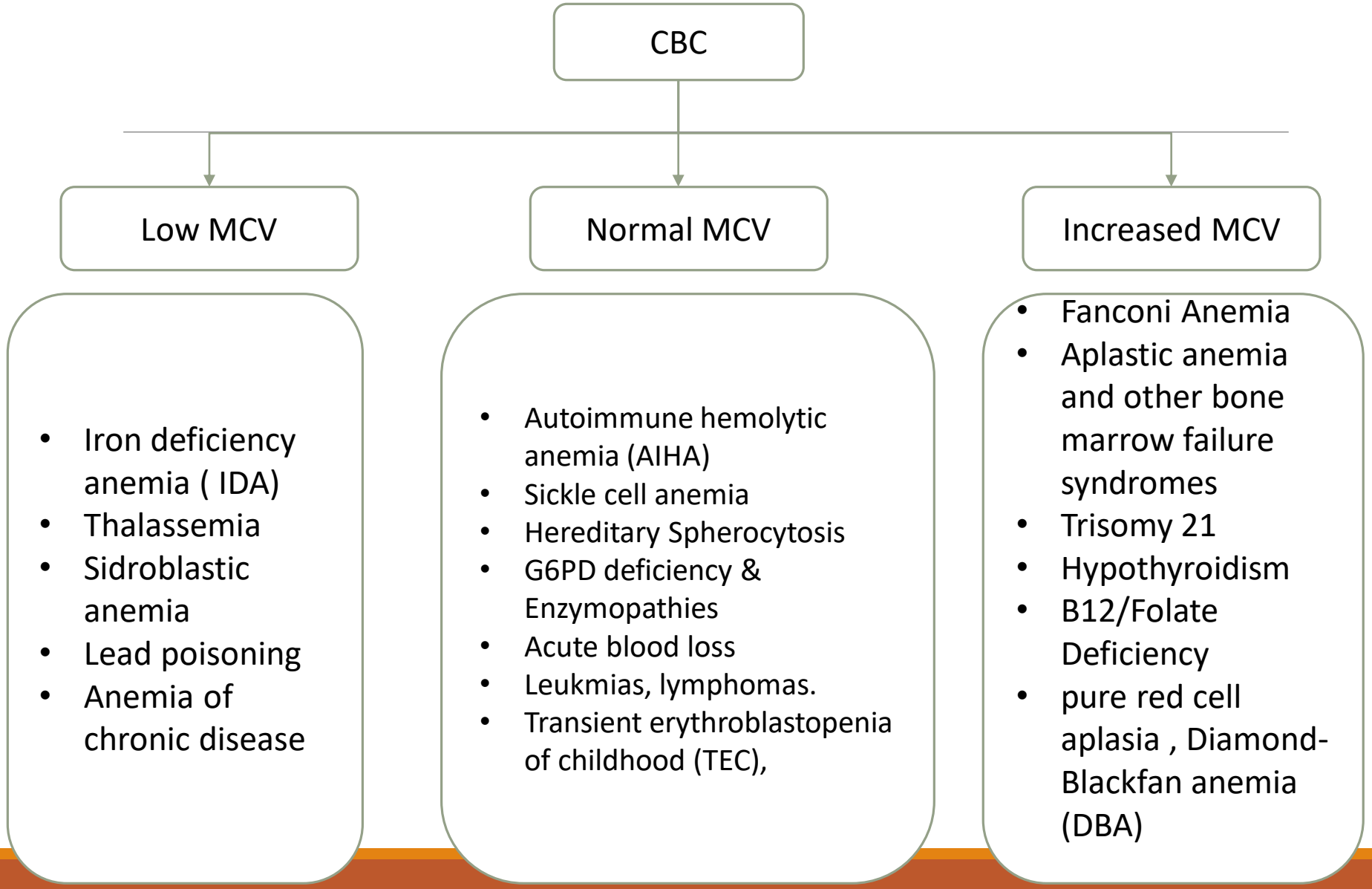
Normal blood smear with red blood cells (majority of cells shown), white blood cells (segmented neutrophils) and platelets (small purple dots)

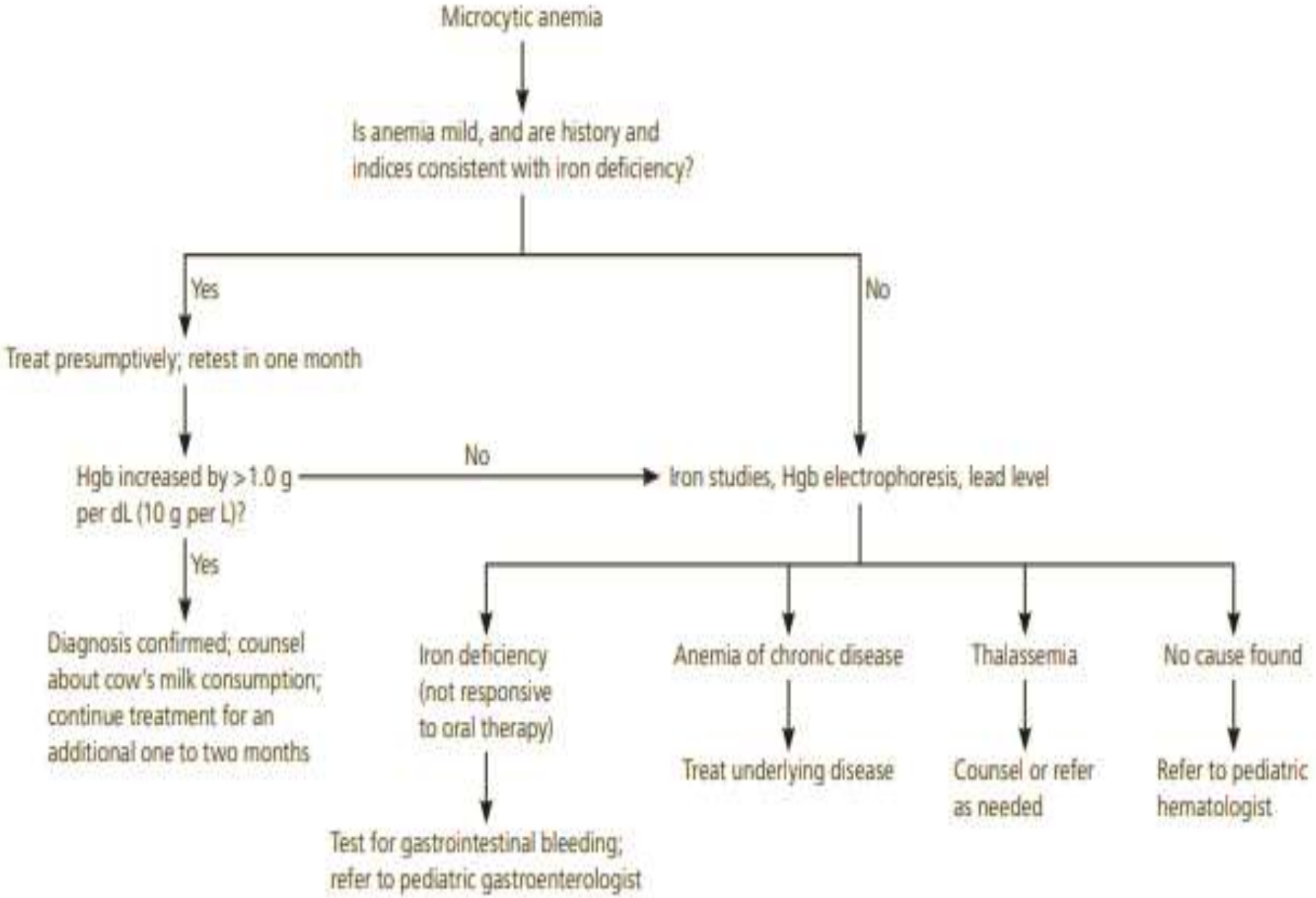
Classifications of Anemias

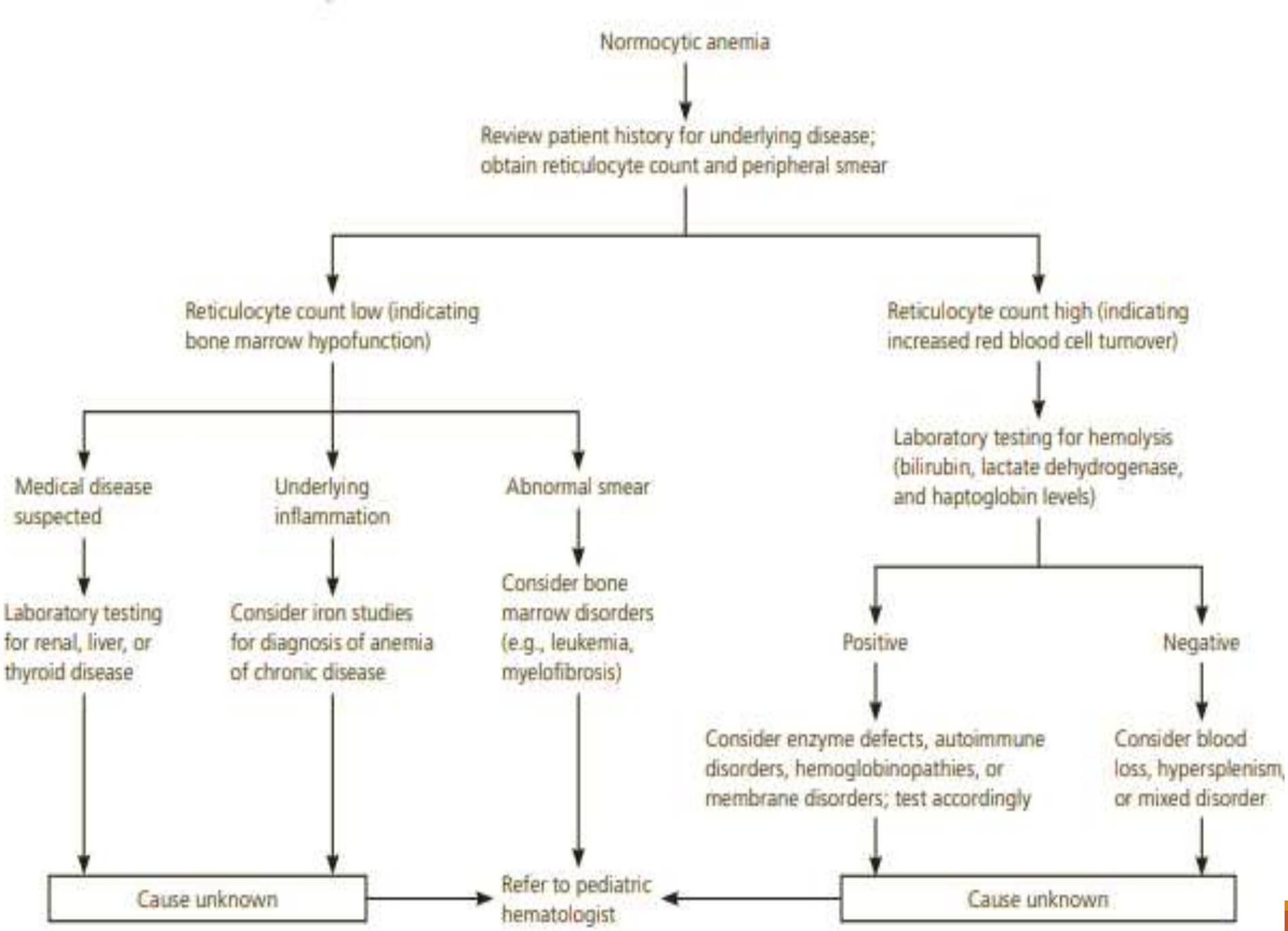
1. Physiologic :
   - Disorders of effective red cell production
   - rapid erythrocytes destruction or loss

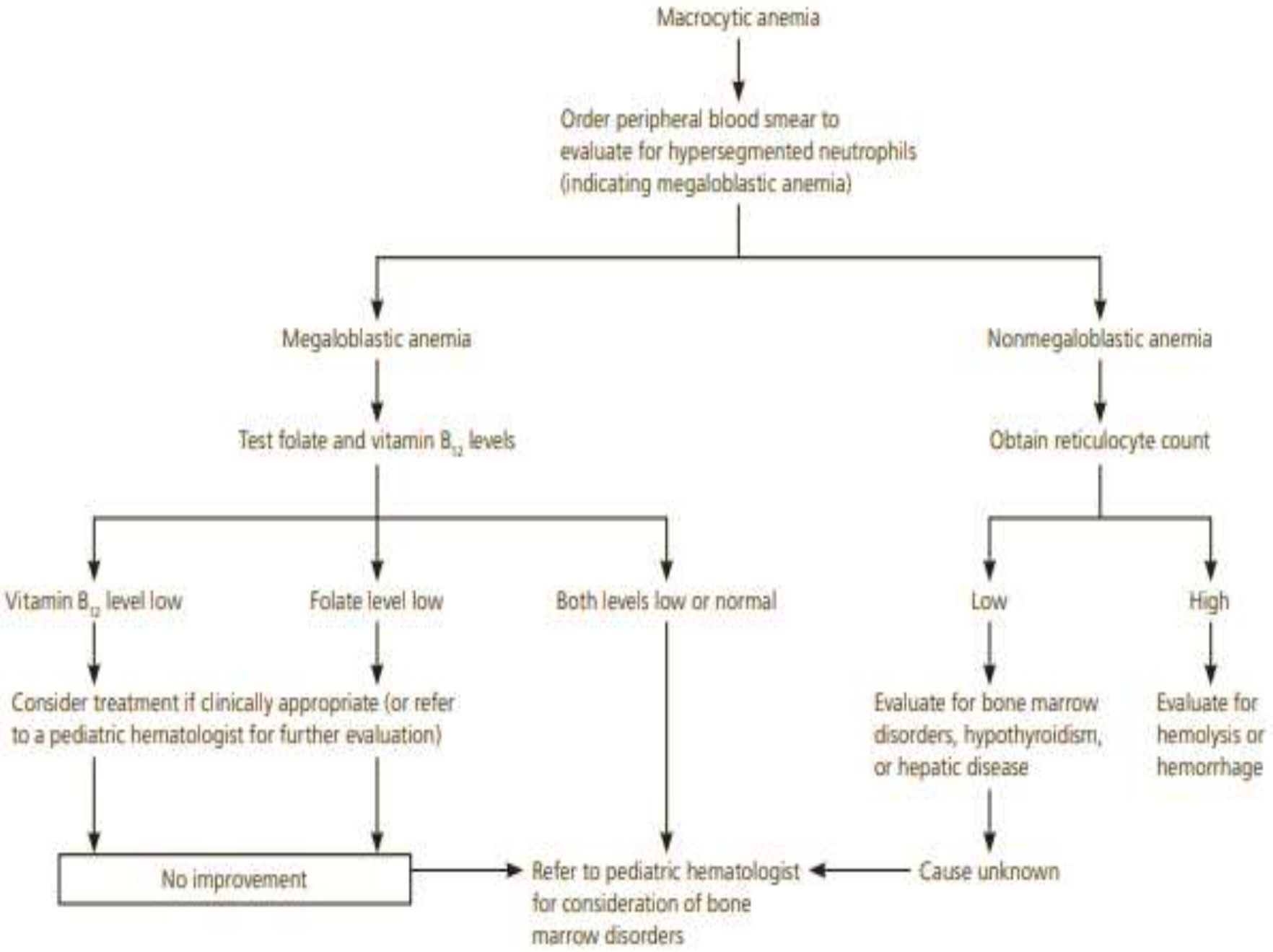
2. Red cell size; MCV:
   - macrocytic anemias
   - microcytic anemias
   - normocytic anemias

Anemia classification by RBC size




Microcytic anemia
Is anemia mild, and are history and indices consistent with iron deficiency?
Yes
No
Treat presumptively; retest in one month
Hgb increased by >1.0 g per dL (10 g per L)?
No
Iron studies, Hgb electrophoresis, lead level
Yes
Diagnosis confirmed; counsel about cow's milk consumption; continue treatment for an additional one to two months
Iron deficiency (not responsive to oral therapy)
Anemia of chronic disease
Thalassemia
No cause found
Test for gastrointestinal bleeding; refer to pediatric gastroenterologist
Treat underlying disease
Counsel or refer as needed
Refer to pediatric hematologist


Normocytic anemia
Review patient history for underlying disease; obtain reticulocyte count and peripheral smear
Reticulocyte count low (indicating bone marrow hypofunction)
Reticulocyte count high (indicating increased red blood cell turnover)
Medical disease suspected
Underlying inflammation
Abnormal smear
Laboratory testing for hemolysis (bilirubin, lactate dehydrogenase, and haptoglobin levels)
Laboratory testing for renal, liver, or thyroid disease
Consider iron studies for diagnosis of anemia of chronic disease
Consider bone marrow disorders (e.g., leukemia, myelofibrosis)
Positive
Negative
Consider enzyme defects, autoimmune disorders, hemoglobinopathies, or membrane disorders; test accordingly
Consider blood loss, hypersplenism, or mixed disorder
Cause unknown
Refer to pediatric hematologist
Cause unknown


Macrocytic anemia
Order peripheral blood smear to evaluate for hypersegmented neutrophils (indicating megaloblastic anemia)
Megaloblastic anemia
Nonmegaloblastic anemia
Test folate and vitamin B_{12} levels
Obtain reticulocyte count
Vitamin B_{12} level low
Folate level low
Both levels low or normal
Low
High
Consider treatment if clinically appropriate (or refer to a pediatric hematologist for further evaluation)
Evaluate for bone marrow disorders, hypothyroidism, or hepatic disease
Evaluate for hemolysis or hemorrhage
No improvement
Refer to pediatric hematologist for consideration of bone marrow disorders
Cause unknown

Macrocytic anemia

- Megaloblastic anemia:
  - B12 , folate deficiency
- Non-megaloblastic anemia:
  - Fanconi anemia
  - Diamond-Blackfan anemia (DBA)
  - Aplastic anemia
  - Pearson syndrome
  - Chronic liver disease

Megaloblastic anemia

- Megaloblasts in bone marrow
- High MCV
- Peripheral blood shows hypersegmented neutrophils
- Causes: Folic acid and vitamin B12 deficiency
- Both vitamins are required for DNA synthesis and red cell maturation

Folate deficiency

- Causes:
  - Malnutrition, malabsorption, goat's milk consumption
  - Antimetabolite (e.g., methotrexate), phenytoin, trimethoprim/sulfa
- Clinical manifestation:
  - glossitis, symptoms of anemia (weakness, pallor, shortness of breath), and GI problems (weight loss and infertility)
- Treatment:
  - diet modification, treat underlying cause, folate therapy.

Vitamin B12 (Cobalamin) Deficiency

- Causes:
  - Pernicious anemia, ileal resection,
  - strict vegetarian,
  - congenital intrinsic factor or transcobalamin deficiency
- Main manifestations
  - same as those for folate but may be a more serious presentation with peripheral neuropathy, degeneration of the spinal cord, or demyelination of white matter of brain.
- Treatment:
  - diet modification, treat underlying cause, B12 therapy.

Fanconi anemia

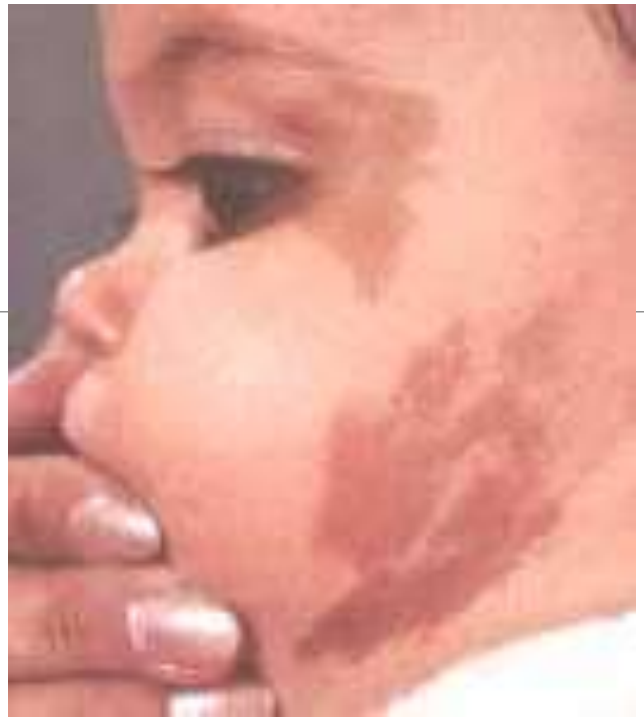
- inherited bone marrow failure
- Autosomal recessive.
- Many patients eventually develop acute myelogenous leukemia at an early age.

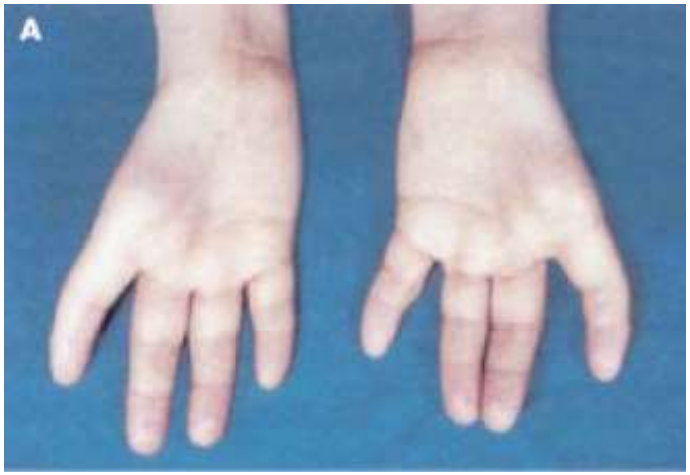
Fanconi anemia

Presents with:

- Pancytopenia: develops between 4 and 12 years of age
- Short stature
- Absence of or malformation in hands and arms, for example the absence of a thumb or the presence of polydactyly
- Single kidney or of a horseshoe kidney
- Café-au-lait spots

Fanconi anemia





Fanconi anemia

- Diagnosis: positive chromosome-breaking effect to diepoxybutane (DEB) or mitomycin C (MMC) tests

- Treatments include:
  - Bone marrow transplant.
  - Hematopoietic (blood-stimulating) growth factors are used to stimulate WBC production.
  - Androgens: stimulate the production of RBCs and platelets.
  - Future: gene therapy
- Genetic counseling

Diamond-Blackfan anemia (DBA)

- Bone Marrow Failure
- Autosomal dominant, May be sporadic or inherited
- Congenital Anomalies mainly involve cranio-orofacial, upper extremity, genitourinary, cardiac
- Cancer Predisposition

DBA

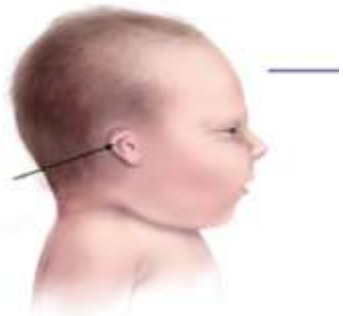
Treatment:

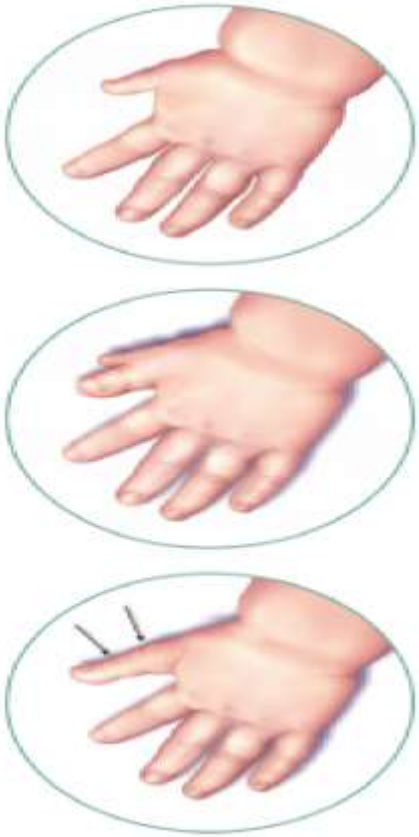
- Prednisone: 2 mg/kg for up to 8-12 weeks before declaring failure
- chronic red cell transfusions. Chelation therapy for Iron overload
- HSCT for transfusion dependent patients

Outcome:

- Remission of anemia ~ 20%
- cancer predisposition: e.g., AML/ MDS, osteosarcoma.

DBA





- Cleft palate
- Microcephaly
- small ears
- Ptosis
- congenital cataract
- Strabismus
- short webbed neck
- Single kidney, horseshoe kidney

VSD (VENTRICULAR SEPTAL DEFECT)

ASD (ATRIAL SEPTAL DEFECT)

COARCTATION OF THE AORTA

Pearson Syndrome

- Refractory sideroblastic anemia by 6 months of age
- Exocrine pancreatic dysfunction (fat malabsorption)
- Associated usually mild neutropenia, thrombocytopenia
- Bone Marrow: Vacuolated precursors/ringed sideroblasts
- Death usually as a consequence of acidosis, sepsis, liver or renal failure related to tubular dysfunction
- Median survival 3 years
- Genetics: Mitochondrial DNA deletion. Pathognomonic, maternal inheritance

Acquired aplastic anemia

2 of 3 peripheral blood criteria:

- ANC < 500/ml
- Platelets < 20,000/ml
- Reticulocytes < 1% corrected (ARC < 40,000/ul)

1 of 2 bone marrow criteria:

- < 25% cellularity on biopsy
- 25 – 50% with < 30% hematopoietic cells

Causes of acquired aplastic anemia

- Idiopathic (70%)
- Radiation
- Drugs/Chemicals
  - Cytotoxic agents, benzene
  - Idiosyncratic: chloramphenicol, anti-epileptic, anti-inflammatory, and psychotropic medications
- Viruses:
  - EBV, CMV, sero-negative hepatitis, HHV6, HIV, **parvovirus**
- Immunologic disorders: GvHD. Preleukemia, MDS, thymoma
- Malnutrition
- Paroxysmal nocturnal hemoglobinuria

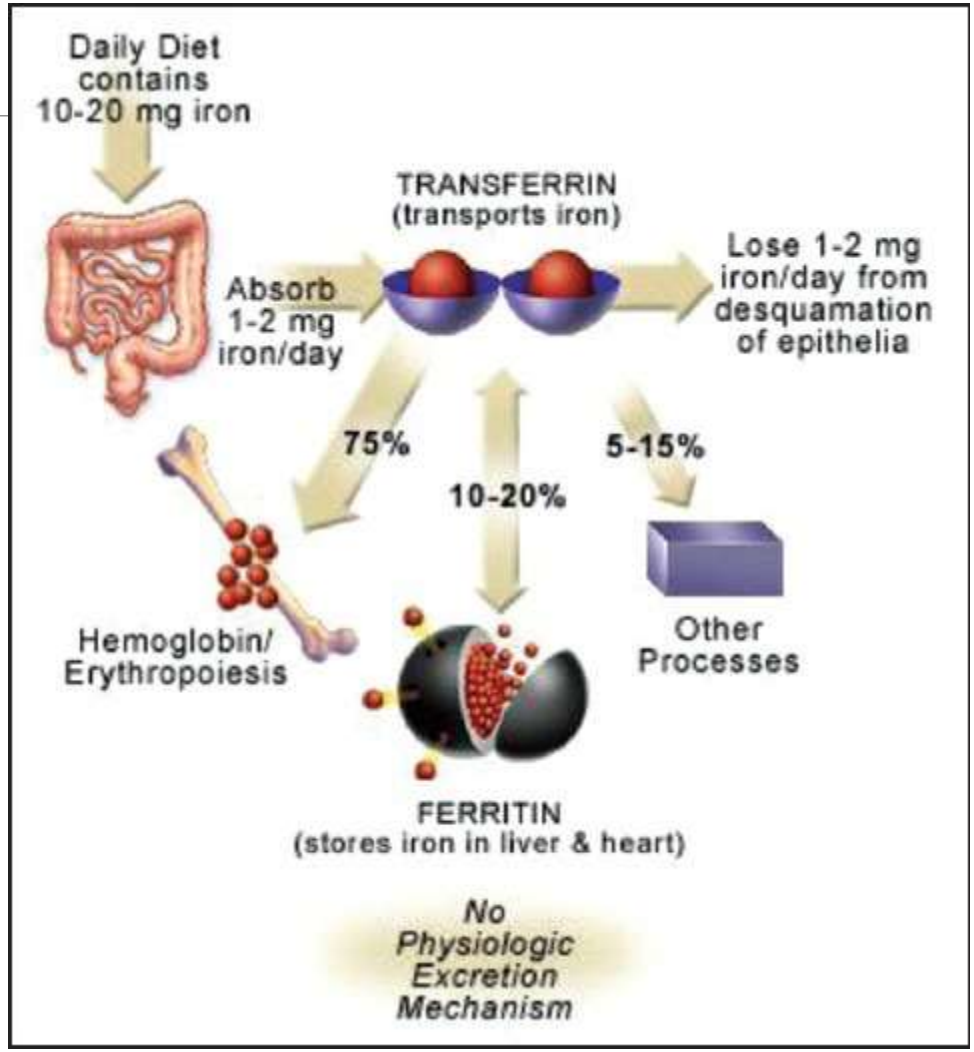
Transient erythroblastopenia of childhood (TEC)

- Most common acquired red cell aplasia in previously healthy children
- Age: 6 months and 3 years of age
- Neutropenia 10%, Thrombocytosis 50 % of cases.
- Typically self limited within 1-2 mo – close supportive care
- Transfusion if necessary:
  - Hgb<5 with reticulocytopenia
- Follow to resolution

Microcytic anemias

Iron Deficiency Anemia

- Most common cause of anemia
- Iron is essential for DNA synthesis



Etiology

- Excessive Cow's Milk Intake
  - Chronic low grade hemorrhagic enteropathy
  - Low iron content
  - Poor bioavailability of iron (50% in BM, 5-10% cow's milk)
  - Prevention of eating iron-rich foods
- impaired absorption (e.g. celiac disease)
- Vegan/Poor Meat Intake
- Growth spurts
- Blood Loss
  - Menorrhagia
  - GI (celiac, IBD), Parasite/Worm (#1 cause of GI blood loss worldwide)

Clinical manifestations

- Neurocognitive effects (Apathy, irritability, poor concentration)
- Pica: compulsive consumption of nonnutritive substances
- Anorexia, poor weight gain
- Epithelial changes: angular stomatitis, glossitis, finger nails koilonychias or spooning. dry skin, thin hair.

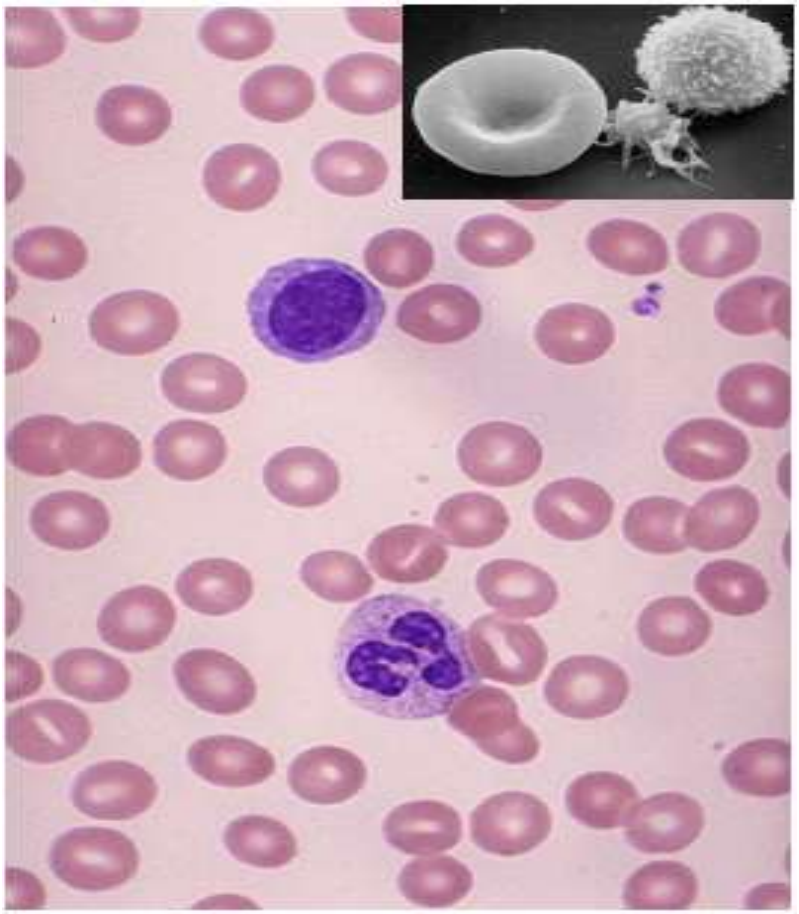
Diagnostic laboratory tests

- CBC:
  - low hb , normal WBCs, normal or high paltelets. Low MCV and MCH. High RDW. Low reticulocytes
- Blood Film:
  - hypochromic microcytic RBC, anisopoikilocytosis (variable sizes and shapes)
- Iron metabolism tests:
  - low ferritin, Low serum iron, low transferrin saturation, high total iron-binding capacity,

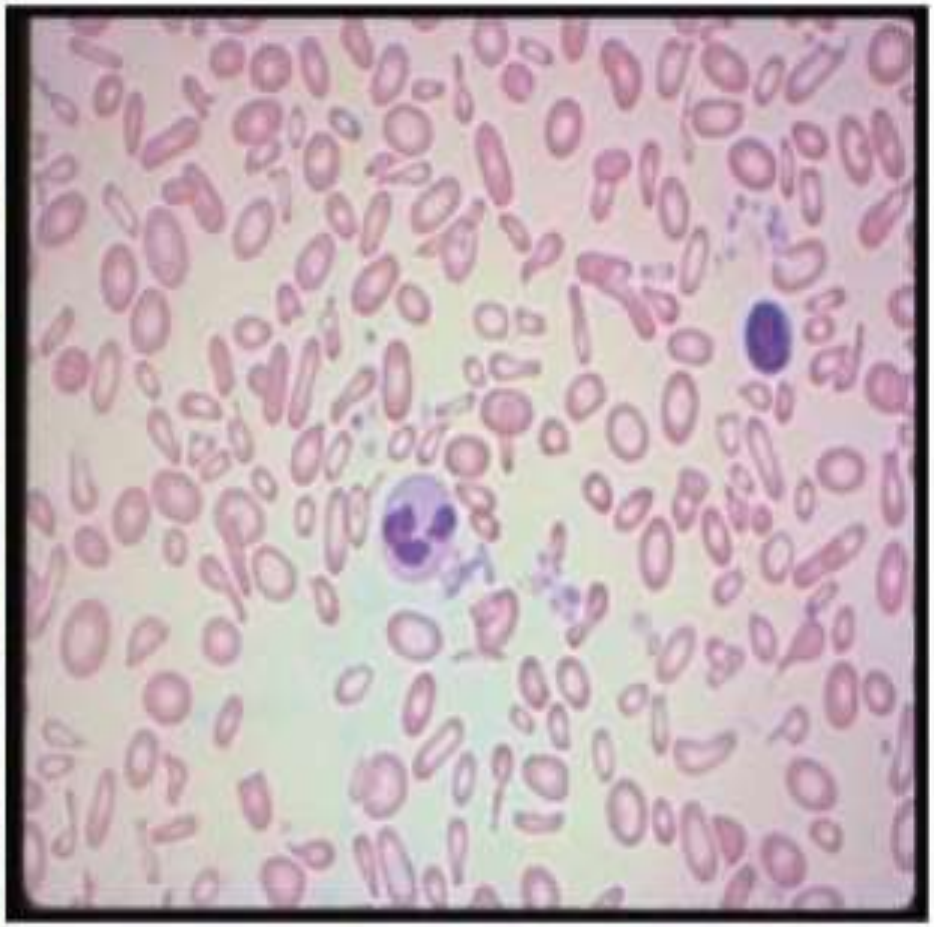
Differentiating features of iron deficiency anemia from other microcytic anemia

	Fe deficiency anemia	Anemia of chronic Inflammation	Thalassemia	Sideroblastic anemia
Smear	Micro/Hypo	Normal Micro/Hypo	Micro Hypo an targeting	Variable
SI	<30	<50	N / η	N / η
TIBC	> 360	<300	Normal	Normal
%, saturation	<10	10-20	30-80	30-80
S.Ferritin	<15	30-20	50-300	50-300
Hb pattern	N	N	Abnormal	N

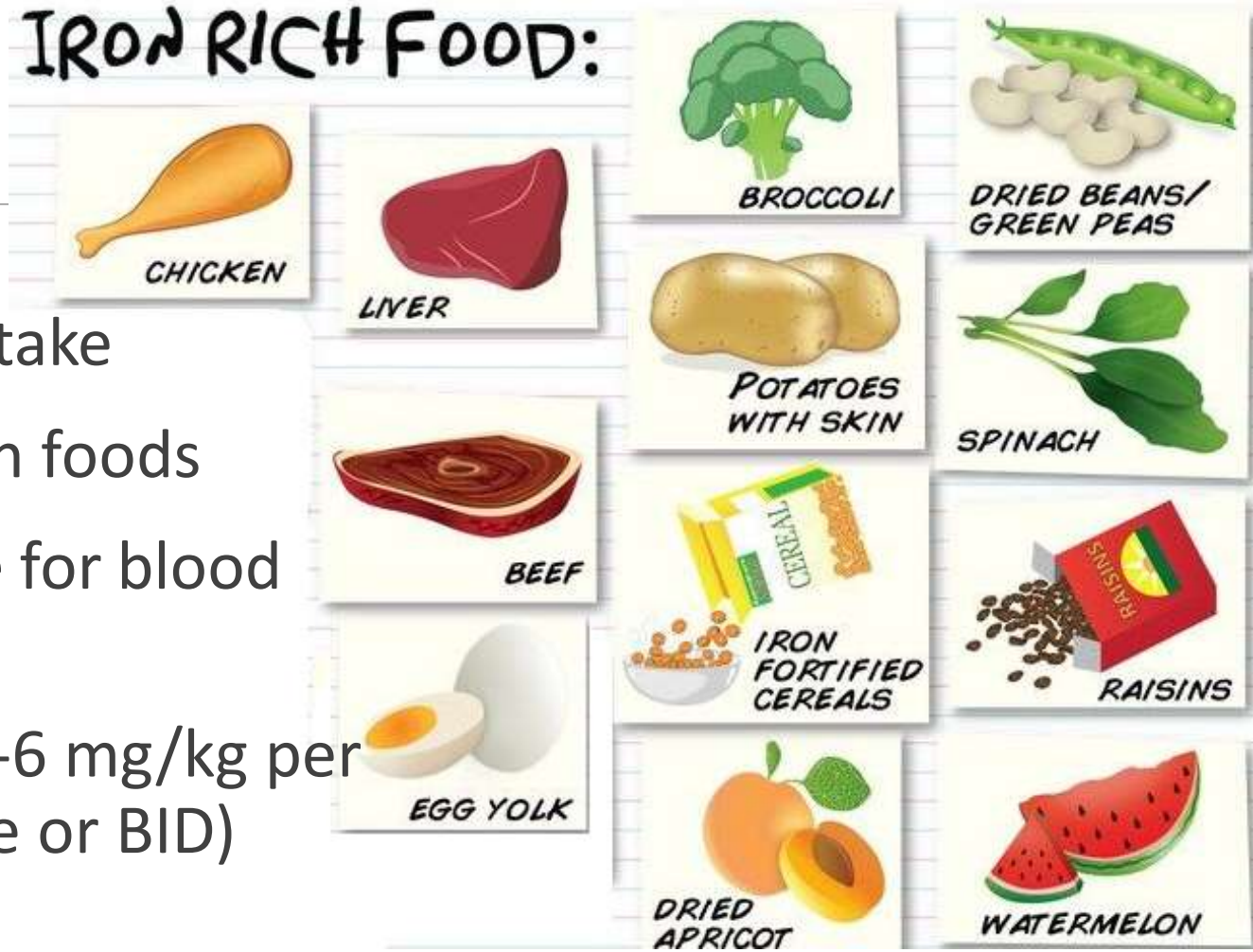
Normal blood film



IDA
Hypochromic microcytic, anisopokilocytosis

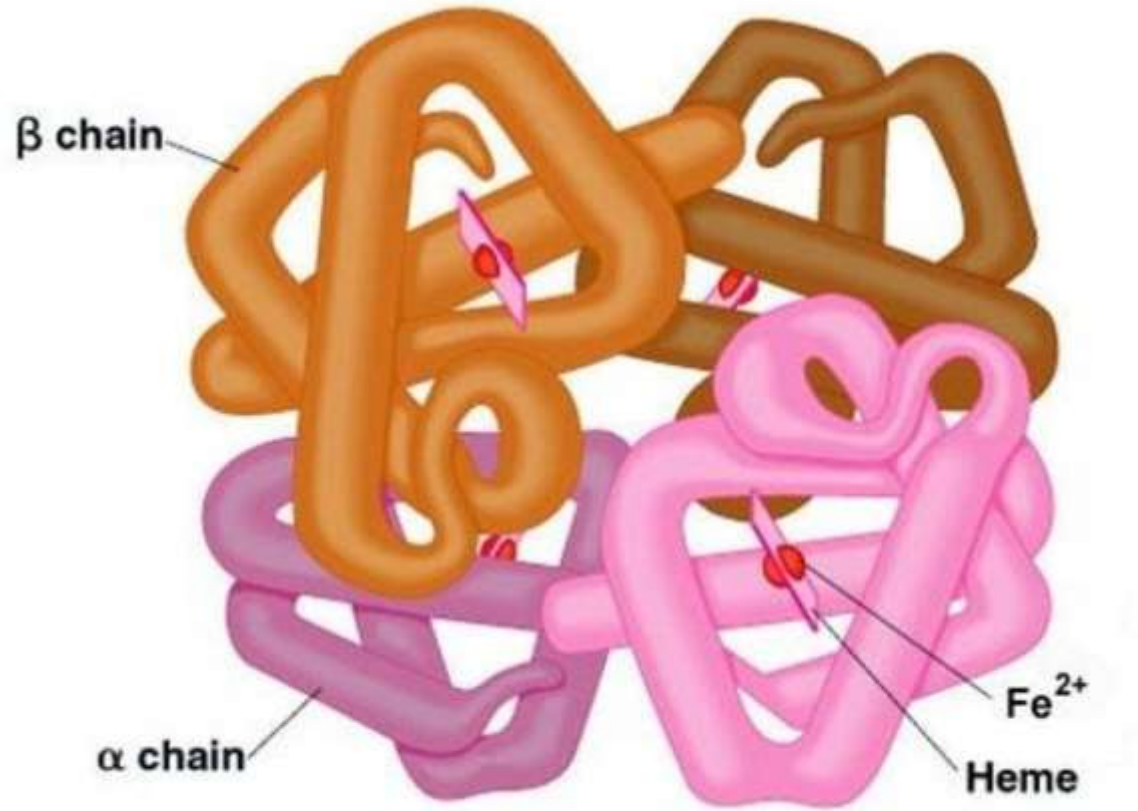


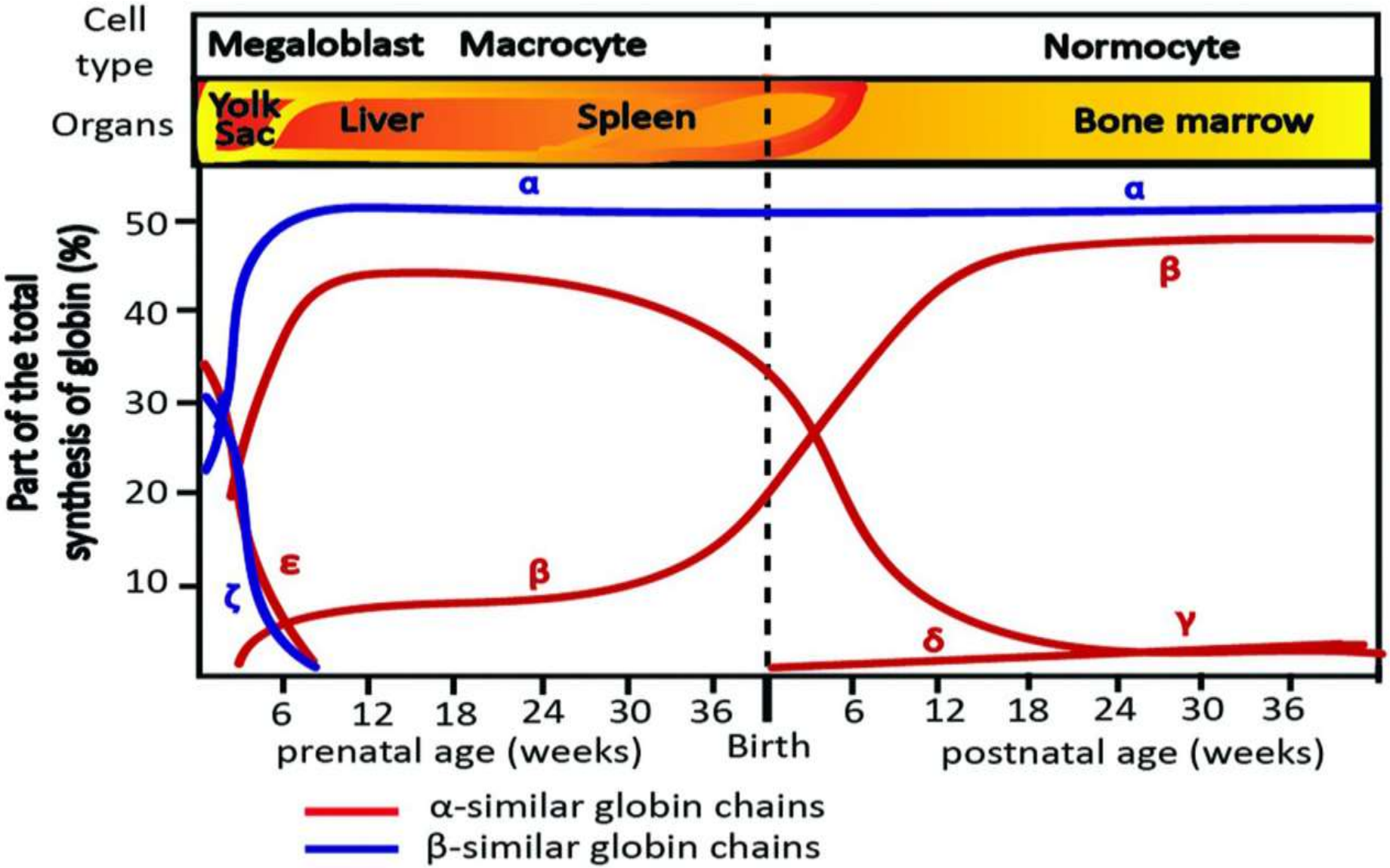
Treatment



- Decrease milk intake
- Promote iron rich foods
- Control/evaluate for blood loss
- Elemental iron 4-6 mg/kg per day (divided once or BID) orally
- IV iron if malabsorption suspected

Hemoglobinopathies





Expression of globin genes during prenatal and postnatal development in humans.

Normal and Variant Hemoglobin at Birth and in Older Children

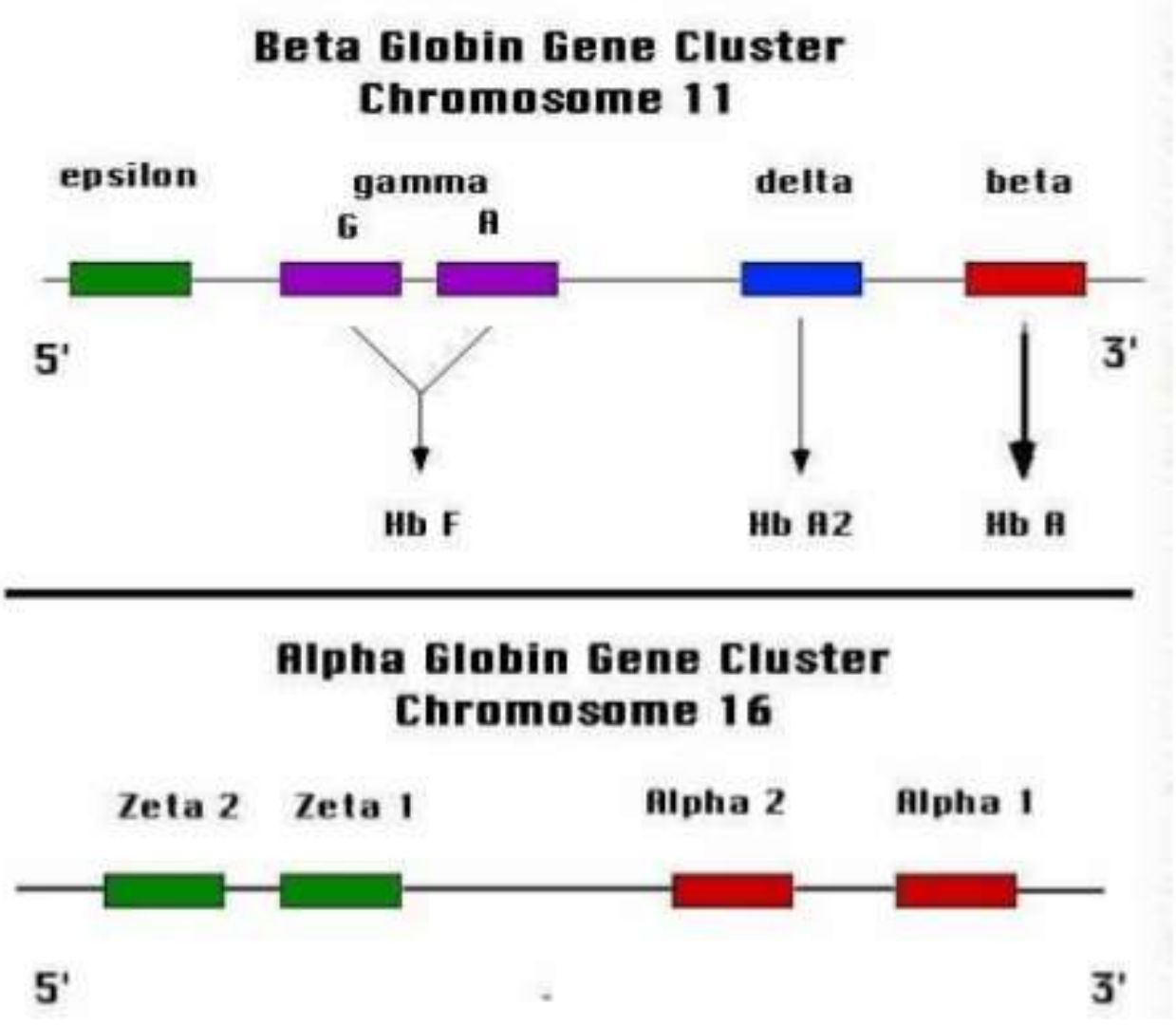
Hemoglobin	Structure	Levels at Birth	Levels in Adults	Comments
A	$\alpha_2\beta_2$	20%-25%	97%	Reaches adult levels by 1 year of age
A_2	$\alpha_2\delta_2$	0.5%	2.5%	Elevated in β thalassemia trait
F	$\alpha_2\gamma_2$	75%-80%	< 1%	Reaches adult levels by 1 year of age
HbH	β_4	15%-20% in HbH disease	NA	HbH produces Heinz bodies in the erythrocytes and hemolysis
Hb Bart	γ_4	100% in hydrops fetalis, 15%-25% in HbH disease	NA	Increased in carriers of α thalassemia trait at birth

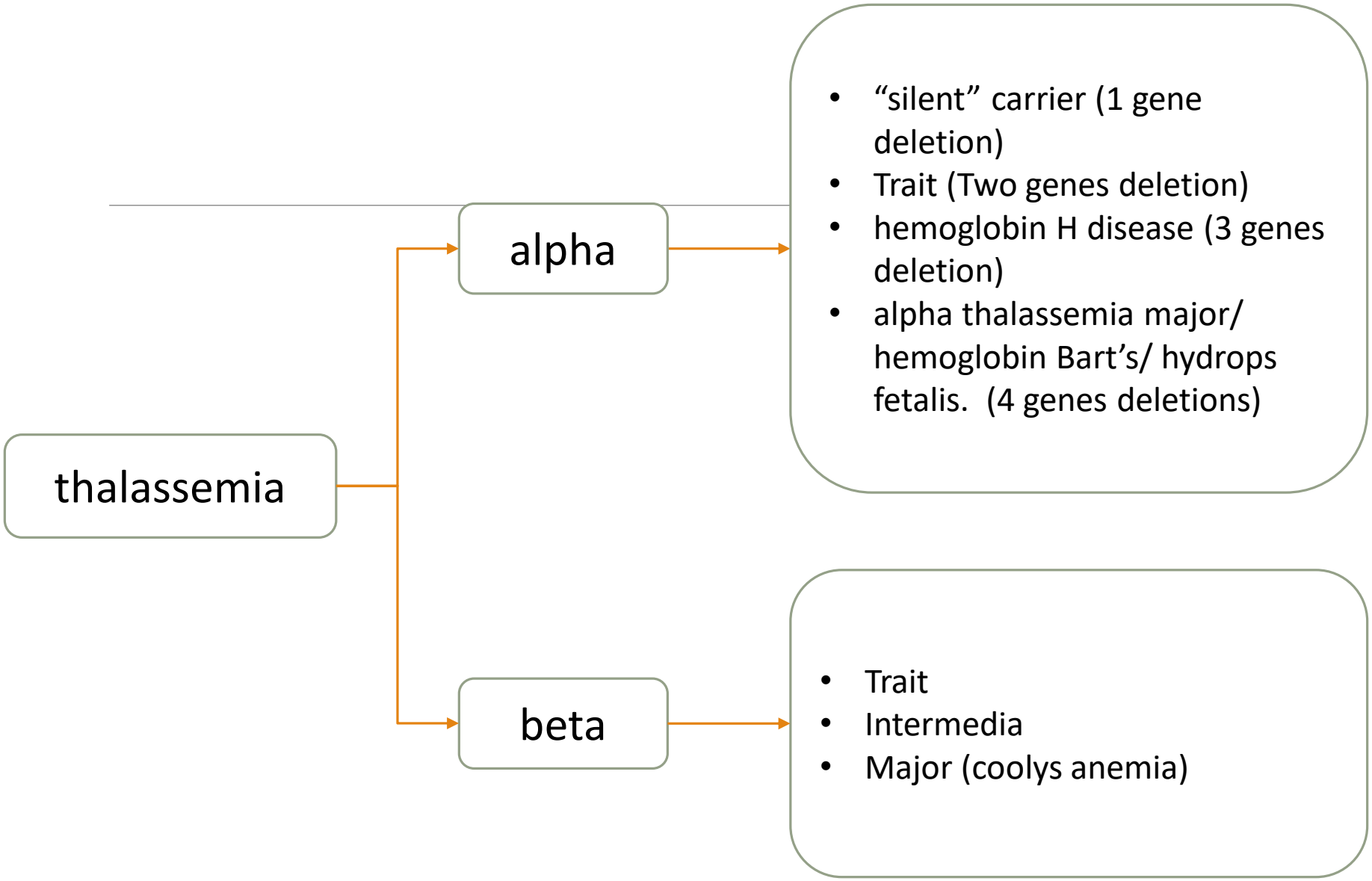
NA = not applicable.

Thalassemia

- A group of hemoglobin disorders in which the production of normal hemoglobin is partially or completely suppressed as a result of defected synthesis of one or more globin chains
- Inherited as autosomal recessive
- Hypochromic microcytic anemia as a result of ineffective erythropoiesis and increased hemolysis
- High incidence in Asia, Africa, Mideast, and Mediterranean countries

Globin genes




thalassemia
alpha
beta
• “silent” carrier (1 gene deletion)
• Trait (Two genes deletion)
• hemoglobin H disease (3 genes deletion)
• alpha thalassemia major/ hemoglobin Bart’s/ hydrops fetalis. (4 genes deletions)
• Trait
• Intermedia
• Major (coolys anemia)

Alpha thalassemia

- Alpha globin genes are coded on chromosome 16 (Two genes on each chromosome)
- The majority result from gene deletions
  - One deletion: Silent carrier; no clinical significance
  - Two deletions: α Thalassemia trait; mild hypochromic microcytic anemia
  - Three deletions: Hgb H; variable severity, but less severe than Beta Thalassemia Major
  - Four deletions: Bart's Hgb; Hydrops Fetalis; In Utero or early neonatal death

Beta thalassemia

Beta globin genes are coded on chromosome 11 (one gene on each chromosome)

Point mutations result in most of Beta-Thalassemias

- Thalassemia minor (trait) ß+: Affected individuals have only one affected ß gene. Anemia is either not present or very mild
- Thalassemia intermedia ß+: both ß genes , anemia is relatively mild-moderate with no or rare transfusion requirement
- Thalassemia major ß0: both ß genes are affected, anemia is sever. Patients are transfusion dependent.

Beta thalassemia (major and intermedia) sequelae

- Hyperplastic expanded bone marrow and bone abnormalities
- Iron overload /hemochromatosis (mainly from recurrent blood transfusions)
  - Liver fibrosis/cirrhosis
  - Endocrine disturbances (e.g., DM, hypothyroidism, hypogonadism, hypoparathyroidism, etc)
  - Cardiac hemochromatosis, arrhythmias, and failure
  - Skin hyperpigmentation
- Hypersplenism:
  - Low RBC, WBC, and platelets

Clinical features

- Presentation at about 2-4 months of age (after HbF to HbA switch)
- Sever anemia
- Progressive pallor and jaundice
- Hepatosplenomegaly
- Failure to thrive, gross motor delay, short stature
- Cardiomyopathy, heart failure
- Recurrent infections

- Skeletal changes: prominence of malar eminence, frontal
- bossing, depression of bridge of the nose, exposure of
- upper central teeth
- primary amenorrhea, delayed puberty in males
- Diabetes mellitus
- Leg ulcers, gallstones
- Skin bronzing
- If untreated, 80% of patients die in the first decade of life

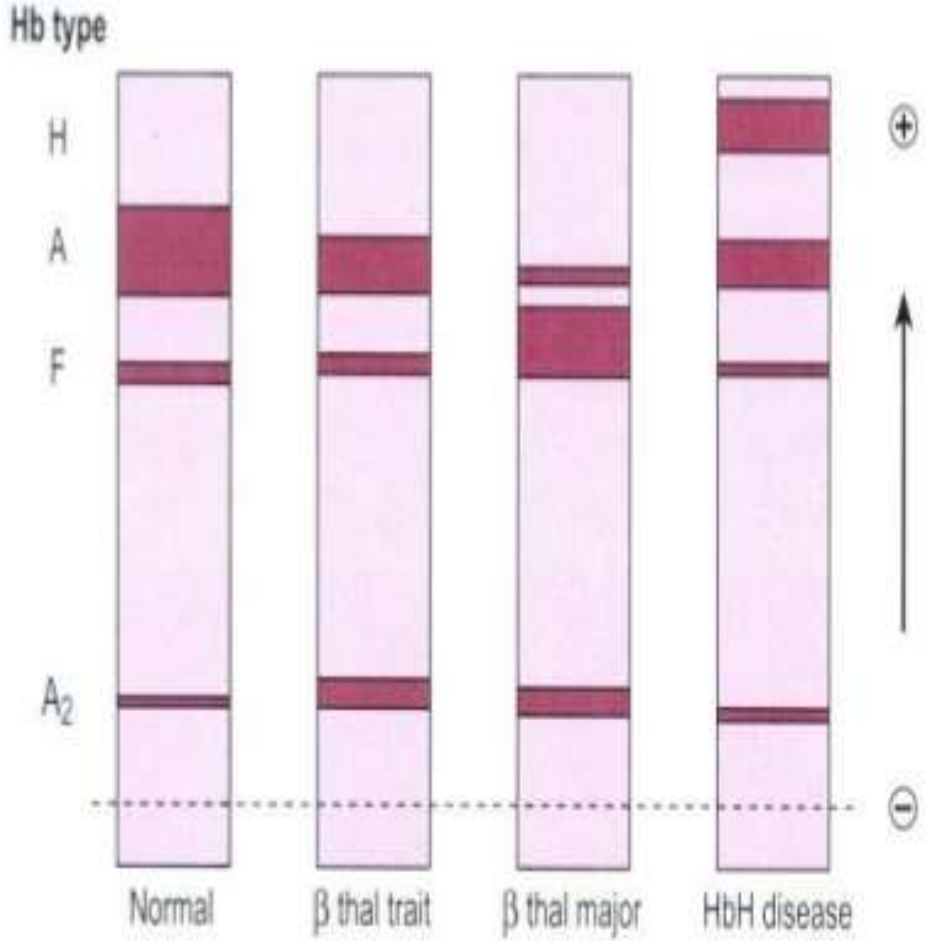
Laboratory findings

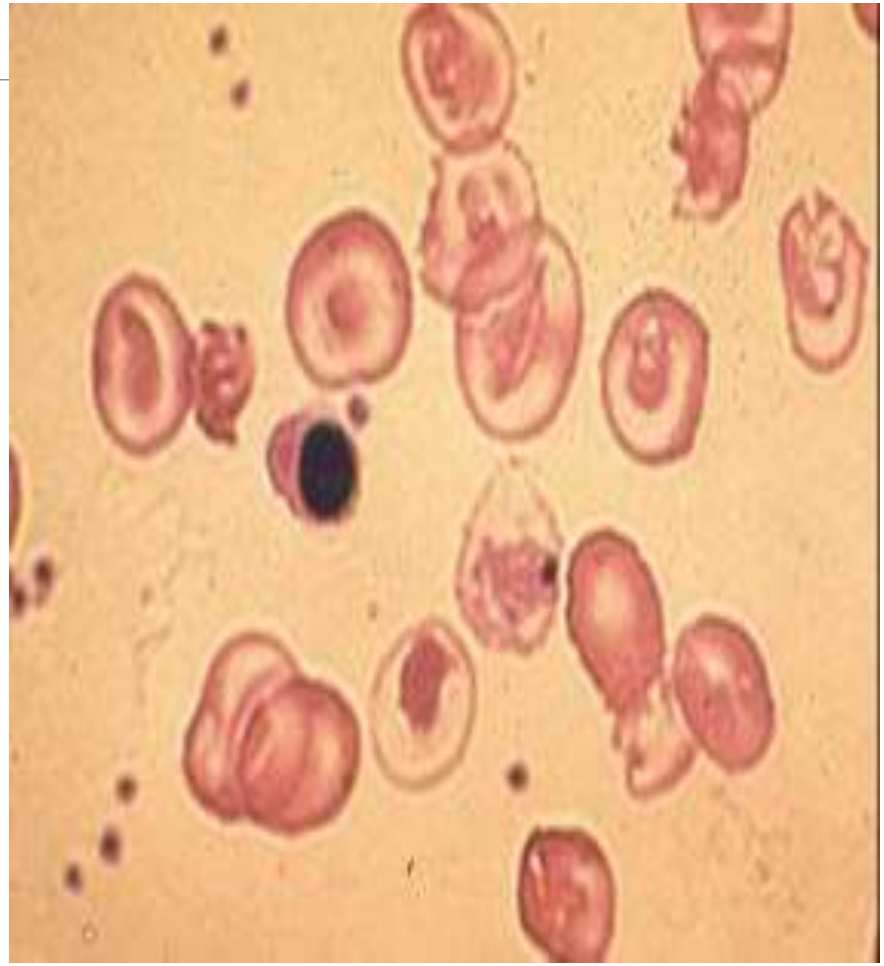
- Hematological:
  - Anemia: hypochromic microcytic.
  - Mentzer index (MCV/RBC) < 13 (not diagnostic)
  - Reticulocytosis
  - Leukopenia and thrombocytopenia
  - Blood smear: Target cells, nucleated RBCs, extreme anisocytosis
  - Hemoglobin electrophoresis (**diagnostic**): HbF raised; HbA2 increased
  - Megaloblastic bone marrow (due to folate deficiency)

- Biochemistry
  - High bilirubin.
  - Evidence of liver dysfunction
  - Evidence of endocrine abnormalities
  - Elevated ferritin and transferrin levels

Hgb Electrophoresis

target cells and nucleated RBC





Treatment

- Blood transfusion every 4-6 weeks, to keep Hgb> 10g\dl to suppresses ineffective erythropoiesis
- Iron chelating therapy: maintain serum ferritin close to 1000 ng/ml
- Splenectomy: deferred as long as possible, at least till age 5-6 years
- Bone marrow transplant : curative
- Hydroxyurea?: enhance HbF production
- Gene therapy: future ??

Supportive therapy

- Diet modification: restrict iron-rich food intake. Drink more tea
- Folic acid
- Hormonal therapy
- Treatment of congestive heart failure
- Psychological support
- Genetic counselling

Anemia of chronic disease

- Anemia of inflammation
- Causes:
  - infections, e.g., Osteomyelitis, Tuberculosis
  - Malignancies
  - autoimmunity, and graft-versus-host disease, Familial Mediterranean Fever, Ulcerative Colitis, Crohn's Disease, SLE, RA
  - chronic kidney disease.
- It is typically a mild to moderate normocytic, normochromic, hypo proliferative anemia associated with a decreased serum iron and low transferrin saturation

Normocytic anemias and Hemolytic anemias

Enzyme defects

Pyruvate Kinase deficiency:

defective red cell glycolysis

Red cell rigid, deformed and metabolically and physically vulnerable

Autosomal –recessive inheritance

Nonspherocytic hemolytic anemia

Variable severity: moderate severe anemia

Neonatal jaundice, splenomegaly, heosiderosis

Splenomegaly, Gallstones, hemosiderosis, bone changes

Treatment: folic acid supplementation, transfusions, splenectomy

Enzyme defects

- **Glucose-6-Phosphate Dehydrogenase deficiency (G6PD):**
- Also known as Favism, is the most common enzymopathy
- X-linked recessive
- G6PD is particularly important for the survival of red blood cells and their ability to respond to oxidative stress
- There are many different variants and Mediterranean variant is the most common mutation in the world

- Most deficient people do not show any symptoms until following exposure to oxidative drugs, infections, or some foods e.g. Fava beans.

Table 1 Drugs To Be Avoided by G6PD-Deficient Patients[16,19]

- Diaminodiphenyl sulfone (Dapsone)
- Flutamide (Eulexin)
- Furazolidone (Furoxone)
- Isobutyl nitrite
- Methylene blue
- Niridazole (Ambilhar)
- Nitrofurantoin (Furadantin)
- Phenazopyridine (Pyridium)
- Primaquine
- Rasburicase (Elitek)
- Sulfacetamide
- Sulfanilamide
- Sulfapyridine

G6PD

Clinical features:

- Neonatal jaundice is the earliest indication of G6PD deficiency.
- The most common presenting symptom is fatigue as a result of the decreased red blood cell count.
- Acute hemolysis may also lead to back or abdominal pain, shortness of breath, dizziness, headache, cold extremities, pallor, and chest pain.
- If hemolysis is severe enough, jaundice and hemoglobinuria (dark urine) may occur.
- Treatment: avoidance of oxidative stressors, Blood transfusion, Folic acid.

Hereditary spherocytosis

- Autosomal-dominant inheritance (75%), sporadic–25%
- Membrane instability due to dysfunction or deficiency of a red cell skeletal protein: ankyrin (75-90%) and/or spectrin (50%)
- Mild- moderate microcytic anemia
- Reticulocytosis. Blood film: microspherocytes, hyperdense cells , polychromasia
- Direct antiglobulin test (DAT) negative
- Increased osmotic fragility

Hereditary spherocytosis

- Anemia and jaundice- severity depends on rate of hemolysis, degree of compensation of anemia by reticulocytosis, and ability of liver to conjugate and excrete indirect hyperbilirubinemia
- Splenomegally
- Neonatal hyperbilirubinemia

HS- Complications

- Hemolytic crisis – with pronounced jaundice due to accelerated hemolysis (may be precipitated by infection)
- Erythroblastopenic crisis – dramatic fall in Hb level and reticulocyte count, usually associated with parvovirus B19 infection
- Folate deficiency caused by increased red cell turnover, may lead to superimposed megaloblastic anemia
- Gallstones in 50% of untreated patients, incidence increases with age
- Rarely hemochromatosis

HS- Treatment

- Folic acid supplement 1mg/day
- Leukocyte-depleted packed red cell transfusion for severe erythroblastopenic crisis
- Splenectomy and cholecystectomy for moderate to severe cases

Sickle cell disease

- Autosomal recessive disorder
- Arises from a mutation substituting thymine for adenine in the sixth codon of the beta-chain gene, which results in production of abnormal hemoglobin
- The disorder typically affects Africans and people of Mediterranean ancestry
- Common sickle cell syndromes:
  - Sickle Cell Trait (HbS gene)
  - Sickle Cell Anemia (HbS/HbS): the most common type
  - Hgb SC Disease
  - Sickle Beta-Thalassemia

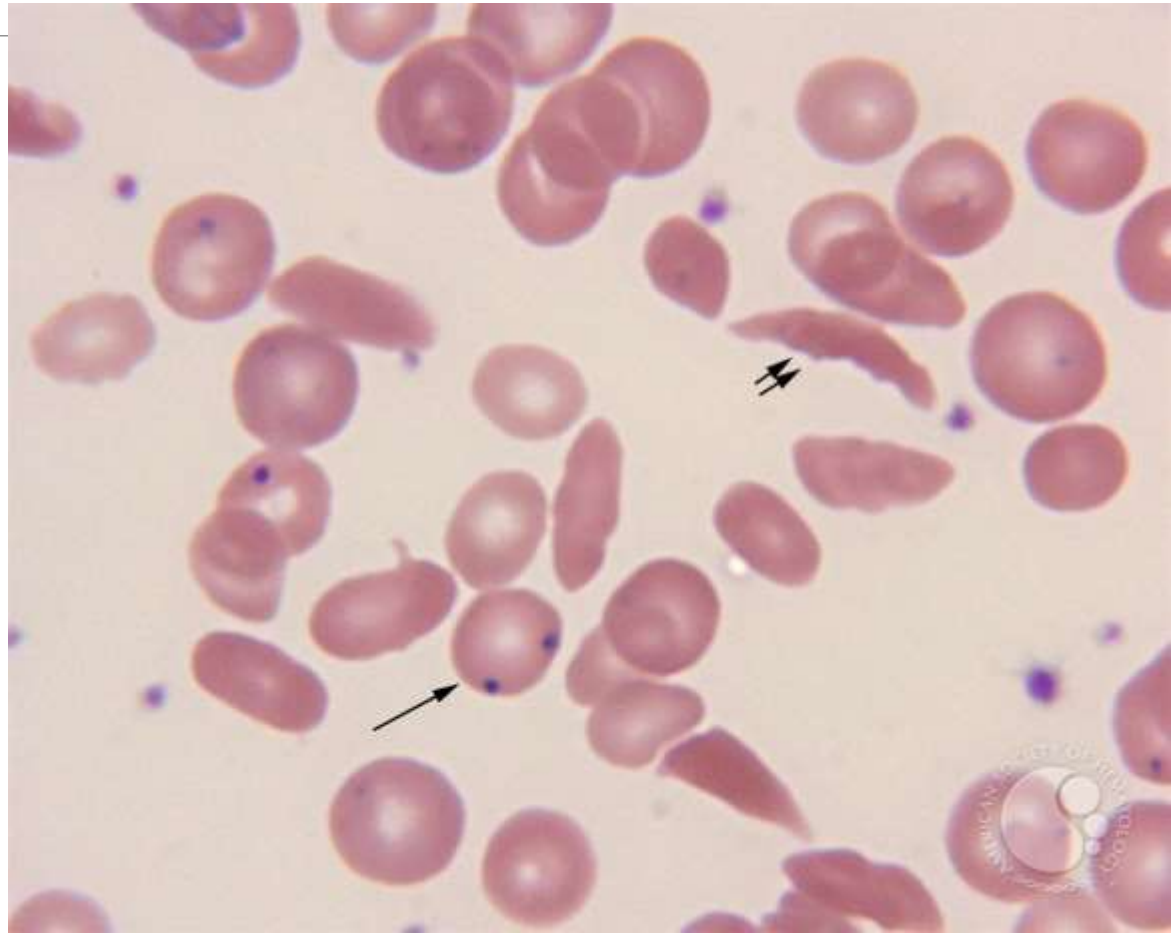
Sickle cell disease

- Clinical manifestations do not appear until after ~ 6 months
- By 5 yeras of age, most children with sickle cell anemia have complete functional asplenia.
- With low oxygen levels, the shape of red cells becomes distorted. They appear elongated and sickle shaped
- Red blood cells become very fragile, short lived, and can occlude blood vessels
- The sickling phenomena is exacerbated by hypoxia, acidosis, fever, hypothermia, and dehydration
- Diagnosis by Hgb electrophoresis

Clinical features

- Hematology:
  - Mild to sever anemia (MCV low or normal)
  - Reticulocytosis
  - Neutrophilia and thrombocytosis are often present
  - ESR low despite inflammation
  - Blood film : sickle cells, target cells , Howell-jolly bodies, nucleated RBCs

Crescent-shaped sickle cells are noted (double arrow). Several RBCs with Howell-Jolly bodies are also present (single arrow)



Acute complications (crises)

1. Vaso-occlusive pain crisis:
   - Microvascular occlusion
   - Mimic osteomyelitis,
   - Sites: hands/feet (dactylitis), long bones, spine, pelvis, and abdomen (mesenteric infarction)
   - Treatment: analgesia, hydration, oxygen
2. Overt stroke
   - Treatment: exchange transfusion and supportive therapy
3. Priapism:
   - Sustained, painful erection of the penis, may last > 3 h.
   - Analgesia , hydration, pseudonephrine
   - Urological consultation for episodes lasting > 4 h.

4. Acute chest syndrome (ACS)
   - Development of new pulmonary infiltrate accompanied with fever, chest pain, hypoxia, and shortness of breath.
   - Most common cause of death in sickle patients
   - ACS is caused by infections, infarctions, and/or fat embolism, and iatrogenically by overhydration.
   - Treatment:
     1. chest imaging, infections workup. ICU admission.
     2. Pain management, iv fluids , broad spectrum antibiotics plus atypical bacteria coverage
     3. Oxygen if hypoxemic, mechanical ventilation if needed
     4. Simple and/ or exchange transfusions.

5. Splenic sequestrations
   - Between 5 and 24 months, pooling of large amount of blood in the spleen
   - Hypovolemic shock
   - Treatment: cardiovascular support. Blood transfusion, and pain management

6. Transient pure red cell aplasia
   - Spontaneous termination at around 10 days
   - Human parvovirus B19

Chronic complications

- Silent stroke
- Pulmonary hypertension
- cardiac failure
- Pulmonary fibrosis
- Renal failure
- Chronic liver disease
- Bone abnormalities, vascular necrosis of the femoral head, leg ulcers
- Retinopathy, sensorineural hearing loss
- Functional hyposplenism

Fever and sickle cell anemia

- Due to functional hyposplenism patients are at high risk to develop overwhelming sepsis.
- Encapsulated organism, gram negative enteric organisms, and salmonella.
- Febrile sickle cell patient is a medical emergency.
- early administration broad spectrum antibiotic is crucial

Management

- Patient education (e.g., good hydration) and psychological support
- Oral analgesia
- Penicillin pophylaxis, vaccinations
- Hydroxyurea for induction of fetal Hgb
- Hematopoitic stem cell transplantation: curative

Extracorpuscular hemolytic anemias

Autoimmune hemolytic anemia

Features of Warm & Cold AIHA

Features	Warm (37.0 C)	Cold (<37.0 C)
Immunoglobulin	IgG	IgM
Typical Pattern on Coombs	IgG +, C3 ±	IgG -,C3 +
Peripheral Smear	Spherocytes	Erythrocyte agglutination
Clinical Manifestations	Fatigue, Dyspnea, Jaundice, Splenomegaly	Fatigue, Dyspnea, Jaundice, acrocyanosis, splenomegaly
Associated Condition	Autoimmune, CLL, NHL, drugs	Infections (Mycoplasma, Mono), MGUS, Waldenstrom, other B-cell Lymphomas

Nonimmune hemolytic anemia

- Microangiopathic hemolytic anemia caused by renal, cardiac, liver disease, infections. Like hemolytic uremic syndrome

Thank You