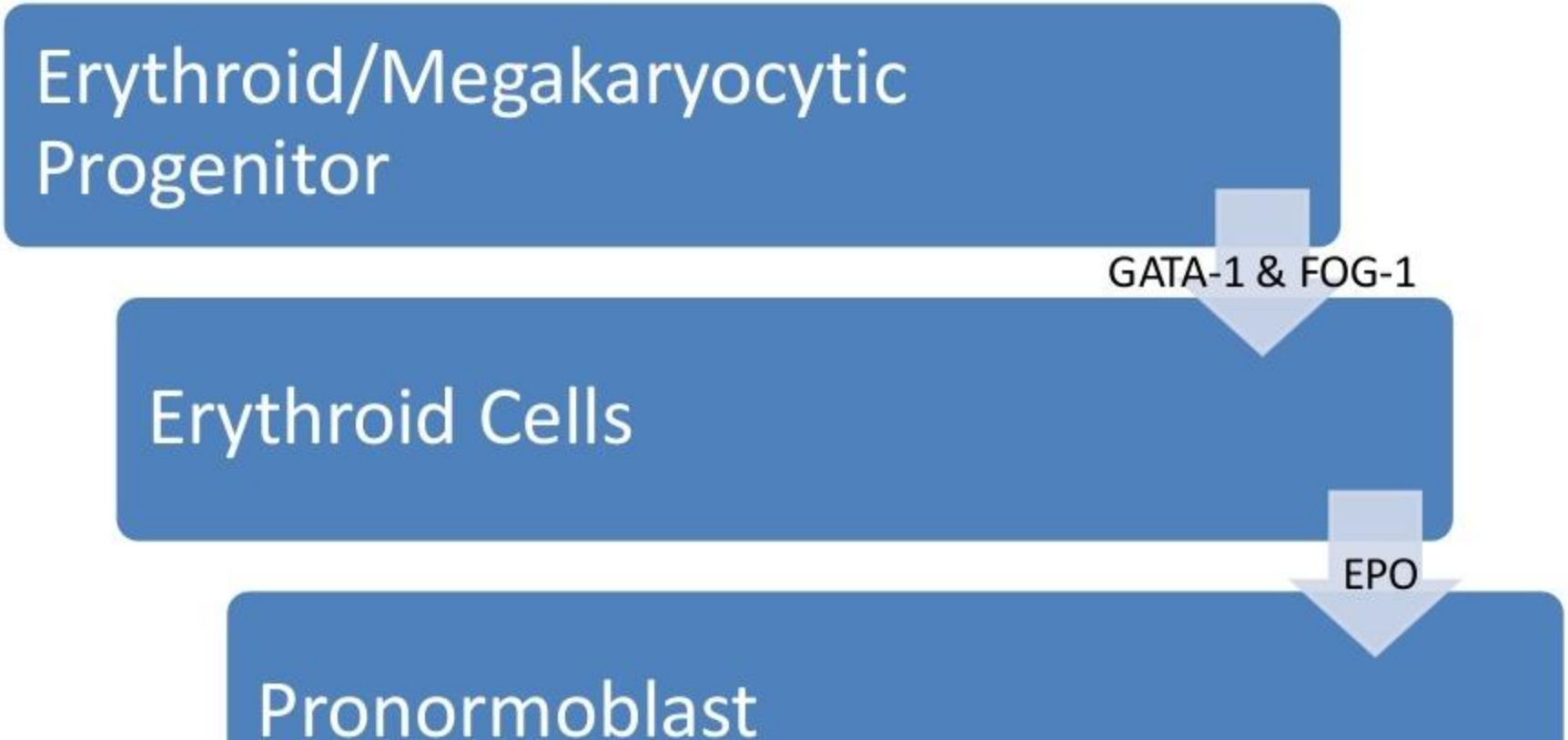
APPROACH TO ANEMIA

ERYTHROPOESIS



WHO Definition :

Anaemia is a condition in which the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body's physiologic needs.

Clinical Key

- Classical symptoms :
  - Fatigue, Malaise
  - Dyspnoea on exertion
  - Loss of stamina
  - Palpitations
  - Complaints related to Exertion
  - Reduced exercise capacity
  - Pounding sensation in ears
  - Night sweats

Clinical Key

- Symptoms suggestive of Nutritional anemia :
  - Blood in stools
  - Loose stools/ Clay colour stools
  - Constipation
  - Blood in urine
  - Pregnancy
  - Recurrent/Recent foetal loss
  - History of Neural Tube Defects in offspring
  - Cleft palate/lip in offspring

Clinical Key

- Symptoms of Haemolysis :
  - Yellowish discoloration of eyes and skin
  - Reversible skin pigmentation
- Symptoms suggestive of marrow disorders :
  - Recurrent upper respiratory tract infections
  - Episodic jaundice/ abdominal pain/ lumbar pain/ hematuria
  - Easy bruising/ Gum bleed/ Nose bleed/ Heavy menstrual flow/ Hemiparesis/ Vision loss

Clinical Key

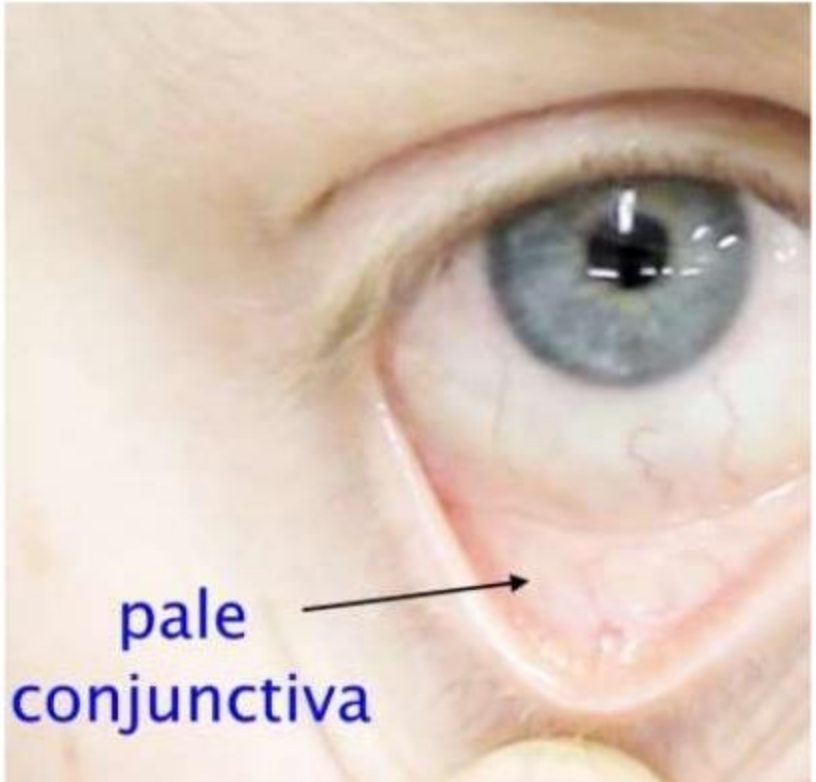
- Symptoms suggestive of genetic disorders :
  - Early hair greying
  - Short stature
  - Dystrophic nails

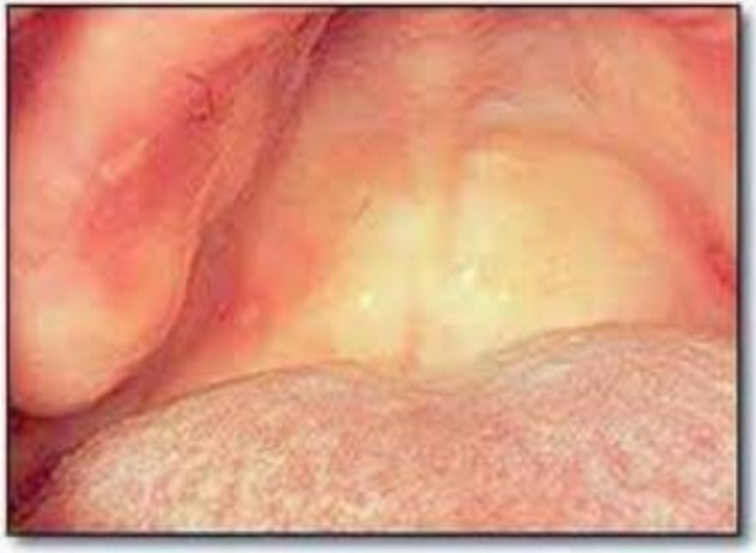
- Past History :
  - Blood donation history
  - Phlebotomy history

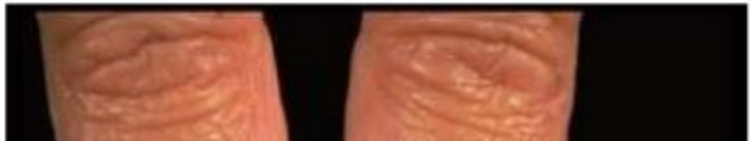
Clinical Key

- O/e :
  - Mental state
  - Signs of dehydration
  - Cheilosis (Fissures at corners of mouth)
  - Koilonychia (Spooning of finger nails)
  - Pallor (< 8-9 gm/dL)
    - Mucus membranes
      - Palpebral conjunctiva

Clinical Key







Clinical Key

  - Icterus
  - Clubbing
  - Cyanosis
  - Lymphdenopathy
  - Pedal edema
  - Petechiae/ Ecchymosis
- Systemic Examination :
  - Splenomegaly
  - Hepatomegaly
  - Forceful Heart beat

Clinical Key

- Also Look for :
  - Ascites
  - Heart failure
  - Cirrhosis
  - Endocrinopathies
  - Pseudoxanthoma elasticum

Lab Investigations

- Complete Blood counts
  - Hb :

Occasion	Normal Value (mg/dL)
At Birth	17
Childhood	12
Adolescence	13
Adult Man	16 ± 2

Lab Investigations

– Hematocrit :

	Normal Values (%)
Adult Male	47 ± 5
Adult Female	42 ± 5

– Reticulocyte Count

– Absolute reticulocyte Count

Lab Investigations

- RBC Indices

Indices	Normal
MCV	90 ± 8 fL
MCH	30 ± 3 pg
MCHC	33 ± 2 %
RDW	11.5 – 14.5 %

- Other Counts
  - TLC

Lab Investigations

- Red cell Morphology
  - Cell size
    - Mirocytic (<80 fL)
    - Macrocytic (>100 fL)
    - Anisocytosis (Variable size)
    - Poikilocytosis (Variable Shape)
    - Polychromasia
      - » (Slightly larger than normal cells, greyish blue in Wright Giemsa stain

Lab Investigations

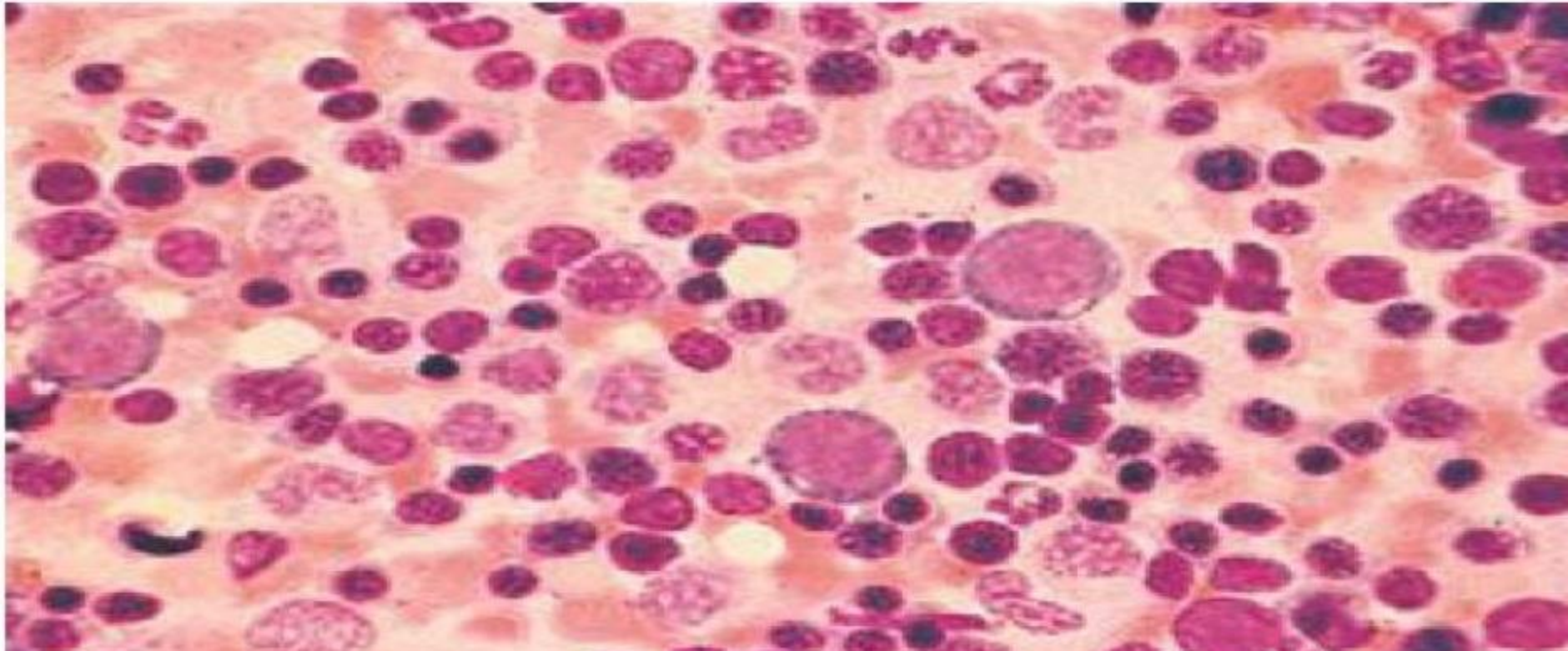
- Iron Studies

Study	Normal Range
Serum Iron	50-150 µg/dL
TIBC	300-360 µg/dL
Serum Ferritin	Males – 100 µg/ L Females – 30 µg/ L
Transferrin Saturation	25-50 %

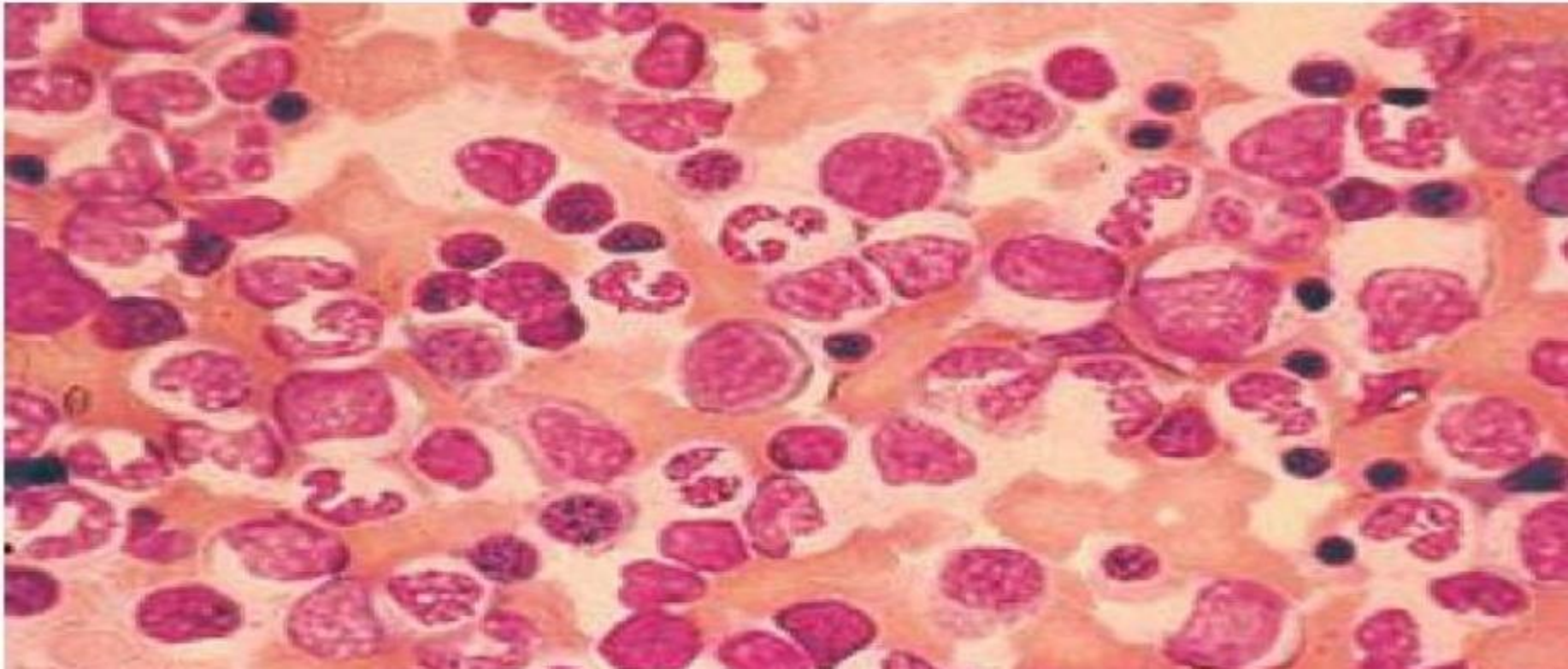
Lab Investigations

- Marrow Examination
  - Aspirate :
    - M/E ratio (1:1)
    - Cell Morphology
    - Iron Stain
  - Biopsy
    - Cellularity (1:1)
    - Morphology
- Signs of Hemolysis

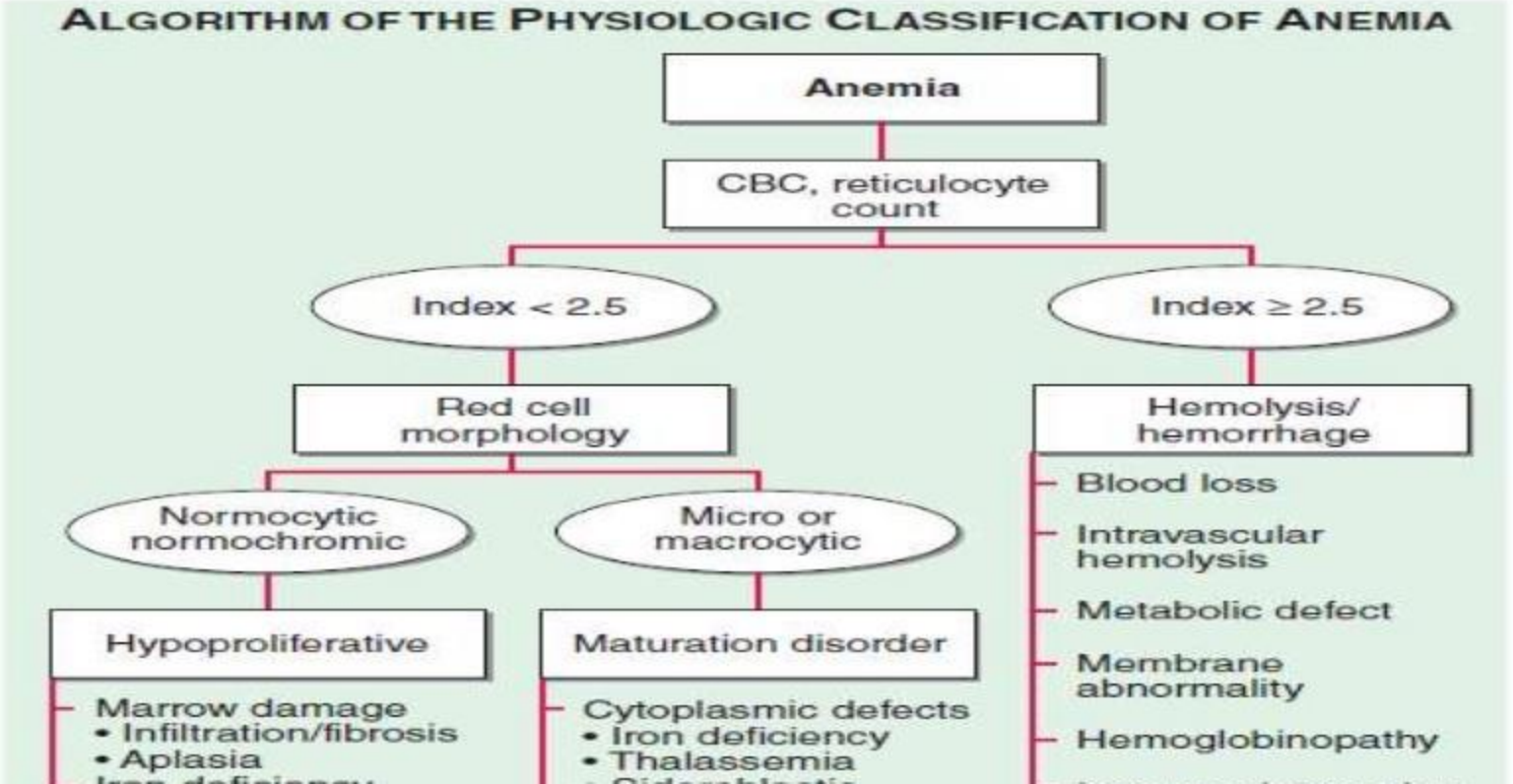
Lab Investigation



Lab Investigation



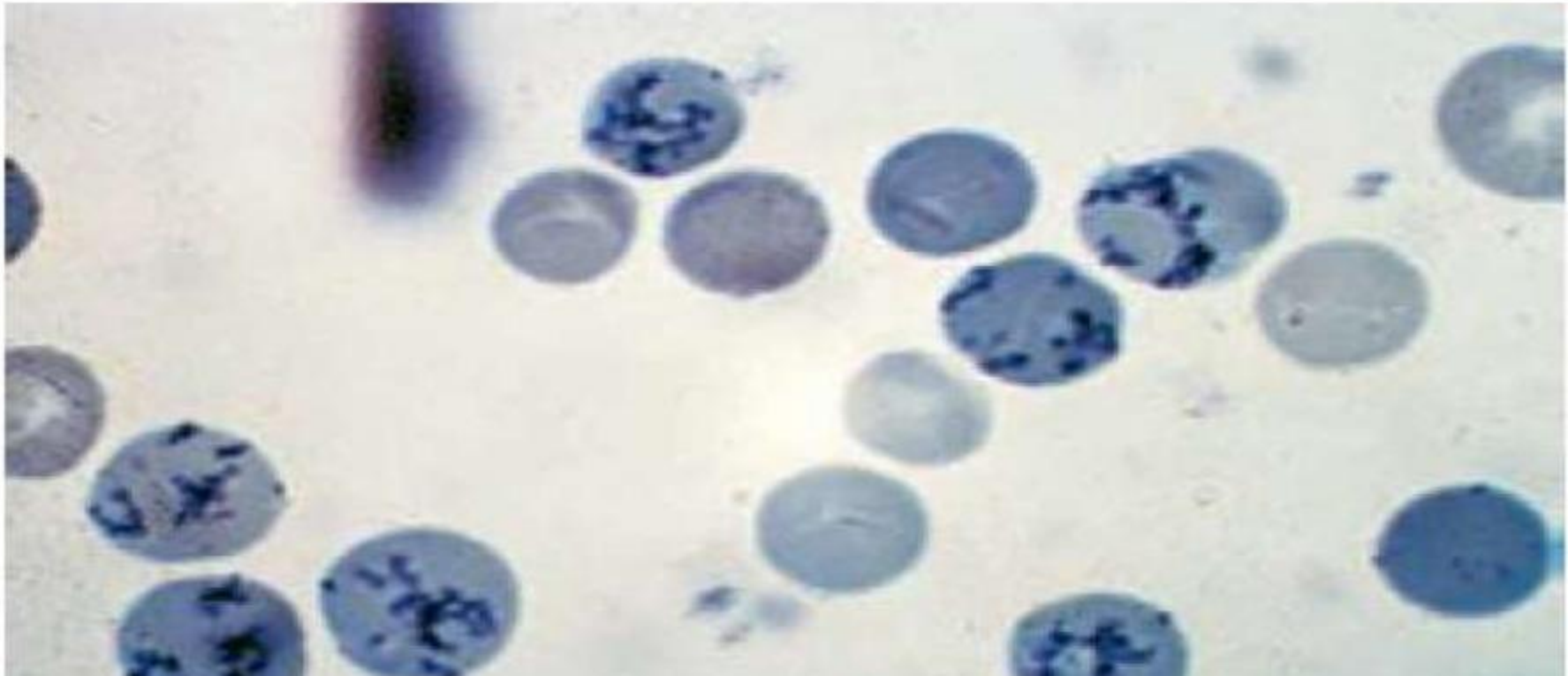
Clinical Classification of Anaemia



Reticulocyte Count

- By Supra vital stains – Blue, black punctate spots (precipitated rRNA)
- Life – 24 to 36 hrs
- Normal range – 1-2%
- Daily replacement – 0.8 to 1%
- Response depends on

Reticulocyte count



Reticulocyte count

- Correction for Anemia

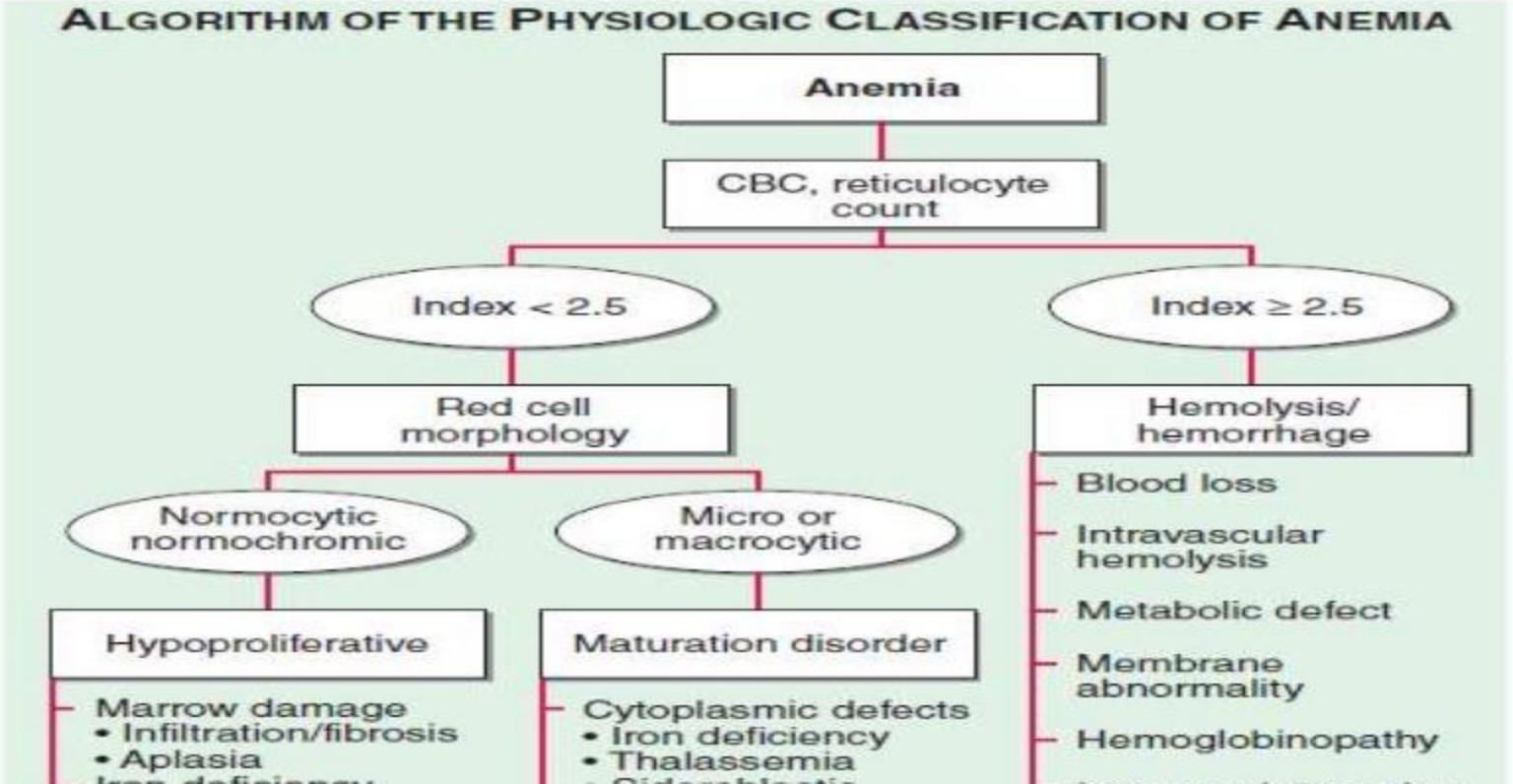
$$- Absolute\ Reticulocyte\ count\ =$$

$$reticulocyte\ count\ x\ Hb/15\ or\ Hmt/45$$

- Correction for prematurely released reticulocytes (only when you see ‘shift’ cells)

$$- Reticulocyte\ Production\ Index\ =$$

Clinical Classification of Anaemia



Hypo-proliferative Anemia

- Causes :
  - Mild to Moderate Anemia
  - Marrow Damage
  - Inadequate EPO stimulation
    - Inflammation (IL -1, TNF α, etc..)
    - Metabolic Disorders (Hypothyrodism, ..)
    - Renal Failure (in DM & Myeloma – marked EPO def seen than actual failure)

Hypoproliferative Anemia

Parameter	Mild – Mod Iron Def	Chr. Inflammation
S.Iron	↓	↓
TIBC	↑↑	↓/N
% Saturation	↓	↓

Maturation Disorder

- BM shows erythroid hyperplasia (M/E < 1:1)
  - But fails to release into peripheral circulation

Nuclear maturation defects	Cytoplasmic maturation defects
Macrocytosis	Microcytic, Hypochromic
Vit B12/ Folate Deficiency	Severe Iron Deficiency
Drugs (Methotrexate/ Alkylating agents/	Globin chain/Heme synth Defects

Blood Loss

- Normocytic/ Slightly Macrocytic

Acute Blood Loss

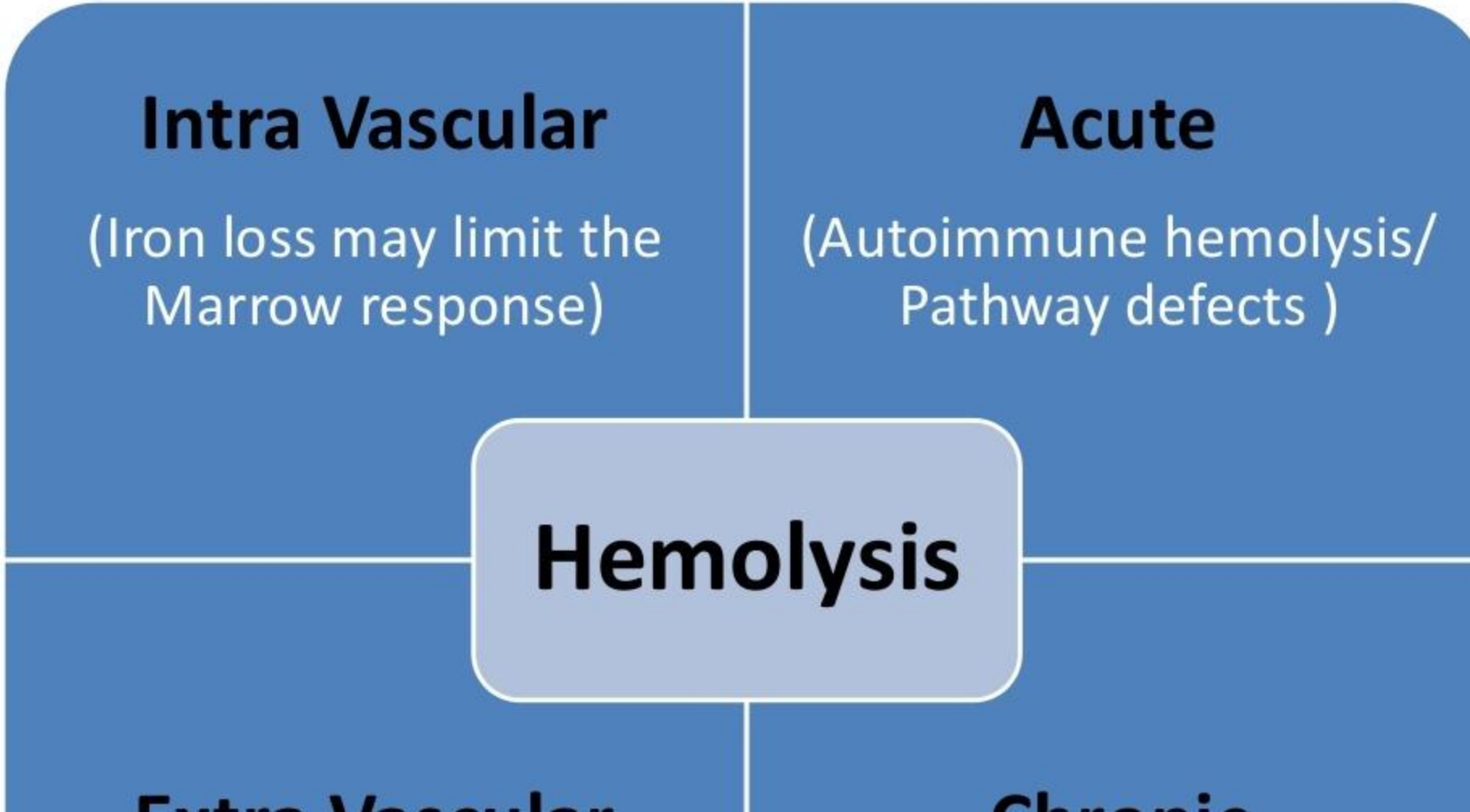
- No Increase in RPI
- Signs of

Sub Acute Blood Loss

- Modest Reticulocytosis

Chronic Blood Loss

- Iron Deficiency picture dominates


Intra Vascular
(Iron loss may limit the Marrow response)
Acute
(Autoimmune hemolysis/ Pathway defects)
Hemolysis

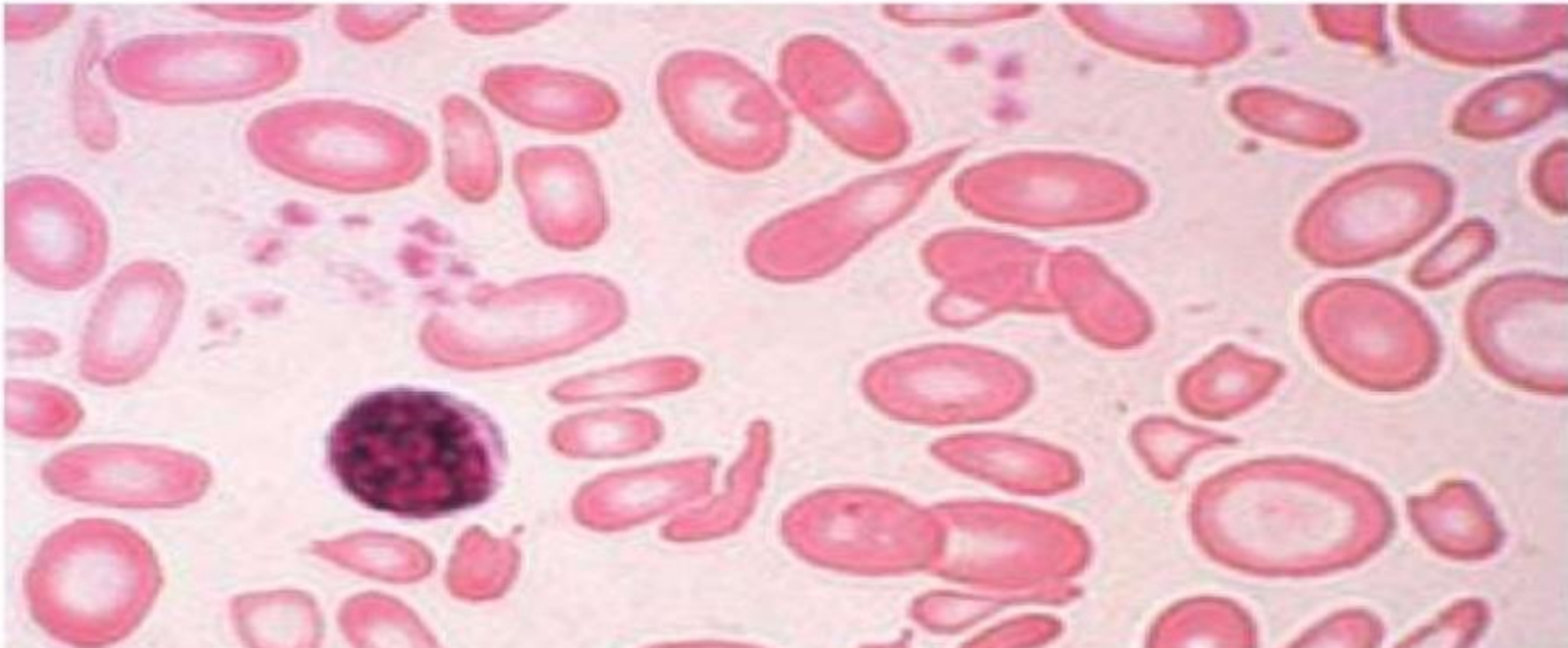
Iron Deficiency Anemia

- C/f :
  - Pregnancy/ Adolescence/ Blood Loss/ Phlebotomy
  - Advanced tissue iron def
    - » Cheilosis
    - » Koilonychia
  - In adult male – GI loss, until proven otherwise

Iron Deficiency Anemia

- RBC Indices
  - Microcytic, Hypochromic, Aniso-Poikilocytosis
- Iron Studies
- Marrow Iron (Normal : 20-40% sideroblasts, with ferritin granules)
  - Decreases

Iron Deficiency Anemia

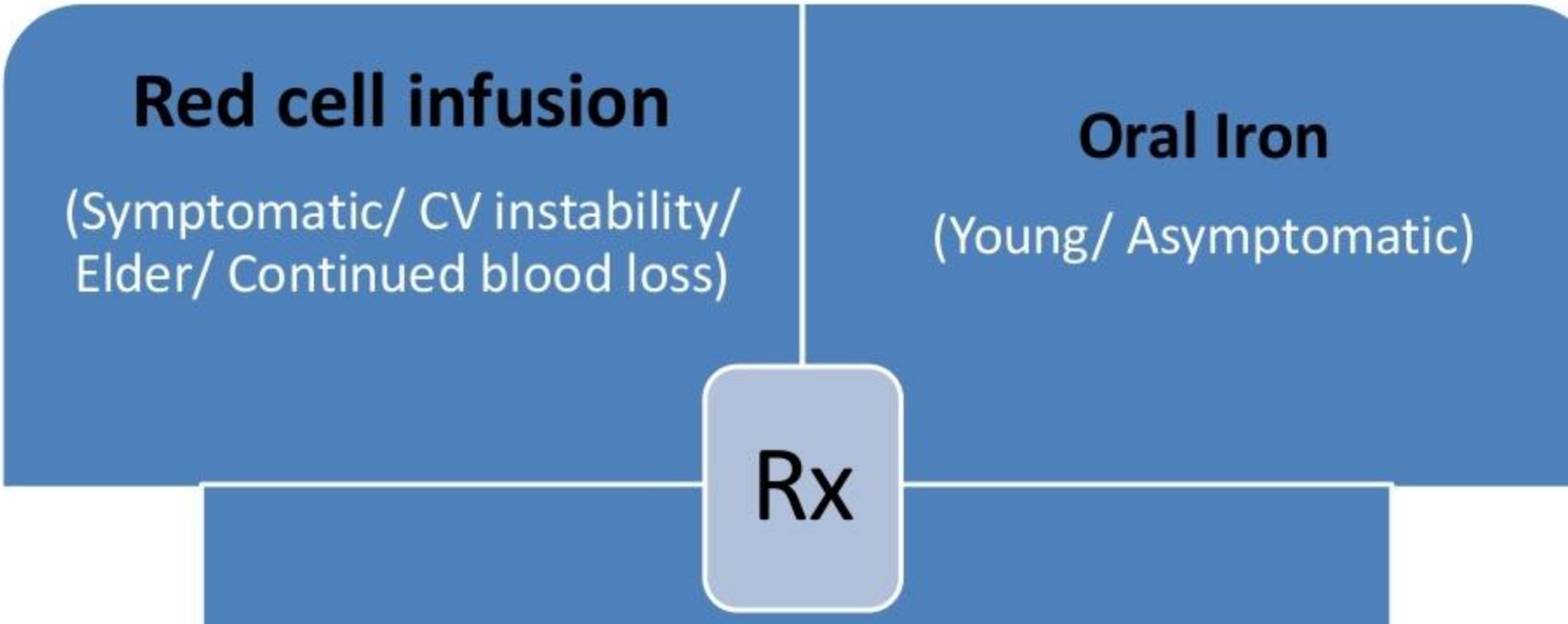


DD for Microcytic Anemia

TABLE 126-4 DIAGNOSIS OF MICROCYTIC ANEMIA

Tests	Iron Deficiency	Inflammation	Thalassemia	Sideroblastic Anemia
Smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
Serum iron (µg/dL)	<30	<50	Normal to high	Normal to high
TIBC (µg/dL)	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin (µg/L)	<15	30–200	50–300	50–300

Iron Deficiency Anemia



G6PD Deficiency

- Asymptomatic
- Classical :
  - Malaise, weakness, abd & lumbar pain
  - In 3 days
  - Jaundice & dark urine
- Primaquine mass prophylaxis is a danger
- Blood :
  - Normocytic Normochromic (Mod to Severe)

Iron Deficiency Anemia

- Oral Iron:
  - 200mg elemental Iron/day
  - Absorption will be upto 50mg/d (with good retention capacity)
  - Supports 2-3x production
  - Add Ascorbic acid for increased absorption (if cost effective)
  - 3-4 tabs/day for 6-12 months

Iron Deficiency Anemia

– Iron Tolerance test

- 2 Iron tabs on empty stomach
- Serial S.Iron for 2 hrs
- At least 100 mcg/dL increase

Preparation	Amount (Elemental Iron)
Ferrous sulphate	325 (65)

Iron Deficiency Anemia

- Parenteral Iron :

Needed = { Body wt in Kg x 2.3 x (15 – pt. Hb)}
+ 500-1000mg for stores

– 500mg at a time/ repeated small doses

Preparation	Amount of Iron per injection
Sodium ferric gloconate	125 mg

Anemia of chronic inflammation

- Iron restricted erythropoesis with inflammation.
    - IL – 1 -> INF $^{\gamma}$
    - TNF α -> INF β
    - Suppresses EPO
- Mixed blood picture
    - Inflammatory component (Normocytic Normochromic)

Anemia of chronic inflammation

TABLE 126-6 DIAGNOSIS OF HYPOPROLIFERATIVE ANEMIAS

Tests	Iron Deficiency	Inflammation	Renal Disease	Hypometabolic States
Anemia	Mild to severe	Mild	Mild to severe	Mild
MCV (fL)	60–90	80–90	90	90
Morphology	Normo-microcytic	Normocytic	Normocytic	Normocytic
SI (µg/dL)	<30	<50	Normal	Normal
TIBC (µg/dL)	>360	<300	Normal	Normal
Saturation (%)	<10	10–20	Normal	Normal

Anemia of chronic inflammation

- Rx :
  - Transfusion : symptomatic/ terminal disease
    - Wait up to 7-8 g/dL
    - If compromised, maintain at 11 g/dL
    - Liberal use in ICU leads to ↑ morbidity & mortality
  - EPO : Glycoprotein, from peritubular capillary cells in kidney & hepatocytes, regulated by HIF 1 α

Anemia of chronic inflammation

- Recombinant EPO therapy :
  - Check for iron stores
  - 50-150 U/kg 3 times/week IV
  - Up to 300 U/kg, (in chemo induced anemia)
  - 10-12 g/dL Hb in 4-6 weeks
  - Stop if acute inf/ iron depletion/ Al toxicity/ hyperpaarthyroidism

Megaloblastic Anemia

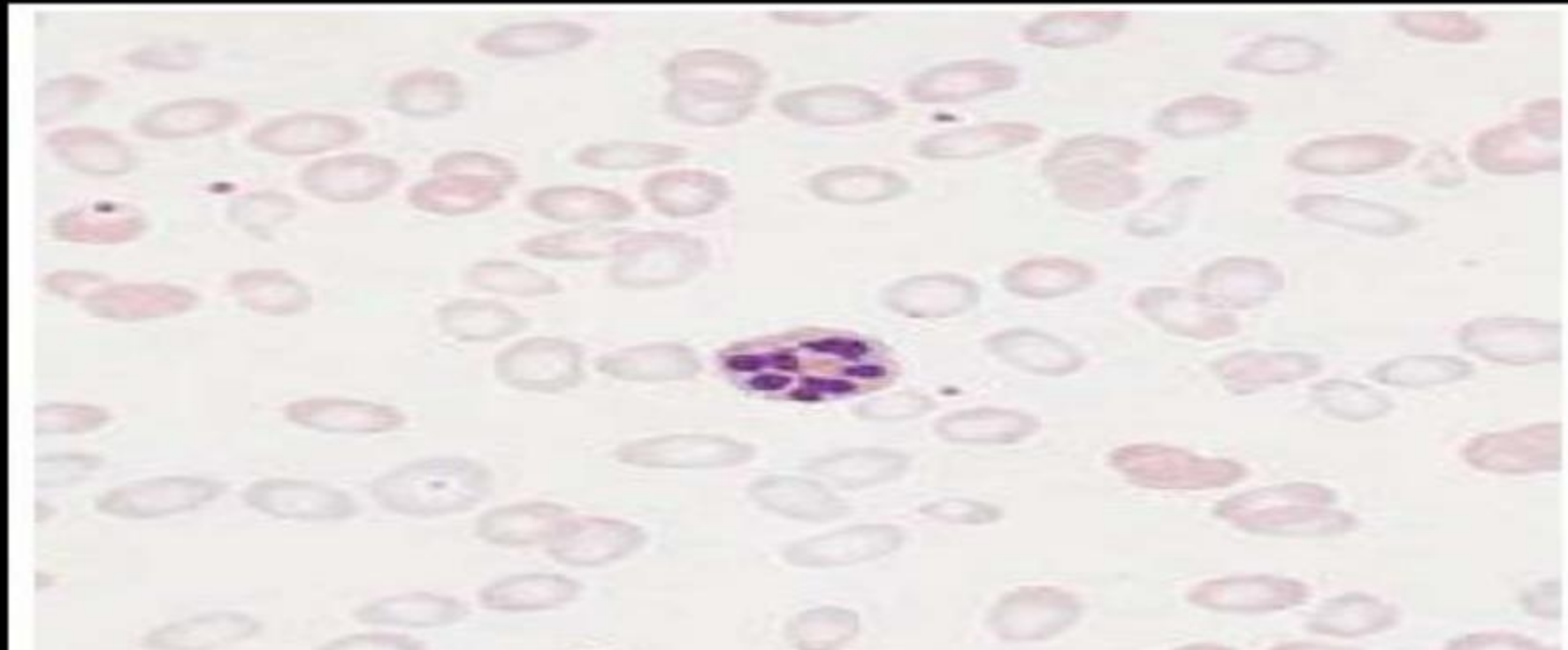
Megaloblastic	Megaloblastoid
Immature appearing nuclei with large blast like cells with normal hemoglobinisation. Seen in B12/Folate deficiency.	Immature appearing nuclei with defective hemoglobinisation. Seen in Myelodysplasia.

CLINICAL FEATURES

Anorexia, Wt. loss, Diarrohea/ constipation, Mild fever

Tissue effects	Hematological effects
Mucosal damage	Macrocytsis

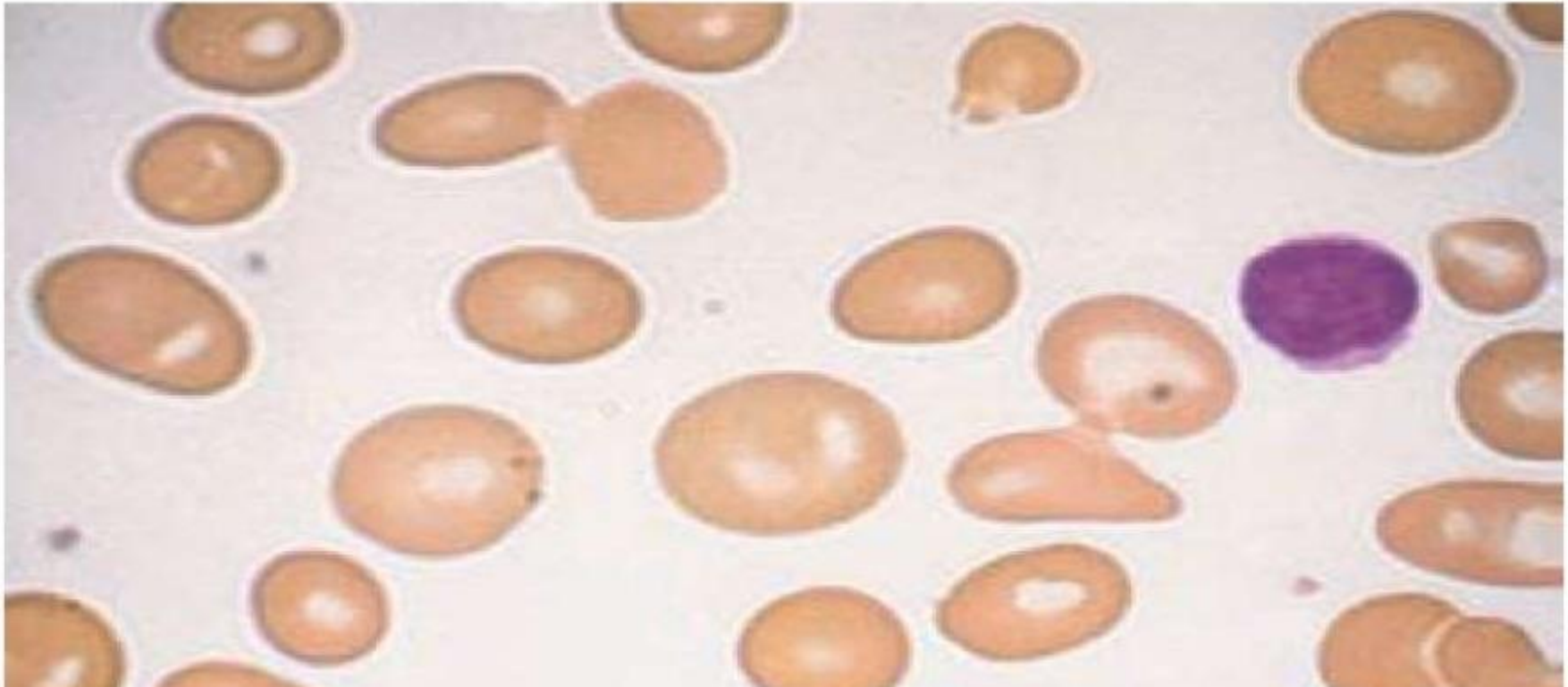
Megaloblastic Anemia



Megaloblastic Anemia

B12 deficiency	Folate Deficiency
S.Cobalamin <100 ng/L	S. Folate < 2µg/L ↑ - severe B12 def & Intestinal stagnant loop synd
S. MMA & Homocystein – Increases	S. MMA & Homocystein – Increases
B12 absorption tests are obsolete S. Gastrin ↑ S. Pepsinogen I ↓ (for Pernicious Anemia)	RBC Folate < 160 µg/L False + in Recent transfusion/ ↑Retic count

Megaloblastic Anemia



Megaloblastic Anemia

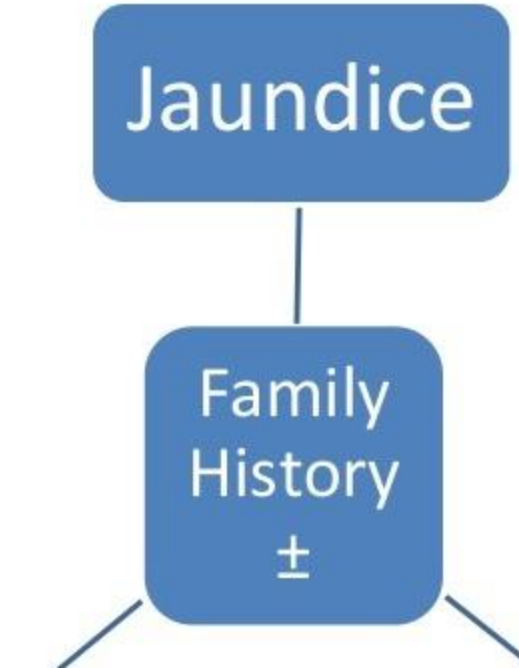
- Rx :
  - Treat appropriate vitamin only (always B12 first)
  - Transfusion is usually unnecessary & inadvisable
  - ↑ platelet count after 1-2 weeks (start aspirin, if >8 lakh/cumm)

B12 deficiency	Folate deficiency
Hydroxy/ cyano cobalamine life long therapy is best Routinue in GIT resections/ longterm PPI therapy Always low threshold for therapy	Oral 5-15 mg/ day For 4 months

Hemolytic Anemias

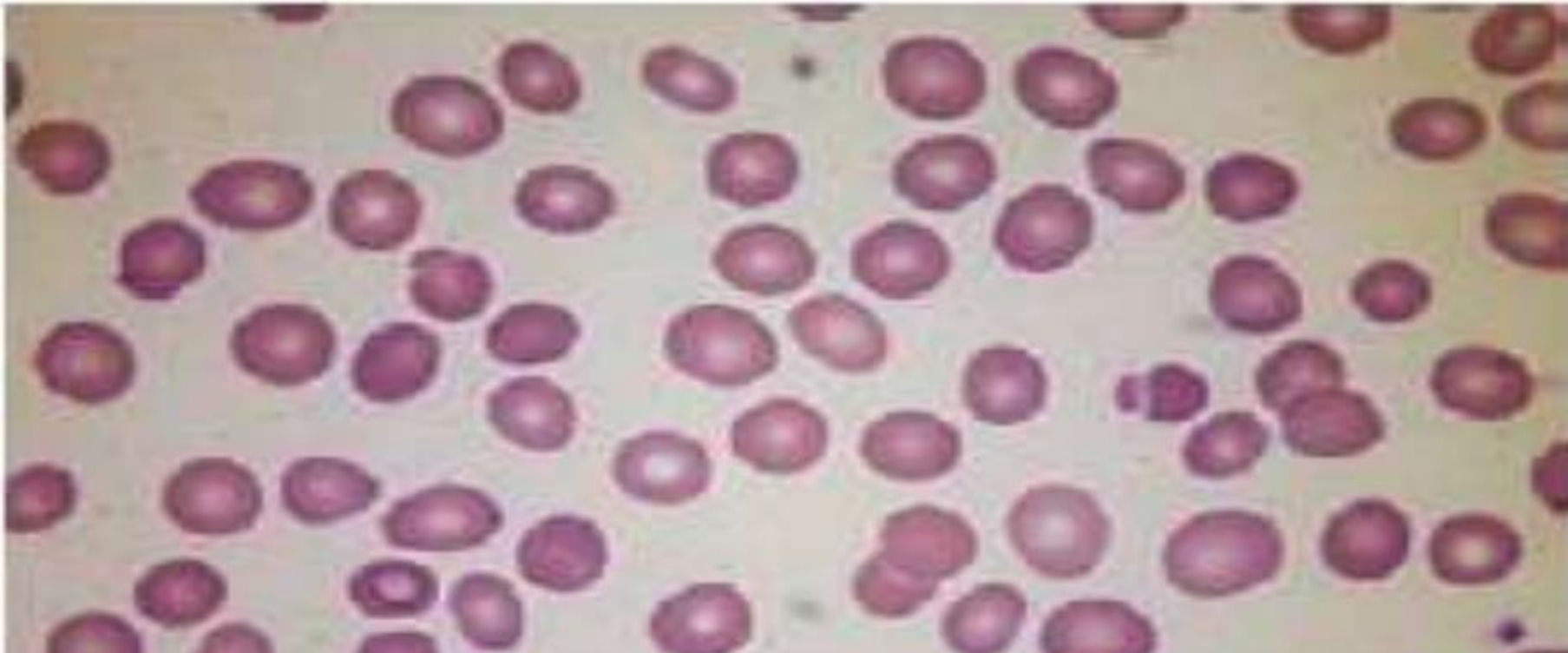
Hereditary Spherocytosis

Mild : Young adult/ adult

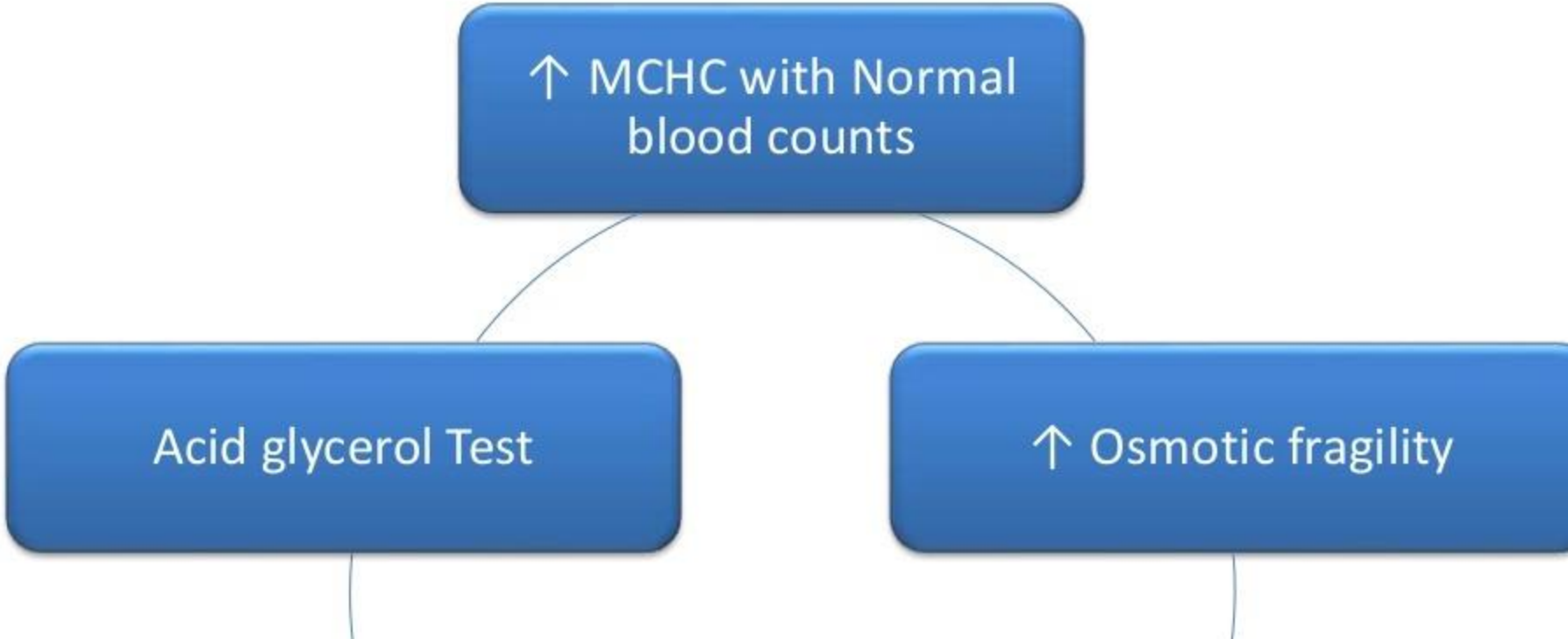


Severe : Infancy

Hereditary Spherocytosis



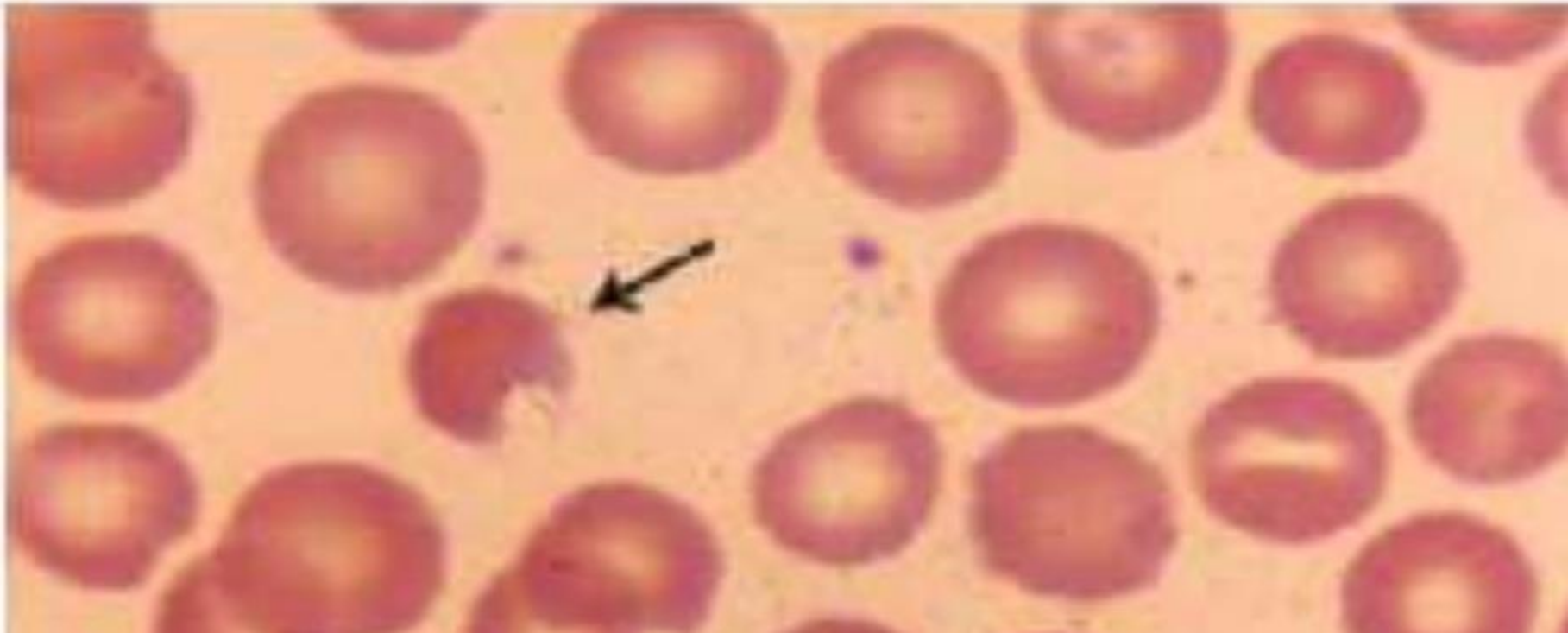
Hereditary Spherocytosis



Hereditary Spherocytosis

- Rx:
  - No causal treatment
  - Splenectomy
    - Mild cases : Defer Splenectomy
    - Moderate cases : delay until puberty
    - Sever cases : delay until 4-6 years of age
  - Anti pneumococcal vaccination before surgery

G6PD Deficiency



G6PD Deficiency

- Diagnosis :
  - DNA testing
  - During hemolytic attack – quantitative test done for heterozygotes and hemi zygotes
- Rx :
  - No cure

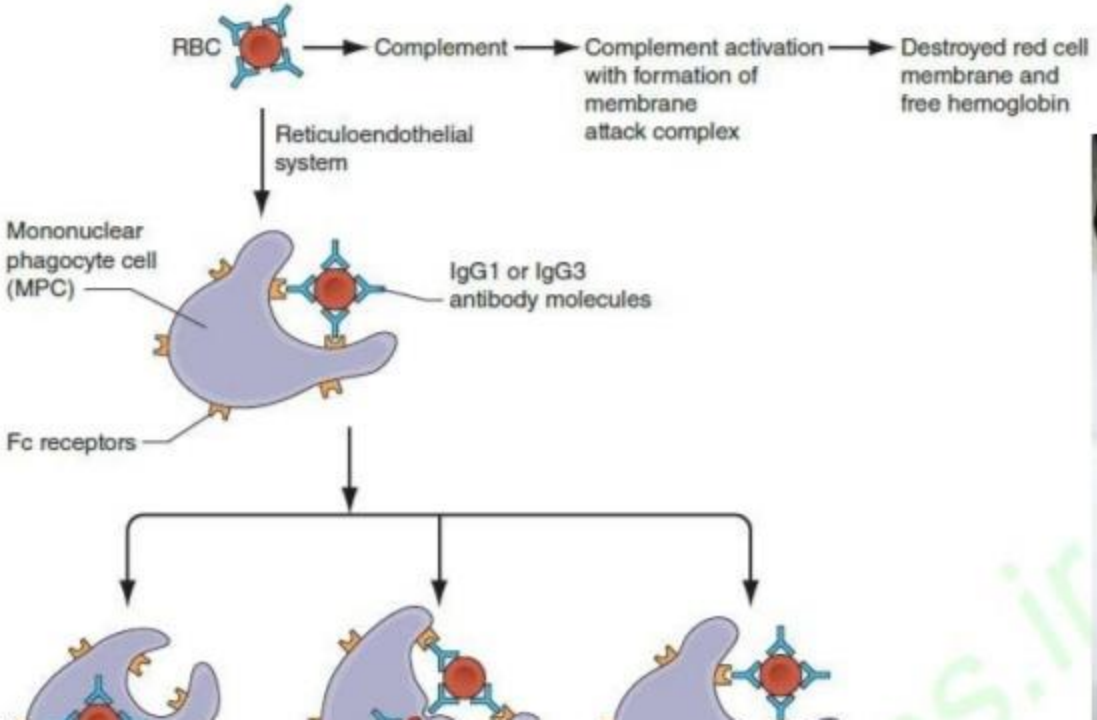
AIHA

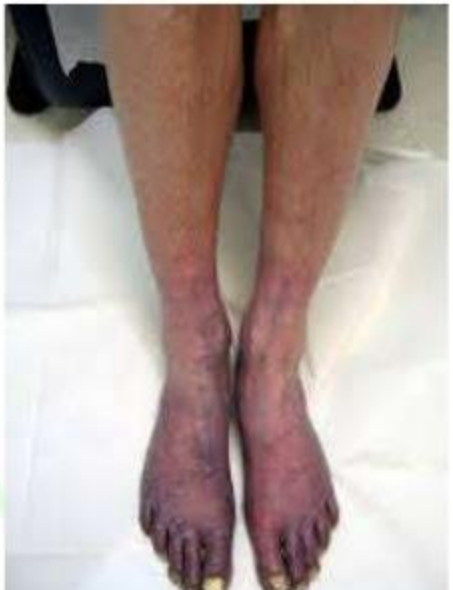
Anemia + Splenomegaly + Jaundice

Warm Ab disease	Cold Ab disease

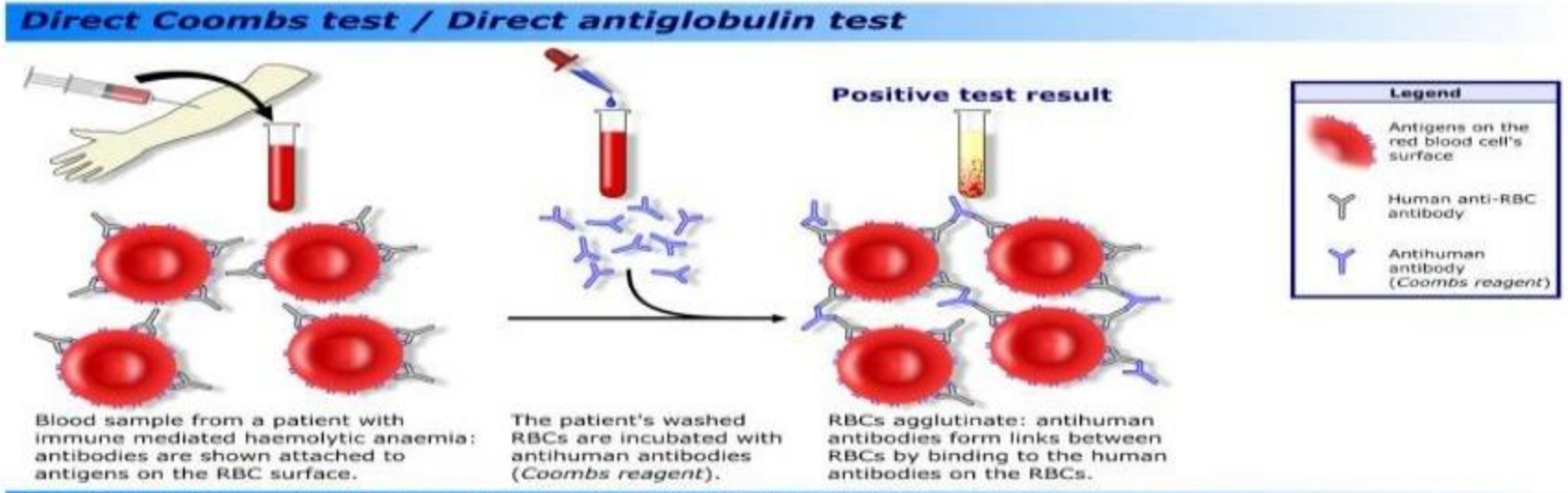
• Ig G1/ G3 mediated
• 37° C
• Extravascular hemolysis
  • Phagocytosis
  • Fragmentation
  • Cytotoxicity
	• Ig M mediated
	• 0-4°C
	• Intravascular hemolysis
	  • Membrane attacking complex

AIHA


RBC
Complement
Complement activation with formation of membrane attack complex
Destroyed red cell membrane and free hemoglobin
Reticuloendothelial system
Mononuclear phagocyte cell (MPC)
IgG1 or IgG3 antibody molecules
Fc receptors



AIHA


Direct Coombs test / Direct antiglobulin test
Positive test result
Legend
Antigens on the red blood cell's surface
Human anti-RBC antibody
Antihuman antibody (Coombs reagent)
Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.
The patient's washed RBCs are incubated with antihuman antibodies (Coombs reagent).
RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.
Indirect Coombs test / Indirect antiglobulin test
Positive test result

AIHA

- Medical Emergency, needs transfusion.
- Abs are commonly non specific against ‘e’ Ag of Rh system.
- So all most all the blood groups will be incompatible
- Start incompatible blood transfusion to keep the pt alive (with hold when condition improves)

PNH

Hemolysis + Pancytopenia + Venous thrombosis

- Classical :
  - Early morning bloody urine
- Recurrent severe abdominal pain (thrombotic event)
- Acute hepatomegaly, ascites without liver or cardiac disease
- MC COD : Venous thrombosis > Infections

PNH

- Reticulocytosis (up to 400,000/µL)
- ↑ MCV, Normo-Macrocytic
- Signs of Hemolysis
- Signs of Iron def (persistent loss)
- BM : cellular with massive erythroid hyperplasia
- Definitive : ↑susceptibility to complement
  - Sucrose hemolysis (not reliable)

PNH

- Life long condition
- Filtered RBC (retain WBC)
- S. Iron maintanance
- Folate >3mg/d
- Never long term corticosteroids
- ECULIZUMAB IV/ Fort night (↓Compliment mediated hemolysis)

Aplastic Anemia

- Sudden/ insidious Bleeding (MC 1st symp)
- Easy bruising, gum bleed, nose bleed, heavy menstrual flow, petechia, Hemorrhagic CVA, Retinal hemorrhage
- Symptoms of Anemia
- History of Drugs (allopurinol, gold, pencillamine)/ Viral illness/ Chemical exposure

- Early hair greying – telomeropathy

Aplastic Anemia

- PS : large RBC, paucity of platelets & granulocytes, ↓↓↓ Retic count

- Immature myeloid forms – Leukaemia/MDS
- Nucleated RBC – Marrow fibrosis/ tumor invasion
- Abnormal platelets - MDS

Aplastic Anemia

Aplastic anemia	Hypocellular MDS/Leukemia
• ↓ myeloid/ megakaryocytes • Normal eyrthroblasts	• ↑ myeloblasts • Abnormal karyotype of erythroblasts

Aplastic anemia	Hairy cell leukaemia

Aplastic Anemia

Mild	• Supportive • Epoetin/ Darbepoetin + Filgrastim/ Sargramostim • Transfusions, AMD
Severe (<500/µL neutrophils <20000/µL thrombocytes <1% retic count	• <40 yrs + HLA matched donor = allogenic BMT • <40 yrs – HLA matched donor/ • >40 yrs =Immunosuppressive therapy

Aplastic Anemia

Immunosuppressive therapy

Initially

- Equine Anti thymocyte globulin (40mg/kg/day x 4)
- Cyclosporin A (6mg/kg BD x 6months)
- Methyl prednisolone (1-2mg/kg/day x 7day)

After 1-3 months

- Patient becomes partially transfusion free

Thalassemia

α- thalassemia	β- thalassemia
• (α, α/α,-) Silent carrier	(β0/β0 or β +/β +) Thalassemia Major Transfusion dependent
• (α,-/α,-) type I α- thalassemia trait • (α, α/-,-) type II α- thalassemia trait Mild Microcytic anemia	(β+/β+ with more β chain synth) T. Intermedia Transfusion at aplastic crisis/ stress
• (α,-/-,-) Hb H disease Chronic hemolytic anemia of variable	(β/β0 or β/β+) T. Minor Mild Microcytic hypochromic anemia

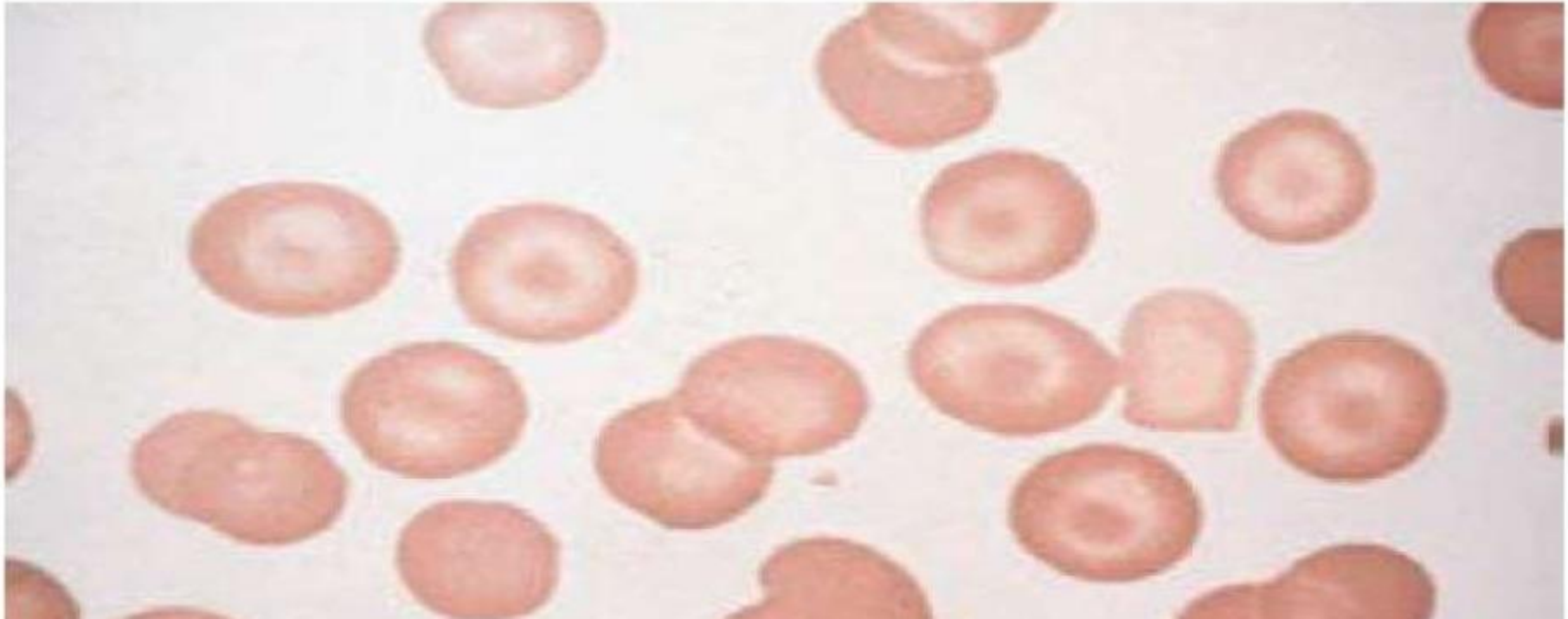
Thalassemia

- C/f : Onset 4-6 months
  - Stunted growth
  - Bony deformities
  - Hepatosplenomegaly
  - Jaundice (gallstones, hepatitis)
  - Thrombophilia
  - Over load symptoms
    - Heart failure

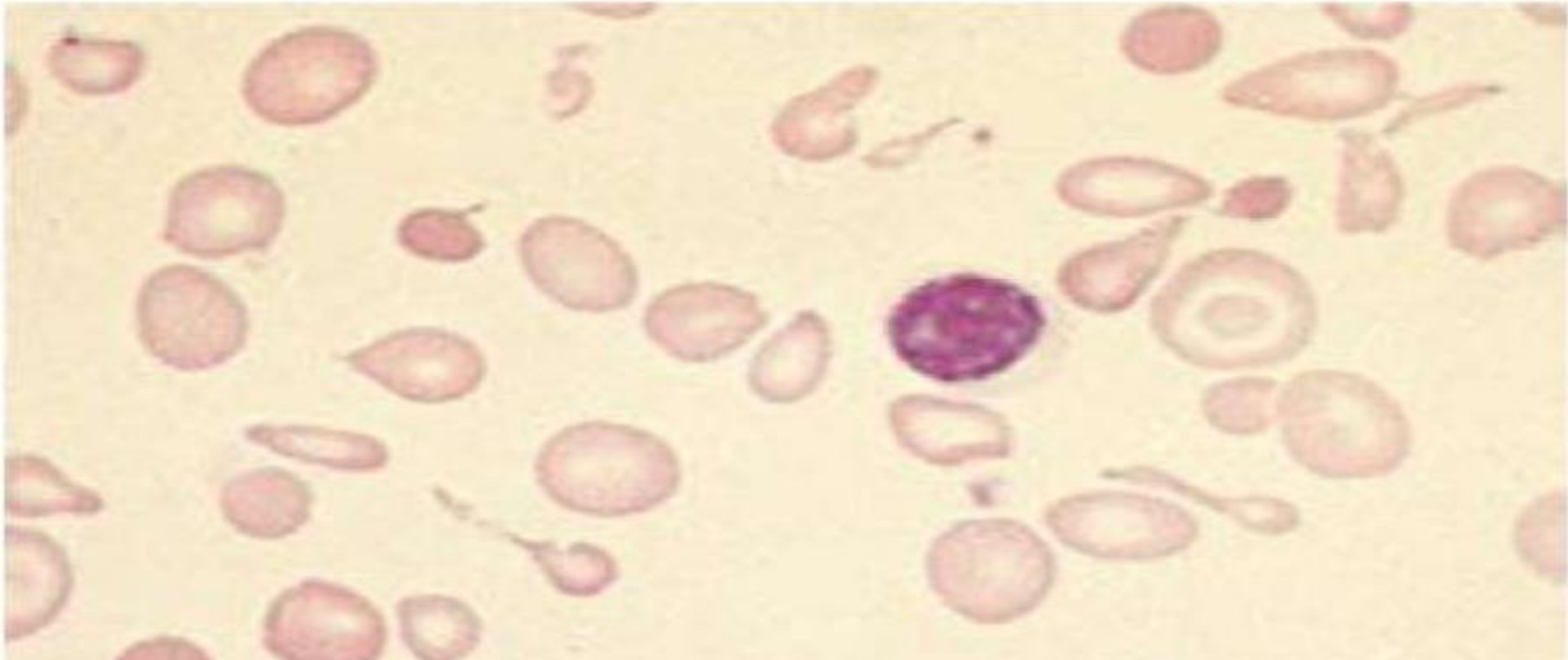
Thalassemia

- Microcytic hypochromic
- 60 – 70 fL MCV
- 22-32 % Hematocrit
- Target cells
- Acanthocytes (irregular spikes)
- Basophilic stippling (β thalassemias)

Thalassemia



Thalassemia



Thalassemia

- Electrophoresis (definitive)

Diesase	Electrophoresis finding
Hb H disease	10-40% migrating Hb
T. Minor	4-8% Hb A2 1-5% Hb F
T. Intermedia	0-30% Hb A 0-10% Hb A2

Thalassemia

- Mild – No Rx
- Hb H
  - Folate 1mg/day oral
  - No oxidative drugs/ iron
  - Transfusion
- Splenectomy (if hypersplenism is seen)

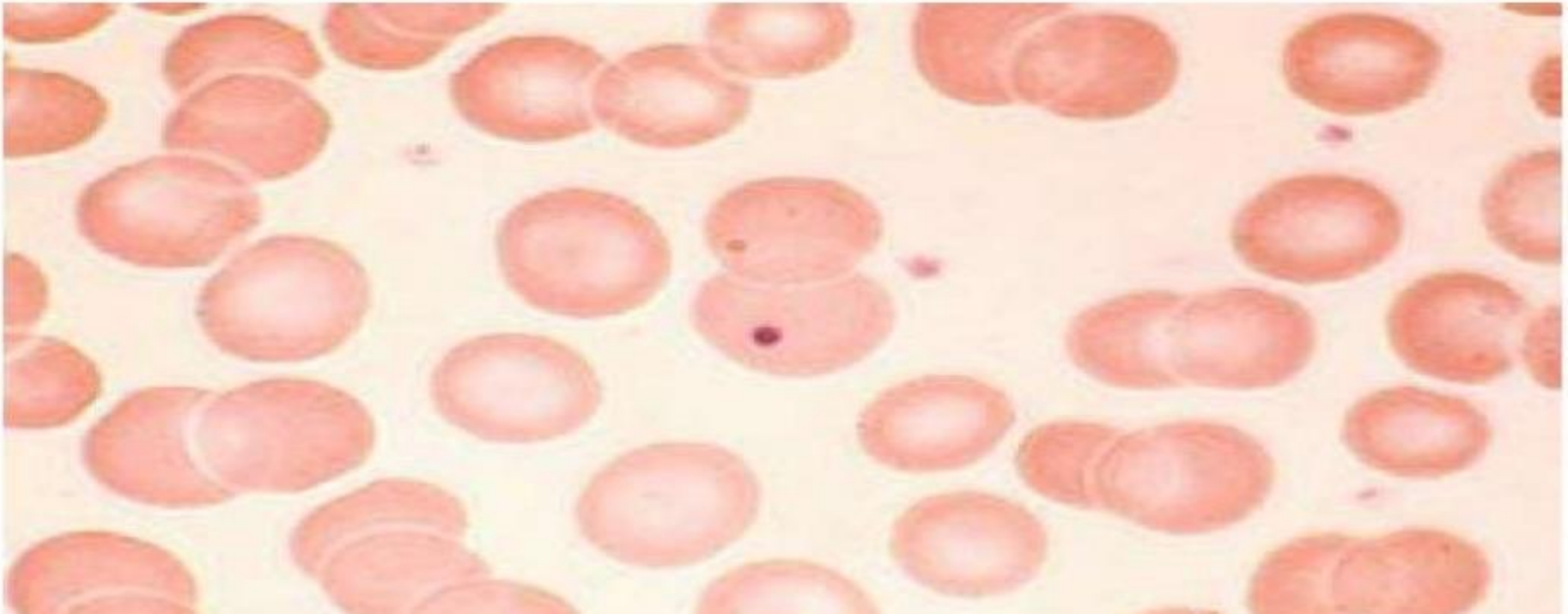
Sickle Cell Anemia

- C/f : Onset 4 – 6 months
  - Chronic hemolytic jaundice
  - Aplastic crisis with viral illness
  - Acute painful syndrome (acute vaso occlusion)
    - Episodes last for hrs to days + low grade fever
  - Repeated occlusion
    - Enlarged heart
    - PAH
    - Cirrhosis liver
    - Osteonecrosis (salmonella > staph)
    - Renal papillary infarction (gross hematuria)
    - Retinopathy (similar to DM)

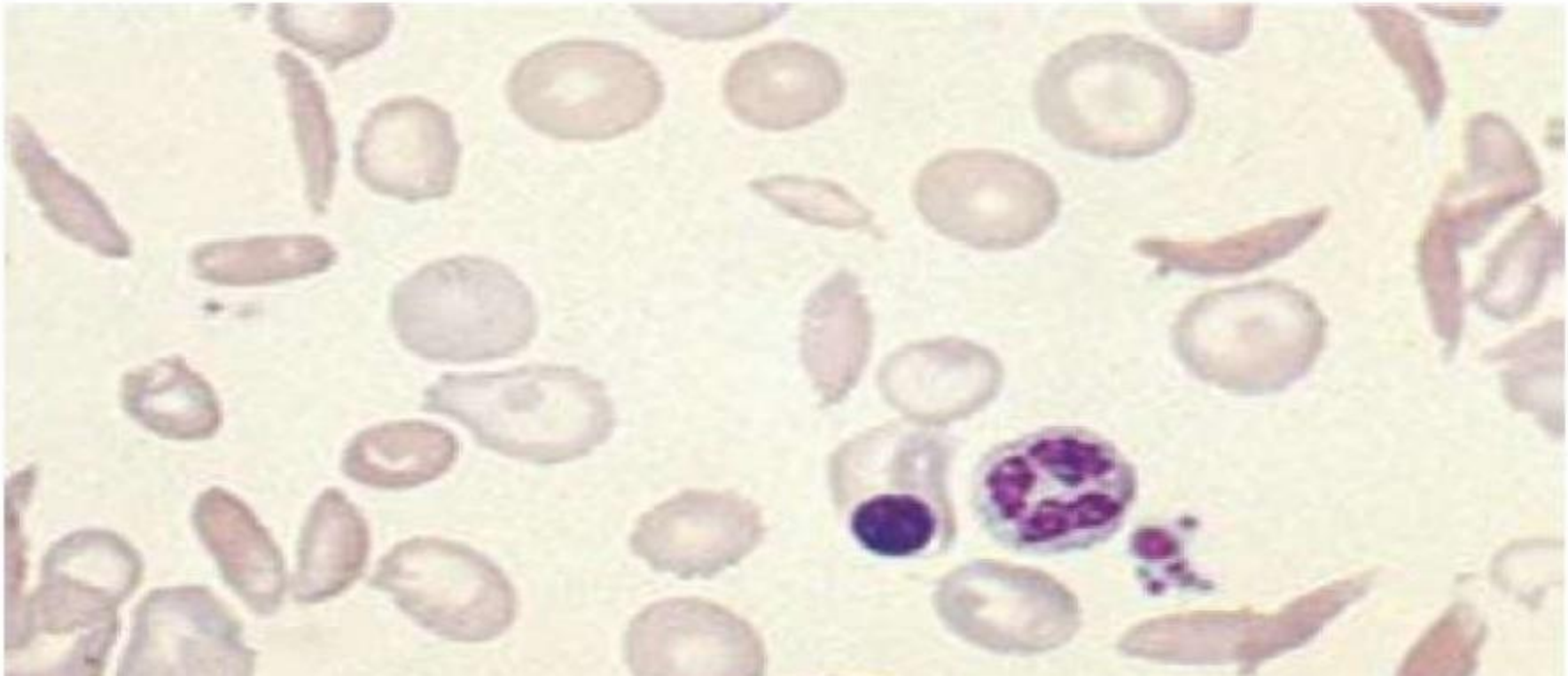
Sickle Cell Anemia

- Sickled cells (5 – 50%)
- Reticulocytes (10 – 25%)
- Howel jolley bodies (d/t hyposplenism)
- Target cells
- Leukocytosis (12000 -15000/cumm)
- Reactive thrombocytosis

Sickle Cell Anemia



Sickle Cell Anemia



Sickle cell anemia

- Allogenic BMT (Curative in child)
- Omega 3 FA
- Folate 1mg/day
- Transfusions
- Pneumococcal vaccination
- Hydroxy Urea 500-750 mg/OD
- Painful crisis :
  - Hydration, NSAIDS, O2
- Vaso-occlusive/ Intractable pain/ Acute chest synd/ priapism/ stroke

THANK YOU