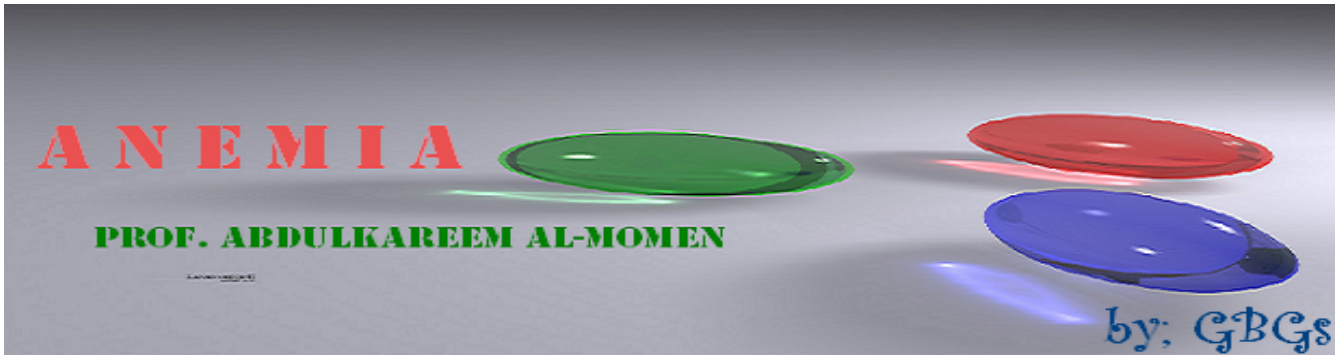


-Anemia is operationally defined as a reduction in one or more of the major RBC measurements:

Hb concentration, PCV (hematocrit), or RBC count

(adjusted to age, gender & sea level)

"Keep in mind these are all concentration measures"

<u>Examples :(Hb/PCV)</u>

Newborn Hb= 200 g/l +/- 20
PCV= 60 %

Childhood Hb = 110 g/l +/- 20
PCV= 33 %

Adult: Male:Hb = 160 g/l +/-30
PCV = 48 %
Female: Hb = 140 g/l +/- 20
PCV = 42 %

High altitude increased Hb & PCV

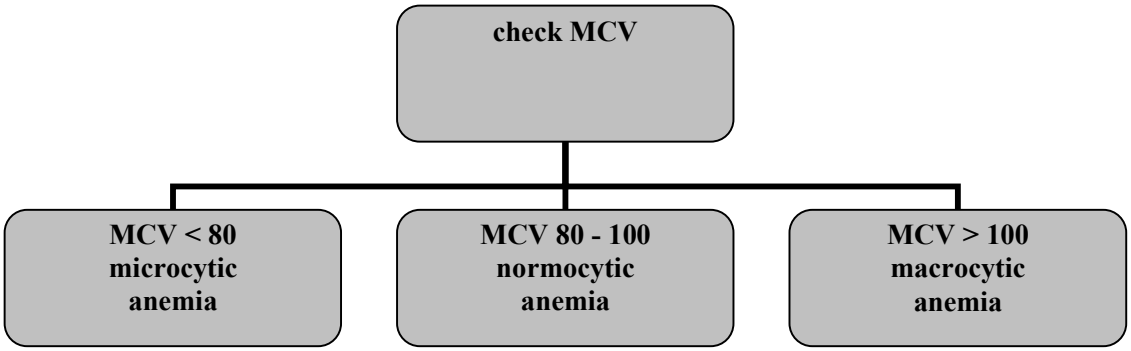
CAUSES

1. RBC Loss (Hemorrhage)

2. Decreased RBC production

3. Increased RBC destruction

APPROACH TO ANEMIA



1- MCV >115

- B12, Folate

- Drugs that impair DNA synthesis (AZT, chemo., azathioprine)

- MDS (Myelodysplastic syndrome)

2-MCV 100 – 115

- Liver disease

- Endocrinopathy (hypothyroidism)

- Reticulocytosis

- MDS

3-Normocytic

- Acute bleeding
- Anemia of chronic disease
- Mixed deficiencies
- Renal failure

4-Microcytic

- Iron deficiency
- Thal. trait
- Anemia of chronic disease (30-40%)
- sideroblastic anemias

Laboratory Evaluation of Anemia:

-Complete blood count
-Reticulocyte count
-Peripheral smear

Reticulocyte Count

- Increased reticulocytes (greater than 2-3% or 100,000/mm3 total) are seen in blood loss and hemolytic processes, if response is normal
- Retic counts are most helpful if extremely low (<0.1%) or extremely high (more than 3% or 100,000/mm3 total).
-To be useful the reticulocyte count must be adjusted for the patient's hematocrit.

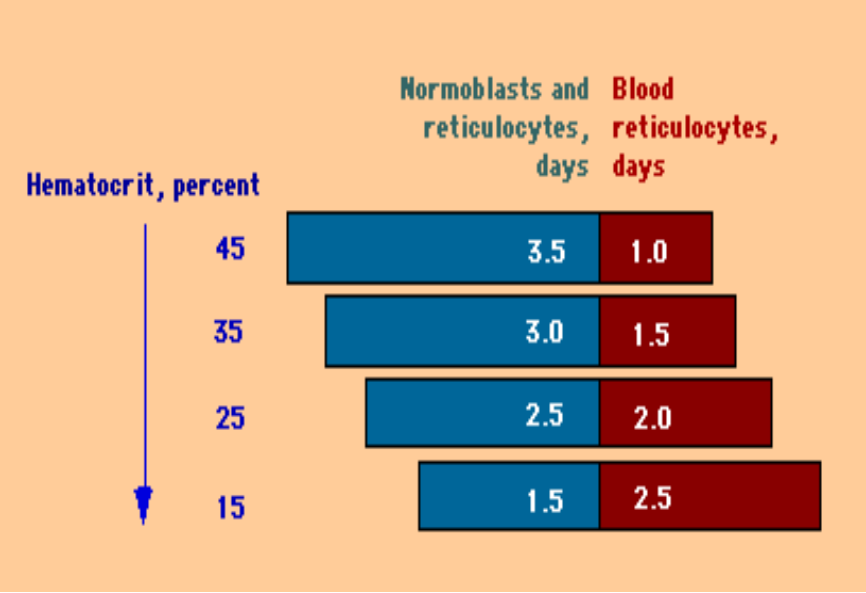
- Also when the hematocrit is lower, reticulocytes are released earlier from the marrow so one can adjust for this phenomenon. Thus:

Corrected retic. = Patients retic. x (Patients Hct/45)

Reticulocyte index (RPI) = corrected retic. count / Maturation time

(Maturation time = 1 for Hct=45%,
1.5 for 35%,
2 for 25%, and
2.5 for 15%.)

Absolute reticulocyte count = retic x RBC number.



Example

Hb= 75 g/l, PCV= 22%, Retics.= 12%

Corrected retics.= 12 x 22/45 = 6

Retic.Index = 6/2.5 = 2.5 %

- Absolute reticulocyte count = retic x RBC number = 80,000 /m3
(Normal = 0.5 – 1.5 % of normal RBC count,)
(In good responders, lower PCV leads to higher Retic. Count)

IRON DEFICIENCY ANEMIA

- **A world-wide problem**
- **3% of toddlers age 1-2 years**
- **2-5% of women of child bearing age**

Iron Compartments in a 70 kg person

Compartment	Fe content (mg)	Total body Fe (%)
Hemoglobin Fe	2000	67
Storage (ferritin, hemosiderin)	1000	27
Myoglobin Fe	130	3.5
Labile pool	80	2.2
Other tissue Fe	8	0.2
Transport Fe	3	0.08

Causes of Iron Deficiency

(Iron deficiency is a symptom, not a disease)

1-Increased iron requirements:

- Blood loss

- Gastrointestinal disorders (esophageal varices, hemorrhoids)

- Extensive and prolonged menstruation

- Pregnancy

- Dialysis

- Hookworm infestation

- Intravascular hemolysis with hemoglobinuria

- Paroxysmal nocturnal hemoglobinuria

- Cardiac valve prostheses

- Rapid growth in body size between 2 and 36 months of age

2-Inadequate iron supply:

- Poor nutritional intake in children (not a common independent mechanism in adults but often a contributing factor)

- Malabsorption

- Gastric bypass surgery for ulcers or obesity

- Achlorhydria from gastritis or drug therapy

- Severe malabsorption (for example, celiac disease [nontropical sprue])

Systemic Manifestations of Iron Deficiency

-Behavioral and neuropsychiatric manifestations

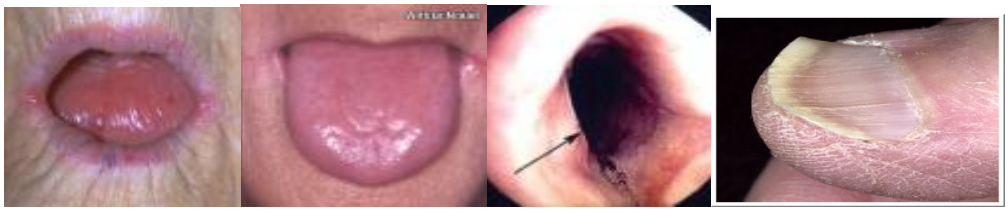
-Pica (pagophagia)

-Angular stomatitis

-Glossitis

-Esophageal webs and strictures

-Koilonychia



Treatment with Oral Iron

- Ferrous salts (sulfate,fumerate,gluconate) .

(Ferrous salts are absorbed better than ferric)

- Ascorbic acid increases absorption and toxicity

- Iron should not be given with antacids

- Iron is absorbed best on an empty stomach ,absorption is impaired by food (vegetables, milk).

- Heme iron (meat,liver) absorption is not affected

- Iron polysaccharide complex (Ferose) seems to be better tolerated than iron salts, and is taken with food.

Oral iron failure

- Incorrect diagnosis (eg, thalassemia)

- Anemia of chronic disease?

- Patient is not taking the medication

- Not absorbed (enteric coated?)

- Rapid iron loss?

Use of Intravenous Iron

Iron Saccharate (ferosac), 200 mg in normal saline intravenously/day

Total dose = Body weight x target Hb – current Hb x 4

Indications

-Malabsorption

-Iron-limited response to erythropoietin

-Toxicity/noncompliance with oral iron

Iron Deficiency Anemia vs. Inflammatory Block

Smear

- Hypochromic and microcytic (low MCV) RBCs, usually not seen unless Hct < 30%

- Platelet count is often elevated

↓ Ferritin:

a measure of total body iron stores, but also an acute phase reactant

<15μg/l = Fe deficiency

>150 μg/l = Not Fe deficiency

15-150 μg/l = ?

- Low Iron Saturation (Fe/TIBC ratio)

↓ Fe (not reliable)

↑ TIBC

Fe/TIBC (% saturation) <15%

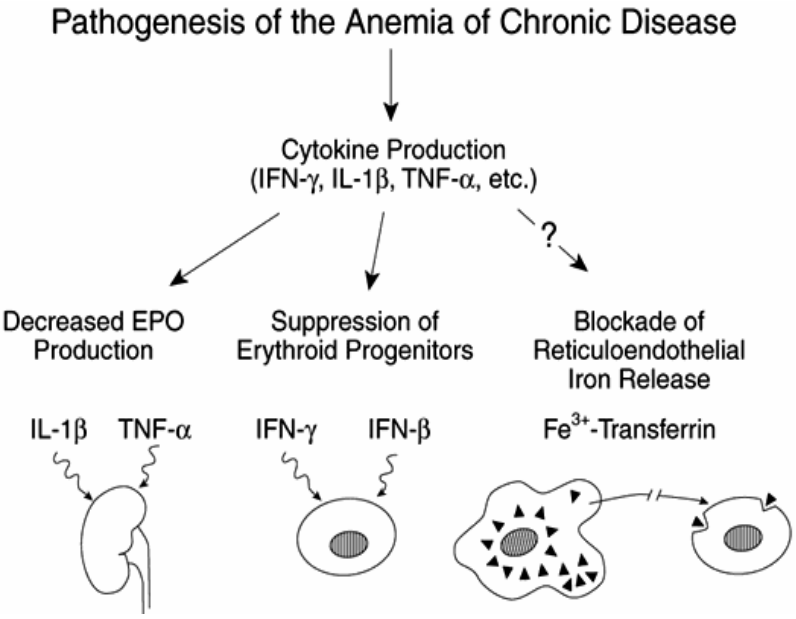
-BM bx: absent Fe stores

Gold standard

-Therapeutic Trial of Oral Iron

Differentiation of anemia of chronic disease and iron deficiency anemia by laboratory measures

Lab measure	ACD	Iron-def. anemia
Plasma Fe	Reduced (normal)	Reduced
Plasma transferrin	Reduced (normal)	Increased
Transferrin sat.	Reduced (normal)	Reduced
Plasma ferritin	Increased (normal)*	Reduced
Plasma TfR	Normal	Increased
TfR/log ferritin	Low (<1)	High (>4)



B12/FOLATE DEFICIENCY

ETIOLOGY

- Vitamin B12 and folate are needed for DNA synthesis deoxyuridate to thymidylate , including RBC precursors

- Deficiency :

B12

- Low dietary intake

- Impaired absorption:

*** Stomach [pernicious anemia, gasterectomy]**

*** Small bowel [ileal disease or resection (eg; Crohn's disease) , celiac disease, tropical spru, bacterial overgrowth, fish tapeworm (Cbl-IF)]**

*** Low pancreatic proteases**

PERNICIOUS ANEMIA : (Common cause of vit. B12 deficiency)

Autoimmune disease in which there is atrophy of the gastric mucosa → insufficiency of gastric secretions of acid, pepsin & intrinsic factor (important for B12 absorbtion)

Folate

- Poor dietary intake ± EtOH (alcohol !)

- Malabsorption

- Increased demand (pregnancy, hemolytic anemias)

- Inhibitors of DHF reductase enzyme (eg ; methotrexate, trimethoprim)

DIAGNOSIS

- Smear :

Macrocytic (High MCV) RBCs

+/- hyper-segmented neutrophils

+/- modest neutropenia,

B12

Low serum B12

Elevated serum methylmalonic acid levels

Anti-IF Abs

Pernicious anemia accounts for 75%

Folate

Serum folate level -- can normalize with a single good meal

TREATMENT

B12 deficiency:

B12 1 mg/month IM,

or 1-2 mg/day po

Folate deficiency:

Improved diet,

folate 1 mg/day

*** Monitor for a response to therapy.**

*** Pernicious Anemia → monitor for gastric cancers.**

Cobalamin deficiency and neurological problems

- Subacute combined degeneration of the dorsal and lateral spinal columns.

- There is well known study of B12 deficiency in the nursing home population .

- Vitamin B-12 deficiency is present in up to 15% of the elderly population as documented by elevated methylmalonic acid in combination with low or low-normal vitamin B-12 concentrations.

- Association between nitrous oxide anesthesia and development of neurological symptoms responsive to B12 in patients with subclinical cobalamin deficiency (methionine?).

SIDEROBLASTIC ANEMIAS

- Heterogenous grouping of anemias defined by presence of ringed sideroblasts in the BM

ETIOLOGY

- Hereditary (rare), type of porphyria

- Myelodysplasia

- EtOH (alcohol)

- Drugs (INH, Chloramphenicol)

TREATMENT

Trial of pyridoxine for hereditary or INH induced SA

HEMOLYTIC ANEMIAS

Anemia of increased destruction

- Normochromic, normochromic anemia

- Shortened RBC survival

- Reticulocytosis - response to increased RBC destruction

- Increased indirect bilirubin

- Increased LDH

CAUSES

A) INTRACORPUSCULAR HEMOLYSIS

1- Membrane abnormalities

- Microskeletal defects (Hereditary spherocytosis)

- Membrane permeability defects (Hereditary stomatocytosis)

- Increased sensitivity to complement (Paroxysmal nocturnal hemoglobinuria)

2- Metabolic abnormalities (Enzymopathies)

- Deficiencies in Hexose Monophosphate Shunt (G6PD Deficiency)

- Deficiencies in the EM Pathway (Pyruvate Kinase Deficiency)

3- Hemoglobinopathies

B) EXTRACORPUSCULAR HEMOLYSIS

1 – Nonimmune

- Mechanical or traumatic (Microangiopathic Hemolytic Anemia - MAHA)

- Infectious

- Chemical

- Thermal

- Osmotic

2 - Immune

HEREDITARY SPHEROCYTOSIS

- Defective or absent spectrin molecule

- Leads to loss of RBC membrane, leading to spherocytosis

- Decreased deformability of cell

- Increased osmotic fragility

- Extravascular hemolysis in spleen

- Treatment → Splenectomy

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

- Clonal cell disorder

- Ongoing Intra- & Extravascular hemolysis; classically at night

- Testing :

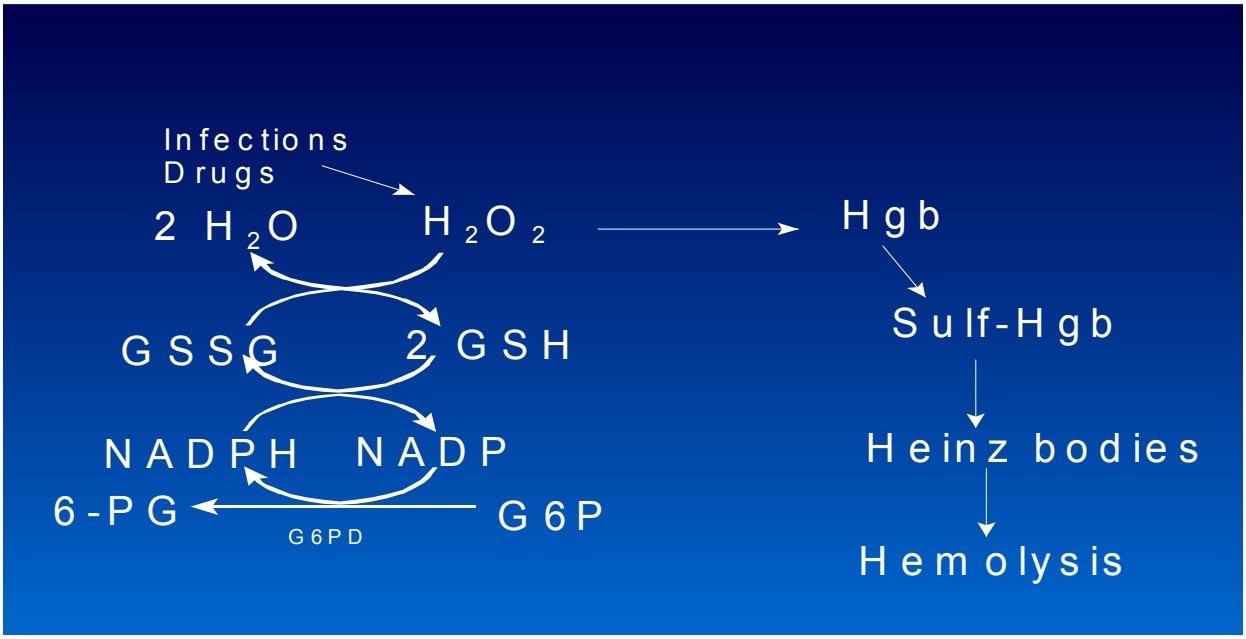
Acid hemolysis (Ham test)

Sucrose hemolysis

CD-59 negative (Product of PIG-A gene)

- Acquired deficit of GPI-Associated proteins (including Decay Activating Factor)

G6PD DEFICIENCY



Functions of G6PD:

- Regenerates NADPH, allowing regeneration of glutathione

- Protects against oxidative stress

- Lack of G6PD leads to hemolysis during oxidative stress (infection, medications, Fava beans)

- Oxidative stress leads to Heinz body formation, extravascular hemolysis

HEEMOGLOBINOPATHIES

Structural hemoglobinopathy:

Amino acid substitution in the globin chain e.g. sickle hemoglobin (HbS)

~ SICKLE CELL ANEMIA

CLINICAL FEATURES

1) Hemolysis

2) Occlusion of blood vessels

- **bone (‘painful crisis’)**
- **lung (‘acute chest syndrome’)**
- **brain**
- **heart**
- **spleen (‘Acute splenic sequestration’)**
- **hands (dactylitis in children)**
- **other**

DIAGNOSIS

*** Smear : sickle-shaped RBCs and Howell-Jolly bodies .**

*** Hb electrophoresis**

TREATMENT

- Opiates and hydration for painful crises

- Pneumococcal vaccination

- Retinal surveillance

- Transfusion for serious manifestations (eg stroke)

- Hydroxyurea
- Stem cell transplant

Sickle Cell Trait

- Heterozygous state for HbS (HbAS)
- No serious clinical consequences
- Sudden death during intensive training
- Hematuria, isosthenuria (renal papillary necrosis)
-Protection against malaria

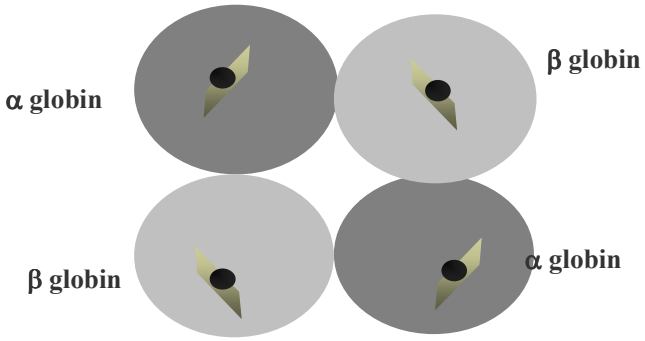
~ THALASSEMIA

- Normally, there is a balance in the production of ά and β chains in Hb (Hb A)
- In Thalassemia, there is impaired Globin Gene production.
- The imbalanced globin chain production → precipitation of chains within red cells → cell damage → death of cells in bone marrow (ineffective erythropoiesis), and haemolysis .

-α thalassemia –deficiency of α gene(s)

-β thalassemia - deficiency of β gene(s)

HbA tetramer($ά_2,β_2$)



1-Alpha Thalassemia:

α CHAINS	HEMOGLOBIN ANALYSIS
αα/αα	Normal
αα/-α	Mild microcytosis
α-/α- or --/αα	Mild microcytosis
--/-α	Hemoglobin H disease
- - / --	Hemoglobin Barts – Hydrops Fetalis

2-Beta Thalassemia:

Beta thalassemia minor – heterozygous (or trait)

-No symptoms

-Mild microcytic anemia

Beta thalassemia major - homozygous

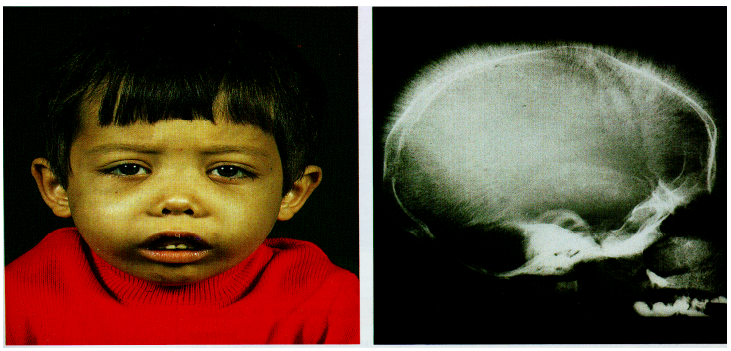
- No beta chain produced (no HbA)

- Severe microcytic anemia occurs gradually in the first year of life (*Cooley's anemia*)

- Marrow expansion → bony abnormalities : thalassemia facies

- Iron overload

- Growth failure and death



Beta thalassemia major -Treatment

- Transfusion
- Iron chelation
- Stem cell transplant

MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA)

CAUSES

***Vascular abnormalities.**

- Thrombotic thrombocytopenic purpura.

- Renal lesions :
  - Malignant hypertension
  - Glomerulonephritis
  - Pre-eclampsia
  - Transplant rejection

- Vasculitis :

Polyarteritis nodosa

Rocky mountain spotted fever

Wegener's granulomatosis

Autoimmune Hemolytic Anemia

~ WARM TYPE

- Usually IgG antibodies
- Fix complement only to level of C3,if at all
- Immunoglobulin binding occurs at all temps
- Fc receptors/C3b recognized by macrophages
-Hemolysis primarily extravascular
- 70% associated with other illnesses
- Responsive to steroids/splenectomy

~ COLD TYPE

- Most commonly IgM mediated
- Antibodies bind best at 30º or lower
- Fix entire complement cascade
- Leads to formation of membrane attack complex, which leads to RBC lysis in vasculature
- Typically only complement found on cells
- 90% associated with other illnesses
- Poorly responsive to steroids, splenectomy; responsive to plasmapheresis

HEMOLYTIC ANEMIA

~SUMMARY~

- Myriad causes of increased RBC destruction

- Marrow function usually normal

- Often requires extra folic acid to maintain hematopoiesis

- Anything that turns off the bone marrow can result in acute, life-threatening anemia

CHOICE

is a divine teacher;

for when we choose..

We learn that nothing is ever put in our path

Without a REASON !

COMMON QS

Concerning anemia:

1)in sickle cell anemia, HbS is elevated (T)
2)ß-thalasemia associated with low plasma iron (F)
3) ß-thalasemia caused by HbF (F)
4)autoimmune disease can cause anemia (T)

Hereditary spherocytosis(H.S) is associated with:

1)leg ulcer (T)
2) gall stone (T)
3)splenomegally (T)
4)spherical RBCs (T)

Sickle cell crisis can be precipitated by:

1)infection (T)
b)alkalosis
c)cold whether (T)
c)hypoxia (T)
d)acidosis (T)
e)dehydration (T)

Peripheral blood finding in dietary iron deficiency anemia:

1)microcytosis preceding the development of hypochromic (T)
2)ovoilocytosis and ellipocytosis (T)

3)MCHC < 50% of normal (F)

4)numerous target cells and Howell-Jolly bodies (F)

5)neutrophil hypersegmention and thrombpcytosis (T)

Microcytic anemia is atypical finding in all Except:

1)folic acid deficiency

2)hemolytic anemia

3)alcohol abuse

4)primary sedroplastic anemia

5)meylodysplastic syndrome

Regarding to iron which of the following is correct:

1)folic acid should be given if the anemia is sever

2)treatment should be stopped when Hb become normal

3)Hb should rise 1mg/h/day

4)reticulocyte count rise withen 7-10 days

5)parentral iron is more affected than oral iron

Iron deficiency anemia may occore with:

1)chronic peptic ulcer (T)

2) rheumatoid arthritis

3)deficiency of Vit.B12 (T)

4)crohn's disease (T)

5)food deficient in iron (T)