Anaemia

by Dr.Khalid AlSaleh

Done by: Lena Alaseem

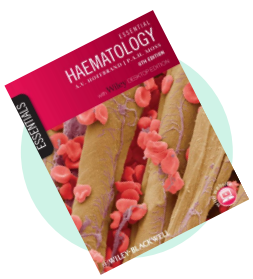
Revised by: Sarah Almubrik & Mohanad Alsuhaim

Objectives:

- **Not given yet!**

References:
Slides - Black
Doctor's notes - Red
Master the board - Blue
Extra explanation - Grey

Optional:



Chapter 3,5,6,7

Editing file

Introduction

- **The principle function of hemoglobin "Hb" is to carry & deliver Oxygen to tissues from the lungs.**
- **Hb is a tetramer formed of one pair alpha chains & one pair of non-alpha chains**
- **Anemia present when there is decrease of Hb in the blood below reference range of the age & sex if the individual .**
- **In general elderly can tolerate anemia less well than young people.**

Whatever speciality you're dreaming for , whether it's dermatology , medicine or surgery you will order CBC & **always when you read CBC you have to correlate it with the clinical context** ,I can give you 2 identical CBC each with different clinical picture each will have a different Dx & this is very important we can challenge you in the exam!

What control our RBC production ?

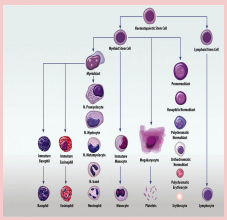
Erythropoietin from Juxtaglomerular apparatus of the proximal tubules of the Kidney.

What is the difference between plasma & serum ?

Plasma is fluid that carries blood clotting agents, while serum is the water fluid from blood without the clotting factors.

CBC: is one of the commonest investigation we use and you need to understand it. Many items listed and some of them tell the same information in different way.

- **CBC is dealing with the cellular compartments of the blood only! it <u>will not</u> tell you about the plasma proteins!**
- **Most of the CBC now done in automated way.**
- **Contents of CBC:**
- WBC and diff, RBC, HB, Htc : Hematocrit also called"Packed cell volume"
- MCV "Mean corpuscular volume" : size of the RBCs,MCH,MCHC, Platlets and MPV, ESR, Blood film
- RDW "random distribution with " : it tells you how variable is your RBCs , our RBCs are quite variable but it need to be of limited variability , Reticlocytes "immature RBC" very important , One way of Stem cells differentiation is RBCs Note : RDW is either Normal or High it won't be low
- "see the picture".



Click for Maximum view!

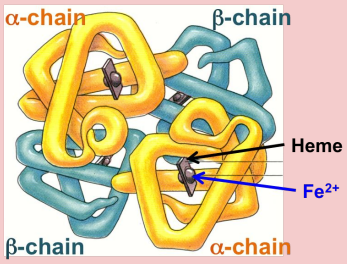
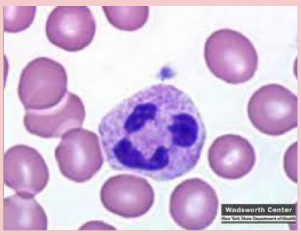
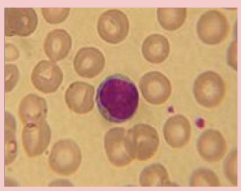
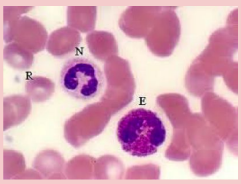
Some formula for interest: 🤔

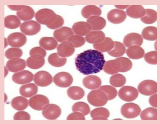
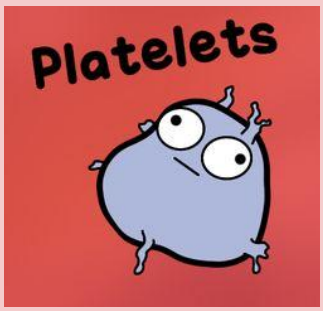
- **MCV = Hct (L/L) 1,000/red cell count (10^12/L) → To measure the average size of RBCs**
- **MCH = hemoglobin (g/L)/red cell count (10^12/L) → To measure the average Hb weight in RBCs**
- **MCHC =hemoglobin (g/dl)/Hct (L/L) → To measure the average concentration of Hb in RBCs**

Interpret results in clinical context: All haematology results need to be interpreted in the context of a thorough history and physical examination, as well as previous results.

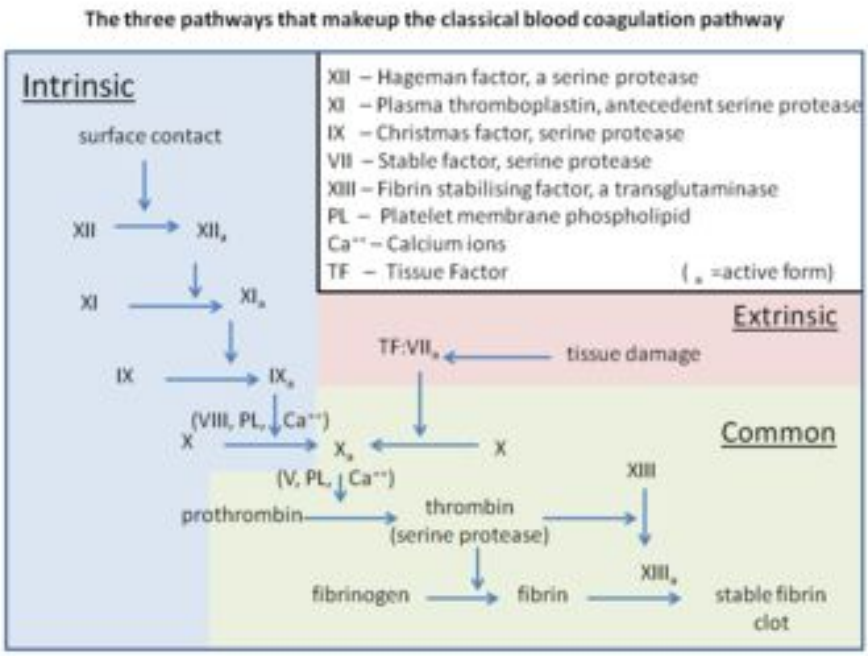
History and clinical examination: pallor, jaundice, fever, lymphadenopathy, bleeding/bruising, hepatomegaly, splenomegaly, frequency and severity of infections,mouth ulcers, recent viral illness, exposure to drugs and toxins, fatigue/weight loss.

interpretation of cellular components in CBC !

Type / amount	Low ↓	High ↑
HB 	-	⇧ Hb often accompanied by ⇧ PCV • Can reflect decreased plasma volume (eg: dehydration, alcohol, cigarette smoking, diuretics) or • Increased red cell mass (eg polycythaemia) This can be primary or secondary
Neutrophils 	Significant levels < 0.5 x 10^9/L (high risk infection) Most common causes: viral (overt or occult),autoimmune/idiopathic, drugs) Red flags: person particularly unwell,severity, lymphadenopathy, hepatosplenomegaly.	Most common causes: infection/inflammation Necrosis/malignancy. any stressor/heavy exercise. Drugs. CML. Red flags: person particularly unwell, Severity, presence of left shift or blast.
Lymphocyte 	Not usually clinically significant	isolated elevated count not usually significant Causes: acute infection (viral, bacterial), smoking , hyposplenism, acute stress response, autoimmune thyroiditis, CLL
Monocytes 	Not clinically significant	Usually not significant watch levels > 1.5 x10^9/L more closely
Eosinophils 	No real cause for concern	Most common causes: allergy/atopy: asthma/hay fever ,parasites (less common in developed countries) Rare causes :Hodgkins ,myeloproliferative disorders,Churg-Strauss syndrome

Type / amount	Low ↓	High ↑
Basophils 	**Difficult to demonstrate/no clinical significance.**	**Associated with myeloproliferative disorders and other rare causes.**
Platelets 	**Significant levels < 100 x10^9/L** **<u>Most common causes:</u> viral infection,idiopathic thrombocytopenic purpura,liver disease,drugs, hypersplenism,autoimmune disease,P regnancy, Artificial à confirm on blood film** **<u>Red flags:</u>bruising,petechiae,signs of bleeding**	**Significant levels > 500x10^9/L** **<u>Most likely causes:</u> reactive conditions eg infection, inflammation,pregnancy, iron deficiency,post splenectomy,essential thrombocythemia.**

❖ Coagulation Cascade



4:16 min

- **Prolonged PT is seen in:** Vitamin K deficiency، Warfarin therapy & Liver disease.
- **Prolonged PTT is seen in:** von Willebrand ,**hemophilia**، Heparin therapy، Antiphospholipid syndrome

★ Prolonged PT and PTT is seen in deficiencies of the final common pathway factors such as factor V, prothrombin, fibrinogen, or factor X. Liver disease, DIC.

Anemia

"Basic Principle"

Anemia is a Reduction in the total amount of red blood cells (RBCs) or hemoglobin in the blood. The Normal Hb values in males (13.5-17.5 g/dl) while in females is (12.5-16g/dl) Q:why it less in female? due to menstrual cycle.

So, in case of Anemia:

In Males: Hb < 13.5 g/dl

In Females: Hb < 12.5 g/dl

Important when you say patient has Anemia this is useless so you have to specify whether it is Normo , Macro or Microcytic Anemia so you will know how to interfere with this case, this classification is by MCV which is measured with the CBC.

- Anemia can be classified <u>According to MCV</u> into:

Low haemoglobin

Microcytic, MCV < 80 fl

Most common causes are:

Iron deficiency Anemia "IDA", Thalassaemia & Anaemia of Chronic disease

-rare cause is sideroblastic anemia caused by lead poisoning & it's very rare forget about it:)

Normocytic, MCV 80 – 100 fl

Causes:Bleeding, Early nutritional anaemia (iron, B12, folate deficiencies), Anaemia of renal insufficiency,Anaemia of chronic disease/chronic inflammation,Haemolysis,Primary bone marrow disorder

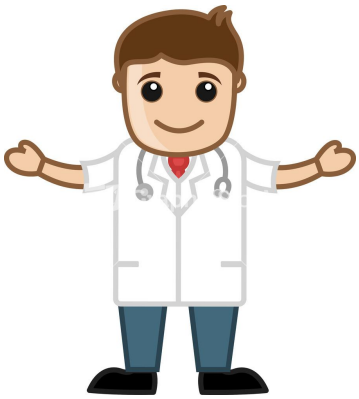
Macrocytic, MCV > 100 fl

Common causes:

- Alcohol
- Liver disease
- B12 or folate deficiency
- Thyroid disease
- Some drugs (especially hydroxyurea -used in SCA)

so if the pt with Normal RBC & he swear that he is taking the drug he is lying or he is under dose..

Why macrocytic anemia causes large RBC? is the result of impaired DNA synthesis. leading to a buildup of cytoplasmic components in a slowly dividing cell. This results in a larger-than-normal cell.remember immature cell are big , actually when we get rid of the DNA the cells becomes smaller



Given by the Doctor

Case1

- 20 YO Lady **came with Hb=7, Normal WBC & Platelets complaining of fatigue, SOB, Tachycardia what is the next thing you would like to know?** MCV=67 (Low) so she has Microcytic Anemia **What is your differential ?** IDA*, Anemia of chronic disease & Thalassemia.
  She has no blood disorder Nor chronic disease so most likely she has IDA & the most common causes in young ladies are Menorrhagia & pregnancy is she hasn't Hx of these 2 we will think of Celiac disease or GI blood loss

Case2

- 60 YO lady **with same Hb & symptoms of the Previous case she is healthy otherwise she doesn't have DM nor bleeding disorder ?**
  it's impossible to be menorrhagia or Pregnancy at her age
- **What is the most important thing to rule out ?**
  Cancer & GI blood loss so in this case u gonna do colonoscopy.

Case3

- **20 YO male came with microcytic anemia , No Hx of chronic illness or bleeding disorder so what do you think ?**
  most likely IDA we have to 1-rule out GI blood loss & scope the patient up & down because he might have an ulcer , ulcerative colitis .
- what else you could think of ? 2-Malabsorption like celiac "**celiac disease** is a serious genetic autoimmune disorder where the ingestion of gluten leads to damage in the small intestine causing malabsorption." , 3- Bariatric surgery which causes intentional malabsorption so those patient will have IDA & they'll be connected to I.V iron all of the time.

❖ Signs and Symptoms of Anemia:

Correlation of Levels of Anemia with Symptoms	
Hematocrit (Normal ranges are 39%–49% in men, 35%–45% in women)	**Symptoms**
30–35	Generally asymptomatic
25–30	Fatigue, tiredness
20–25	Dyspnea, especially on exertion, some will be lightheaded
<20–25	Lightheadedness, confusion, incapacitating fatigue and dyspnea

❖ Diagnostic tests:

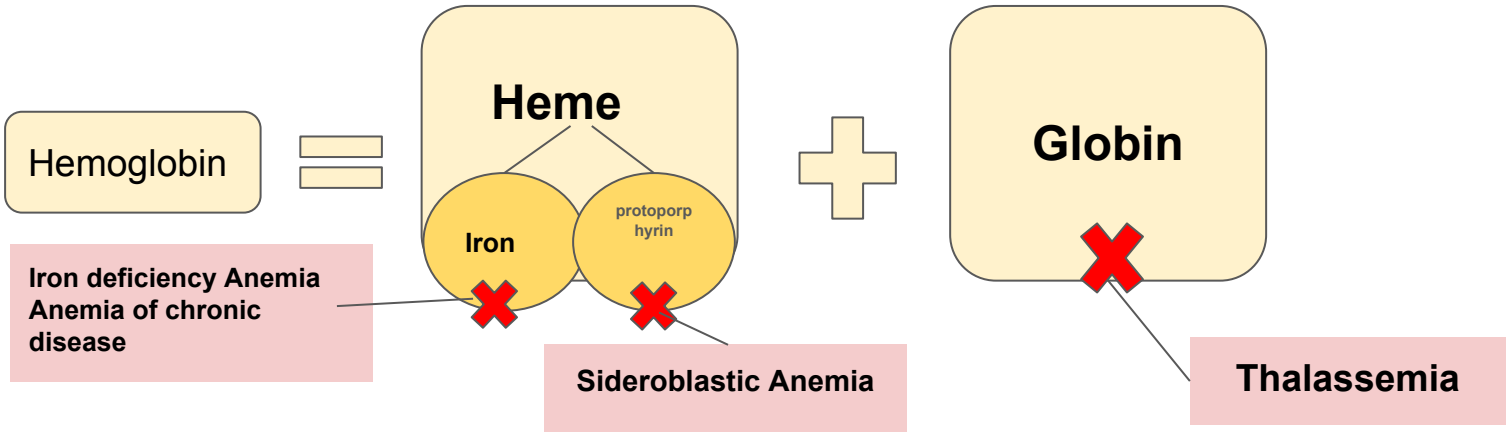
TABLE 9-1 Iron Studies in Microcytic Anemias

	Serum Ferritin	Serum Iron	TIBC	RDW
Iron deficiency anemia	Low	Low	High	High
Anemia of chronic disease	Normal/high	Low	Normal/low	Normal
Thalassemia	Normal/high	Normal/high	Normal	Normal/high

IDA = iron deficiency anemia

Microcytic Anemia

- Anemia with **MCV < 80 fl**
- Microcytic anemias are due to ↓ production of Hb.
- **Recall: Hemoglobin = Heme(Fe+protoporphyrin) & Globin.**
- **So, any defect in each part of these components will reduce hemoglobin production giving rise to a specific microcytic Anemia.**



❖ Iron deficiency anemia: (Heme part of hemoglobin is affected)

The most common cause of Microcytic Anemia
Causes include:-
Chronic Blood loss ***most common cause**

- Dietary deficiency
- Increase demand as in Infants and toddlers as they are growing
- Pregnancy
- Menstruation.

Investigations :
↓ ferritin it's the most reliable test available.
↑ TIBC
peripheral smear → Microcytic hypochromic RBCs
Bone marrow biopsy the gold standard but rarely done.
if GI bleeding is suspected - guaiac stool test or colonoscopy.
*Colon cancer is a common cause of GI bleeding in the elderly.

! Causes According to Age & Gender:
Infants → Breast feeding
Children → Poor diet
Adult:
In Males → Peptic Ulcer
In Females → Menorrhagia & Pregnancy
In elderly → Colon Cancer

Tx:

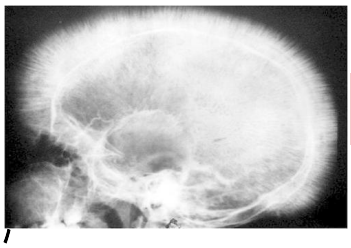
- Oral iron given to menstruating women however in postmenopausal & males determine the underlying cause.
- Parenteral iron dextran I.V or I.M rarely because most of the pt respond to oral , given only if pt can't tolerate ferrous sulfate , poor absorption or require more iron than the oral therapy can provide.
- Make sure that you're treating the diseases that can cause IDA (Ex: Colon cancer)

Tx= Treatment , Dx=diagnosis

❖ Thalassemia: (Globin part of hemoglobin is affected)

It's inherited disorder characterized by inadequate production of either alpha OR beta globin chain of hemoglobin

1-Beta-Thalassemia	2-Alpha-Thalassemia
The cause of it is due to **Mutation** of ß genes There are 2 copies of ß genes are located on chromosome 11 and it depends on how many of ß genes get mutated so beta chain production will be deficient , and it found mostly in people of mediterranean, middle east and indian ancestry. Three types are found in ß thalassemia: • **Minor (heterozygous)** → usually asymptomatic, **Dx**: Hb electrophoresis , **Tx**: no need • **Major (homozygous)** → severe anemia , massive hepatosplenomegaly , skull x-ray may show "crew cut" appearance **Dx** : Hb electrophoresis Hb F & Hb A2 will be high , peripheral blood smear microcytic hypochromic & **Target cell** may be seen. **Tx**: frequent PRBC transfusion .	The cause of it is usually due to **Deletion** of α genes there are 4 copies of α genes are located on chromosome 16 each deletion of any of the 4 genes will increase the degree of severity - deletion of one alpha → Asymptomatic - deletion of two alpha (Trait or minor) → Mild Anemia - deletion of 3 alpha (**Hb H disease**) → **Severe Anemia** - deletion of all 4 alpha (**Hydrops fetalis**) → **Lethal in utero "fetus will die in the uterus"**



Crew cut appearance

MCV will be much more affected than Hb level.
Important Hint : RDW will be normal or close to normal-if the normal 14 they'll have 15 - while on IDA it'll be quite big more than 20 because it take few of iron the Bone marrow start to produce a lot of Large RBC without taking it it goes small.
so RDW is the clue another clue to differentiate between IDA & Thalassemia is Platelets on IDA it goes up while on thalassemia it'll be normal **But the simplest and clearest way to differentiate** is to measure the serum ferritin **WHY?** "because it's the shedding of the cell which reflect the intracellular concentration-true store

Nutshell

- Thalassemia is inherited disorder affect the globin part of hemoglobin
- it divided into 2 types: Alpha and Beta
- Beta-Thalassemia is concerned about mutation in ß genes
- Alpha-Thalassemia is concerned about deletion in α genes
- Thalassemia is diagnosed by Hb electrophoresis

❖ Anemia of chronic disease

typically it's normocytic but in 25% of the cases it'll be microcytic, mechanism: there is increase of protein called hepcidin which block iron release from macrophages , the patient usually have Hx of Rheumatoid arthritis , Autoimmune , somebody who has been sick in the hospital for long time or chronic inflammation. ESR will be high, **Clue** Ferritin-iron store- will be high **why ?** because it's an acute phase reactant, & the inflammation makes Iron utilization difficult.

Anemia of chronic disease won't drop Hb below 9 while if Hb=7 there is definitely element of IDA so i'll give Iron despite his normal ferritin.

Macrocytic Anemia

- Anemia with **MCV > 100 fl**
- Most common causes are Vit B12 OR folate deficiency
- Vit B12 & folate deficiency also called "Megaloblastic Anemia"
- Vit B12 is found in meat & fish" while Folate can be found in vegetables & fruits
- Vit B12 is absorbed in the ilium & Folate is absorbed in jejunum
- other causes include: Alcoholism, liver disease,Thyroid disease, Drugs(Ex: hydroxyurea)
- Both Vit B12 & Folate deficiency have similar findings! , except there is **NO** neurological symptoms in Folate deficiency

B12 absorption
9:50 min

❖ Vit B12 deficiency

causes include:-
- lack of IF due to autoantibodies attacking the parietal cell of stomach, also called **"pernicious anemia"**
-Poor diet "strict vegetarianism"
-Crohn's Disease
-ileal resection

Signs & symptoms: stomatitis & glossitis, Neurological symptoms "ataxia loss of position/vibration".
Dx : Hyper-Segmented Neutrophils, B12 <100 pg/mL, antibody against IF can help in Dx of pernicious Anemia.

How long does it take anyone to develop B12 deficiency?
3 years

❖ Folate deficiency

causes include:-
-Alcoholism
-increased demand situation:(eg:pregnancy)
-use of folate antagonists as methotrexate

signs & symptoms: stomatitis & glossitis **Without** neurological symptoms.

why we need IF? because B12 is very complex & it's easily digested by acidity it need something to protect it that's why we need healthy stomach , when we do total gastrectomy-as in cancer- we can lose it completely.

! When you have very huge MCV going beyond 120 this is B12 deficiency almost 100% of the time the only exception to that is if you have someone using HIV antiretroviral agents.

Normocytic Anemia

❖ Anemia of chronic disease

As Anemia of chronic disease e.g chronic infection, cancer, inflammation "RA*, SLE". the release of inflammatory cytokines has suppressive effect on erythropoiesis. Lab finding: serum ferritin will be High, Low iron & Low TIBC. Usually normocytic but can be microcytic also, No specific **Tx** other than Treating the underlying cause , Don't give iron because the anemia is usually mild & well tolerated.

important thing to look in anemia is WBC & Platelets if everything is going down with low Hb especially if it's a normocytic we should suspect Bone marrow problem the production is off. Best Ex: Aplastic Anemia

Note: Ok, I know you may get confused about which category "Anemia of chronic disease" belongs whether to microcytic OR normocytic. Well,Actually it belongs to both as in the beginning it would be normocytic and while progression of the disease eventually will turn to be microcytic.

❖ Hemolytic Anemia "High reticulocytes"

Classification:

A- factors external to RBC as immune hemolysis , medication or infection.

B- Intrinsic RBC defects: 1- Hb abnormality as Sickle cell anemia.2-membrane defect as hereditary spherocytosis.3-Enzyme defect: (i.e: G6PD deficiency)

Symptoms : symptoms of anemia , dark urine , hepatospleenomegaly & cholelithaisis.

Another Classification:

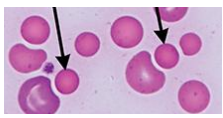
A-intravascular hemolysis within the circulation.

B- Extravascular in the reticuloendothelial system primarily spleen.

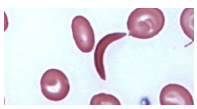
Dx:

- Schistocytes suggest intravascular hemolysis.
- Spherocytes or helmet cells suggest Extravascular hemolysis.
- Sickled RBCs - SCA.
- Heinz bodies in G6PD deficiency.

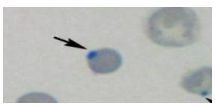
Schistocytes



Spherocytes



SCA



Heinz bodies

❖ Sickle cell anemia

Caused by Autosomal recessive when normal Hb A replaced by Hb S.

Clinical features:

- Severe life long hemolytic anemia:
  Jaundice, pallor, gallstone disease,Heart Failure and aplastic crises.
- Findings secondary to vaso-occlusion(occluded vessels):
  Painful crises, Hand foot syndrome, acute chest syndrome
  episodes of splenic infarction, avascular necrosis of joints, priapism, stroke, ophthalmologic complications, renal papillary necrosis, chronic leg ulcers,infectious complications and delayed growth and sexual maturation.

Dx: sickled RBCs on peripheral blood smear. Diagnosis confirmed by Hb electrophoresis

Tx : 1- educate pt to avoid High altitude , Treat infection promptly. 2- Hydroxyurea which improve Hb F levels which interfere with sickling process & decrease painful crisis & it accelerate healing of leg ulcers.

RA = Rheumatoid arthritis, SCA = Sickle cell anemia

MCQ's

Q1: A 35-year-old man befog treated with phenytoin for epilepsy comes to the physician for a routine check-up examination. He has been seizure-free for the past year. Physical examination reveals pallor of skin and mucosae, slightly jaundiced discoloration of sclera, and a red and shiny tongue. He denies paresthesias, and sensation is normal on neurologic examination. Significant results of blood and serum studies include:

Hematocrit	**28%**
Hemoglobin	**8.5 g/dL**
Mean corpuscular volume	**130 fl**
Reticulocytes	**0.2%**
Platelets	**140,000/mm3**

A peripheral blood smear reveals microcytes, ovalocytes, and hypersegmented neutrophils, which of the following is the most likely cause of this patient's anemia?
(A) Autoimmune hemolysis
(B) Bone marrow aplasia
(C Folate deficiency
(D) Iron deficiency
(E) Vitamin B12 deficiency

Q2:A 17-year-old girl complains of fatigue. She has difficulty making it through the entire school day. She recently began to feel her heart beating in her chest. Examination shows pale mucosal membranes. A peripheral blood 'smear shows hypochromic, microcytic red blood cells
Which of the following is the most likely diagnosis?
(A) Folate Deficiency
(B) Hereditary spherocytosis
(c) Iron deficiency anemia
(D) Sickle cell anemia
(E) Vitamin B12 deficient

Q3:A 20-year-old black woman' with a history of multiple small bowel resections for Crohn's disease presents complaining of fatigue and dyspnea on exertion. Her physical examination is notable for pallor and a wide-based unsteady gait. Her lab studies reveal a hemoglobin of 10.0 g/dL, witli a mean corpuscular volume(MCV) of 120 μm3. Examination of the peripheral blood smear showed macrocytosis, anisocytosis, poikilocytosis, and neutrophils with 6 to 8 nuclear lobulations.
Which one of the following is most likely cause of this patient's anemia?
(A) Beta-thalassemia trait
(B) Folate deficiency
(C) Iron deficiency
(D) Sickle cell trait
(E) vitamin B12 deficiency

Q4: A 4 year old girl is brought to her pediatrician for a check up. The child's skin is slightly jaundiced, and she has mild splenomegaly. Her hemoglobin and hematocrit are reduced. Her mean corpuscular volume(MCV) is 90 μm3 and her reticulocyte count is 7%、A Coombs test is performed and is negative. A hemoglobin electrophoresis shows an abnormal component, constituting less than 25% of the total. A blood smear shows inclusion bodies within the RBCs
Which of the following is tine most likely diagnosis?
(A) Beta thalassemia
(B) Heinz body anemia
(C) Hereditary spherocytosis
(D) Pernicious anemia
(E) Sickle cell anemia

Answers: 1.C, 2.C, 3.E, 4.B

Thank you

If you have any question please contact with us at:
Internalmedicineteam434@gmail.com