

HEMATOLOGY

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SHORT ANSWER QUESTIONS

1. What are different types/causes of anaemia?
2. Management of iron deficiency anemia.
3. Hemolytic Anemia.
4. Sickle cell anemia.

Answer any one of the above.....

Approach to Anemia

OUTLINE

- INTRODUCTION
- HOW TO APPROACH A PATIENT WITH ANEMIA?
- CLASSIFICATION
- CASES
- SUMMARY
- REFERENCES

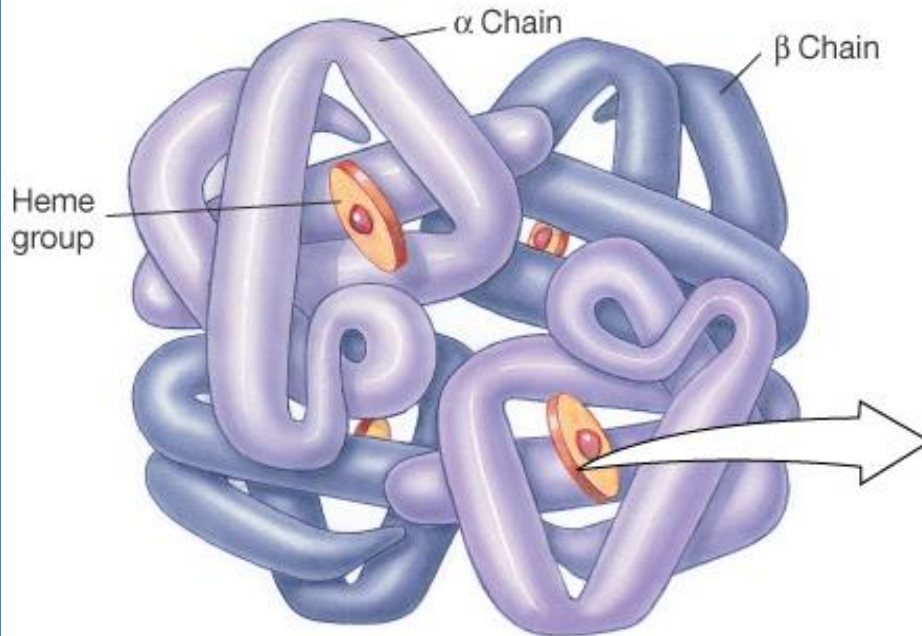
INTRODUCTION

Anemia is defined as Hemoglobin of :

- < 12g/dL in females
- < 14 g/dL in males
- Anemia is one of the most common blood disorders affecting about more than 3 million Americans.
- Though it affects all ages and gender, non- pregnant women are affected the most world wide.
- All anemias cannot be prevented . But the most common anemia worldwide- IDA can definitely be prevented and treated.

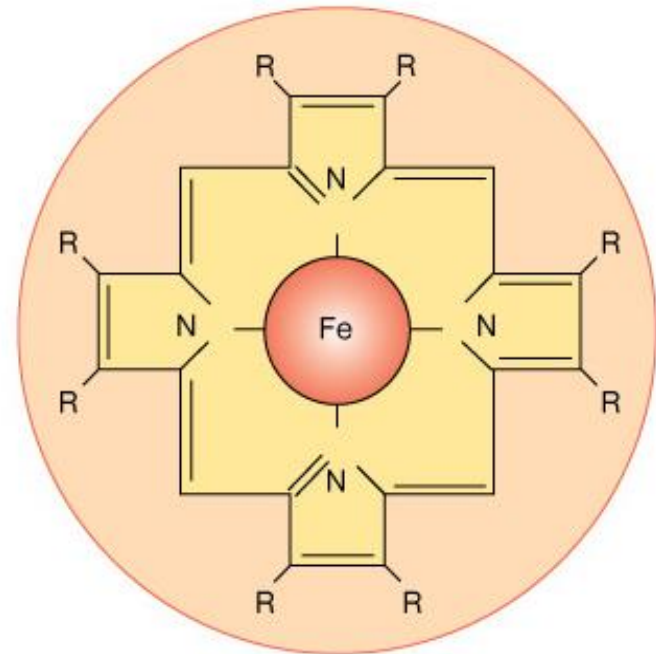
Hemoglobin (Hb)

(a) A hemoglobin molecule is composed of four protein globin chains, each centered around a heme group.



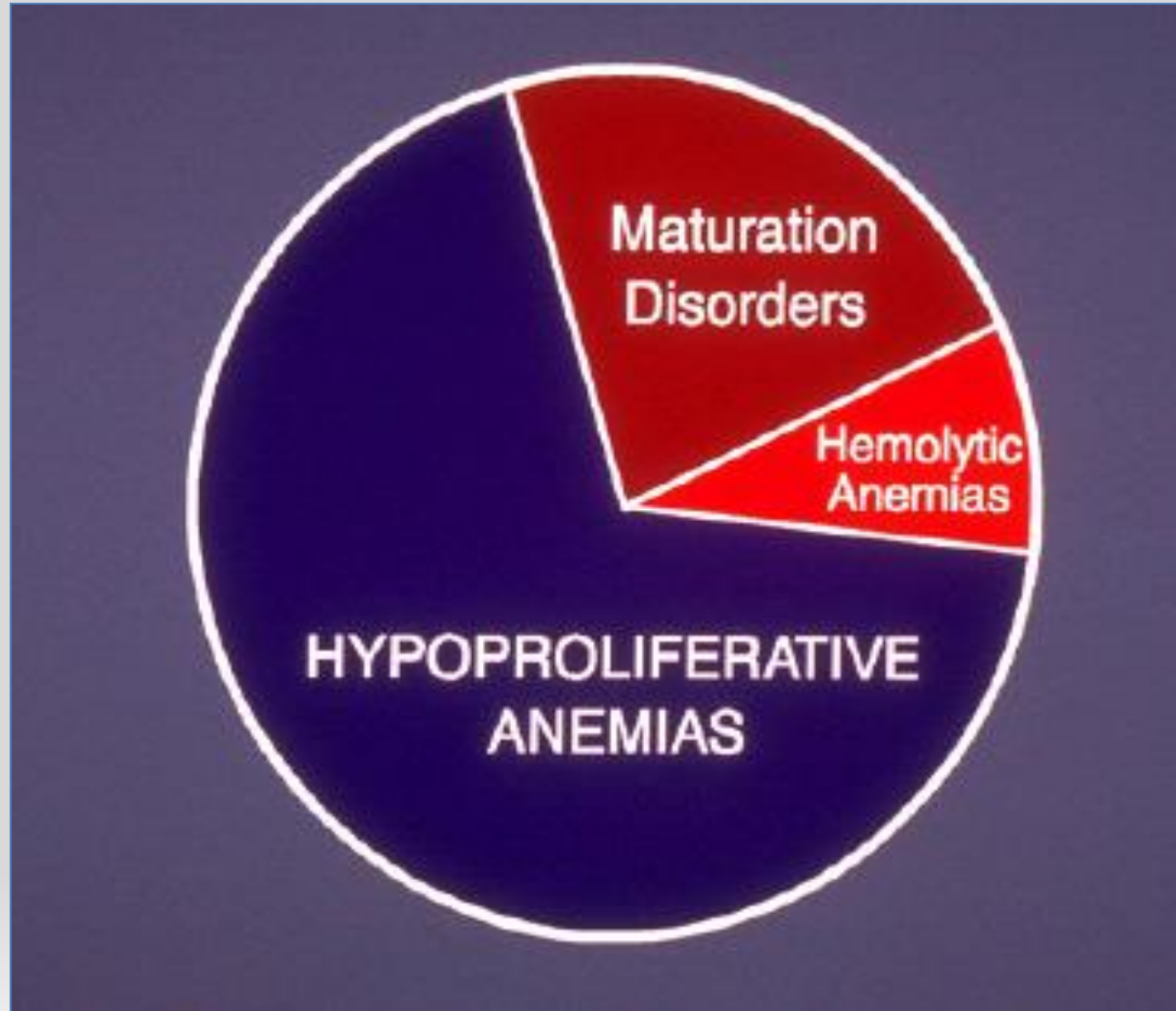
In most adult hemoglobin, there are two alpha chains and two beta chains as shown.

(b) Each heme group consists of a porphyrin ring with an iron atom in the center.



R = additional C, H, O groups

Types of Anaemia



How to Approach a patient with anemia?

History

- Symptoms
- Medical conditions
- Medication Hx
- Family History

Physical Examination

- Signs of anemia
- Signs of renal disease
- Signs of chronic disease
- Hepatomegaly and splenomegaly
- Petichae, bruises, infections

Labs:

- CBC
- Reticulocyte count
- Peripheral Blood smear
- Bilirubin level (Indirect)

Other investigations based on the preliminary results.

The Three Basic Measures

Measurement	Normal	
Range		
A. RBC count	5 million	4 to 6
B. Hemoglobin	15 g%	12 to 17
C. Hematocrit	45	38 to 50

$$A \times 3 = B$$

$B \times 3 = C$ - This is the rule of thumb

Check whether this holds good in given results

If not -indicates micro or macrocytosis or hypochro.

The Three Derived Indices

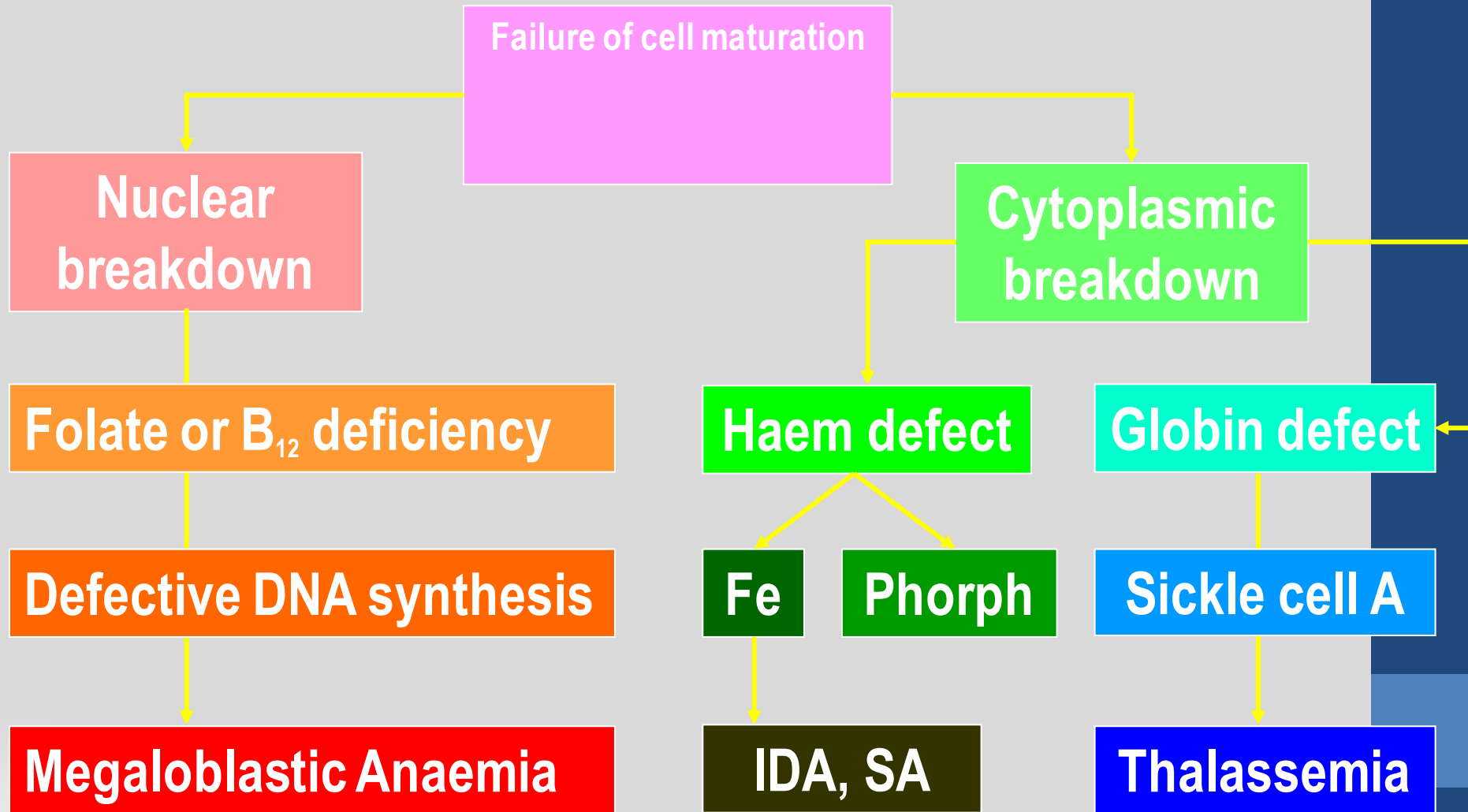
Measurement	Normal Range	
A. RBC count	5 million	4 to 6
B. Hemoglobin	15 g%	12 to 17
C. Hematocrit	45	38 to 50

MCV	$C \div A \times 10$	=	90 fl
MCH	$B \div A \times 10$	=	30 pg
MCHC	$B \div C \times 100$	=	33%

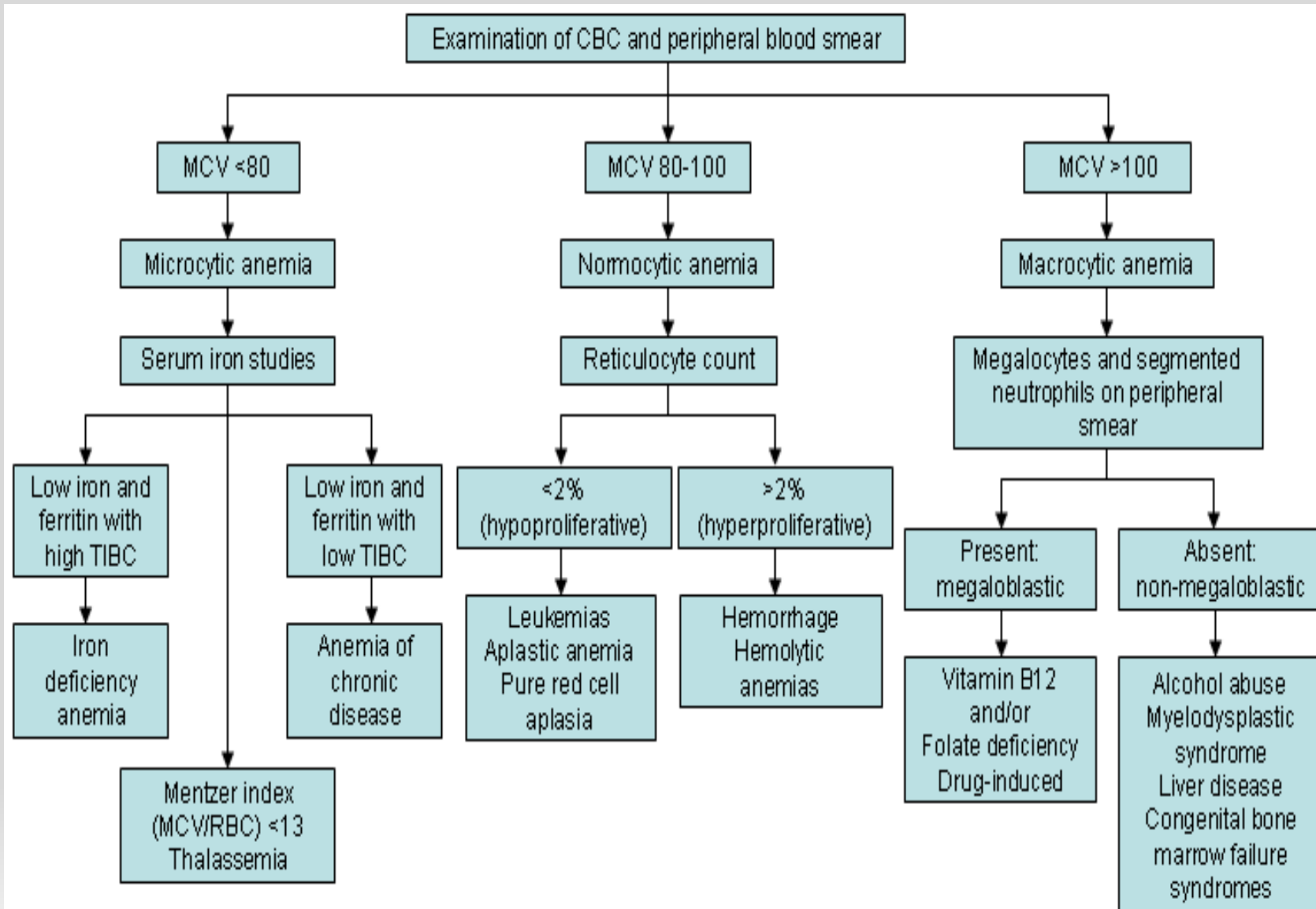
Causes of Anaemia

1. Decreased production of Red Cells
 - Hypo proliferative, marrow failure
2. Increased destruction of Red Cells
 - Hemolysis (decreased survival of RBC)
3. Loss of Red Cells due to bleeding
 - Acute / chronic blood loss (hemorrhagic)

Hypoproliferative Anaemias



CLASSIFICATION



Anaemia

Hb% < 12, Hct < 38%

Decreased Production

Increased Destruction

Hypoproliferative

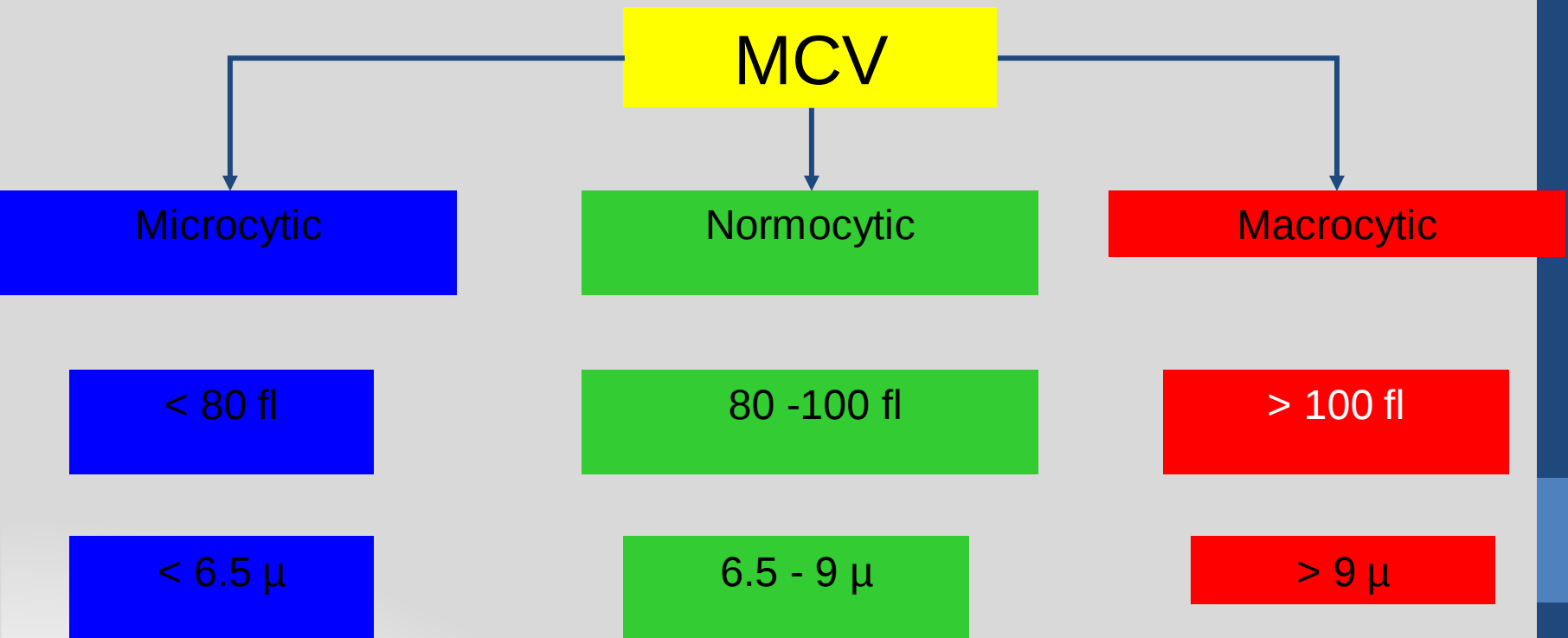
Hemolytic

RPI < 2

RPI > 2

Mean Cell Volume (MCV)

RBC volume (rather) is measured by
The Mean Cell Volume or MCV and RDW



Anaemia – First Test

RETICULOCYTE COUNT %

- ‘RBC to be’ or Apprentice RBC
- Fragments of nuclear material
- RNA strands which stain blue

Normal

Less than 2%

Reticulocyte Production Index

For example the RPI is calculated as follows

Reticulocyte count	9%
Hb content	7.5 g%

1. Correction for Anaemia
 $= 9 \times (7.5 \div 15) = 9 \times 0.5 = 4.5 \%$
2. Correction for increased life span
 $4.5 \div 2 = 2.25 \%$
3. Thus, the RPI is 2.25

Workup – Second Test

The next step is ‘What is the size of RBC’ ?

MCV indicates the Red cell volume (size)

Both the MCH & MCHC tell Hb content of RBC

If the RPI is 2 or less

We are dealing with either

- Hypoproliferative anaemia (lack of raw material)

- Maturation defect with less production

- Bone marrow suppression (primary/ secondary)

Anaemia Workup - MCV

MCV

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graph TD; MCV[MCV] --> Microcytic[Microcytic]; MCV --> Normocytic[Normocytic]; MCV --> Macrocytic[Macrocytic];
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Microcytic

Iron Deficiency IDA
Chronic Infections
Thalassemias
Hemoglobinopathies
Sideroblastic Anemia

Normocytic

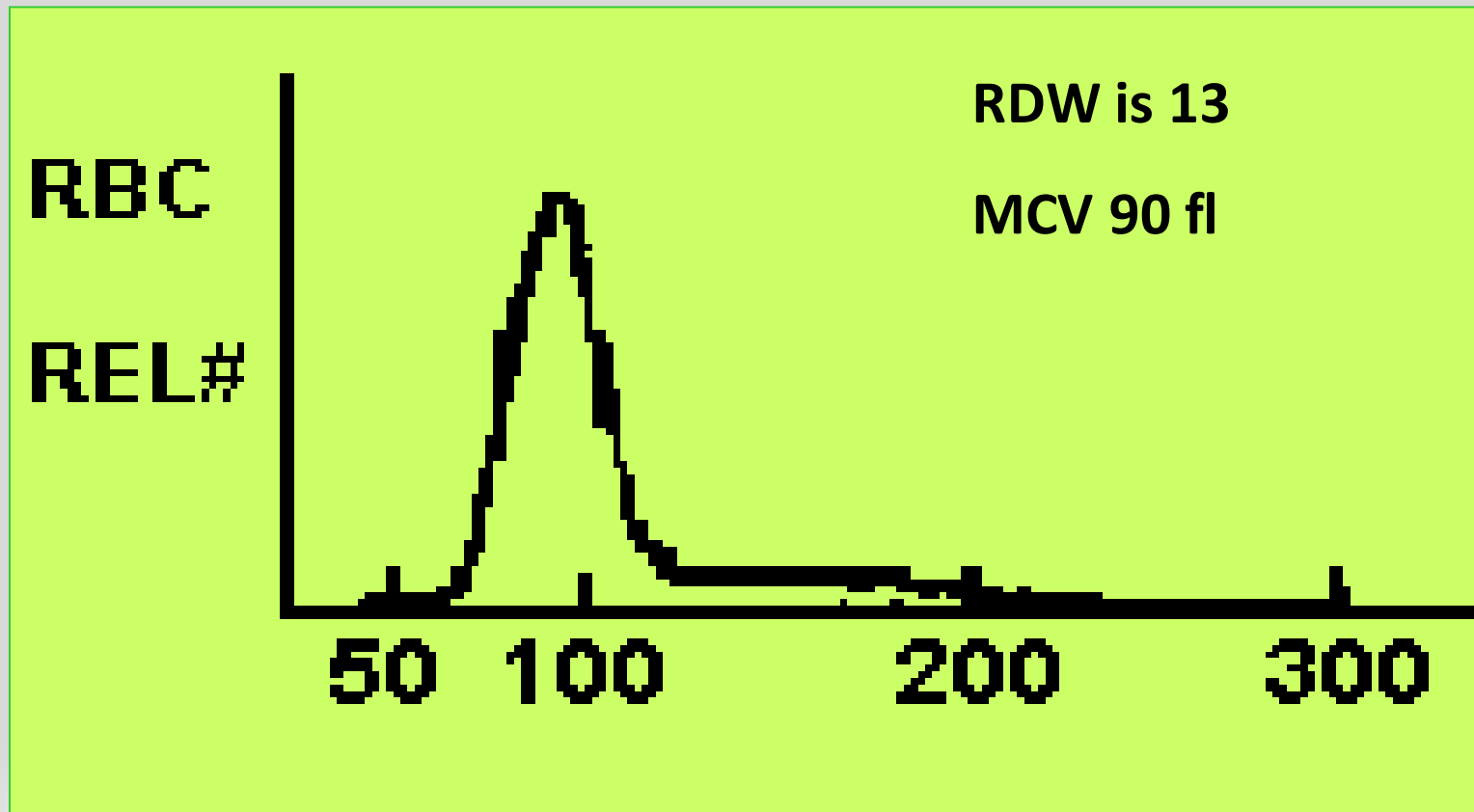
Chronic disease
Early IDA
Hemoglobinopathies
Primary marrow disorders
Combined deficiencies
Increased destruction

Macrocytic

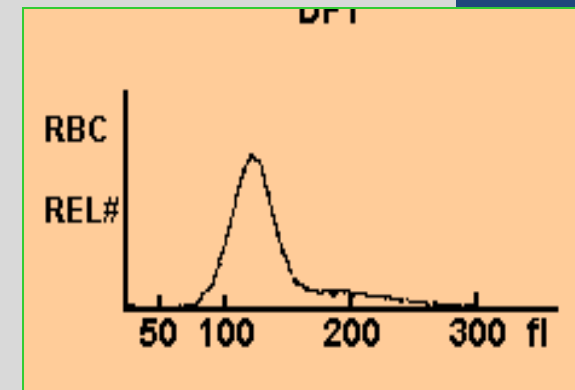
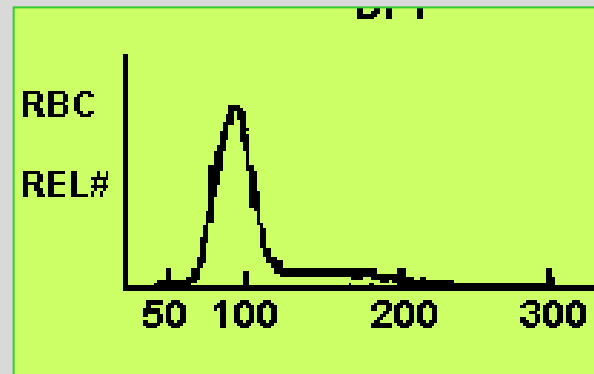
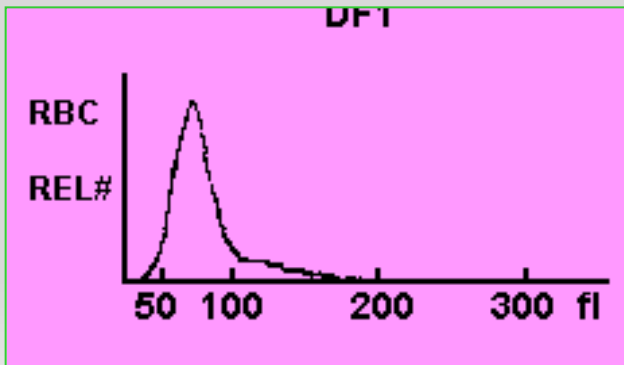
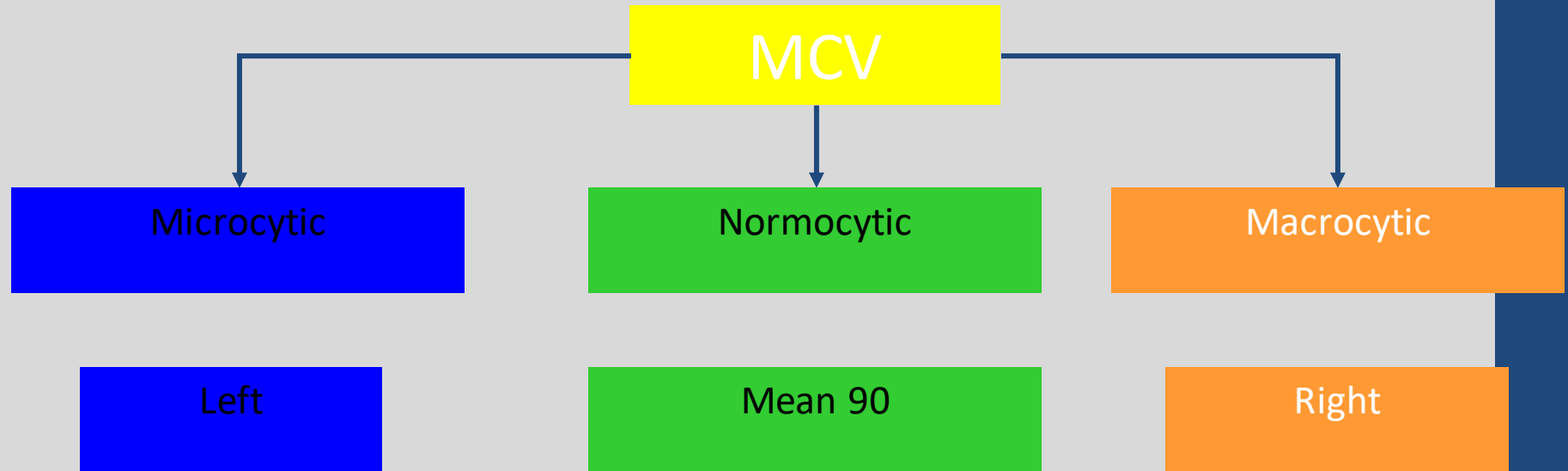
Megaloblastic
anemias
Liver disease/alcohol
Hemoglobinopathies
Metabolic disorders
Marrow disorders
Increased destruction

Anaemia Workup – 3rd Test

Red cell Distribution Width – RDW



Red cell Distribution Width - RDW



Anaemia Workup - 4th Test

Peripheral Smear Study

Are all RBC of the same size ?

Are all RBC of the same normal discoid shape ?

How is the colour (Hb content) saturation ?

Are all the RBC of same colour/ multi coloured ?

Are there any RBC inclusions ?

Are intra RBC there any hemo-parasites ?

Are leucocytes normal in number and D.C ?

Is platelet distribution adequate ?

CASE 1

- A 12 year old white female came to the physician complaining of weakness, lethargy and inability to do work for the past 2 month. Upon questioning she revealed that she just had her first menstrual cycle (menarche) last month and it lasted for 20 days. Also this month she is having heavy periods. Today is her 15th day . She has breathlessness and palpitations while climbing stairs. Also she had episodes of dizziness but no fainting. Family hx is positive for menorrhagia.
- Vitals: BP= 110/ 74; HR= 115; RR= 16; T= 36.8
- Examination showed overall pallor, pale nail bed , pale conjunctiva and pale gums. No yellow discoloration of the sclera or skin.
- CVS= Heart murmur II/VI.
- Respiratory – Normal breath sound
- Abdomen- Soft lax and non- tender.
- Pelvic- Normal

What is the next step?

CASE 1

CBC:

WBC- 6000

Hb- 5g/dl

RBC count: 3 million/
mm³ Hct= 18%

MCV- 56 fl

MCH- 20 pg

MCHC- 26 g/dl Platelet-
200,000/mm

Reticulocyte-8%

What do you infer from
here?

**Microcytic Hypochromic
Anemia**

What additional tests you
want to do?

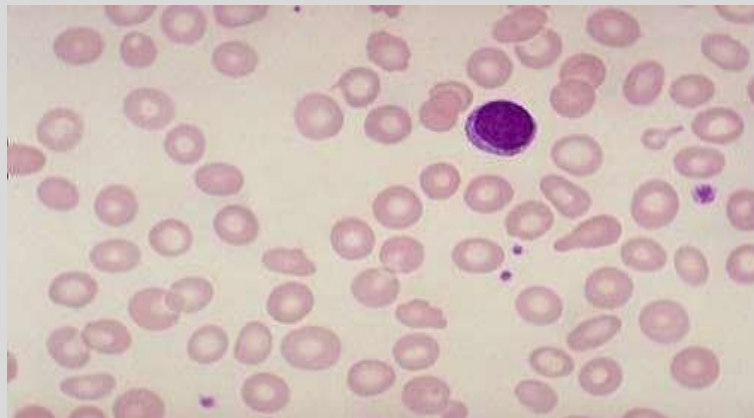
Serum Iron- 30mcg/dL

TIBC- 450

Ferritin-9 ng/ml Transferrin
saturation- 7%

What kind of anemia is this?

Iron Deficiency Anemia



CASE1

- **How will you manage the patient?**
 - Admit the patient
 - Blood typing and cross match
 - Packed RBCs transfusion
 - IV tranexamic acid
 - Upon Discharge prescribe iron supplements-Ferrous sulphate/
ferrous fumarate.
 - referral for gynecology for further management of the underlying cause
- **What is the most likely cause of menorrhagia in this age group?**

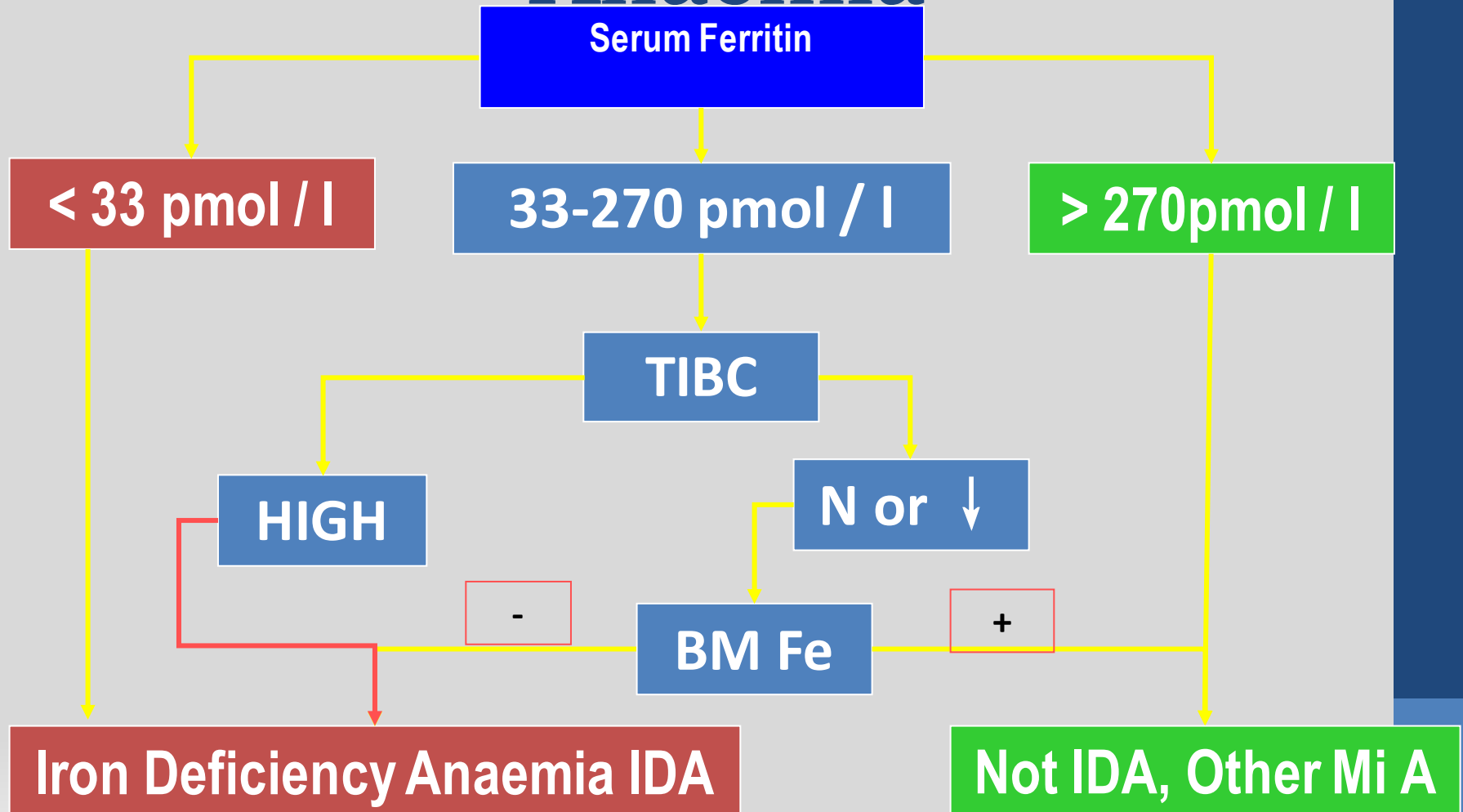
IDA

- Most common type of anemia worldwide.
- **Causes:**
 - Blood loss- overt/ occult
 - Decreased Iron absorption- Celiac disease, atrophic gastritis, H.pylori gastritis
 - Gastric Bypass surgery

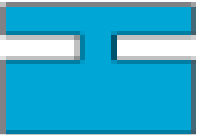
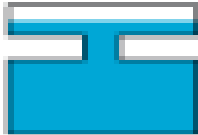
Clinical Presentation- weakness, headache, irritability, fatigue, exercise intolerance and pica

Diagnosis- Microcytic hypochromic anemia with high RDW, low serum Iron, Low ferritin, low transferrin saturation and High TBC

Microcytic Hypochromic Anaemia



IDA – Special Tests

	Normal	Negative iron balance	Iron-deficient erythropoiesis	Iron-deficiency anemia
Iron stores				
Erythron iron				
Iron related tests	Normal	IDA		
Serum Ferritin (pmo/L)	33-270	< 33		
TIBC (µg/dL)	300-340	> 400		
Serum Iron (µg/dL)	50-150	< 30		
Saturation %	30-50	< 10		
Bone marrow Iron	++	Absent		

Microcytic Anaemias

MCV < 80 fl	Serum Iron	TIBC	BM Perls stain
Iron Def. Anemia	↓ ↓	↑ ↑	0
Chronic Infection	↓ ↓	↓ ↓	+ +
Thalassemia	↑ ↑	N	+ + + +
Hemoglobinopathy	N	N	+ +
Lead poisoning	N	N	+ +
Sideroblastic	↑ ↑	N	+ + + +

IDA

- **Treatment**
- Oral Iron Therapy
 - The recommended dose for IDA in adults is 150-200mg/day.
 - Three forms are available:
 - Ferrous fumarate- 106 mg of elemental Iron/tablet
 - Ferrous Sulfate- 65mg of EI/tablet
 - Ferrous gluconate- 28- 36mg of EI/ tablet
- Parental Iron therapy
 - Indication-Excessive bleeding, IBD, CKD, Cancer patient or unable tolerate orally.
 - Ferric gluconate 125 mg diluted in 100ml of isotonic saline over 30-60 minutes
 - **Total iron deficit = Body weight [kg] x (Target Hb – Actual Hb) [g/l] x 2.4 + Iron stores [mg]**
 - 500 mg iron for iron stores
- Blood Transfusion
 - Hemodynamically unstable
 - Evidence of end-organ damage due to ischemia
 - In HF patient

CASE 2

- A 19 year old male presented to the clinic in tertiary care due to fatigue, abdominal pain, joint pain and a general feeling of being unwell since 2-3 months. He says that he was diagnosed to have a blood disorder at the age of 1 year. Since then he has received several blood transfusion.
- Upon examination, he is a thin built with relatively short stature
,sitting comfortably, not in distress. He is vitally stable.
- General Exam showed pallor, hyperpigmentation of the skin and yellowish discoloration of the sclera
- Head and neck examination reveal depressed cranial vault, frontal bossing, maxillary expansion and exposure of upper teeth.
- Abdominal examination shows hepatomegaly and splenomegaly

CASE 2

CBC:

- Hb- 8.4 g/dL
- MCV- 90.1 fl/
- WBC-11.6x 10⁹/L
- Platelets- 161x 10⁶/L

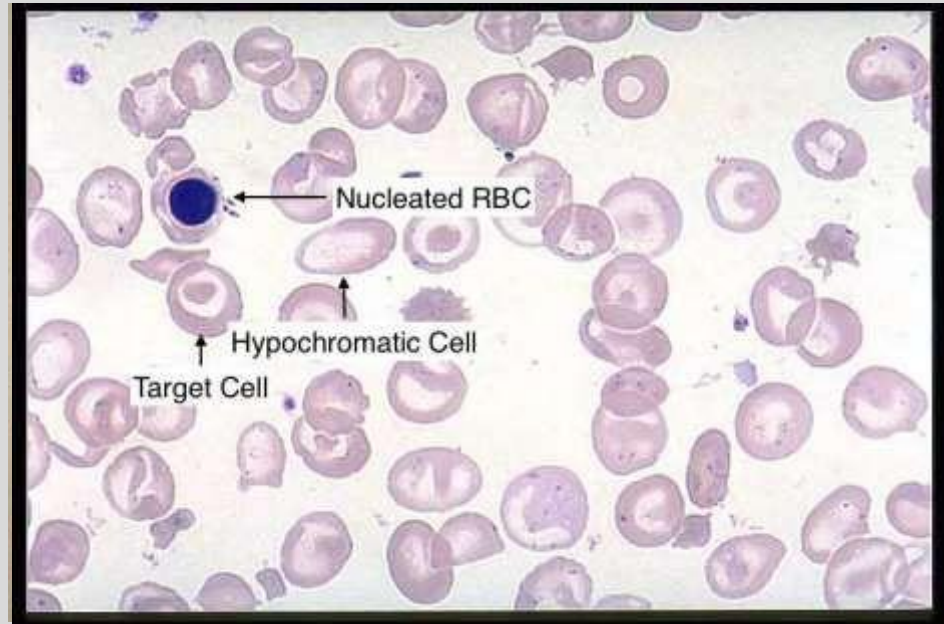
Reticulocytes- 5%

PBS- microcytic, hypochromic, polychromasia, nucleated RBCs target cells, poikilocytosis and anisocytosis

Bilirubin (Indirect)-1.9

What is the additional test that will help you to reach diagnosis?

Hb Electrophoresis- HbA- 87.5%; Hb A2-2.2%; Hb F- 10.3%



CASE 2

What is diagnosis?

Beta-thalassemia (Major) What

other tests would you do? Iron

Studies:

- Serum Iron-219 mcg/dL
- Ferritin-1000ng/ml
- TIBC- 250mcg/dL

LFTs:

- ALT- 90 U/L
- AST- 75 U/L

What do you infer from above tests?

Iron overload

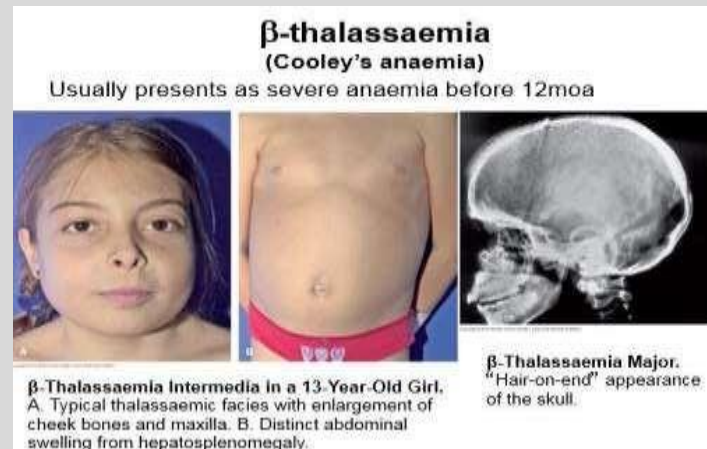
Case 2

How to manage this patient?

- Admit the patient
- Packed RBC transfusion
- Chelation therapy- deferoxamine
- Also do cardiac and liver MRI.
- Other investigations: TSH, LH, FSH, testosterone, FBS, HbA1c

B-THALASSEMIA

- Thalassemia results when mutations affecting the genes involved in Hb biosynthesis lead to decreased Hb production
- Beta thalassemia is a common blood disorder world wide
- **Clinical presentation:** fatigue, weakness, palpitation, short stature, frontal bossing maxillary expansion, abnormal teeth, hepatomegaly, splenomegaly etc.
- If Iron overload: joint pain, abdominal pain, bronze skin, palpitations, depression.



Hair on end - Thalassemia Major



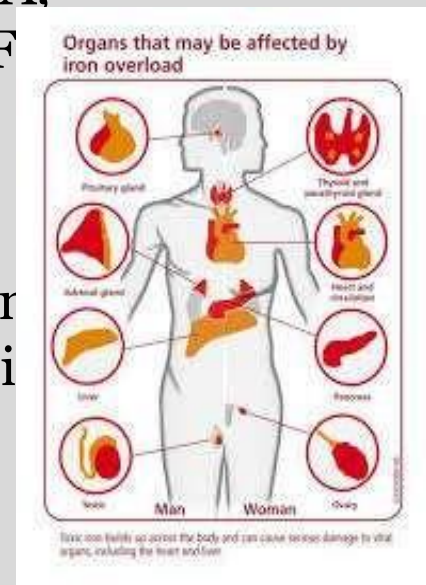
B- THALASSEMIA

- **Diagnosis:**

- Microcytic hypochromic anemia.
- Peripheral blood film shows- microcytosis, hypochromia, polychromasia, target cells and nucleated RBCs
- .Hb Electrophoresis- decreased amount of hbA, variable amount of Hb A2 and increased HbF

- **Complications-**

- Iron overload (cirrhosis, cardiomyopathy),
- Endocrinopathies,
- Cortical destruction and impaired bone function
- Arterial venous thromboembolism



B- THALASSEMIA

Management:

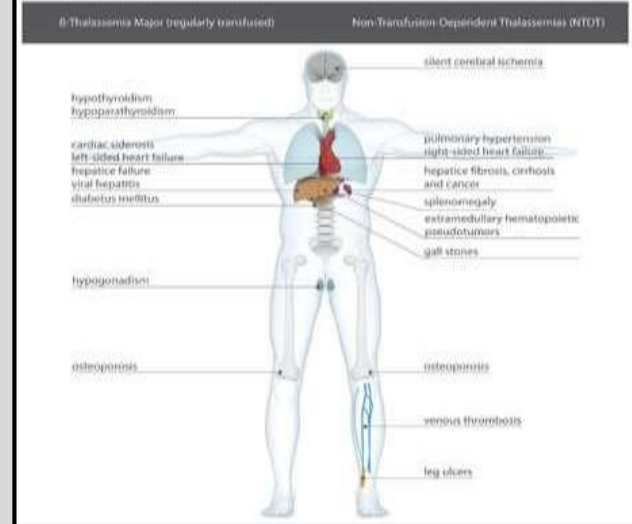
• Transfusion:

- Chronic transfusion has become the accepted regimen for BTM patients in order to maintain a Hb of 9-10 g/dL
- The usual transfusion regimen involves infusion of one to three

units of packed red cells every three to five weeks.

• Chelation therapy:

- Initiated usually after 20-25 unit of transfusion.
- Current regimens for DFO treatment in transfusion-dependent beta thalassemia call for a nightly 10 to 12 hour continuous subcutaneous infusion of about 2 g of DFO using a small battery-driven pump.



B- THALASSEMIA

- Endocrine therapy:
 - Administration of deficient hormones (sex and thyroid hormones)
 - Treatment of Diabetes
 - Use of fertility agent
- Supportive care- cardiac monitoring, monitoring for osteoporosis and osteopenia, folic acid , zinc replacement etc.
- Splenectomy: Indicated in patients with beta-thalassemia major and intermedia requiring an increase of 50 percent or more in the red cell transfusion over a one-year
- HCT- definitive treatment for appropriately selected patients

CASE 3

- An 25 year old man comes to the clinic for evaluation of weakness and fatigue lasting for 6 weeks. Before the past 6 weeks he reports being fairly healthy. He did however had a recent case of 'flu'. On reviewing his medical records it seems that approximately two months ago patient had a mild hepatitis (serology for Hep A, B & C were negative). Before this illness, he has been healthy, takes no medication and has no family history of any disease. No history of blood transfusion
- He does not smoke or use illicit drugs and is sexually inactive.
- Physical examination revealed marked pallor and a 2/6 non-radiating systolic murmur heard best at the right upper sternal border. Abdominal examination reveals few scattered petichae but no hepato splenomegaly.

CASE 3

Labs:

- Hb-5.0g /dL
- Hct= 15 %
- WBC- 4000
- Differentials normal
- Reticulocytes- 0.5%

What do you infer from the results?

Pancytopenia

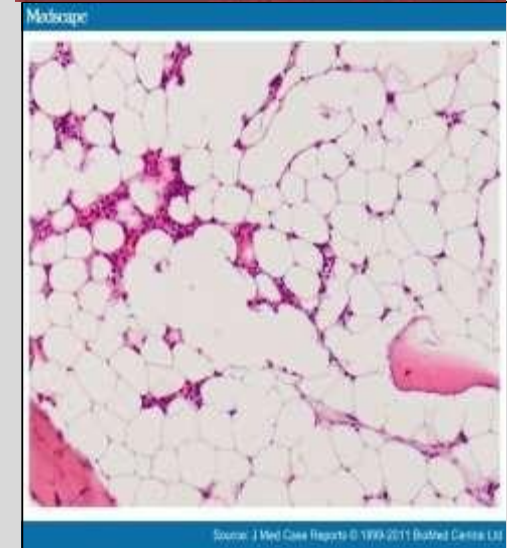
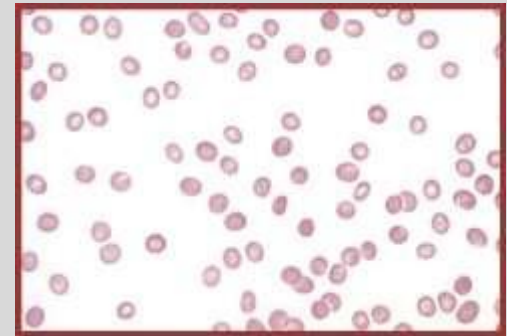
- Other chemistries and liver function was normal.

- What is the next most important test you would do? **BMB**

Bone marrow biopsy- It showed cellularity of < 5% with normal cellular morphology and no organism on gram stain.

- **Diagnosis:** **Aplastic Anemia**

PBS



Source: J Med Case Reports © 1999-2011 StatSoft Central Ltd

APLASTIC ANEMIA

- Aplastic anemia is characterized by diminished or absent hematopoietic precursors in the bone marrow, most often due to injury to the pluripotent stem cell.
- **Causes**- drugs (antiepileptic drugs, nifedipine), viral infections (hepatitis), radiation
- **Clinical presentation**: fatigue, dizziness, palpitations, infections, fever, petechiae, pallor, easy bruising, menorrhagia, etc.
- **Lab findings**: pancytopenia, low reticulocyte count, reduced cellular elements (morphologically normal). Bone marrow biopsy shows decreased cellularity

APLASTIC ANEMIA

- **Management:**

- Withdrawal of the potentially offending agent.
- Supportive Care (transfusion, Antibiotics/ Antiviral)
- For patients under age of 20 years allogenic HCT is the treatment of choice.
- For patients between 20-45 if the patient is healthy and has a full HLA- matched sibling donor, the Allogenic HCT is the choice.
- Over 45 years Immunosuppressive therapy with combined use of anti-thymocyte globulin, cyclosporine , and corticosteroids, without granulocyte-colony stimulating factor, is recommended
- In older adults, treatment should be provided based upon age and comorbidities present

CASE 4

- A 15 year old African- American presented to the ER with acute onset of Left hemiparesis that started 3 hours ago. The patient has no history of thromboembolic disease, no family history of venous or arterial thrombosis, and no atherosclerotic risk factors for stroke.
- But he says he has a blood disease where he gets frequent pains in legs, joints, chest and needs to come to hospital for IV pain medication.
- Physical Exam shows scleral jaundice, no splenomegaly

CASE 4

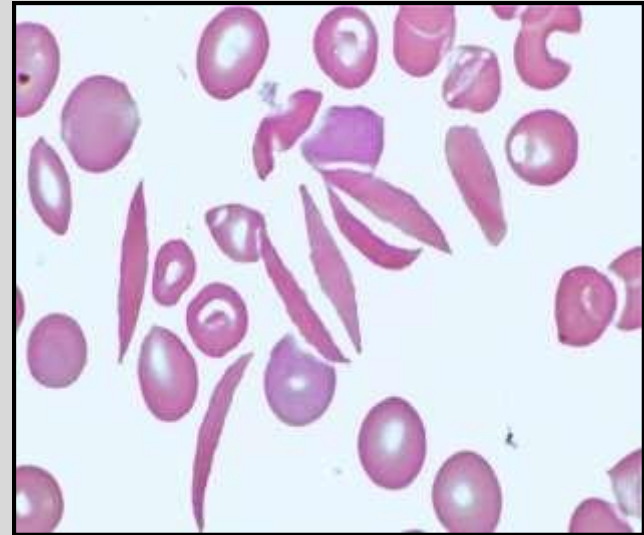
CBC-

- Hb- 8.0g/dL
- MCV- 82.3
- WBC- 9800/mm³
- ANC- 8500
- Platelets- 465000/mm³

Reticulocyte- 7%

Indirect Bilirubin- 84mg/dL

PBS- Numerous Sick cell



Non- contrast CT brain showed acute RT MCA infarct

What is the most likely diagnosis? Sick Cell Crisis

CASE 4

- **How to manage this patient?**
 - Admit the patient
 - Pain medication- opioid
 - Good hydration
 - Red Cell exchange transfusion
 - Hydroxyurea

SICKLE CELL ANEMIA

- AR disease where there is a substitution of valine for glutamic acid in the beta globin chain of Hb which produces Hb tetramer which poorly soluble when deoxygenated.

• Clinical presentation- jaundice and painful episodes, ~~delayed~~ growth and puberty, neurocognitive impairment, osteonecrosis, infections.

• Laboratory findings- Mild to moderate anemia, reticulocytosis, unconjugated hyperbilirubinemia, increased level of LDH and decreased level of Haptoglobin. Peripheral Blood Smear reveal normocytic normochromic red cells sickled red cells, polychromasia and Howell jolly bodies reflecting asplenia.

SICKLECELL ANEMIA

Management:

- Routine Evaluation
- Hydroxyurea
- Pain management with analgesics
- Prophylactic Antibiotics
- Appropriate immunization
- Blood transfusion

Sickle Cell Anaemia



CASE 5

- A 35 year old man being treated with phenytoin for epilepsy comes to the physician for routine check-up examination. He has been seizure free for the past 3 years. Physical exam reveals pallor of the skin and mucosa and slight jaundiced discoloration of the sclera and a red and a shiny tongue. He denies paresthesia and sensation is normal on neurological exam.

CASE 5

- **CBC**

- Hb- 8.5g/dL
- Hct= 28%
- MCV= 130fl
- MCH- 35
- WBC- 4800/mm³
- Platelets- 140,000/mm³
- Reticulocyte- 0.2%

Bilirubin

Total- 2.0mg/dL

Direct- 0.3 mg/dL

- **Peripheral Blood Smear**

- Macrocytes, ovalocytes and hypersegmented neutrophil

LDH- 600U/L

Additional test:

Folate level- 1ng/ml (2-20ng/ml)

Vitamin	B12	level-
300pg/ml		(200pg-
500pg/ml)		

Most likely Diagnosis?

Folate Deficiency Anemia

VITAMIN B₁₂ AND FOLATE DEFICIENCY

Vitamin B₁₂ deficiency

- Takes years to develop
- Neurological

Symptoms are present- ataxia, paresthesia loss of

Lab Findings: macrovalocytic anemia, elevated level of iron, indirect bilirubin and LDH and low level of haptoglobins

PBS: macrovalocytes, occasional megaloblasts and hypersegmented neutrophil

Folate deficiency

- Take months to develop
- No neurological deficits.

How to differentiate between Folate and Vitamin B₁₂ deficiency? Assays of serum or red cell folate, serum B₁₂, methylmalonate, and homocysteine

VITAMIN B₁₂ AND FOLATE DEFICIENCY

Treatment:

• Folate Deficiency Anemia

- Folate deficiency is treated with folic acid (1 to 5 mg/day orally) for one to four months, or until complete hematologic recovery occurs.

• Vitamin B₁₂ Deficiency Anemia

- Parenteral Cobalamin is given to patient with Pernicious Anemia.
- The recommended dose is 1000mcg to 2000mcg I/M

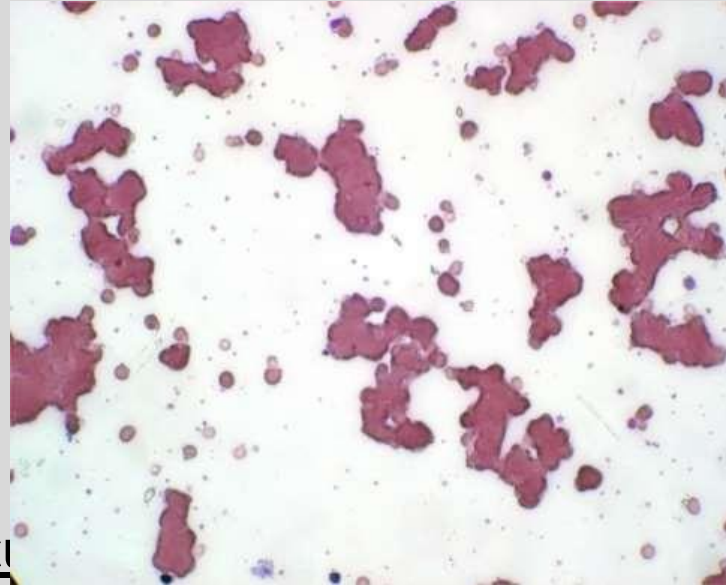
CASE 6

- A 12 year old girl presented to the Emergency Department with fever (38.6 C) headache, abdominal pain, vomiting and yellowish discoloration of eyes of 5 days duration.
- Physical examination revealed marked pallor, fever, tachycardia, tachypnea and icterus. There was no lymphadenopathy, edema, rash, petichae or bruises. Cardio vascular examination revealed a 3/6 systolic murmur along the left sternal border. A non tender soft hepatomegaly with a span of 14 cm and a soft spleen 3 cm below the left costal margin was noted. Lung fields were clear and neurological examination was normal.

CASE 6

CBC

- WBC- 9000/mm³
- Hb- 3g/dL
- MCV- 128 fl
- MCH- 50.9pg
- MCHC- 39.7g/dL
- Platelets- 170,000/mm³ Retic 4.5mg/dL Indirect Bilirubin- 3.2 mg/dL



PBS- Agglutination of RBCs was noted that separated on warming.

Smear showed anisopikilocytosis with predominant macrocytes, hypochromia and nucleated red blood cells.

CASE 6

- LFT & Urinalysis were normal.

What is the next important test to be done?

DAT-strongly positive

Most likely Diagnosis?

Auto Immune Hemolytic Anemia

How to manage this patient?

- Admit the patient
- 2 units Packed RBC transfusion
- IV prednisolone 2mg/kg/day
- IV ceftriaxone

AUTOIMMUNE HEMOLYTIC ANEMIA

- Hemolytic anemias which results from the development of auto antibodies directed against antigens on the surface of patient's own red blood cells.
- Causes- associated with infections, malignancy and other autoimmune disease
- Clinical manifestation- anemia, jaundice, splenomegaly
- Diagnosis: Reticulocytosis, raised serum bilirubin and positive DAT. The presence of agglutination at $T < 37^{\circ}\text{C}$ suggest cold autoantibodies. Monospecific DAT will help to differentiate between warm and cold antibodies

AUTOIMMUNE HEMOLYTIC ANEMIA

Treatment:

- Transfusion of red cell if Hb is considerably low. It is complicated because of cross matching problems and rapid in vivo destruction of transfused cells due to the presence of auto antibodies
- Corticosteroid is the main stay of therapy for warm AIHA.
- Immunosuppressive agent including monoclonal Anti-CD20 (Rituximab) proves useful in CAD and refractory warm AIHA.
- Splenectomy benefit in refractory cases of warm AIHA.

Tests Used to Diagnose Hemolysis

1. Reticulocyte count
2. Combined with serial Hb
3. Serum LDH
4. Serum bilirubin
5. Haptoglobin
6. Urine hemosiderin
7. Hemoglobinuria

Findings in Hemolytic Anaemia

Reticulocyte count and RPI	Increased
Serum Unconjugated Bilirubin	Increased
Serum LDH 1: LDH 2	Increased
Serum Haptoglobin	Decreased
Urine Hemoglobin	Present
Urine Hemosiderin	Present
Urine Urobilinogen	Increased
Cr ⁵¹ labeled RBC life span	Decreased

Tests to define the cause of hemolysis

1. Hemoglobin electrophoresis
2. Hemoglobin A₂ (βeta-Thalassemia trait)
3. RBC enzymes (G6PD, PK, etc)
4. Direct & indirect antiglobulin tests (immune)
5. Cold agglutinins
6. Osmotic fragility (spherocytosis)
7. Acid hemolysis test (PNH)
8. Clotting profile (DIC)

CASE 7

- A 50 year old man comes to the physician because of gingival bleeding, epistaxis and fever for 2 days. He appears acutely ill.
- His temperature is 39 C, BP- 120/70, HR- 120/min and respiration of 22 /min. Bilateral rhonchi is heard on chest auscultation. He is admitted for further evaluation
- Chest x- ray shows bibasilar infiltrates consistent with bronchopneumonia.
- CBC:
 - WBC- 16,900 (numerous blasts)
 - Hb-7.5 g/dL
 - Platelets- 15000/mm³

CASE 7

What will you do next?

- **Bone Marrow Biopsy**- It shows hypercellular bone marrow with 35% blasts.
- Elongated cytoplasmic inclusion could be appreciated in peripheral and marrow blast

What is the diagnosis?

- **AML**

Treatment :

- Induction and consolidation Chemotherapy



TO REMEMBER...

- Anemia is rather a presentation of an underlying condition
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- Anemia due to nutritional deficiencies are common. Early detection is important to prevent permanent neurological deficits.
- CBC , reticulocyte count, PBS, Indirect Bilirubin level are preliminary test in diagnosis of anemia.
- Low Hb with high reticulocyte count indicates normal functioning bone marrow
- Low Hb with normal or low reticulocyte suggests bone marrow failure
- Pancytopenia represent either bone marrow dysfunction or hypersplenism.

TO REMEMBER...

- Jaundice, high indirect bilirubin, presence of schistocytes, increased LDH is suggestive of hemolysis
- Presence of blast cell in the peripheral blood smear point towards malignancy
- Always aim to stabilize the patient first, before investigating for cause of anemia.
- $Hb < 7g/dL$ or patient with acute blood loss and symptomatic is indication for transfusion.
- While diagnosing IDA, GI causes and bleeding disorder should be always kept in mind.
- In patient receiving chronic transfusion, ferritin and iron level should be monitored along with careful observation of signs and symptoms of iron overload.

Anaemia Diagnosis - Algorithm

