

APPROACH TO ANEMIA IN CHILDREN

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DEFINITION

- Anemia is defined as reduction in the blood Hb 2 standard deviations below the mean for the normal population with respect to age, gender.
- Anemia refers to reduction in oxygen carrying capacity of observed by decreased Hb leading to Tissue hypoxia.
- Decreased production and increased breakdown of RBC can lead to anemia.

Pointers towards Anemia

- Growth retardation
- Exercise intolerance
- Behaviour changes
- Child will be irritable, restless, have breath holding spells and temper tantrums.

WHO cut-off values for diagnosis of Anemia

Age	Hb (g/dl)
Newborn	13-14
3 months	9
6-14 yrs	<12
Adult male	<14
Female (non pregnant)	<12
Female (pregnant)	<11

Approach to anemia

3 basic questions

- Is the child anemic?
- How severe the anemia is?
- What is cause and type of anemia?

How severe is the anemia?

- It is important to quickly assess the patient's clinical condition.
- If the patient is severely pale and sick looking, has tachycardia, raised JVP and tender hepatomegaly, it is suggestive of congestive cardiac failure
- Such a patient needs immediate attention and prompt treatment including diuretics, restricted fluids, oxygen support and packed cell transfusion.
- One should not waste time in lengthy diagnostic tests and do as minimum tests as required. Even removing too much blood for various tests can be hazardous as it can precipitate cardiac failure.

Severe Anemia

Hb < 7 gr/dL

- The clinical condition of the patient depends not only on the severity of anemia but also on the rate of drop of Hb.
- A child with 5 g% Hb, when it develops slowly like in iron deficiency, may be comfortable and come by walking whereas, if it develops acutely due to G6PD deficiency, the child may be brought in a collapsed state.

What is the type and cause of anemia?

- Etiological classification
- Morphological classification based on findings of red cell size and indices.
- Anemia can be caused due to
 1. Blood loss
 2. Decreased production of RBC
 3. Increased destruction of RBC
- Detailed h/o, physical examination, lab tests required to know the cause and type of anemia

Clinical approach to anemia

1. Age

- Neonate: neonatal blood loss, fetomaternal hemorrhage, hemolytic disorder.
- Childhood :

6m-3yrs: Nutritional anemia

2. Sex

X-linked diseases will be seen in male

- G6PD deficiency , Only males are affected.
- There will be similar history in male siblings, maternal male cousins, uncles and maternal grandfather.
- In adolescent age, anemia is more common in females due to nutritional deficiency or as a result of menstrual blood loss

3. Family history

- All hemoglobinopathies and **thalassemia syndromes** are inherited in autosomal recessive manner.
- **Spherocytosis** is inherited as autosomal dominant condition.

- **Pica** is both an effect and a cause of iron deficiency besides being seen in lead poisoning.
- Eating clay or mud (geophagia), ice (phagophagia), starch (amylophagia), paper, cloth, raw cereals, paint flakes, etc. is commonly seen in iron deficiency.
- Megaloblastic anemia due to folate deficiency is common in those villagers who consume a lot of goat milk.

5. Drug history

Drugs	Leads to
Salicylates, NSAID, chloramphenicol, analgesics group	Decreased production due to hypoplasia of bone marrow
Penicillins, cephalosporins, alpha methyl dopa	Increased destruction
Sulphadiazine, nitrofurantoin, primaquine, quinidine	Hemolysis
Phenytoin, folate antagonists	Megaloblastic anemia

Physical Examination

- Pulse, blood pressure and respiratory rate should be recorded.
- Look for puffiness, edema, sacral edema, jugulovenous pulse, hepatic tenderness, hepatojugular reflux and basal crepitations.
- Hypertension may be seen in anemia due to renal diseases.

B. Facies:

- Hemolytic facies will have frontal and parietal bossing, large head, depressed bridge of nose, malar prominence, irregular maxillary teeth.
- Diamond Blackfan syndrome will have box like face.
- Hypothyroidism will have typical cretin facies and may be missed unless one looks for it carefully.
- Look for periorbital puffiness which can suggest edema due to anemia, CCF or myxedema.

Eyes:

- Fanconi's anemia will have microcornea.
- Conjunctival vessels tortuosity is seen in sickle cell anemia and so is the presence of retinal hemorrhage or microaneurysms.
- Icterus will suggest hemolytic anemia with indirect hyperbilirubinemia.
- Osteopetrosis patients will develop blindness

Oral cavity: Look for glossitis, angular stomatitis, bald tongue which will suggest nutritional anemia.

E. Nail changes:

- Platynychia, koilonychia, brittle nails are suggestive of iron deficiency. Less common in children than in adults, but when present are pathognomonic of IDA.
- Dyskeratotic nails will be seen in dyskeratosis congenita.

F. Lymphadenopathy:

- Significant lymphadenopathy will suggest tuberculosis, HIV, infectious mononucleosis, leukemia, lymphoma as the cause of anemia.

- ***Hepatosplenomegaly:*** Palpable tender liver with positive hepatojugular reflux is suggestive of CCF.
- ***Significant hepatosplenomegaly*** will suggest tuberculosis, HIV, leukemia, thalassemia, other hemoglobinopathies, lymphoma, myelodysplastic syndrome, malaria, kala azar, disorders as a cause of anemia.
- ***Isolated splenomegaly is*** in favour of enteric fever, malaria, portal hypertension, lymphoma, CML, immune hemolytic anemia, congenital spherocytosis

Bleeding manifestation:

- Presence of bleeding tendencies with petechiae, purpura will suggest thrombocytopenia, which can be seen in benign diseases like ITP.
- In serious diseases like aplastic anemia, malignancies or marrow infiltration.
- Patients with Fanconi's anemia, TAR syndrome, etc. have skeletal malformations like absent radius, absent or bifid thumb, triphalangeal thumb, polydactyly, syndactyly, short stature, microcephaly.
- Look for associated anomalies like mental retardation, skin hyperpigmentation, hypogonadism, renal anomalies in such cases.

Skin changes

- Hyperpigmentation is seen in Fanconi's anemia.
- Icterus is seen in liver diseases as well as hemolytic anemia.
- Non-healing ulcers over lower limbs are seen in any chronic hemolytic anemia especially in HbS.
- Localized DIC like picture with anemia and thrombocytopenia are present in patients with giant cavernous hemangioma as seen in Kasabach-Merrit syndrome.

Laboratory approach to anemia

Screening tests

- CBC, Blood indices (MCV,MCH,MCHC)
- RDW
- Retic count
- Peripheral smear

Reticulocyte count

- It indicates the bone marrow activity.
- increased in hemolytic anemia.
- decreased in bone marrow aplasia or hypoplasia.
- Falsely increased count seen in anemia so reticulocyte index is used.
- $\text{reticulocyte index} = \text{retic count} \times \text{pcv} / 0.45$

Peripheral smear

- It not only suggests the type of anemia but also gives the clue to the underlying disease.

1. RBC Size:

Microcytic cells- smaller than a lymphocyte

Seen in IDA,thalassemia,sideroblastic anemia,
sometimes anemia of chronic disease

Macrocytic Seen in:

- Megaloblastic anemia, hemolysis, hemorrhage, liver disorders, hypoplastic anemia, myelofibrosis.
- In megaloblastic anemia, RBC cell can be hypochromic, oval shaped, and have hypersegmented neutrophils.

Shape of RBC

Table 5 Some peculiar red cell abnormalities on the smear^{1,5}

<i>Morphologic characteristic</i>	<i>Basis of the abnormality</i>	<i>Comment</i>
Howell-Jolly bodies	RBC nuclear remnants	Increased with brisk hemolysis, increased following splenectomy, pernicious anemia, CDA
Basophilic stippling	RNA remnants/ aggregated ribosomes	Impaired globin chain production (thalassemia; lead intoxication), unstable hemoglobinopathies and iron deficiency
Pappenheimer bodies	Iron ferritin granules in cytoplasm	Increased following splenectomy increased with transfusional iron overload
Heinz bodies	Hemoglobin aggregates	Needs brilliant cresyl blue, crystal violet stains. Unstable Hb, enzymopathies, hemoglobin H and thalassemia syndromes
Burr cells	Membrane perturbation	Chronic renal failure, common smear preparation artifact
Acanthocytes (spur cells)	Membrane perturbation	Hepatic insufficiency
Nucleated RBCs	Normoblast nuclei	High with brisk hemolysis present with myelophthisis
Sickle cells	RBC distortion by hemoglobin polymers	Sickle cell disease
Target cells	Low ratio of hemoglobin to red cell membrane; RBC dehydration	Prominent in thalassemia Present with iron deficiency
Spherocytes	Defective membrane protein	Hereditary disorder Immune hemolysis

2. WBC changes

- Leucocytosis can occur in the cases of anemia following hemorrhage, acute hemolysis, megaloblastic anemia, leukemia.

3. Platelets

- Diminished platelet count is seen in hypoplastic anemia and leukemia.

RBC INDICES

- MCV
- MCH
- MCHC
- RDW

Red cell distribution width (RDW)

- It indicates the presence or absence of anisocytosis.
- Expressed in 2 ways
- RDW CV and RDW SD
- Normal value is 12-14
- High RDW indicates presence of anisocytosis
- Normal RDW indicates no anisocytosis.

Bone marrow examination

- It is very useful in diagnosis of aplastic anemia, leukemia, and secondary metastasis.
- Hypercellular bone marrow is seen in hypersplenism, hemolytic syndromes

Other specific investigations for etiological diagnosis

- Serum iron studies
- Serum folate
- Vit B 12 levels
- Hb electrophoresis

Serum iron studies

- TIBC
- Transferrin
- Ferritin
- Serum soluble transferrin receptor
- Free erythrocyte protoporphyrin
- Hepcidin

Classification of anemia

- Etiological classification
- Morphological classification
- Classification based on severity

Classification based on severity

- Mild < 10 g /dl
- Moderate 7-10 g/dl
- Severe < 7 g/dl
- Acute: develops over days
- Chronic: develops over months

Etiological Classification of Anaemias

Anaemias due to impaired red cell production

1. Anaemias due to deficiency of nutrients
 - Iron deficiency anaemia
 - Megaloblastic anaemia due to deficiency of folate or vitamin B₁₂
2. Anaemia of chronic disease
3. Sideroblastic anaemia
4. Aplastic anaemia and related disorders
5. Anaemia of chronic renal disease
6. Anaemia of liver disease
7. Anaemia in endocrine disorders
8. Myelophthisic anaemia (Anaemia due to replacement of marrow by metastatic carcinoma, leukaemia, lymphoma, infections, storage disorders, etc.)
9. Congenital dyserythropoietic anaemia

Anaemias due to excessive red cell destruction (Haemolytic anaemias)

Abnormality intrinsic to red cells

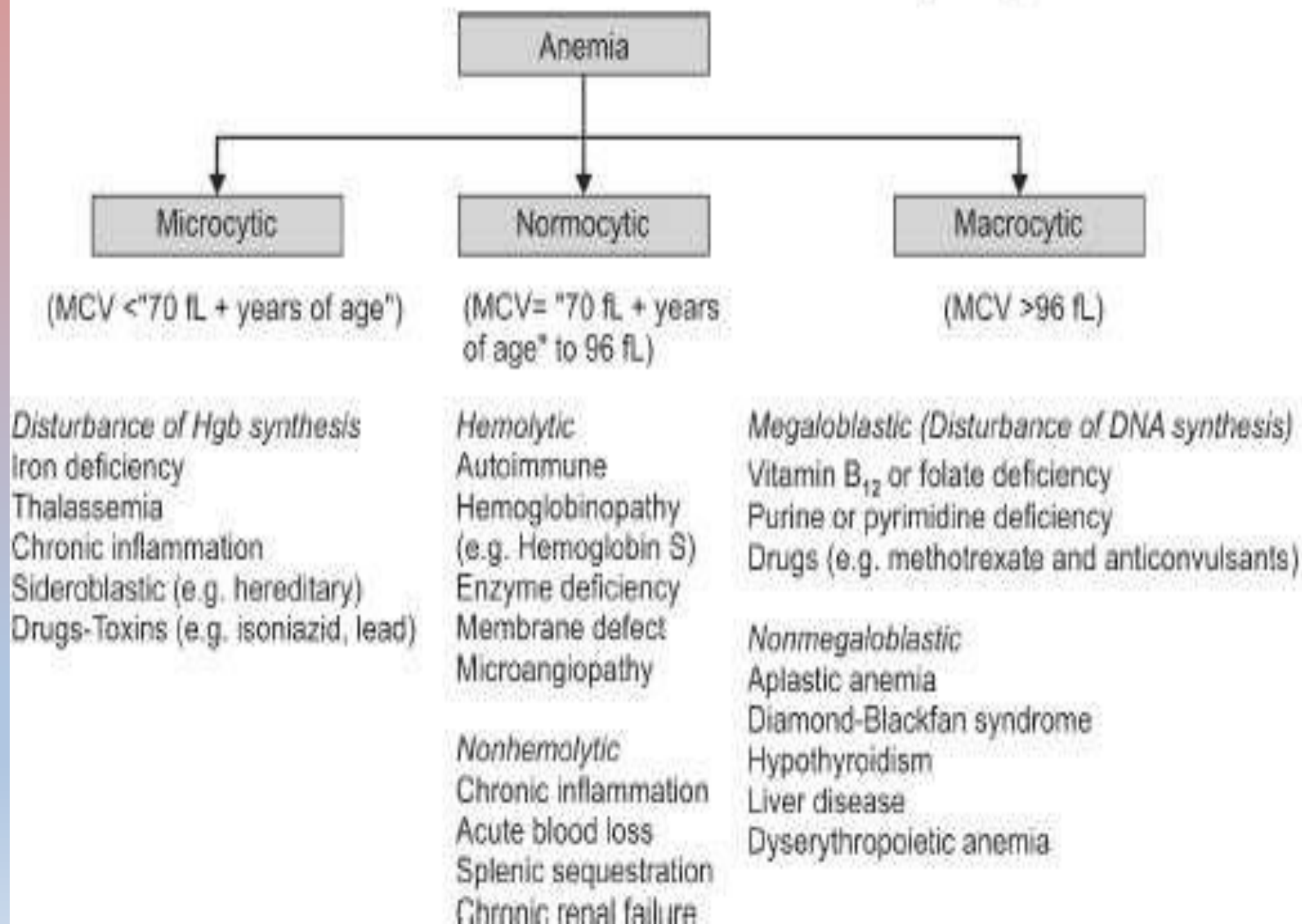
1. **Defects in red cell membrane**
 - Hereditary spherocytosis
 - Hereditary elliptocytosis
2. **Defects in haemoglobin**
 - Quantitative: Thalassaemias
 - Qualitative: Sickle-cell disease; Haemoglobin D, E, or G disease
3. **Defects in enzymes**
 - Glucose-6-phosphate dehydrogenase deficiency
 - Pyruvate kinase deficiency

Abnormality extrinsic to red cells

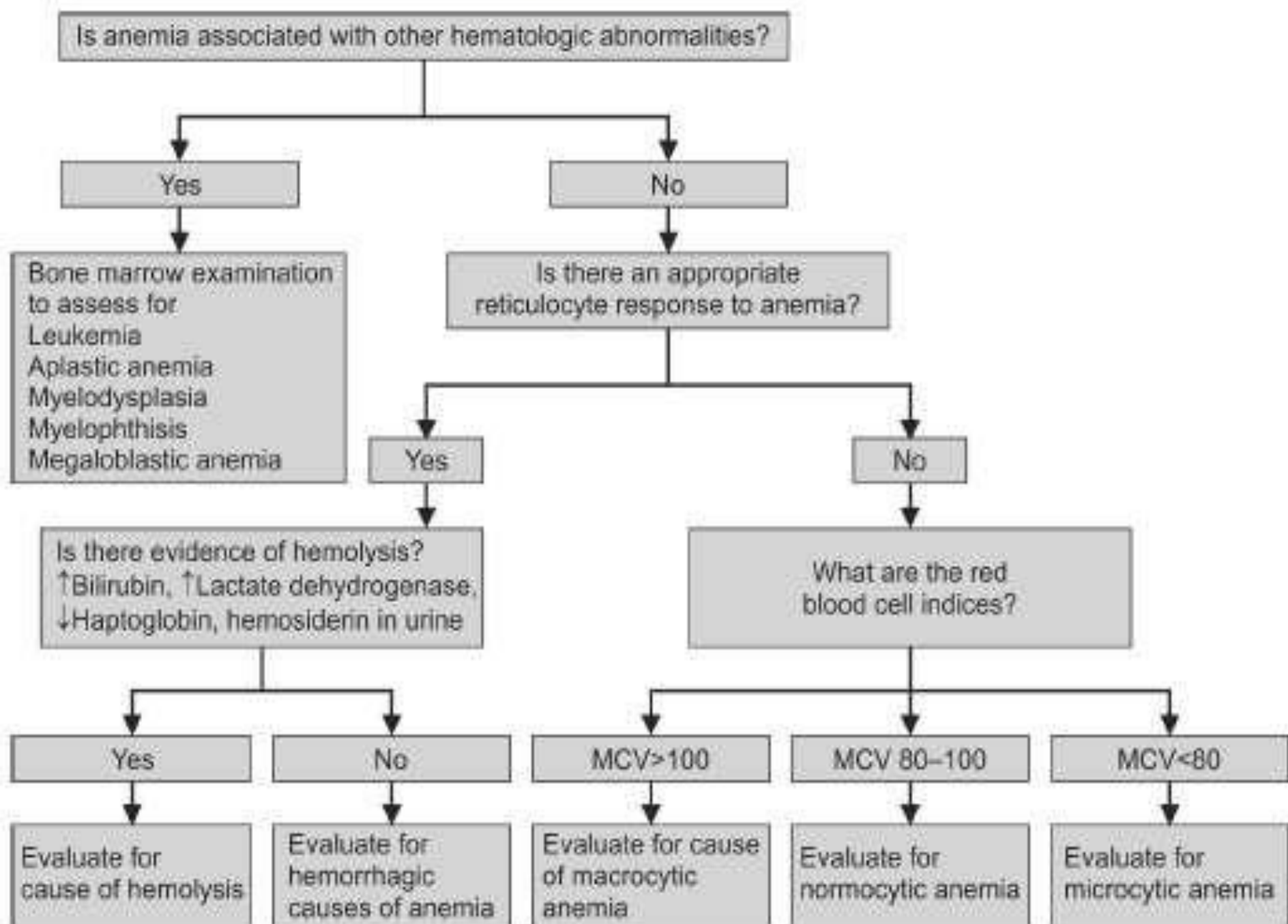
1. **Immune haemolytic anaemias**
 - Autoimmune
 - Alloimmune
 - Drug-induced
2. **Mechanical haemolytic anaemia**
 - Microangiopathic
 - Cardiac
 - March haemoglobinuria
3. **Direct action of physical, chemical, or infectious agents**
4. **Hypersplenism**

Anaemias due to excess blood loss

Flow chart 1 Classification of anemia based on morphology⁴

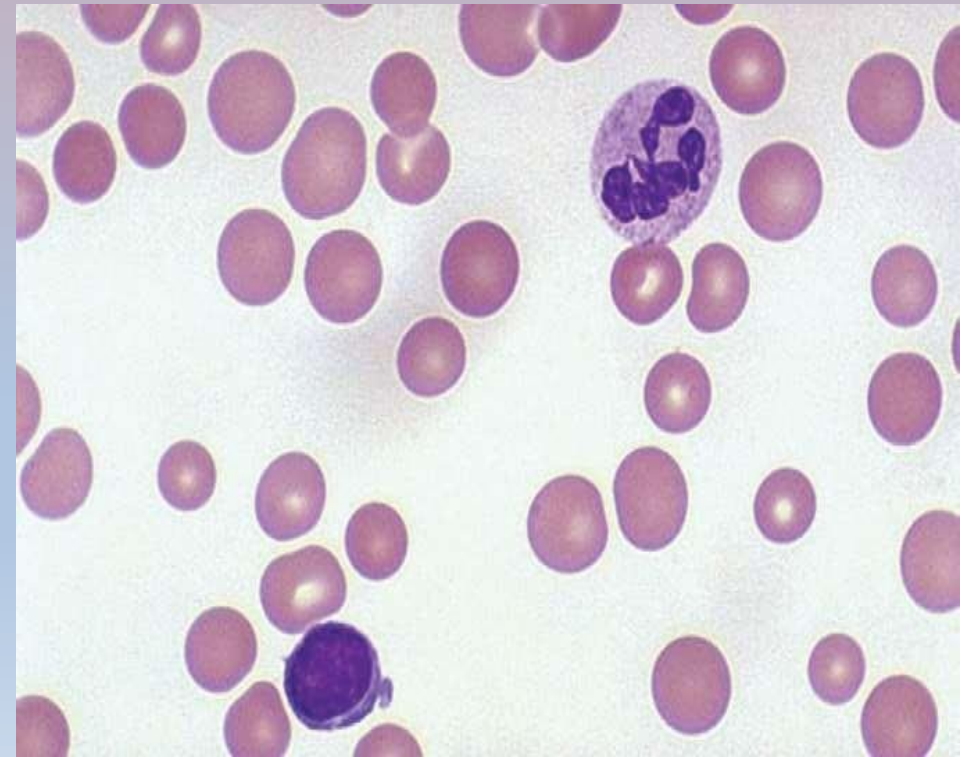
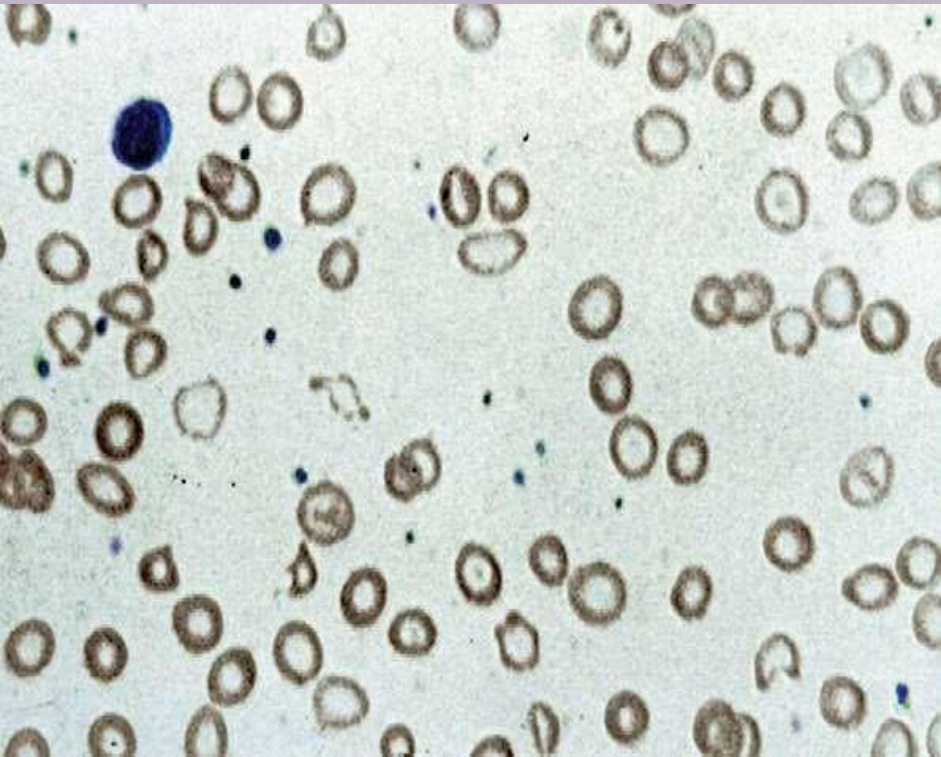


Flow chart 2 Approach to anemia⁵

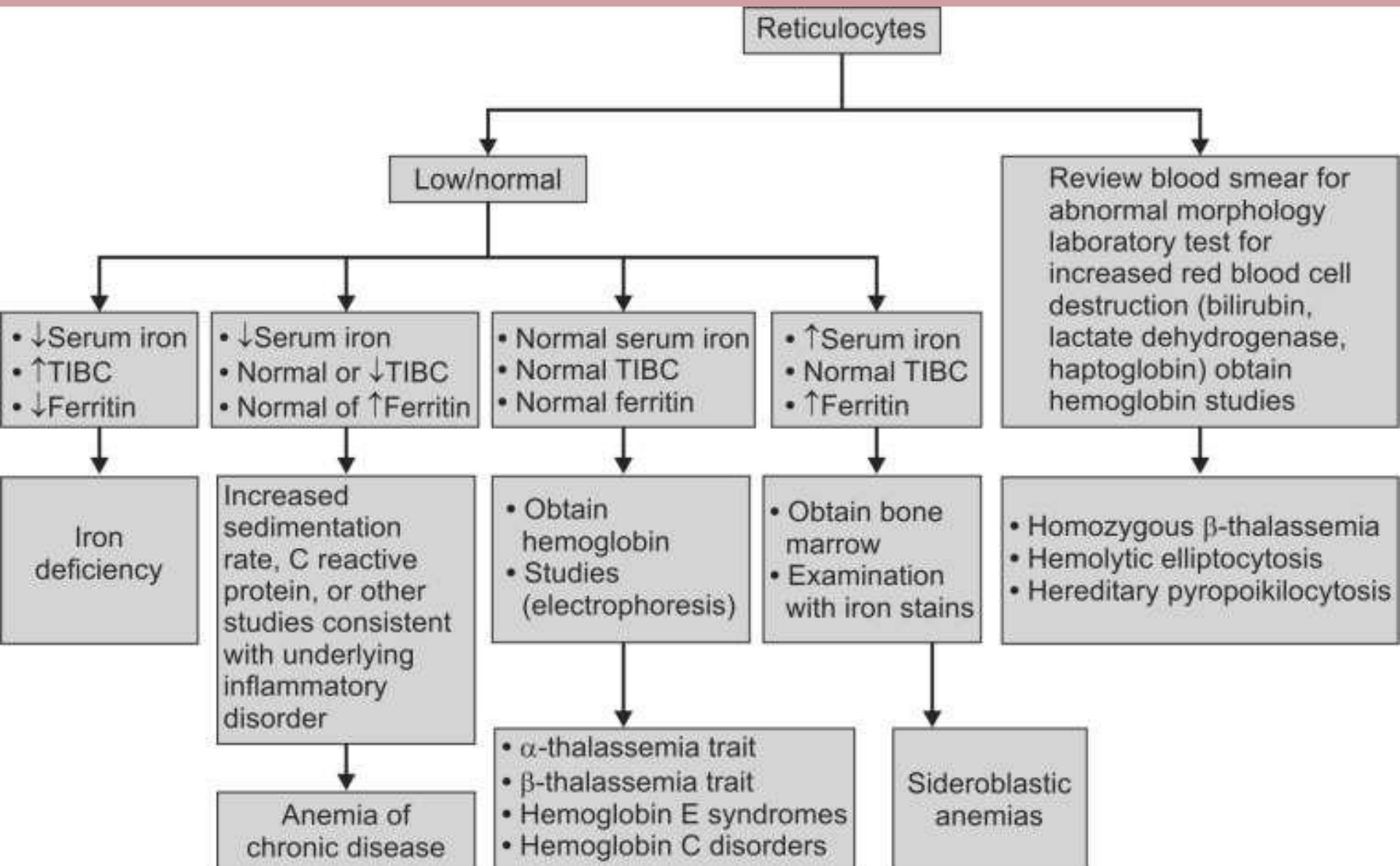


Based on indices, anemia can be classified in to

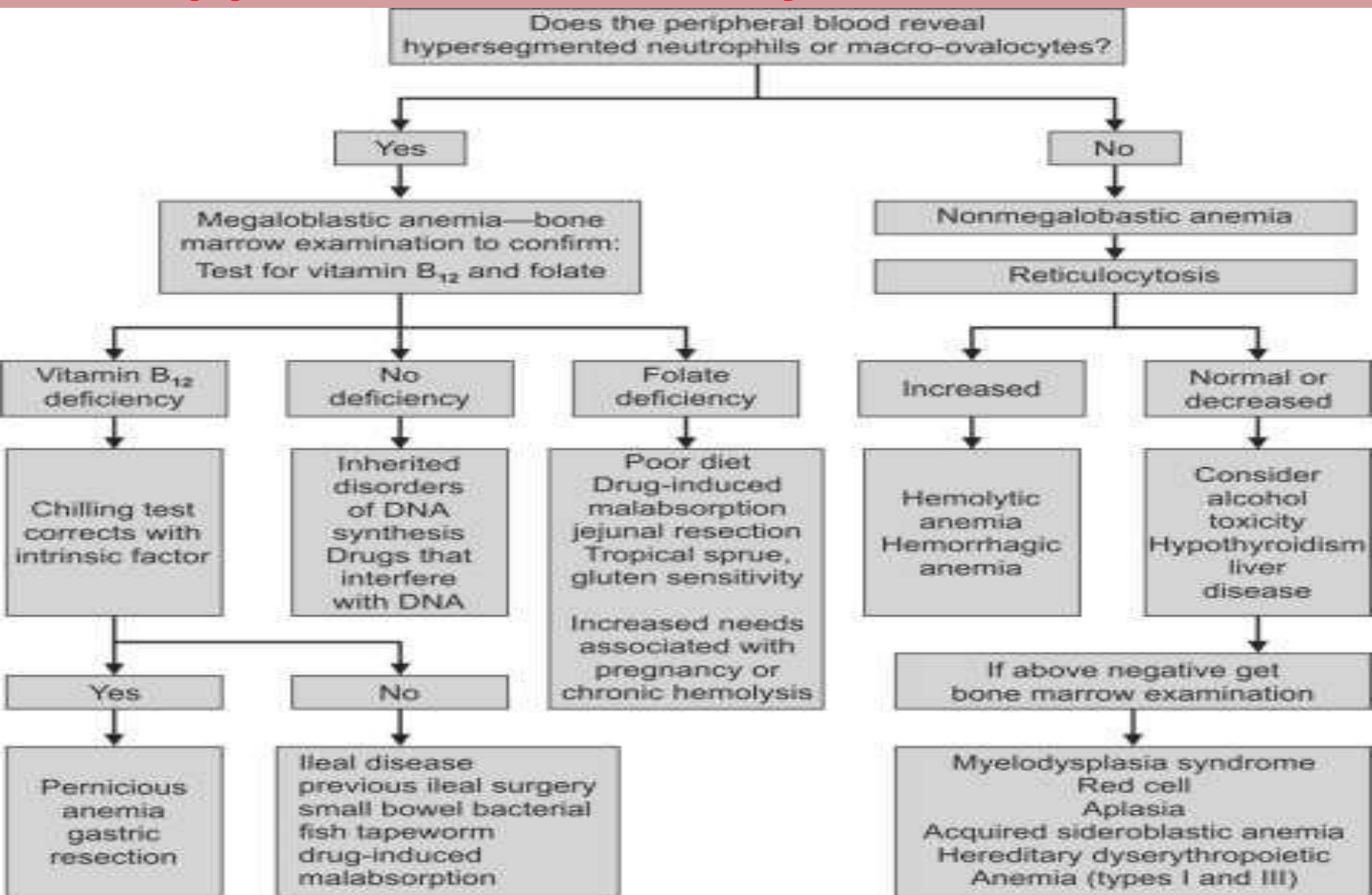
1. Microctic hypochromic
2. Macrocytic
3. Normocytic normochromic



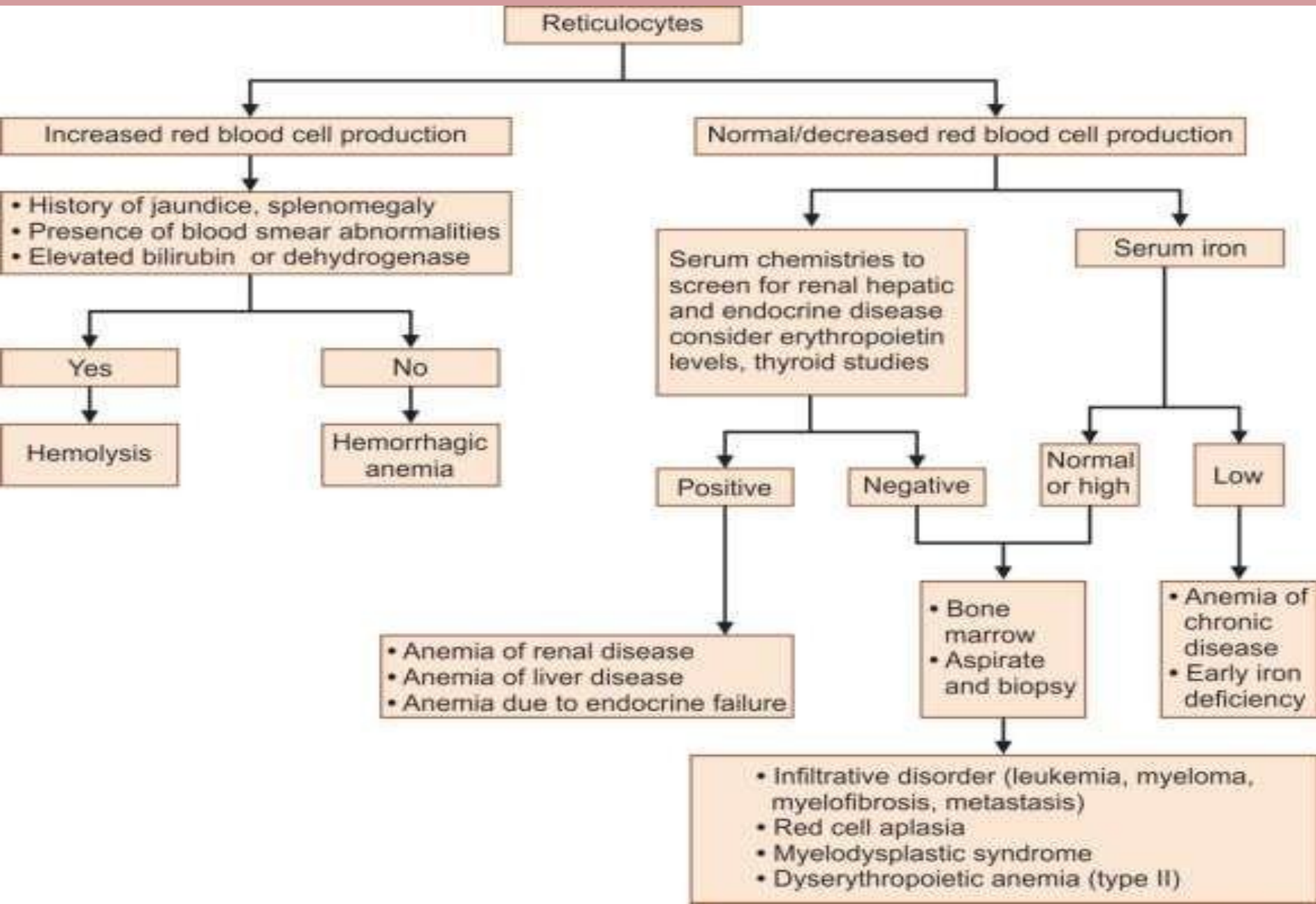
Approach to microcytic hypochromic anemia



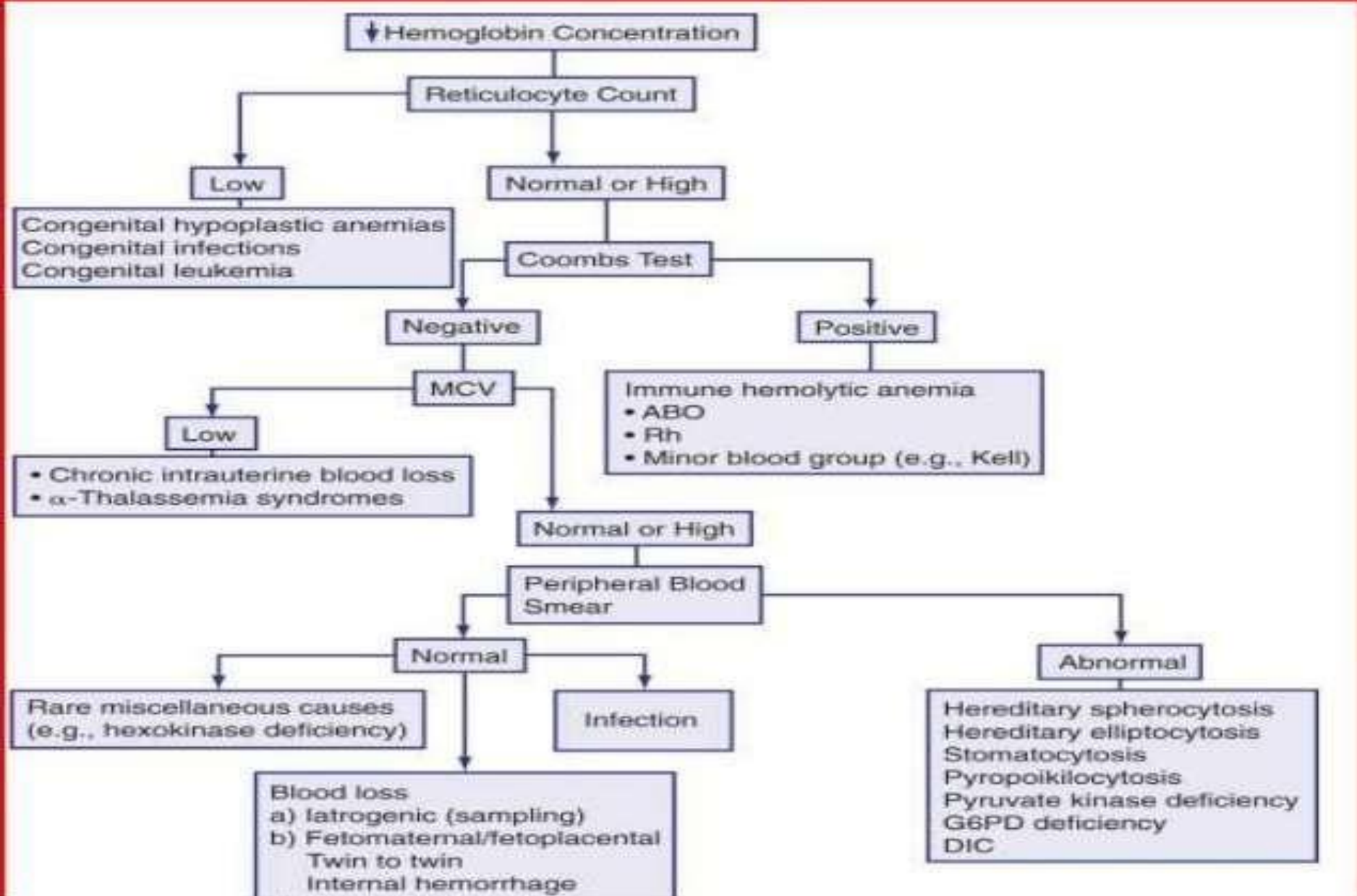
Approach to macrocytic anemia



Approach to normocytic normochromic anemia



Approach to neonatal anemia



Case scenarios

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 . She has breathlessness and palpitations while climbing stairs. Also she had episodes of dizziness .
- 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 present.
- Respiratory – Normal breath sound
- Abdomen- Soft lax and non- tender.

What is the next step?

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%

• Inference ? Microcytic
Hypochromic
Anemia

What additional tests you want
to do
want to do?

Serum IronL 30mcg /dL

- **TIBC- 450**
- **Ferritin-9 ng/ml**
- **Transferrin saturation- 7%**

What kind of anemia is this?

- **Iron Deficiency Anemia**

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 to hematology and gynecology for
further management of the underlying cause

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 TIBC

CASE 2

- A 9 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.
- What to do next?

CBC:

- Hb: 8.4 g/dL, MCV- 90 fl/
- WBC: 11600
- Platelets: 161000
- **Reticulocytes- 5%**
- **PBS- microcytic, hypochromic, polychromasia, nucleated RBCs, target cells, poikilocytosis and anisocytosis**
- **Bilirubin (Indirect):**
- **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%**

- **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

How to manage this patient?

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

BETA- 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.

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

Management:

Transfusion:

- Blood 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.

Endocrine therapy-

- Administration of deficient hormones (thyroid hormones)
- Treatment of Diabetes

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

- A 5 year old boy comes to the clinic for evaluation of weakness and fatigue lasting for 6 weeks.
- 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).
- Physical examination revealed marked pallor
- Abdominal examination reveals few scattered petichae but no hepatosplenomegaly

Labs:

- Hb-5 g /dL
- Hct= 15%
- WBC 1500
- 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?

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

Diagnosis: Aplastic Anemia

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 etc.
- Lab findings: pancytopenia, low reticulocyte count, reduced cellular elements (morphologically normal). Bone marrow biopsy shows decreased cellularity

TREATMENT of Aplastic Anemia

SUPPORTIVE CARE-

- Removal of causative drugs
- Maintenance of vitals
- Control of bleeding if present
- Replacement with blood and blood products

SPECIFIC TREATMENT-

Bone marrow transplantation

CASE 4

- A 11 year old male presented with frequent pains in legs, joints, chest and needs to come to hospital for IV pain medication.
- Physical Exam shows scleral jaundice, no splenomegaly

CBC-

- **Hb- 8.0g/dL, MCV- 82**
- **WBC- 9800/mm³**
- **Platelets- 465000/mm³**
- **Reticulocyte: 7%**
- **Indirect Bilirubin: 84mg/dL**
- **PBS- Numerous Sickle cell**

What is the most likely diagnosis?

- **Sickle Cell anemia**

- **How to manage this patient?**
- Admit the patient
- Pain medication- opioid
- Good hydration
- Red Cell exchange transfusion to maintain HBS at <50%
- Hydroxyurea-decreases the painful episodes,raises the HB level,raises the HbF level.

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- anemia, jaundice and painful episodes, delayed growth and puberty, 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.

Treatment of sickle cell

- Management of pain and anemia.
- Management of sickle cell crisis.
- Management of complications.
- Prevention of infections by capsulated organisms

CASE 5

- 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.

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 (220ng/ml)
- Vitamin B12 level- 300pg/ml (200pg - 500pg/ml)

Most likely Diagnosis?

- Folate Deficiency Anemia

CASE 6

- A 12 year old girl presented to the Emergency Department with fever, 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.
- A non tender soft hepatomegaly with a span of 14 cm and a soft spleen 3 cm below the left costal margin was noted.

- **WBC- 9000/mm³, Hb- 3g/dL, MCV- 128 fl, MCH- 50 pg, MCHC- 39.7g/dL**
- **Platelets- 170,000/mm³**
- **Reticulocyte- 10%**
- **Total Bilirubin- 4.5mg/dL, Indirect Bilirubin- 3.2 mg/dL**
- **PBS: Agglutination of RBCs noted.**
- **Smear showed anisopikilocytosis with predominant macrocytes, hypochromia and nucleated red blood cells.**
- **DAT- strongly positive**

AUTOIMMUNE HEMOLYTIC ANEMIA

- Hemolytic anemias which results from the development of auto antibodies 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.

Treatment of AIHA

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

THANK YOU