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Hematology Notes

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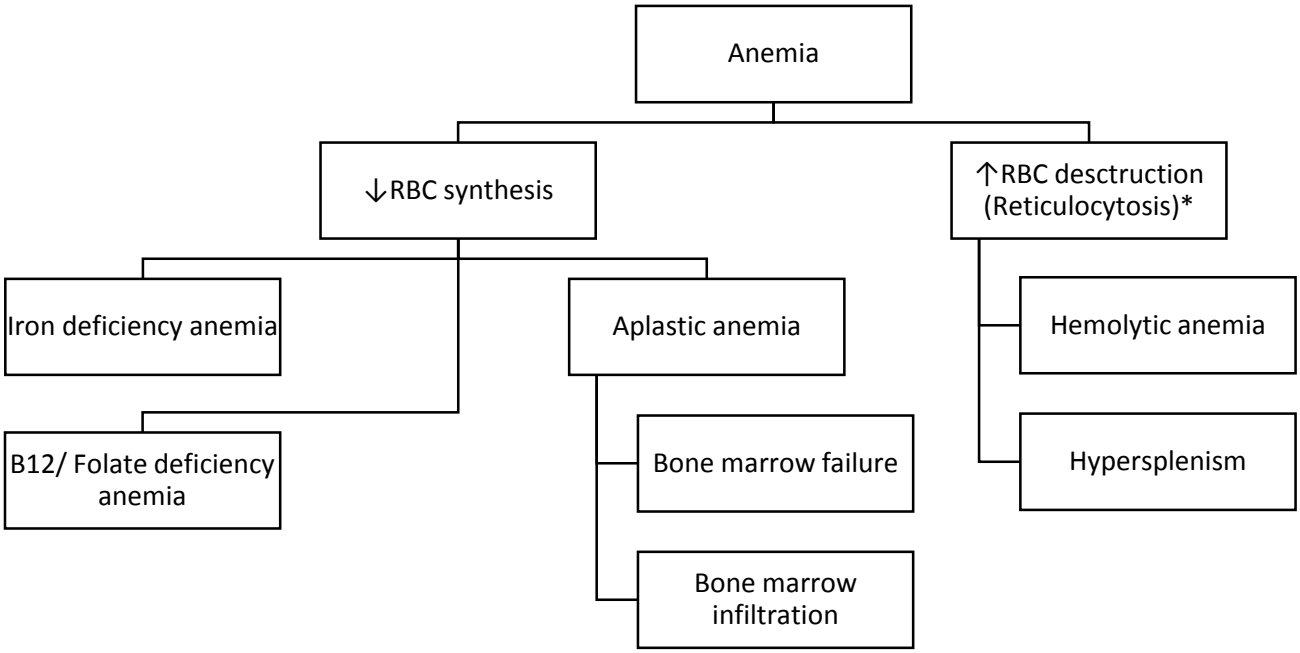
Anemia



*Reticulocytosis occurs due to:

- Hyperfunctioning bone marrow
- Iron replenishment in iron deficiency.

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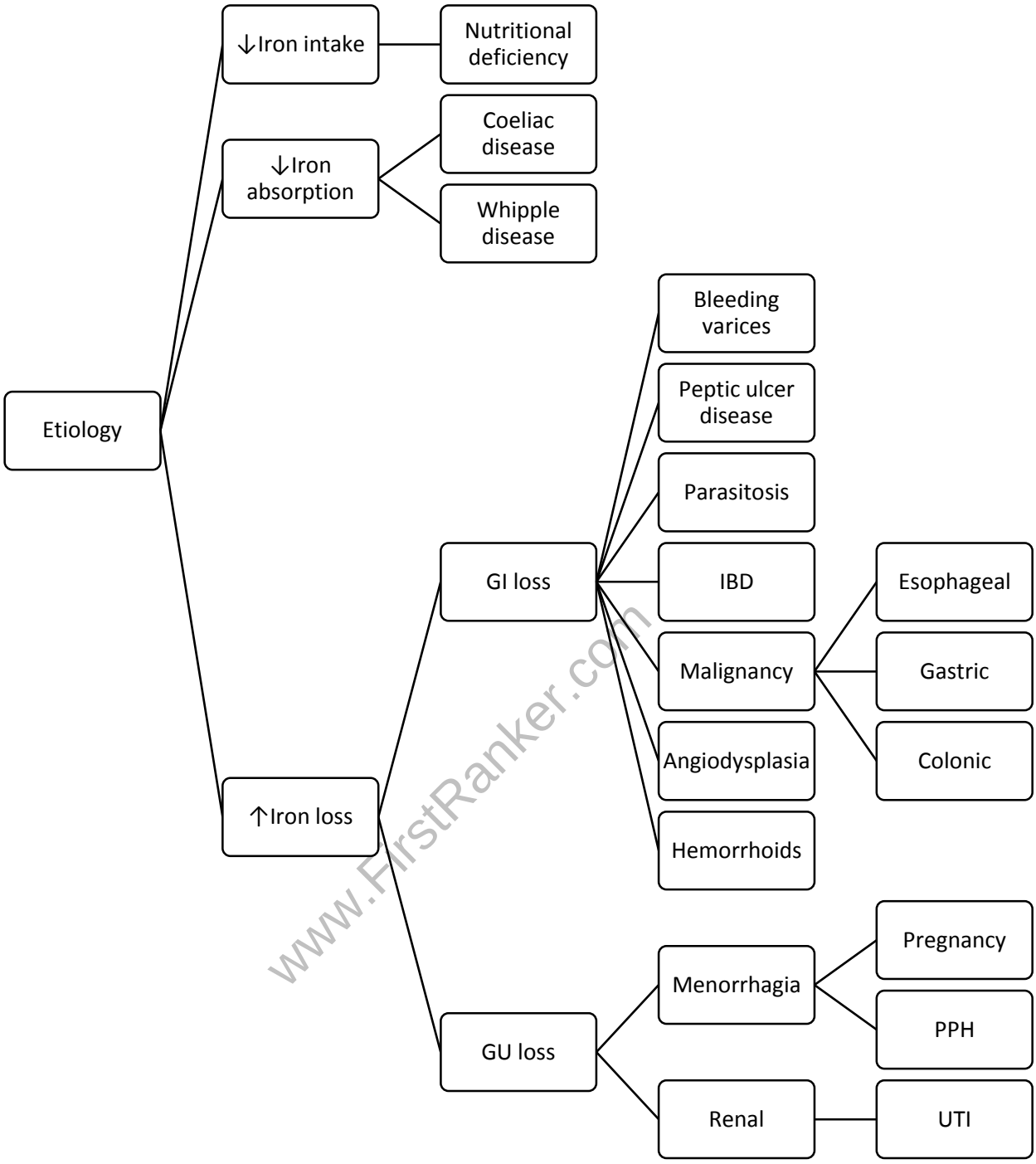
Iron deficiency anemia



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Clinical features:

I	Features due to iron deficiency
D	Features due to underlying disease
A	Features due to anemia

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Features due to iron deficiency:

1. Spoon shaped nail: Koilonychia
2. Glossitis, cheilitis
3. Pica: Abnormal craving due to non-iron rich food (appetite for substances largely non-nutritive, such as ice, clay, chalk, soil, etc. sand).

Features due to underlying disease:

Any evidence of GI/ GU bleed must be looked for; however, bleeding may be occult.

Features due to anemia:

A. Anemic look
B. Breathlessness
C. Cardiac palpitation
D. Dizziness
E. Exercise intolerance
F. Fatigue.

Investigations

1. Blood: Hb, TC, DC, CRP
   Hb: ↓
2. Peripheral film: Anisopoikilocytosis (variation in size and shape of RBC)
3. RBC indices: MCV:↓/Normal
4. Serum iron studies:
   I. Serum iron: ↓
   II. Serum ferritin: ↓ (but may be falsely normal or ↑ due to any co-existing inflammatory condition)
   III. Serum transferrin saturation: ↓
   IV. Total iron binding capacity (TIBC): ↑
5. Other relevant investigation(s) to look for underlying disease(s).
6. In suspected GI loss of iron:
   I. Fecal occult blood test (FOBT)
   II. Examination of stool for ovum, parasite, cyst (OPC)
   III. GI endoscopy:
      ✓ Upper GI endoscopy
      ✓ Colonoscopy
      ✓ Capsule endoscopy.

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Treatment

1. Treatment of anemia:
    - IV fluid resuscitation
    - Blood transfusion
    - Iron replacement therapy:
        I. Per oral:
        $FeSO_4$ /Fe-gluconate (Side effects: Black stool, constipation)
        Usually continued for another 2-3 months after hematological parameters normalize.
        II. IV iron therapy:
        Indications:
            - ✓ Per oral iron intolerance
            - ✓ Non-compliance to oral therapy
            - ✓ Presence of malabsorption.
    - Dietary modifications:
        I. Green leafy vegetables
        II. Meat
        III. Vitamin C rich food (vitamin C increases iron absorption).
2. Treatment of the underlying cause.

Differential diagnosis of microcytic anemia

1. Iron deficiency anemia
2. Thalassemia
3. Anemia of chronic disease
4. Sideroblastic anemia
5. Lead poisoning.

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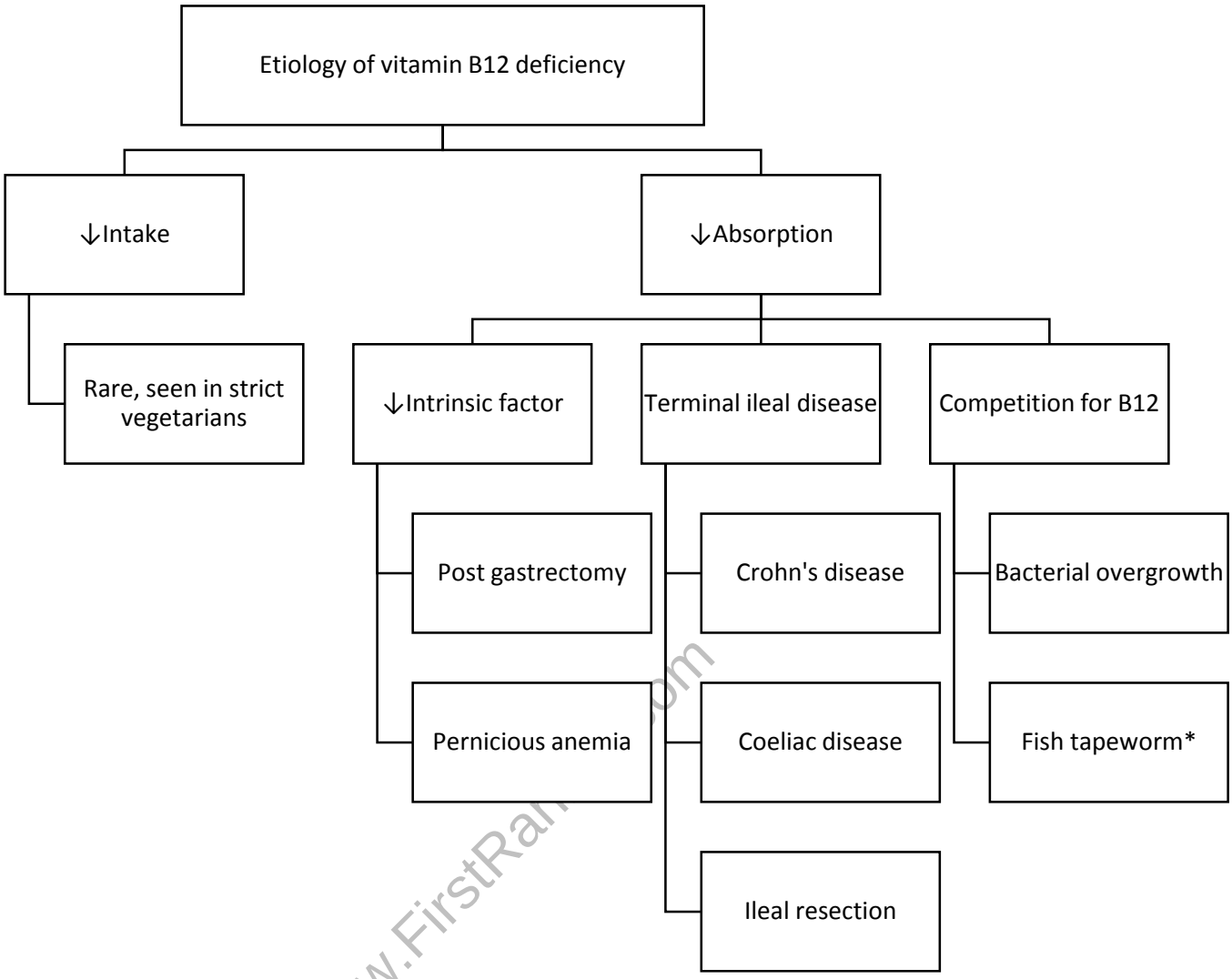
Vitamin B12/ Folate deficiency anemia



[**Diphyllobothrium latum*]

Note: It takes almost 3 years for vitamin B12 deficiency to develop after intake/ absorption is stopped.

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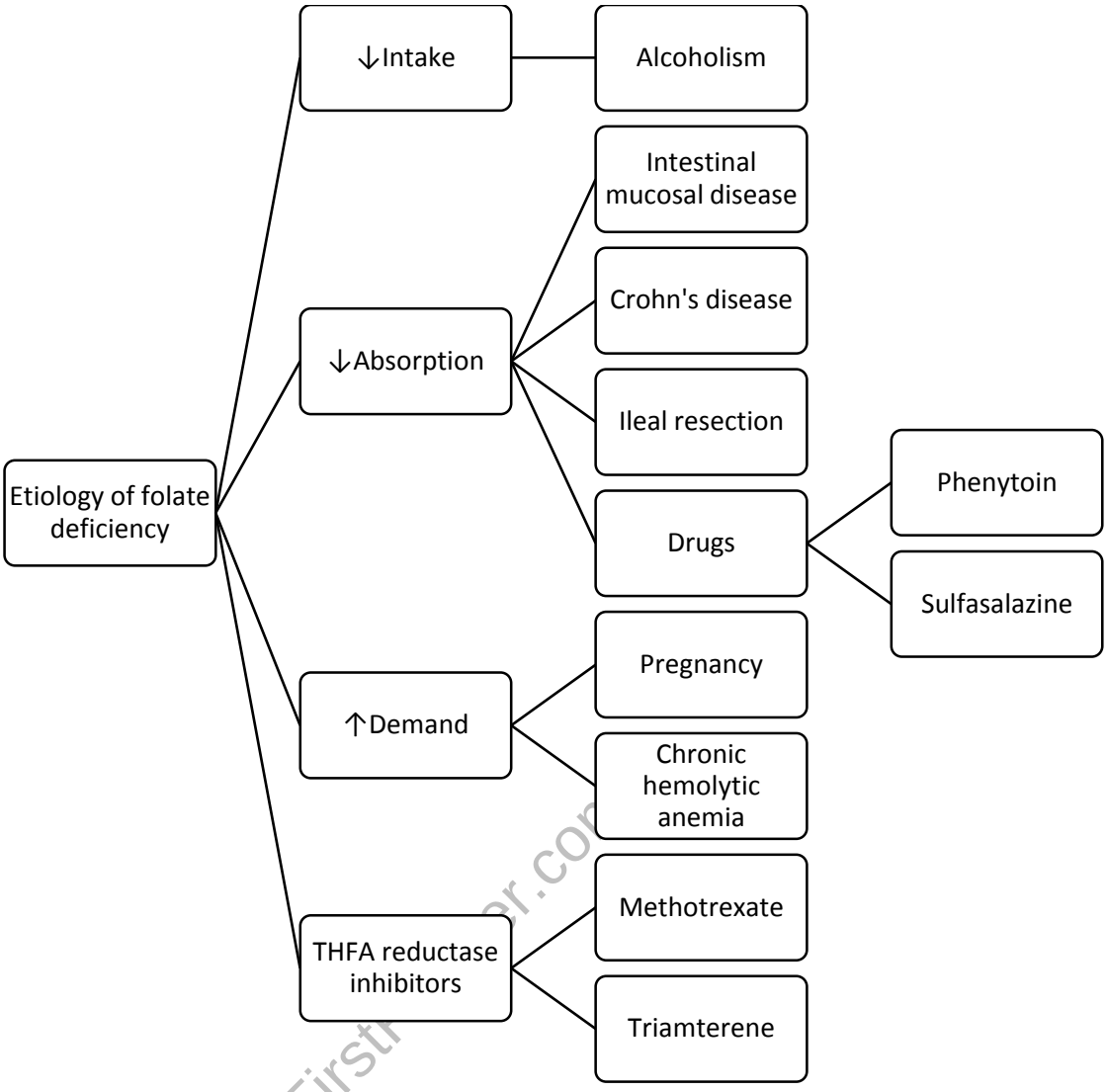

Clinical features of vitamin B12 and folate deficiency anemia:

System	***Hematological***	***CNS***	***Gastrointestinal***
Mechanism	Anemia	Subacute combined degeneration (SACD) of spinal cord	Damage to rapidly proliferating GI mucosal cells due to impaired DNA synthesis
Clinical features	✓ Anemic look ✓ Breathlessness ✓ Cardiac palpitation ✓ Dizziness ✓ Exercise intolerance ✓ Fatigue.	Degeneration of: ✓ Pyramidal tract ✓ Posterior column ✓ Peripheral nerves Higher function abnormalities	✓ Diarrhea ✓ Abdominal pain ✓ Glossitis (Red beefy tongue).

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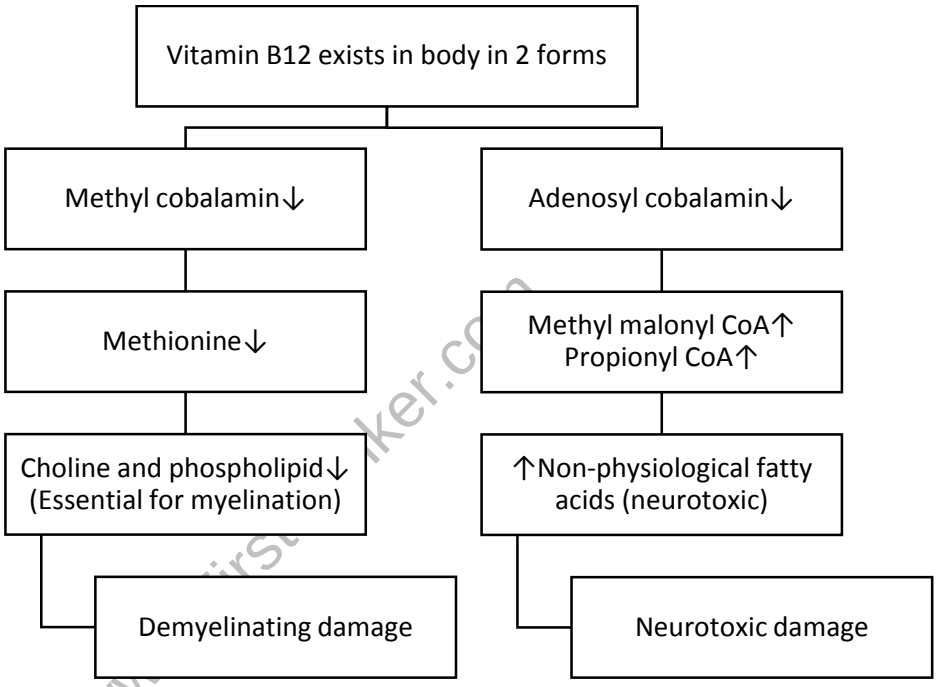
In folate deficiency, only hematological + GI manifestations are present.

Mechanism of clinical manifestations:

In B12/ folate deficiency, impaired DNA synthesis of hematological and other rapidly proliferating cells occur, giving rise to the following manifestations:

1. RBC:
   Cytoplasmic maturation continues normally, but nuclear maturation lags behind; giving rise to *nucleocytoplasmic asynchrony*.
   Same problems occurs in WBCs and platelets also.
2. GI mucosal cells damage
3. Neurological manifestations:



Investigations

1. Blood: Hb, TC, DC, CRP, Platelet
   - Hb: ↓
   - TC: Normal/↓
   - Platelet: Normal/↓
   - Pancytopenia: All the 3 series may be affected due to accelerated destruction secondary to ineffective hematopoiesis.
2. Peripheral film:
   - RBC: Macrocytes
   - WBC: Hypersegmented neutrophils (4-6 lobes)

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- Platelets: Abnormally looking.

3. RBC indices:
   MCV: ↑
4. Bone marrow:
   Erythroid hyperplasia + megaloblasts.
5. Estimation of serum vitamin B12/ folate level
6. Other relevant investigations to diagnose the underlying cause/ neurologic complications.

Treatment

1. Vitamin supplementation:
   a. Vitamin B12: IM
   b. Folate: Oral.
      - Often both of them are administered together as combined deficiency is not uncommon.
      - Always estimate levels of both vitamin B12 and folate in patients of macrocytic anemia.
      - If folate is supplemented alone in a patient with subclinical vitamin B12 deficiency, hematological picture improves satisfactorily but neurological symptoms may aggravate.

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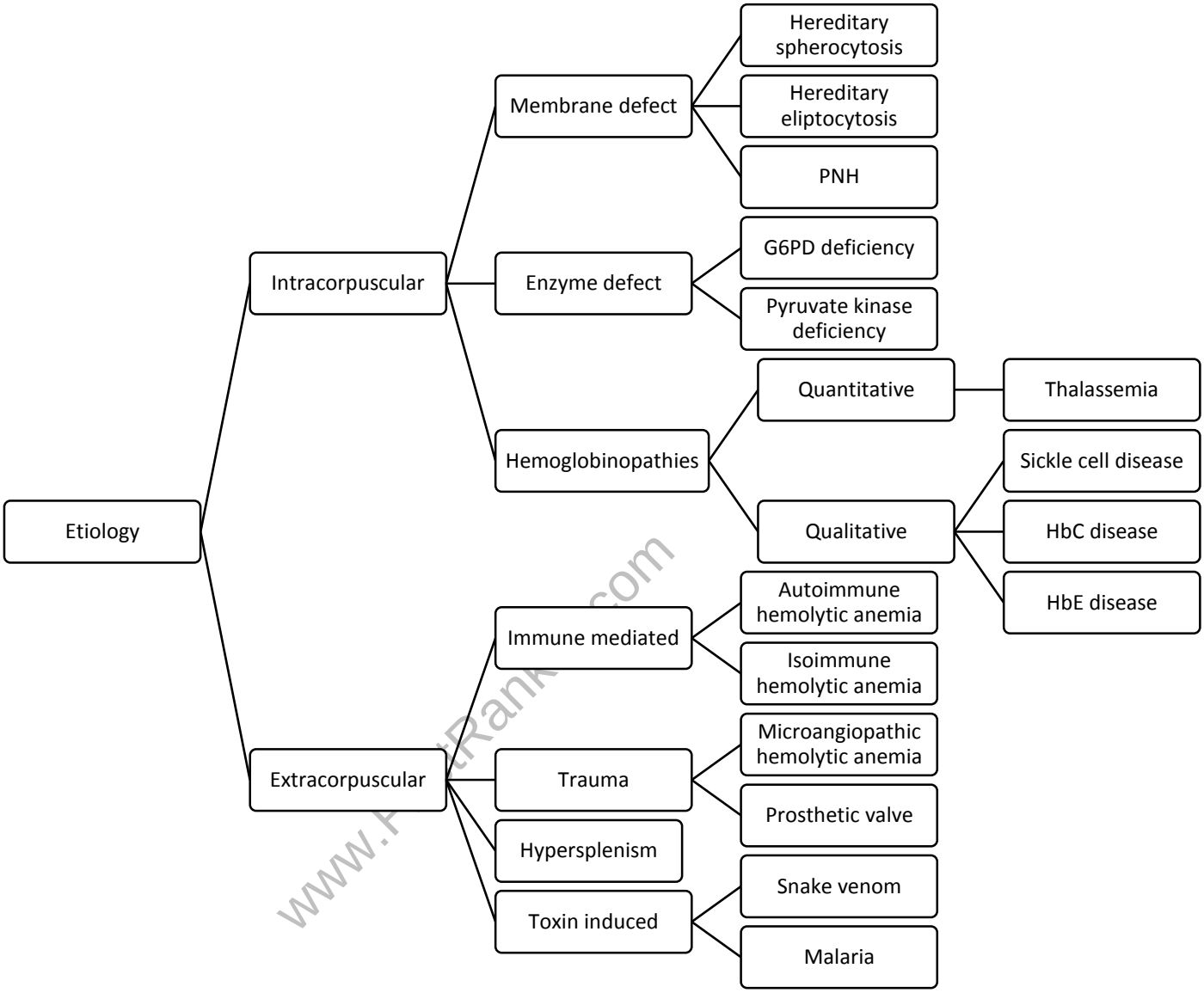
Hemolytic anemia

Anemia characterized by accelerated destruction of RBCs.



Clinical features of hemolytic anemia:

1. Due to anemia:
   - ✓ Anemic look
   - ✓ Breathlessness
   - ✓ Cardiac palpitation
   - ✓ Dizziness
   - ✓ Exercise intolerance

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- ✓ Fatigue.

2. Due to excessive hemolysis:
   - ✓ Icterus
   - ✓ Splenomegaly (if spleen is the site of RBC destruction)
   - ✓ Calculus cholecystitis.
3. Due to extramedullary erythropoiesis:
   - ✓ Liver: Hepatomegaly
   - ✓ Spleen: Splenomegaly
   - ✓ Bones: Skeletal changes.
4. Due to underlying disease
5. Due to complication(s):
   - ✓ Iron overload
   - ✓ Iatrogenic complication (Ex.: blood borne infections).

Investigation

1. Evidence of anemia:
   - ✓ Blood: Hb, TC, DC, CRP
     Hb: ↓
2. Evidence of excessive hemolysis:
   - ✓ Unconjugated bilirubin: ↑
   - ✓ LDH: ↑
   - ✓ AST: ↑
   - ✓ Urinary urobilinogen: ↑
   - ✓ Fecal stercobilinogen: ↑
3. Evidence of accelerated erythropoiesis:
   - ✓ Reticulocyte count: ↑
   - ✓ Erythroid hyperplasia.
4. Investigations to confirm underlying disease
5. Investigations to detect complications:
   - ✓ Iron overload: Serum iron ↑, serum ferritin ↑.
   - ✓ Blood borne infections: Tests for HIV, HBV, HCV.

Treatment

1. Treatment of anemia
2. Treatment of iron overload
3. Treatment of underlying disease (specific treatment)
4. Treatment of complications.

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Mention some differentiating parameters between extracorpuscular/ extravascular and intracorpuscular/ intravascular hemolysis?

Parameter	Intravascular hemolysis	Extravascular hemolysis
Hemoglobin in urine	+	-
Hemosiderin in urine	+	-
Haptoglobin in blood	↓↓	↓

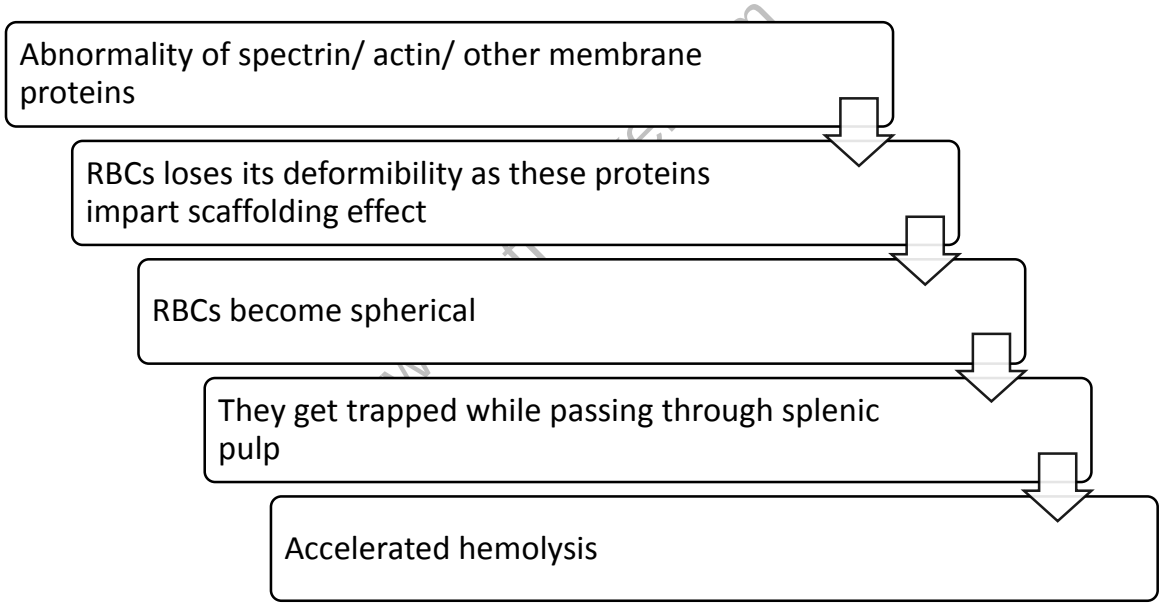
Now we will discuss the individual underlying diseases that cause hemolytic anemia.

Hereditary spherocytosis (HS)

Definition:

Congenital defect of RBC membrane protein resulting in accelerated destruction of RBCs in the spleen.

Pathophysiology:



Clinical features:

1. Due to anemia:
   - ✓ Anemic look
   - ✓ Breathlessness
   - ✓ Cardiac palpitation
   - ✓ Dizziness

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- ✓ Exercise intolerance
- ✓ Fatigue.

2. Due to accelerated erythropoiesis:
   - ✓ Icterus
   - ✓ Splenomegaly
   - ✓ Calculus cholecystitis.
3. Anemia may worsen if bone marrow fails to compensate for accelerated hemolysis. This problem particularly happens if there is associated folate deficiency. This event is therefore known as “aplastic crisis”.

Investigation

1. Blood: Hb, TC, DC, CRP
   Hb: ↓
2. Peripheral blood film: Spherocytosis ++ but it is not diagnostic of hereditary spherocytosis as there are other causes of spherocytosis.
3. Reticulocyte count: ↑ (due to accelerated erythropoiesis)
   Reticulocytopenia suggests impending aplastic crisis.
4. Evidence of excessive hemolysis:
   - ✓ Unconjugated bilirubin: ↑
   - ✓ LDH: ↑
   - ✓ AST: ↑
   - ✓ Urinary urobilinogen: ↑
   - ✓ Fecal stercobilinogen: ↑
5. To confirm hereditary spherocytosis:
   I. Osmotic fragility test:
      Spherocytes are vulnerable to get damaged by a hypotonic media.
   II. Coomb’s test: -Ve
      To rule out autoimmune hemolytic anemia where there is spherocytosis and ↑osmotic fragility as well as HS.

Treatment

1. Uninterrupted folic acid supplementation to prevent aplastic crisis
2. Blood transfusion in case of significant anemia
3. Splenectomy in severe cases.

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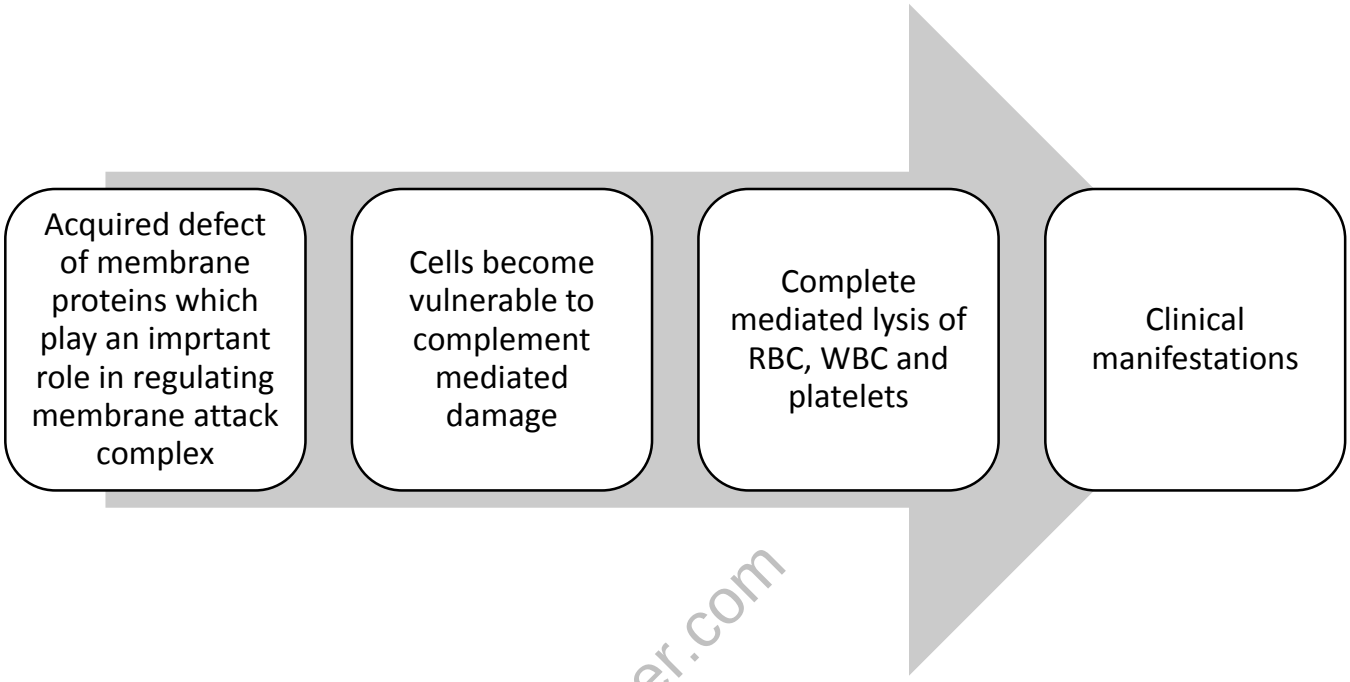
Paroxysmal Nocturnal Hemoglobinuria (PNH)

It is an acquired hematopoietic stem cell disorder characterized by excessive complement mediated lysis of the cells.

Pathogenesis:



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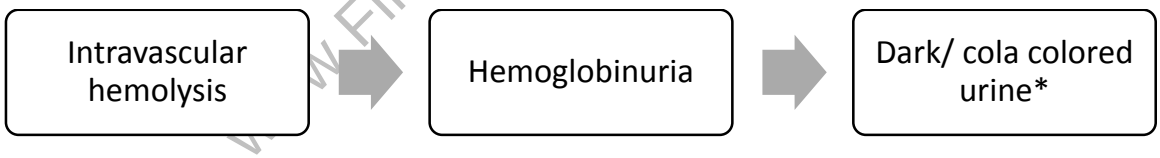
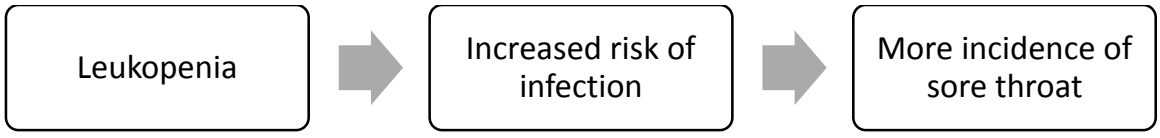
Clinical manifestations due to complement mediated lysis of RBCs:

1. Anemia and its clinical features
2. 

*It particularly occurs in the early morning as CO_2 retention during sleep acidifies the blood which increases hemolysis.

Clinical manifestations due to complement mediated lysis of WBCs:



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Clinical manifestations due to complement mediated lysis of platelets:

1. Thrombocytopenia → Bleeding manifestations
2. Complement mediated clumping → Hypercoagulable state → Deep vein thrombosis (DVT)

Investigations

1. Blood: Hb, TC, DC, CRP, Platelet count
   - ✓ Hb: ↓
   - ✓ TC: ↓
   - ✓ DC: ↓
   - ✓ Platelet count: ↓
2. Evidence of hemolysis:
   - ✓ Unconjugated bilirubin: ↑
   - ✓ LDH: ↑
3. Evidence of intravascular hemolysis:
   - ✓ Urine Hb: ↑↑
   - ✓ Urine hemosiderin: ↑
   - ✓ Blood haptoglobin: ↓↓
4. Confirmation of diagnosis of PNH:
   Flow cytometry detects abnormal proteins:
   - ✓ CD55
   - ✓ CD59.

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Treatment

1. Anemia: Blood transfusion
2. Prevention of venous thrombosis: Anticoagulants
3. Eculizumab: It is a humanized monoclonal antibody that is a terminal complement inhibitor and the first therapy approved for treatment of PNH
4. Corticosteroid: For some unknown reasons.

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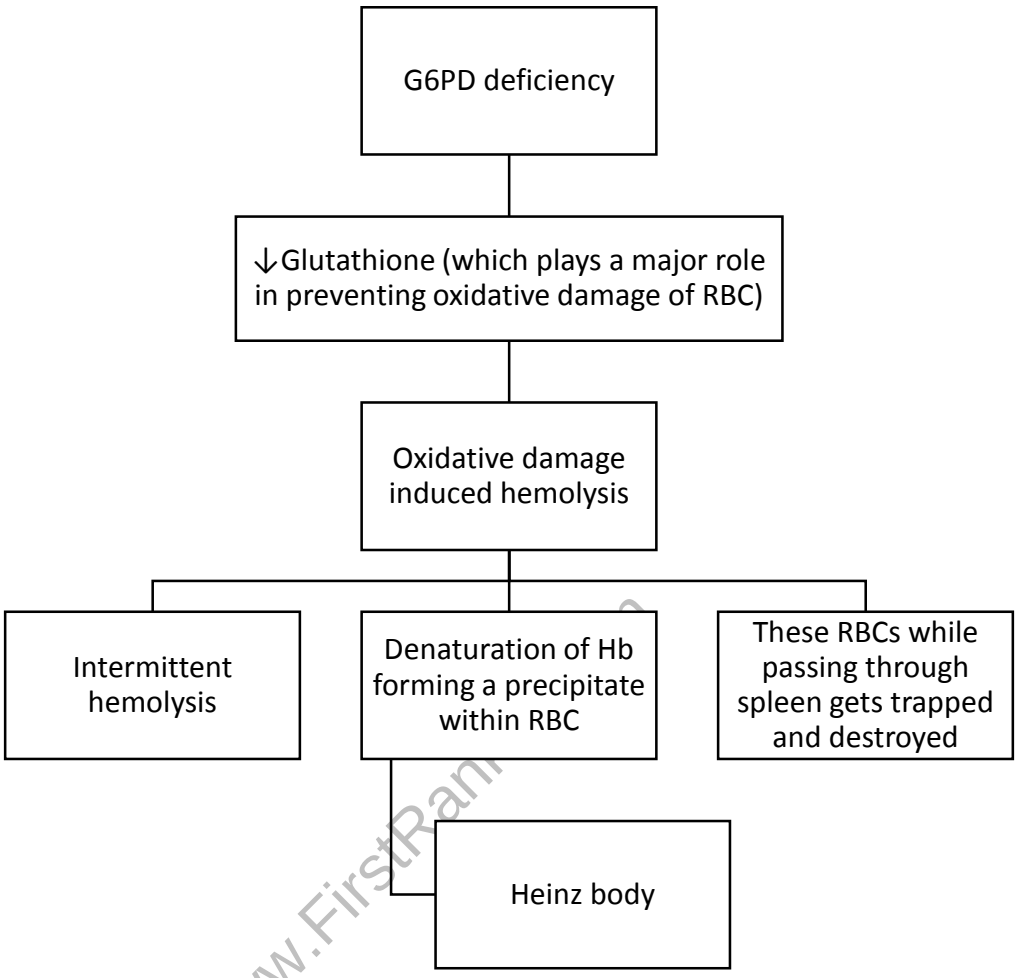
G6PD Deficiency

Hemolytic anemia precipitated by oxidative stress in G6PD deficient individuals.

Pathogenesis:



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Clinical features:

Oxidative stress induced intermittent hemolysis causes:

- Anemia
- Icterus.

Often the oxidative stress is drug induced:

- ✓ Primaquine
- ✓ Nitrofurantoin
- ✓ Sulfonamides.

Investigations

Investigations are abnormal during active hemolytic spells:

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1. Hb: ↓
2. Peripheral film:
   a. Heinz body
   b. Bite cells: Pitted RBCs looks like they have had a bite taken out of it (When a macrophage in the spleen identifies a RBC with a Heinz body, it removes the precipitate and a small piece of the membrane, leading to this characteristic appearance).
3. Evidence of hemolysis:
   a. Unconjugated bilirubin: ↑
   b. LDH: ↑
4. Evidence of hemolysis:
   Reticulocyte count: ↑
5. Confirmation of diagnosis:
   Estimation of G6PD: Ideally should be confirmed after couple of weeks of active hemolytic spells as fresh crops of RBCs (young RBCs) present during hemolysis may contain adequate amount of G6PD giving a false –Ve result.

Treatment

Avoid offending drugs.

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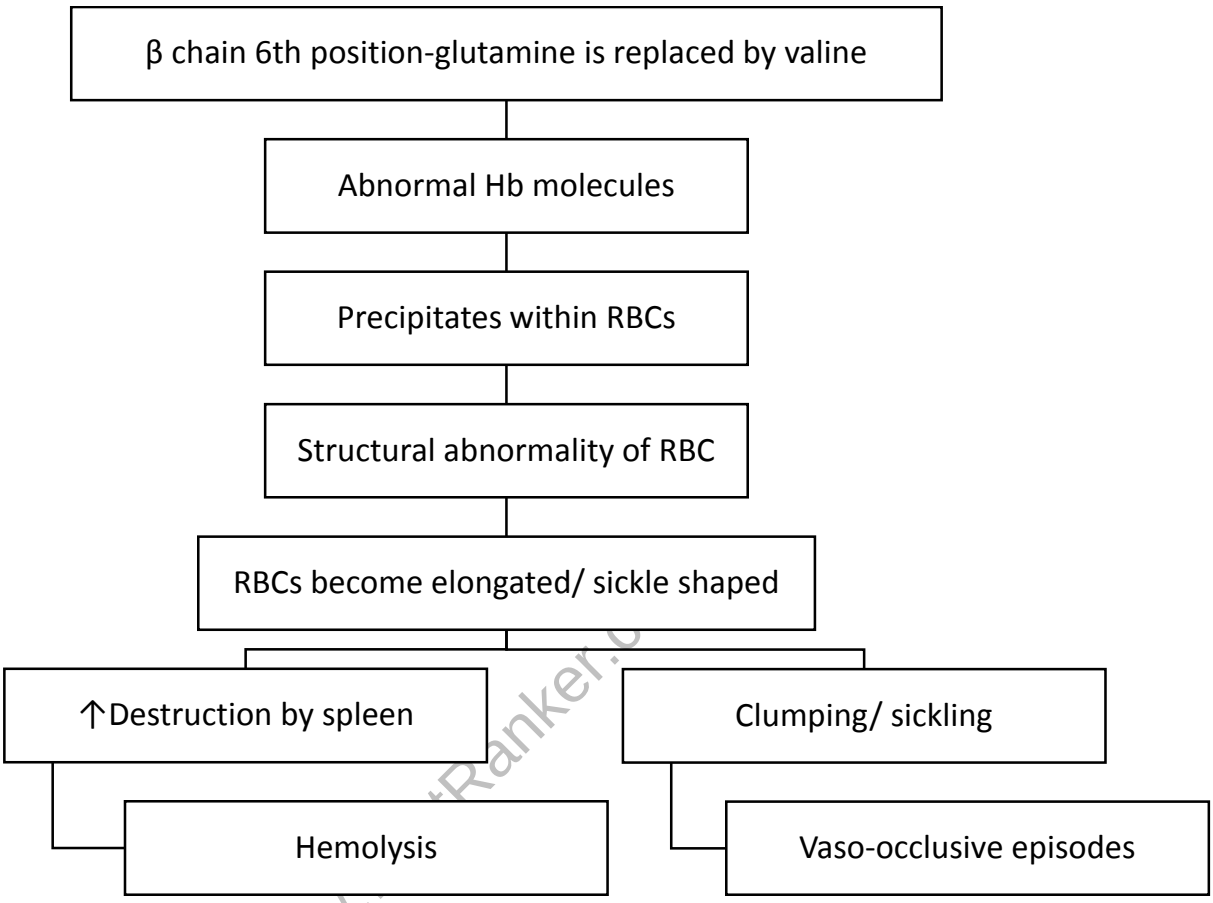
Sickle cell disease

Qualitative hemoglobinopathy characterized by abnormal shaped RBCs which are prone to get destroyed and clumped.

Pathogenesis:



Clinical features:

1. ***Vaso-occlusive spells*** (particularly affecting veins):

Organ involved	***Clinical features***
Brain	Venous sinus occlusion
Lung	Pulmonary artery clot-> Acute chest syndrome
Bones	Ischemic necrosis (severe bony pain) Osteomyelitis (Salmonella is the commonest organism)
Spleen	Splenic infarct causing acute LUQ pain Repeated episodes leads to *autosplenectomy*
Penile blood clots	Priapism (a painful condition where erect penis does not return to its flaccid state in the absence of any stimulation)

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2. ***Evidence of hemolysis***:
   a. Anemia
   b. Icterus
   c. Spleen: May be palpable in children, not palpable in adult due to hyposplenism.

   Tendency of sickling is aggravated by:

   a. Dehydration
   b. Hypoxia
   c. Acidosis.

Investigation

1. Hb: ↓
2. Peripheral blood film:
   a. Howell Jolly bodies: Due to hyposplenism, *nuclear remnant of RBCs* seen
   b. Sickle cells.
3. Evidence of accelerated hemolysis:
   a. Unconjugated bilirubin: ↑
   b. LDH: ↑
4. Evidence of accelerated erythropoiesis:
   a. Reticulocyte count: ↑
   b. A normal reticulocyte count indicates an impending episode of aplastic crisis.
5. Confirmation of diagnosis:
   Hb electrophoresis confirms the diagnosis: shows HbS.

Treatment

1. Treatment of vaso-occlusive spells:
   - ✓ Proper hydration
   - ✓ Oxygen in hypoxia
   - ✓ Treat infections by antibiotics
   - ✓ Analgesics to reduce pain
   - ✓ Exchange transfusion.
2. Definitive treatment:
   - ✓ Curative: Bone marrow/ stem cell transplantation
   - ✓ Hydroxyurea: Decreases tendency of sickling by increasing circulatory HbF levels.

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Pernicious anemia

Vitamin B12 deficiency anemia due to autoantibody mediated *deficiency of intrinsic factor*.

Pathogenesis:

- There is formation of autoantibodies against:
  a. Gastric parietal cell: Causing decreased HCl secretion and atrophic gastritis
  b. Intrinsic factor: Binds and neutralizes them.
- Eventually, there is deficiency of intrinsic factor and impaired absorption of vitamin B12.

Clinical features and Investigations

Same as vitamin B12 deficiency anemia.

Confirmation of diagnosis by:

- Anti-parietal cell antibody
- Anti-intrinsic factor antibody.

Treatment

Lifelong vitamin B12 supplementation (usually IM route is preferred).

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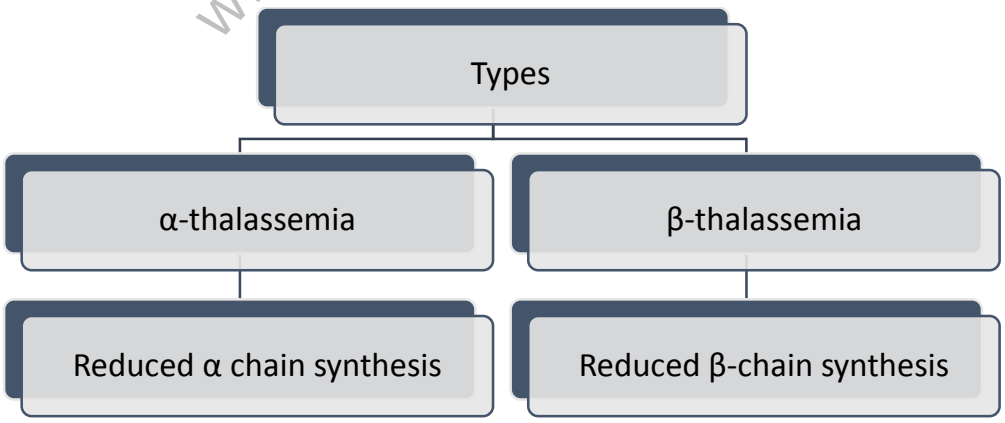
Thalassemia

Quantitative type of hemoglobinopathy.

Quantitative defect in Hb synthesis leads to chronic hemolytic anemia.



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1. ***α-thalassemia***:
   If α-chain deficiency is significant, β-chain gets precipitated forming a tetramer within the RBCs. These RBCs get destroyed by the spleen.
2. ***β-thalassemia***:
   α-chain synthesis goes on but proportion of α2β2 (HbA) gets reduced. Excess α-chain leads to 3 abnormalities:
   a. Precipitation within RBCs: RBCs undergo hemolysis
   b. Increased α2δ2 (HbA2)
   c. Increased α2γ2 (HbF).

Clinical features of thalassemia:

1. Features due to anemia:
   ✓ Anemic look
   ✓ Breathlessness
   ✓ Cardiac palpitation
   ✓ Dizziness
   ✓ Exercise intolerance
   ✓ Fatigue.
2. Features of excess hemolysis:
   a. Icterus
   b. Splenomegaly.
3. Features of accelerated erythropoiesis:
   a. Hepatomegaly
   b. Splenomegaly
   c. Frontal bossing
   d. Prominent parietal eminence
   e. Depressed bridge of nose.
4. Feature of iron overload:
   Cardiomyopathy
5. Features due to iatrogenic complications:
   Blood borne infections (HIV/ HBC/ HCV)

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Investigations

1. Evidence of anemia:
   a. Hb: ↓
   b. TC, DC, CRP: Normal
   c. Peripheral blood smear: Microcytic anemia (microcytosis is out of proportion to the degree of anemia)

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d. MCV: ↓
e. Iron studies:
   - ✓ Serum iron: ↑
   - ✓ Serum ferritin: ↑

2. Evidence of hemolysis:
   Liver function test:
   - ✓ Unconjugated bilirubin: ↑
   - ✓ LDH: ↑
   - ✓ AST: ↑

3. Evidence of accelerated erythropoiesis:
   a. Reticulocyte count: ↑
   b. Bone marrow: Erythroid hyperplasia
   c. Skull X Ray: Hair on end appearance.
4. Evidence of iron overload:
   a. Serum iron/ serum ferritin: ↑
   b. Echocardiogram: To assess cardiac function
   c. MRI heart.
5. Detection of iatrogenic complication:
   Viral serology (for HIV/ HCV): +Ve.
6. Confirmation of diagnosis of thalassemia:
   Hb electrophoresis.

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Treatment

1. Supportive treatment:
   Packed cell transfusion (the frequency of which depends upon severity of symptoms and level of Hb in blood):
   - There are 2 types of regimens:
     - ✓ Supertransfusion: Target Hb > 12 gm %
     - ✓ Hypertransfusion: Target Hb > 8 gm%.
   - There are 2 types of transfusion:
     - ✓ Triple saline wash RBC (to make RBCs WBC depleted)
     - ✓ Neocyte transfusion.
2. Prevent and treat iron overload:
   - Continuous slow SC infusion of Desferrioxamine
   - To avoid iron rich vegetables
   - To avoid citrous fruits.
3. Treatment of complications:

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- Treat infections
- Treat cardiomyopathy.

4. Definitive/ curative treatments:
    - Bone marrow transplantation
    - Splenectomy: As it is the main site of RBC destruction.

Differential diagnoses

1. *Other causes of chronic hemolytic anemia*:
    a. Hereditary spherocytosis
    b. Sickle cell anemia.
2. *Other causes of microcytic anemia*:
    a. Iron deficiency anemia
    b. Anemia of chronic inflammation
    c. Sideroblastic anemia
    d. Lead poisoning.
3. *Other causes of prominent unconjugated hyperbilirubinemia*:
    a. Hemolytic diseases
    b. Inherited liver diseases:
        ✓ Defect in bilirubin **t**ransport: Gilbert syndrome
        ✓ Defect in bilirubin **c**onjugation: **C**rigler-Najjar syndrome
        ✓ Defect in bilirubin **d**elivery: **D**ubin-Johnson syndrome/ **R**otor syndrome.

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Extras (not needed for exam.)

1. RDW (Red cell distribution width):
    - It is a measure of variation of RBC size (anisocytosis).
    - Normal value: 11.5%-14.5%
    - Abnormality:

RDW	***MCV***	***Interpretation***
↑	↓	Iron deficiency anemia
↑	N	Acute hemorrhage
↑	↑	B12/ Folate deficiency
N	↓	Thalassemia/ other causes of chronic hemolytic anemia

2. Mentzer index:

$$Mentzer\ index = \frac{MCV\ (fL)}{RBC\ count\ (lakhs/ml)}$$

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- MI > 13 is suggestive of iron deficiency anemia while a MI <13 is suggestive of thalassemia.
- It takes an extreme change in MCV and RBC count to significantly alter this ratio, which has put the reliability of this index in question.

3. Types of thalassemia according to clinical scenario:

Minor	***Intermediate***	***Major***
Asymptomatic, with only abnormal hematological parameters	Symptomatic, clinical impact of disease not significant	Symptomatic, significant clinical impact
Does not require blood transfusion	Requires occasional blood transfusion	Transfusion dependent

4. An insight into alteration of laboratory parameters in α and β thalassemia:

α-thalassemia

Genes deleted	***Hematocrit (Normal: 45-55%)***	***MCV (Normal: 85-105)***	***Comment***
1	Normal	Normal	Silent carrier
2	30-40%	60-75	α-thalassemia trait
3	20-30%	60-70	Hemoglobin H disease
4	-	-	Hydrops fetalis

β-thalassemia

Type	***HbA (Normal: 95-96%)***	***HbA2 (Normal: 1-3%)***	***HbF (Normal: <1%)***
Minor	85-95%	4-5%	1-5%
Intermediate	0-30%	1-10%	0-100%
Major	0-10%	4-10%	95-96%

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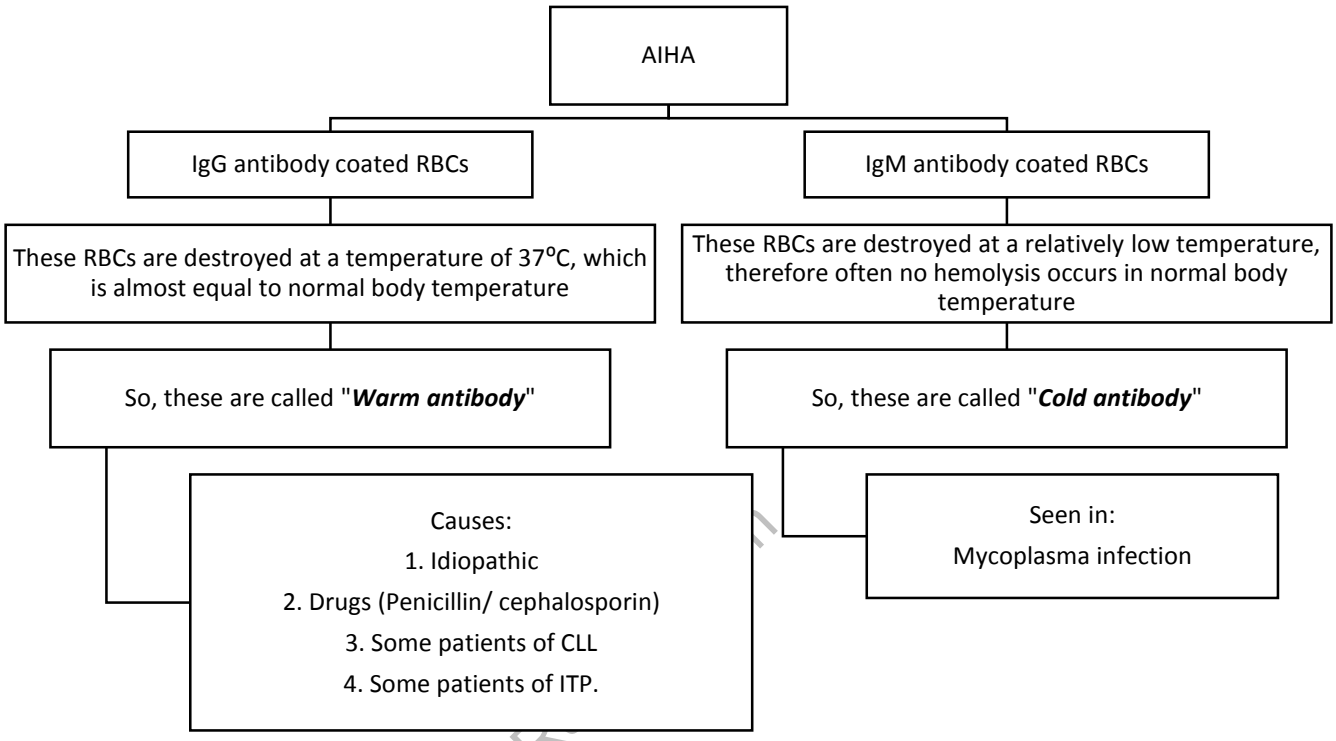
Autoimmune hemolytic anemia (AIHA)

Hemolysis of autoantibody coated RBCs.

Causes/ types:



Clinical features:

1. In many persons, it is completely asymptomatic
2. In case of chronic hemolysis:
   a. Anemia + symptoms due to anemia
   b. Jaundice
   c. Splenomegaly
   d. Features due to the underlying disease.

Investigations

1. Evidence of anemia:
   a. Hb: ↓
   b. Presence of Spherocytes.

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2. Evidence of hemolysis:
   a. Unconjugated bilirubin: ↑
   b. LDH: ↑
3. Evidence of accelerated erythropoiesis:
   a. Reticulocyte count: ↑
   b. Bone marrow: Erythroid hyperplasia
4. ***Coomb's test***:
   a. Direct: Usually +Ve (detects antibody coated RBCs)
   b. Indirect: May/ may not be +Ve (detects free antibody in serum).

Treatment

1. None required in case of insignificant hemolysis
2. In case of significant hemolysis:
   a. Prednisolone
   b. Splenectomy.
3. Treatment of the underlying disease.

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Microangiopathic hemolytic anemia (MAHA)

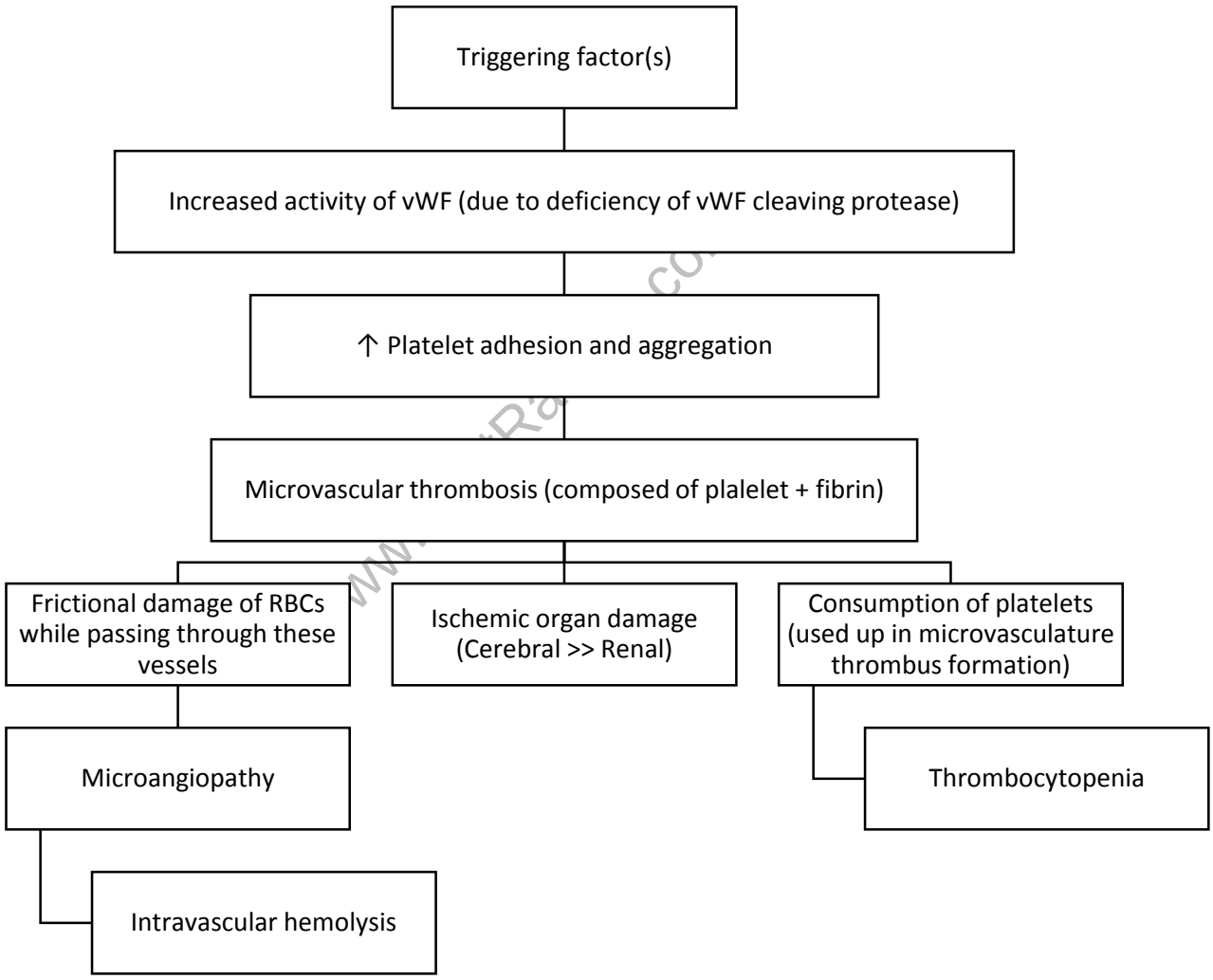
Accelerated intravascular hemolysis due to *damaged microvasculature wall*.

Ex.:

1. Thrombotic thrombocytopenic purpura (TTP)
2. Hemolytic uremic syndrome (HUS).

Thrombotic thrombocytopenic purpura (TTP)

Pathogenesis:



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Clinical features:

T	Features due to **t**hrombosis	CNS thrombosis: ✓ Seizure ✓ Confusion ✓ Delirium ✓ Encephalopathy ✓ Fluctuating focal neurological signs.
T	Features due to **t**hrombocytopenia	Bleeding manifestations: ✓ Purpura ✓ Gum bleeding ✓ Epistaxis ✓ Internal bleeding: Gastrointestinal, Genitourinary, Intracranial.
P		**P**allor + Jaundice

Investigation

1. Blood:
   - Hb: ↓
   - Peripheral film: ***Fragmented RBCs (Schistocytes)***
   - TC: Normal
   - Platelet count: ↓
2. Evidence of hemolysis:
   - Unconjugated bilirubin: ↑
   - LDH: ↑
3. Evidence of intravascular hemolysis:
   - Hemoglobinuria
   - Hemosiderinuria
   - Serum Haptoglobin: ↓.

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Treatment

Supportive (Plasmapheresis).

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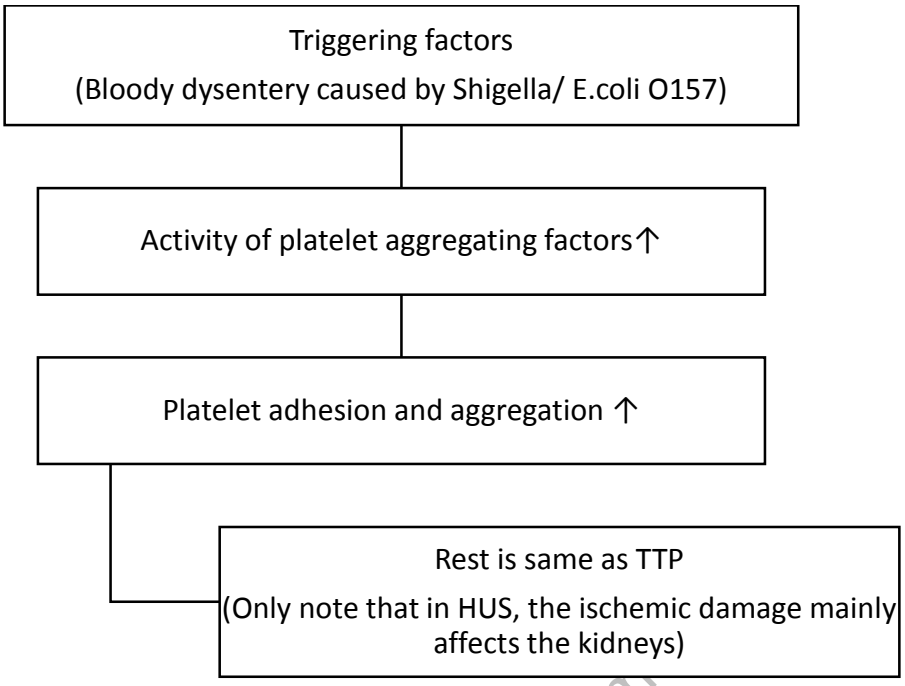
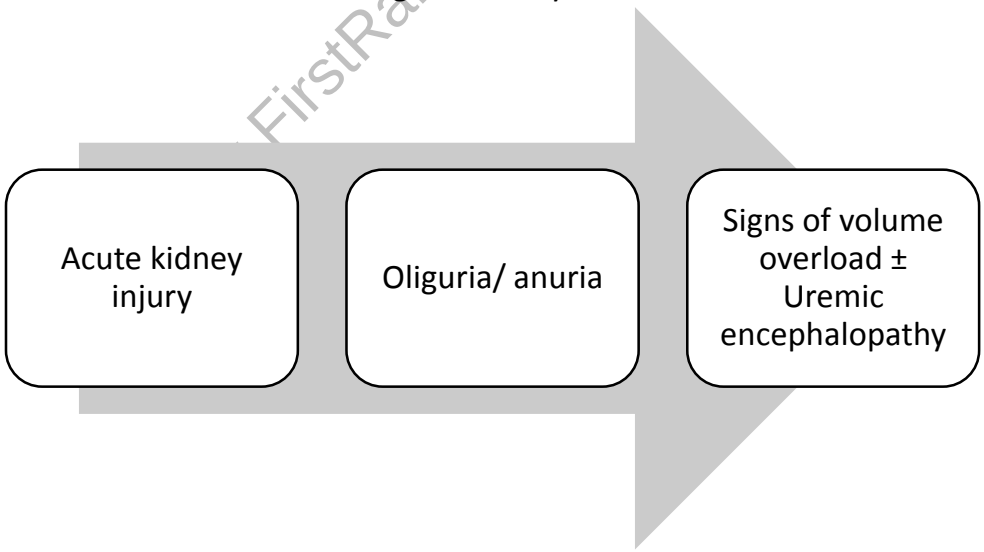
Hemolytic uremic syndrome (HUS)

Pathogenesis:



Clinical features:

1. H/O bloody diarrhea is usually present
2. Features due to thrombotic damage to kidney:



3. Features due to thrombocytopenia:
   Bleeding manifestations:
   Purpura, gum bleeding, epistaxis, internal bleeding (GI/ GU/ IC).
4. Pallor (mild) ± Jaundice (mild).

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Investigations

1. Blood:
    - Hb: ↓
    - Peripheral film: ***Fragmented RBCs (Schistocytes)***
    - Platelet count: ↓
2. Evidence of hemolysis:
    - Unconjugated bilirubin: ↑
    - LDH: ↑
3. Evidence of intravascular hemolysis:
    - Hemoglobinuria
    - Hemosiderinuria
    - Serum haptoglobin: ↓
4. Renal function:
   Urea Creatinine: ↑ (in case of uremic encephalopathy)
   Serum K+: ↑
5. Stool culture and sensitivity.

Treatment

Primarily supportive:

1. In case of acute kidney injury: Dialysis
2. In case of severe hemolysis: Plasmapheresis.

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Sideroblastic anemia

Anemia resulting from *defective haem synthesis/ metabolism*.

Pathophysiology:

Defective haem synthesis ultimately leads to ineffective erythropoiesis; causing anemia.

Causes:

1. Idiopathic
2. Chronic alcohol use
3. Drug: Isoniazid
4. Chronic infection/ inflammation.

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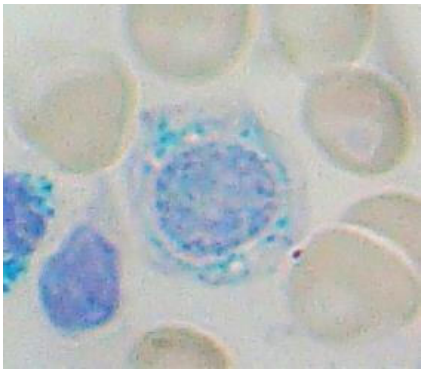
Clinical features:

1. Asymptomatic
2. Symptomatic due to anemia.

Investigations

1. Blood:
   - Hb: ↓
   - WBC/ Platelet: Normal
2. Peripheral film:
   - Microcytic anemia
   - ***Dimorphic picture*** (Small + normal sized RBCs)
   - Reticulocyte: Absent
   - If caused by chronic alcohol use, there is macrocytic anemia.
3. Serum iron studies:
   Picture of iron overload (due to defect in iron metabolism):
   - Serum iron: ↑
   - Transferrin saturation: ↑
   - Serum ferritin: May be ↑
4. Evidence of hemolysis: Absent (to rule out hemolytic anemia)
   - Unconjugated bilirubin: Normal
   - Serum LDH: Normal
5. Bone marrow:
   Shows ***ring sideroblast*** (iron gets deposited within abnormal nucleated RBCs encircling the nucleus).



6. Stool for occult blood test
7. Endoscopy, if missed: colonoscopy.

Treatment

Supportive: Blood/ packed cell transfusion.

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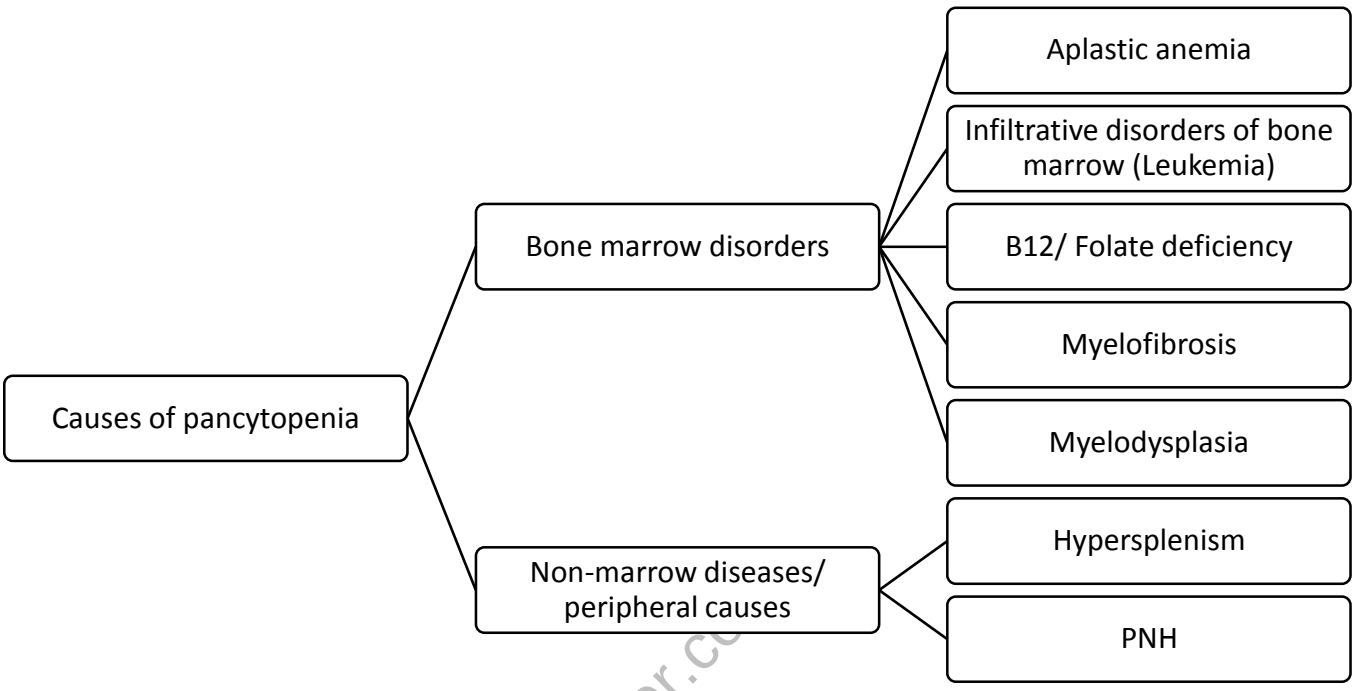
Pancytopenia

Reduction in all 3 series of blood cells.

Causes:



Clinical features of pancytopenia:

- Patient may be completely asymptomatic
- Features due to anemia:
  - ✓ Anemia
  - ✓ Breathlessness
  - ✓ Cardiac palpitations
  - ✓ Dizziness
  - ✓ Exercise intolerance
  - ✓ Fatigue.
- Features due to thrombocytopenia:
  - ✓ Purpura
  - ✓ Gum bleeding
  - ✓ Epistaxis
  - ✓ Internal hemorrhage: GI/ GU/ IC.
- Features due to neutropenia:
  Increased risk of infections:

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- ✓ Fever
- ✓ URTI/ LRTI (Sore throat)
- ✓ Cellulitis/ abscess/ meningitis
- ✓ Fungal infections.

- Features due to the underlying disease.

Investigations

1. Blood:
   a. Full blood count
   b. Peripheral film: To look for abnormal/ immature cells
   c. RBC indices: MCV (if ↑, check for vitamin B12/ Folate deficiency anemia).
2. USG:
   Liver and spleen size
3. Bone marrow:
   a. Hypocellular: Indicates aplastic anemia
   b. Fibrosis: Indicates myelofibrosis
   c. Leukemic cells: Indicates infiltrative disorders of marrow (leukemia).
4. Special tests to confirm the diagnosis.

Treatment of pancytopenia

1. Supportive treatment:
   a. Treatment of anemia:
      Packed cell transfusion, when patient is symptomatic due to anemia.
   b. Treatment of thrombocytopenia:
      Platelet transfusion in case of significant bleeding.
   c. Treatment of neutropenia:
      Neutropenia is defined as an ANC < 1500/µL:
      - Double barrier nursing
      - Febrile patient: IV 3rd generation cephalosporin/ Carbapenem ± Fluconazole/ Itraconazole
      - Septic screen (to find the focus of infection)
      - Granulocyte- Colony Stimulating Factor (G-CSF): Filgrastim.

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Aplastic anemia

Bone marrow hypocellularity leading to pancytopenia in the absence of marrow infiltration and fibrosis.

Causes:

3I

- Idiopathic: Autoantibody mediated
- Iatrogenic:
  Many drugs may potentially cause aplastic anemia:
  - ✓ Anticancer drugs
  - ✓ Antibiotics: Chloramphenicol/ Sulfonamide
  - ✓ NSAIDs: Phenylbutazone
  - ✓ Anti-rheumatic drugs: Gold, Sulfasalazine.
- Infections:
  - ✓ HIV
  - ✓ HBV.

Clinical features:

1. Features of anemia
2. Features of thrombocytopenia
3. Features of neutropenia
4. ***Absence of hepatosplenomegaly***.

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Investigation

1. Blood:
   a. Hb: ↓
   b. RBC count, WBC count, Platelet count: ↓
   c. RBC indices: MCV: Normal.
2. Serum vitamin B12 and folate level:
   To rule out deficiency.
3. Unconjugated bilirubin and serum LDH:
   To rule out hemolysis.
4. Viral serology (HIV, HBV):
   To rule out infections.

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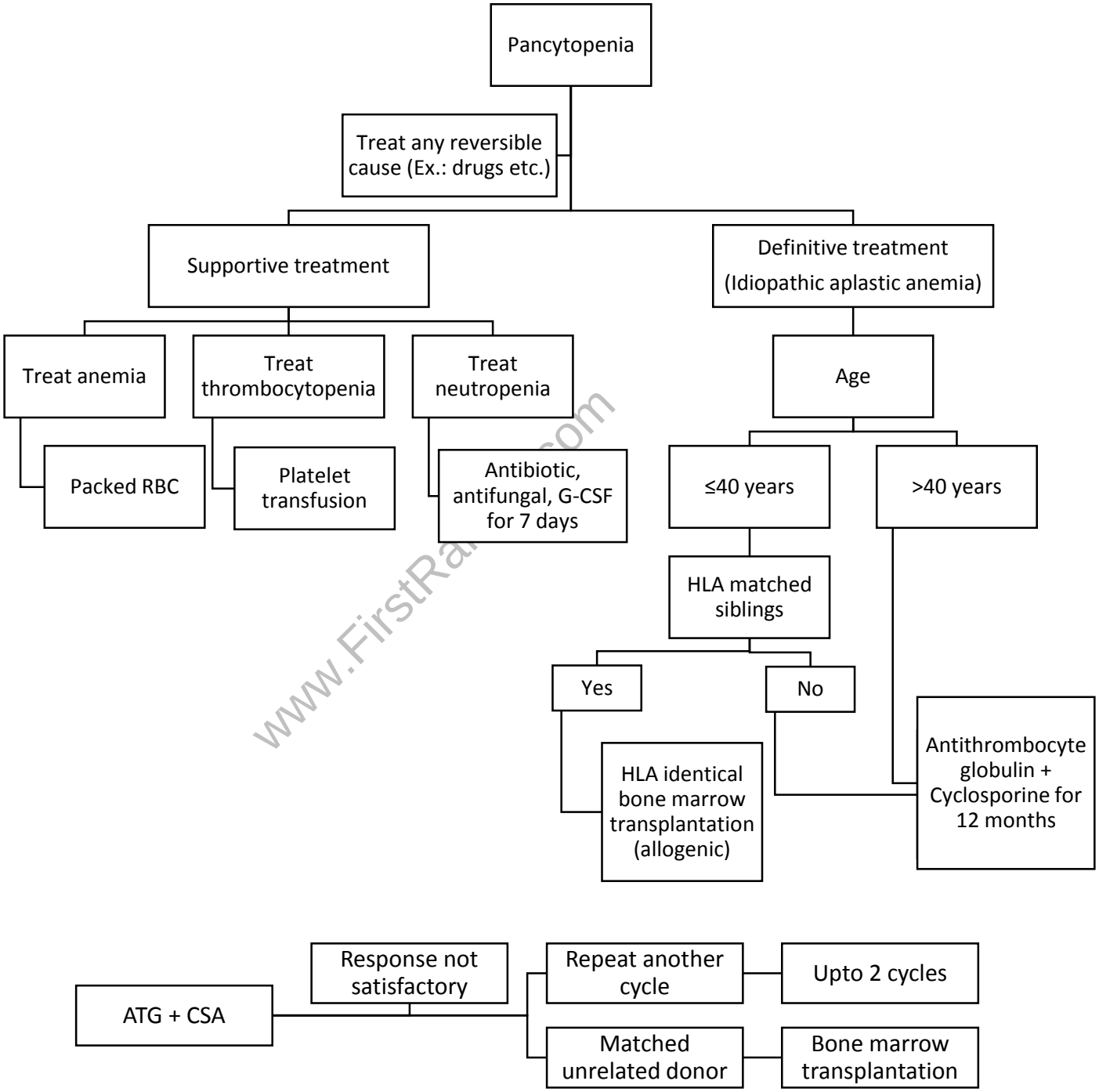
5. USG abdomen:
   To look for organomegaly.
6. Bone marrow examination:
   Trephine biopsy detects hypocellular marrow.

Treatment



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Anemia of chronic inflammation

Causes:

1. Rheumatoid arthritis
2. Inflammatory bowel disease
3. Chronic kidney disease.

Pathogenesis:

It is a multifactorial disorder:

1. Iron depletion (due to increased activity of hepcidin which is an iron absorption regulatory protein)
2. Decreased responsiveness of erythropoietin to its receptors
3. Decreased erythropoietin synthesis (particularly occurs in CKD).

Clinical features:

1. Mild to moderate anemia
2. Features of underlying disease.

Investigations

1. Blood:
   - Hb: ↓
   - MCV: Normal/ ↓
2. Iron studies:
   - Serum iron: Normal/ ↓
   - Serum ferritin: Normal/ ↑

Differentiating among 3 common anemia from iron studies:

Parameters	IDA	Thalassemia	Chr. Inflam.
MCV	↓	↓	N/↓
Serum Fe	↓	↑	N/↓
Serum Ferritin	↓	↑	N/↑

Treatment

1. Treatment of the underlying disease
2. Packed cell transfusion (when anemia is symptomatic)
3. Iron supplementation
4. Regular erythropoietin supplementation (particularly in CKD).

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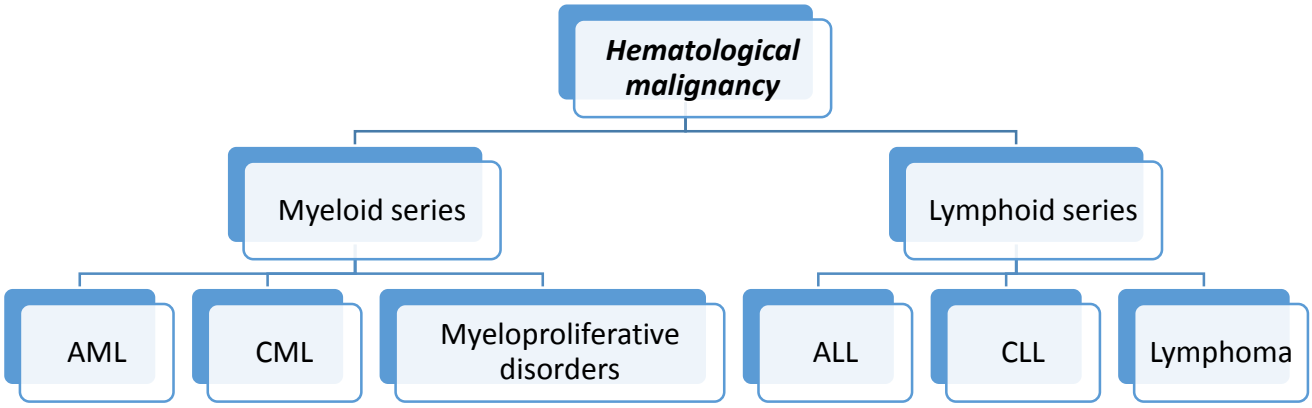


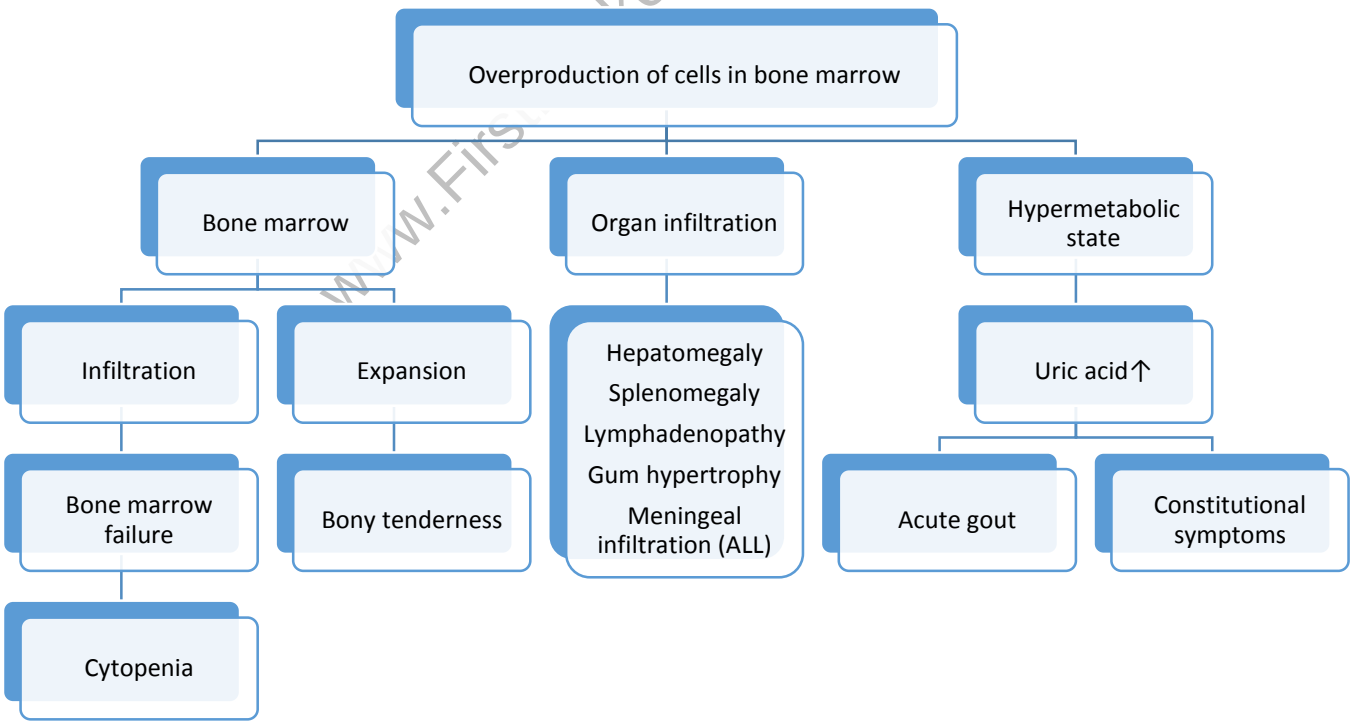
Acute leukemia

Malignant transformation of myeloid/ lymphoid cells characterized by *overproduction* as well as *defective maturation* of cells.

Types:

2 types: ALL and AML.

Mechanisms of clinical manifestations:



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Clinical features:

Age group:

- ALL: Pediatric age group (2-7 years)
- AML: Middle aged/ elderly patients.

Symptoms:

Result from bone marrow infiltration/ failure:

1. Anemia:
   - ✓ Exercise intolerance
   - ✓ Fatigue
2. Bleeding manifestations
3. Infection:
   - ✓ Fever
   - ✓ URTI/ LRTI
   - ✓ Cellulitis/ abscess.

Signs:

1. Due to organ infiltration:
   - ✓ Hepatomegaly
   - ✓ Splenomegaly
   - ✓ Lymphadenopathy
   - ✓ Gum hypertrophy
   - ✓ Meningeal signs (particularly in ALL).
2. Due to marrow expansion:
   Bone tenderness over sternum and pelvic region.
3. Due to hyperuricemia:
   - ✓ Acute gouty arthritis
   - ✓ Constitutional symptoms: Fever, sweating, weight loss etc.

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Investigations

1. Blood:
   - Hb: ↓
   - WBC count: Variable (↑/↓)
   - Platelet count: ↓
2. Peripheral film: Blast cells

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3. Bone marrow:
   Plenty of blast cells (>20% blast cells in marrow confirms an ongoing acute leukemic process):
   - Myeloblast
   - Lymphoblast.
4. Flow cytometry:
   It detects cell surface markers which get expressed in leukemia:
   - ALL: CD10, CD19
   - AML: CD13, CD33.
5. Cytochemistry:
   - AML: Myeloperoxidase (MPO), Butyrate esterase
   - ALL: Detection of Philadelphia chromosome (some of the patients of ALL will show this chromosome).

Diagnosis of complications:

1. Uric acid: ↑ (Due to hypermetabolic state)
2. Serum vitamin B12: ↑ (Due to ↑ levels of transcobalamin 3)
3. CSF: To look for meningeal infiltration (particularly in ALL)
4. Septic screen: To find the focus of infection:
   - ✓ Blood and urine: culture and sensitivity
   - ✓ Chest X Ray
   - ✓ C-reactive protein (CRP)
   - ✓ Throat swab: Gram stain and culture-sensitivity.

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Treatment

1. Supportive treatment:
   a. Treat anemia
   b. Treat thrombocytopenia
   c. Treat neutropenia
   d. Treat hyperuricemia:
      - Allopurinol
      - Febuxostat.
2. Definitive treatment.

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Definitive treatment of ALL

1. Chemotherapy:
   a. ***Induction of remission***:
      Aggressive chemotherapy to destroy most of the leukemic cells.
      Drugs used: Cytarabine + Doxo/ Dauno-rubicin.
   b. ***Consolidation/ intensification of remission***:
      Destroy the rest of the leukemic cells.
      Drug used: Daunorubicin.
   c. ***Maintenance of remission***.
2. Allogenic stem cell transplantation:
   The decision depend on prognostic factors:
   a. Response to chemotherapy
   b. Comorbidities of the patient
   c. Age of the patient.

Definitive treatment of AML

1. Chemotherapy:
   a. ***Induction of remission*** (duration: 4 weeks):
      Drugs used: Vincristine, Prednisone, L-asparaginase, Daunorubicin.
   b. ***Consolidation/ intensification of remission*** (duration: 4 months):
      Drugs used: Methotrexate, L-asparaginase, Cyclophosphamide, Cytarabine, Etoposide.
   c. ***Maintenance of remission*** (duration: >2 years):
      Drugs used: Methotrexate, 6MP, Vincristine, Prednisone.
   Note: If patient is BCR-Abl positive, a tyrosine kinase inhibitor (TKI) is added to the above regimen.
2. Bone marrow transplantation (BMT):
   Post-remission BMT may be indicated in certain patients depending on:
   a. Response to chemotherapy,
   b. Comorbidity,
   c. Age of the patient.
3. Radiotherapy:
   Post- remission prophylactic cranial radiotherapy may be given to treat any meningeal infiltration.

Acute promyelocytic leukemia

1. Often patients present with DIC

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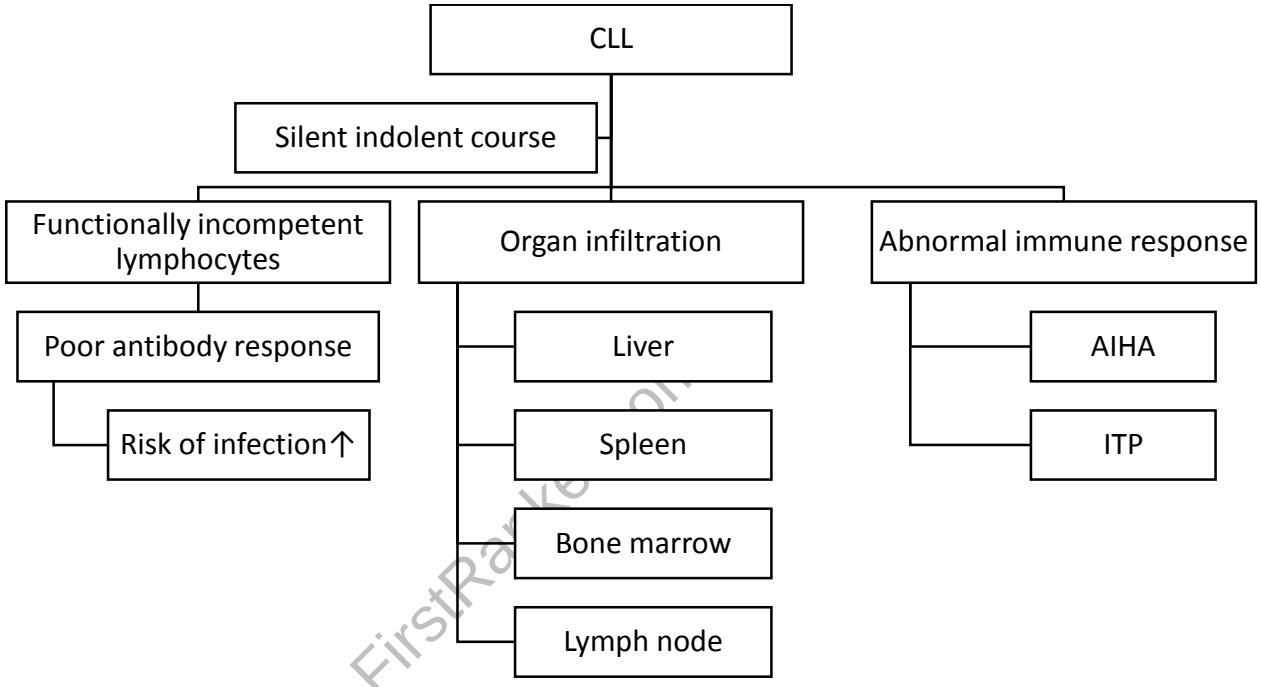
2. Drug of choice in chemotherapy is Retinoic acid.

Chronic leukemia

CLL

Malignant transformation of lymphocytes typically characterized by mature lymphocytosis (B lymphocytes).

Pathogenesis:



Clinical features:

1. Often asymptomatic and diagnosed incidentally
2. Recurrent infection:
    - LRTI
    - URTI
    - Pneumonia
    - Recurrent viral infections
    - Recurrent cellulitis, abscess formation etc.
3. Features of organ infiltration:
    - Hepatomegaly
    - Splenomegaly

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- Lymphadenopathy (usually not generalized)
- Features of lymph node enlargement may be present.

4. Features of anemia
5. Features of bleeding manifestations
6. Icterus.

Investigations

1. Blood:
   - Hb: Normal/ ↓ (in case of AIHA)
   - WBC count: ↑ (mild to moderate): predominantly lymphocytes
   - Peripheral smear: Small mature lymphocytes, presence of smear cells/ smudge cells
   - Platelet count: ↓
2. Liver function test:
   Low γ-globulin level: Hypogammaglobulinemia.
3. Evidence of autoimmune hemolytic anemia:
   - Unconjugated bilirubin: ↑
   - Serum LDH: ↑
   - Coomb's test: +Ve.
4. Serum uric acid: Normal/ ↑
5. Bone marrow: Lymphocytosis
6. CECT abdomen: To detect any organ infiltration
7. Flow cytometry:
   It detects cell surface markers which get expressed in CLL (CD19, CD20, CD5, CD23).

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Treatment

There are 2 approaches in treatment of a CLL patient:

1. Wait and watch approach
2. Proceed to therapeutic intervention.

In the wait and watch approach, only supportive treatments are given:

Supportive treatment:

1. Anemia: Blood transfusion
2. Infection: Antibiotics, Prophylactic IgG
3. AIHA: Corticosteroid and Rituximab.

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Therapeutic interventions:

Options are:

1. Chemotherapy:
    - Fludarabine
    - Cyclophosphamide
    - Rituximab.
2. Bone marrow transplantation:
   In selected patients who have medically refractory CLL
3. Treatment of AIHA/ ITP:
    - Prednisone
    - Rituximab
    - Splenectomy.

Extras: Rai staging system of CLL

Staging	***Description***	
Stage 0	Lymphocytosis	-
Stage 1	Lymphocytosis +	Lymphadenopathy
Stage 2	Lymphocytosis +	Organomegaly
Stage 3	Lymphocytosis +	Anemia
Stage 4	Lymphocytosis +	Significant thrombocytopenia

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Indication for active treatment in CLL

1. Significant lymphadenopathy
2. Significant anemia/ thrombocytopenia.

Therefore, active treatment is required stage 2 and above.

Immunoglobulin therapy

Intermittently given, for treating hypogammaglobulinemia.

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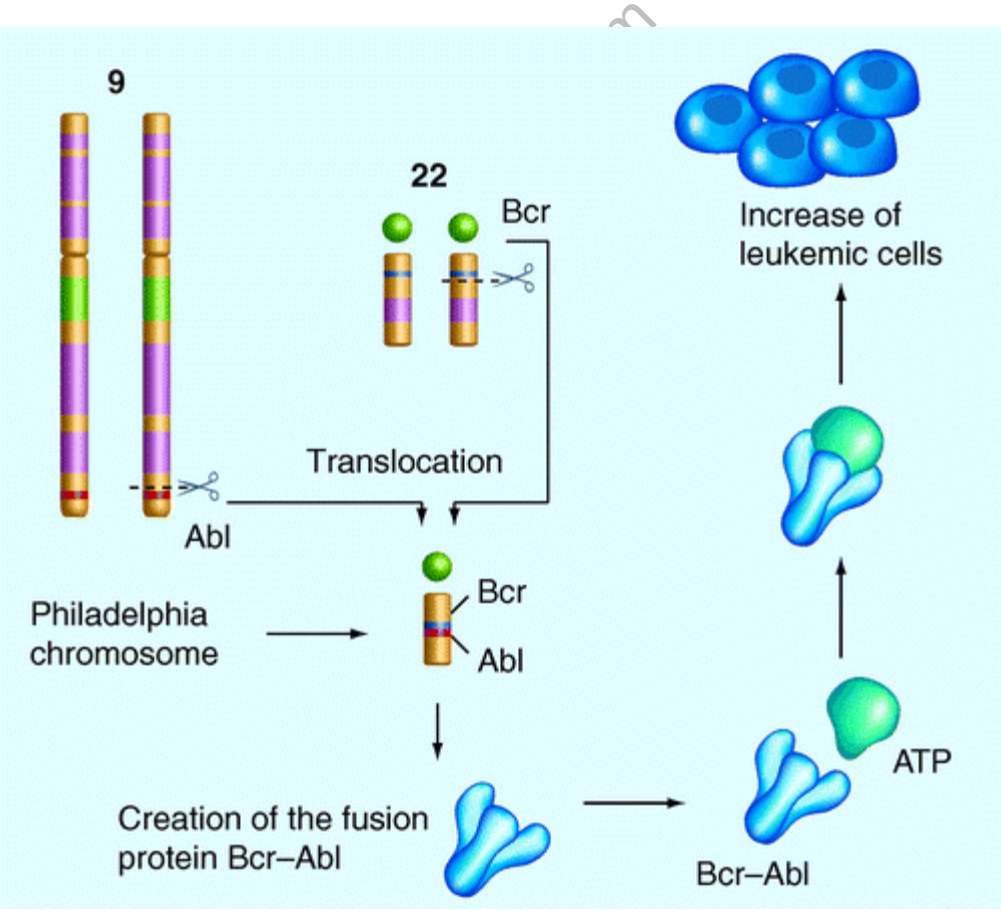
CML

It is a myeloproliferative disease characterized by relentless proliferation of cells of myeloid series (but there is no defect of differentiation/ maturation process).

Pathogenesis:

1. The primary defect is *reciprocal translocation between 2 arms of chromosome 22 and chromosome 9*.
2. The portion of chromosome 9 which gets translocated is called Abl (Abelson murine leukemia viral oncogene).
3. The point on chromosome 22 where the translocated portion of chromosome 9 gets attached to, is called Bcr (Breakpoint cluster region).
4. The fusion gene is called Abl-Bcr, which exhibits abnormally high *tyrosine kinase activity*, which plays a central role in the pathogenesis of CML.
5. The abnormal chromosome is called *Philadelphia chromosome*, which can be detected by cytological studies.
6. The abnormal gene (Abl-Bcr fusion gene) can be quantified using molecular studies.



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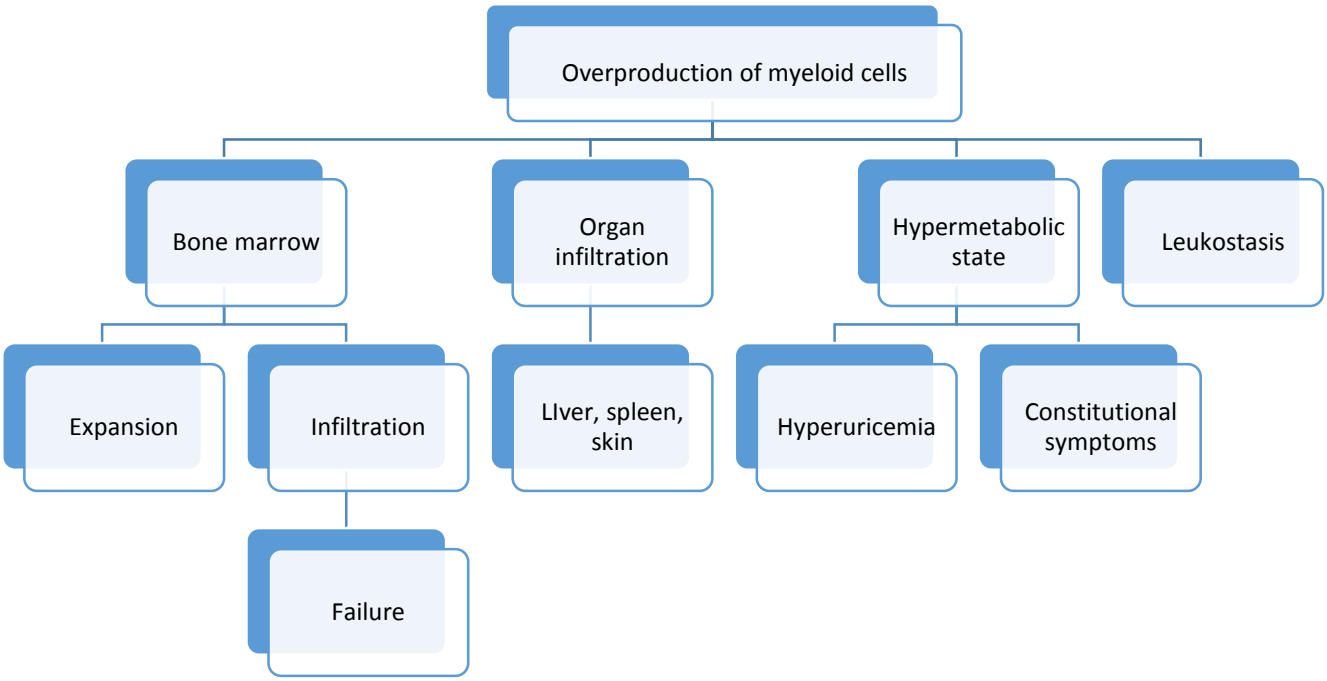
Mechanism of clinical manifestations:



Clinical features:

Symptoms

1. Constitutional symptoms:
    - Fever
    - Night sweat
    - Weight loss.
2. Bone marrow failure:
    - Anemia (early manifestation)
    - Thrombocytopenia (bleeding manifestations)
    - Neutropenia (at late stage).

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Signs

1. Due to organ infiltration: Hepatosplenomegaly
2. Due to marrow expansion: Sternal tenderness
3. Due to leukostasis:
    a. Pulmonary vascular occlusion: Acute chest pain
    b. Cutaneous vascular occlusion: Vasculitic rash
    c. Occlusion of CNS vessels: Temporary focal neurological signs.

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Investigation

1. Blood:
   - Hb: ↓
   - WBC count: ↑↑
   - Platelet count: Normal/ ↓ (due to marrow failure).
2. Peripheral film:
   - Abundant mature WBCs (Promyelocyte/ Metamyelocyte)
   - Myeloblast: Usually very few (Significant number of blast cell is seen in blast crisis phase, i.e. transformation of CML into acute leukemia)
   - *Basophilia*: Indicates an impending episode of blast crisis.
3. Bone marrow:
   - Myeloid hyperplasia
   - Blast cells: Usually <5% (When it is 10-20%, signifies blast crisis)
     Note that: Blast cells of CML usually don't contain Auer rod.
4. Special tests:
   a. Cytogenetic study:
      Detection of Philadelphia chromosome confirms the diagnosis.
   b. Molecular study:
      Quantification of Bcr-Abl gene.

Treatment

1. Supportive treatment:
   a. Treatment of anemia
   b. Treatment of thrombocytopenia
   c. Treatment of neutropenia
   d. Treatment of hyperuricemia.
2. Definitive treatment:
   a. Chemotherapy:
      - ✓ Drug of choice is tyrosine kinase inhibitor:
        1st generation: Imatinib
        2nd generation: Nilotinib, Dasatinib.
      - ✓ In case of accelerated stage/ blast crisis, more aggressive chemotherapy is given.
      - ✓ Response to chemotherapy can be assessed by:

Response	Description
Hematological response	Normalisation of hematological parameters and significant reduction of spleen size by 3 months

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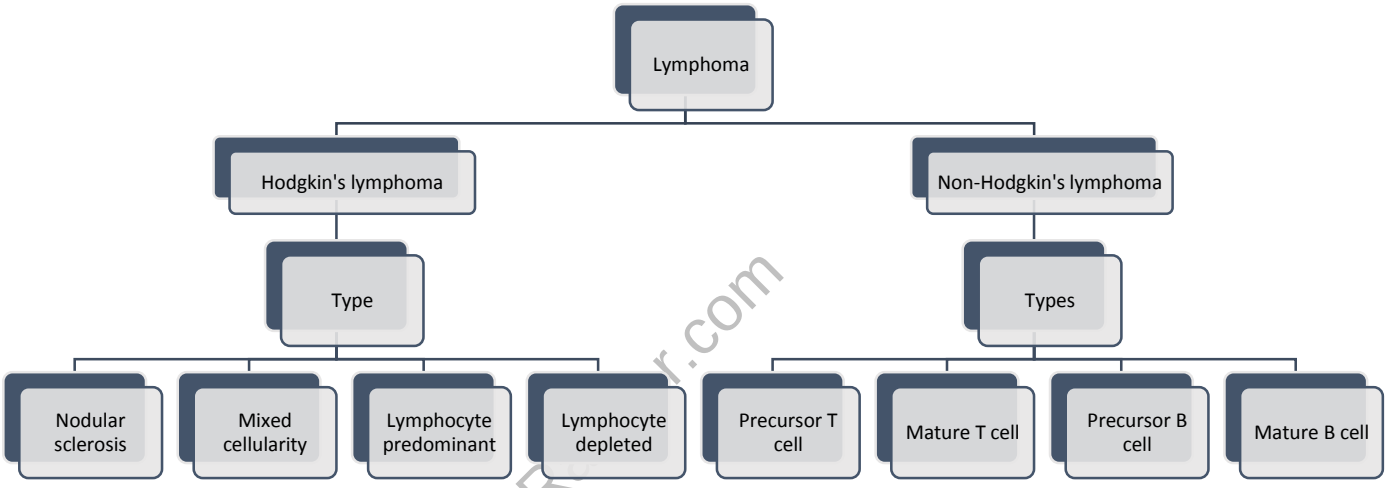
Cytogenetic response	Philadelphia chromosome becomes undetectable by 6 months (latest: by 12 months)
Molecular response	Significant reduction in quantity of Bcr-Abl gene.

b. Bone marrow transplantation:
In case of medically unresponsive/ poorly responsive patients.

Lymphoma

Malignant transformation of lymphocytes.

Classification:



Mechanism of clinical manifestations:

1. Enlargement of lymphoid follicle--------→ Lymphadenopathy
   Lymph nodes commonly involved:
   a. Above diaphragm:
      - ✓ Cervical
      - ✓ Axillary
      - ✓ Epitrochlear
      - ✓ Mediastinal.
   b. Below diaphragm:
      - ✓ Para-aortic
      - ✓ Inguinal.
2. Extranodal spread:
   a. Liver
   b. Spleen

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c. Bone marrow (advanced stage); resulting in marrow infiltration/ failure.

Clinical features:

1. Constitutional symptoms:
    - Fever
    - Sweating
    - Weight loss
2. Features of lymphadenopathy:
    - Palpable lymph nodes: Firm, non-tender, discrete
    - Mediastinal lymphadenopathy: May result in SVC obstruction/ Superior mediastinal syndrome
        - For some unknown reasons, Hodgkin's lymphadenopathy becomes painful after alcohol ingestion.
3. Features due to Extranodal spread:
    - Hepato/spleno-megaly
    - Pleural effusion/ ascites
    - Bone marrow failure at late stage (showing features of anemia, thrombocytopenia, neutropenia).
4. Pal Ebstein's fever:
   In Hodgkin's lymphoma, there is period of high fever followed by prolonged afebrile period after which fever recurs.
5. Acute gouty arthritis.

Investigations

1. Blood:
    - Hb, TC, DC, Platelet count: Normal (cytopenia is a late manifestation)
2. Liver function test:
    - Often normal (but may be non-specifically deranged)
3. Serum uric acid estimation
4. CXR
5. CECT of chest, abdomen and pelvis (to look for lymphadenopathy)
6. Confirmation of diagnosis of lymphoma:
    - FNAB
    - Excisional biopsy.
7. Bone marrow (to look for bone marrow infiltration).

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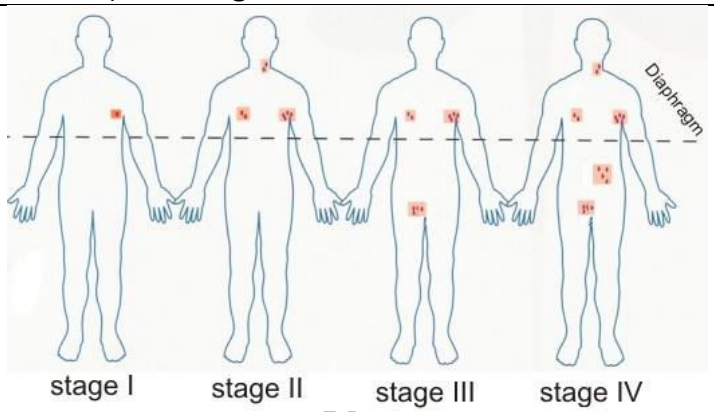
Treatment

Hodgkin's lymphoma

Staging (Ann Arbor classification):

Stage	Description
1	Single lymph node region on one side of diaphragm
2	≥2 lymph node region on one side of diaphragm
3	Involvement of lymph node region on both sides of diaphragm
4	Extranodal spread
A	No constitutional symptoms
B	Constitutional symptoms present (fever, night sweat, ≥10% unintentional weight loss)



Management according to stage

- Stage 1 and 2: Chemotherapy + Local field radiotherapy
- Stage 3 and 4/ any stage B (symptomatic): High dose chemotherapy
- Chemotherapeutic drugs used:
  - ✓ Doxo/ Dauno-rubicin
  - ✓ Bleomycin
  - ✓ Vinblastine
  - ✓ Dacarbazine.

Non-Hodgkin's lymphoma

Chemotherapy (CDPRV):

C. Cyclophosphamide

D. Doxorubicin

P: Prednisolone

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R: Rituximab

V: Vincristine.

Myeloproliferative disorders

Characterized by overproduction of any hematopoietic cell series in an isolated manner/ simultaneously.

Causes:

1. Polycythemia rubra vera
2. Essential thrombocytosis
3. CML
4. Myelofibrosis.

Myelofibrosis

Characterized by marrow fibrosis and exuberant extramedullary hematopoiesis.

Clinical features:

1. Asymptomatic
2. Due to marrow fibrosis:
   a. Marrow failure, leading to features of pancytopenia
   b. Features due to anemia (earliest manifestation)
   c. Features due to thrombocytopenia (bleeding manifestations)
   d. Features due to neutropenia (recurrent infections).
3. Due to extramedullary hematopoiesis:
   a. Significant splenomegaly (causing LUQ discomfort and sensation of fullness) ± hepatomegaly
   b. Usually occurs in elderly population.

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Investigations

1. Blood:
   - Hb: ↓ (earliest and often the only abnormality on presentation)
   - WBC, platelet count: May be ↓
   - Peripheral film:
     - ✓ Poikilocytosis
     - ✓ Teardrop cells
     - ✓ Bizarre looking platelets

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- ✓ Leuko-erythroblastic picture.

2. Bone marrow:
   Marrow aspirate shows reticulin (fibrosis).

Treatment

1. Supportive treatment:
   Treatment of anemia, thrombocytopenia and neutropenia.
2. Definitive treatment:
   a. Medical:
      - ✓ Lenalidomide
      - ✓ Pomalidomide.
   b. Bone marrow transplantation.

Polycythemia rubra vera (PRV)

Hyperproliferation of all 3 series of blood cells.

Pathogenesis:

JAK2 mutation plays a central role in PRV.

Clinical features:

1. Often asymptomatic
2. Features due to ↑RBC count and associated hyper-viscosity state:
   a. Headache
   b. Dizziness
   c. Plethoric appearance.
3. Features due to ↑WBC count:
   Basophilia: Pruritus typically after having a shower (due to increased histamine release)
4. Features due to thrombocytosis:

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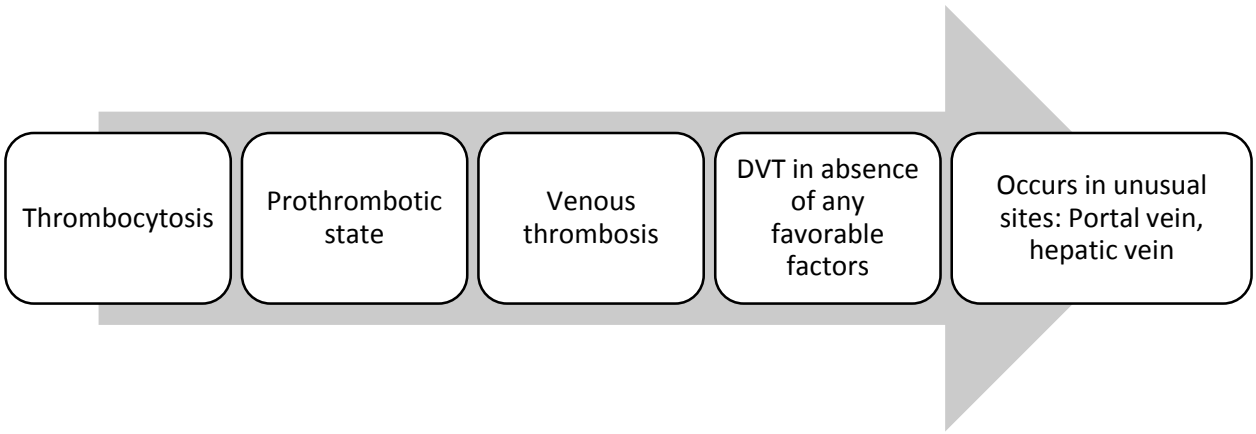

5. Although not common, bleeding manifestations may occur due to functional defect of the platelets.
6. Often splenomegaly is present.

Investigations

1. Blood:
   - Hb: ↑ (often markedly high and usually the earliest manifestation)
   - RBC count: ↑
   - RBC mass: ↑
   - PCV: Abnormally ↑
   - Platelet count: ↑.
2. Diagnosis is confirmed by detecting the presence of JAK2 mutation.

Treatment

1. Regular phlebotomy
2. Medical treatment:
   a. Hydroxyurea
   b. Prophylactic aspirin.

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Extras: Differentiating PRV from secondary polycythemia

Points	***PRV***	***Secondary polycythemia***
Hypoxia in patient	Patients are non-hypoxic	Often patients are chronically hypoxic (COPD/ ILD/ Congenital heart disease etc.); non-hypoxic causes are uncommon (EPO secreting tumor/ RCC/ Cerebellar hemangioblastoma etc.)
Blood cells	RBC↑ WBC↑ Platelet↑	RBC↑

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EPO	↓	↑
JAK2 mutation	+Ve	-Ve

Essential thrombocytosis

Myeloproliferative disorder characterized by *abnormal proliferation of platelets only*.

Clinical features:

1. Often asymptomatic
2. Prothrombotic state, leading to unprovoked DVT at unusual site
3. *Erythromelalgia*: Reddish discoloration of skin due to vascular stasis in cutaneous vessels.

Investigations

1. Blood:
   - RBC/ WBC/ Hb: Normal
   - Platelet count: Abnormally ↑
2. Bone marrow:
   Megakaryocytes are found plenty in number.

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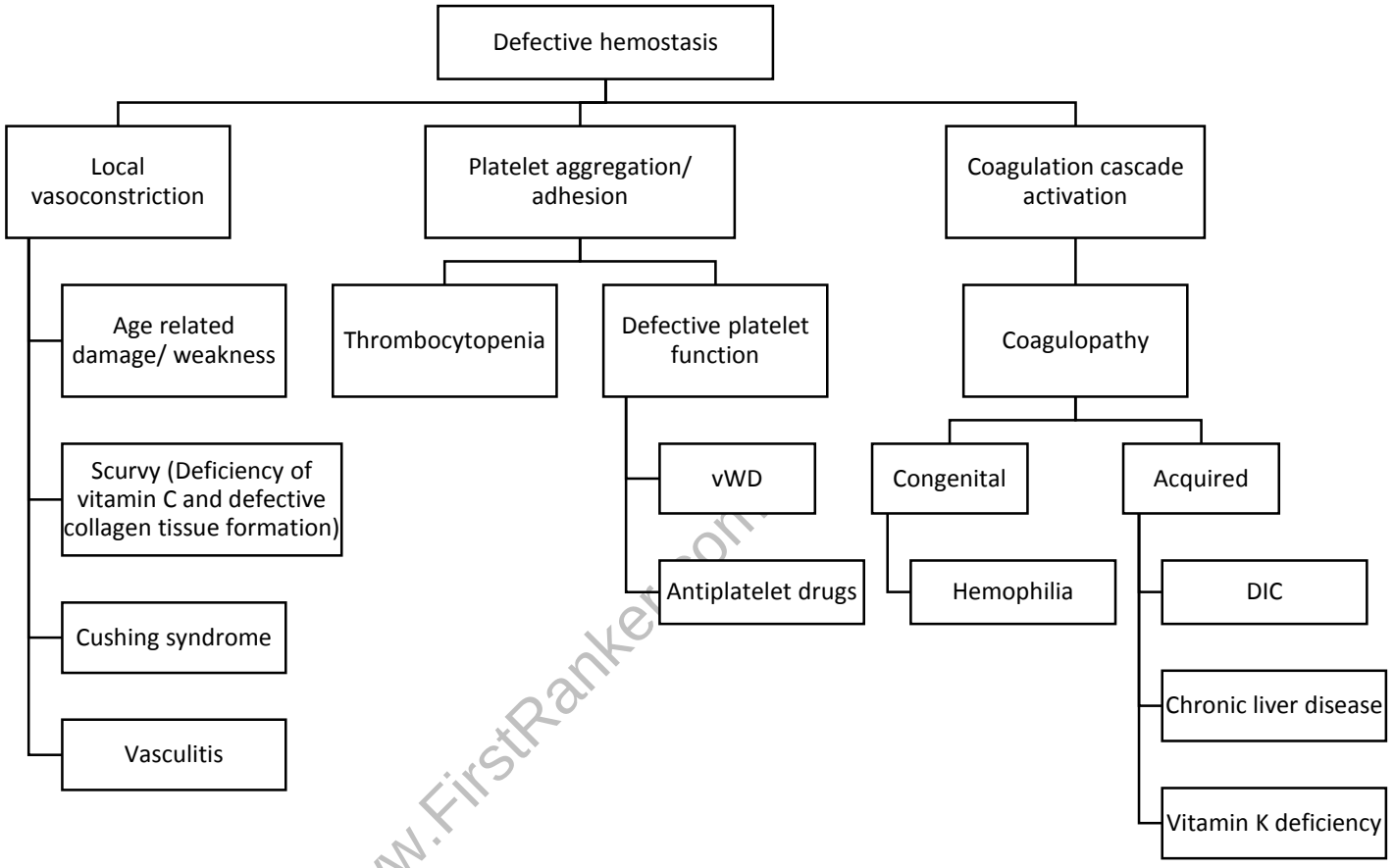
A general discussion on bleeding disorders

Introduction:

Spontaneous bleeding/ abnormal bleeding following minor trauma.

Etiology of bleeding disorders:



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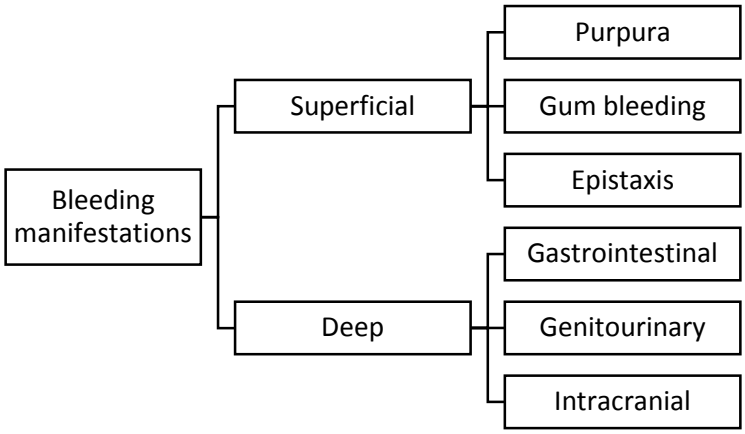
Clinical features:



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Investigations

1. Clotting profile:
   - ✓ Platelet count
   - ✓ BT: Mainly assess the *integrity of blood vessels*, *platelet aggregation and activation* status
   - ✓ CT: Roughly assess the *integrity of coagulation cascade pathway*
   - ✓ PT, INR: Assess the function of extrinsic pathway
   - ✓ aPTT: Assess the function of intrinsic pathway
   - ✓ Thrombin time.
2. Special tests to diagnose the underlying disease.

Treatment of bleeding disorders

1. Treatment of bleeding manifestations:
   - Antifibrinolytic:
     - Tranexamic acid
     - Aminocaproic acid
   - Platelet transfusion
   - Fresh frozen plasma.
2. Treatment of the underlying disease.

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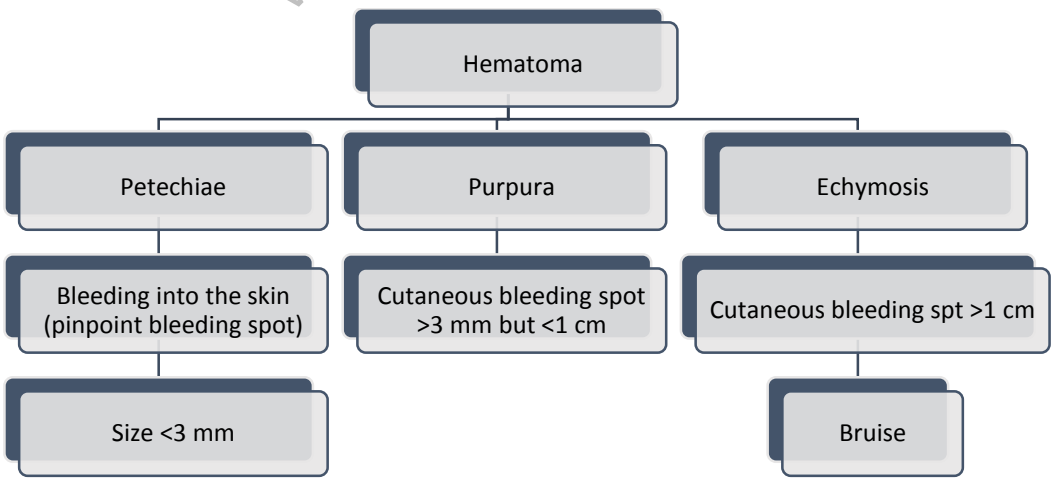
Basic concepts

Hematoma

Collection of blood underneath the skin.

Types:



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Purpura

Reddish discoloration of skin due to bleeding underneath the skin.

Causes:

1. ***Purpura + Thrombocytopenia***:
   a. Part of pancytopenia
   b. Isolated thrombocytopenia.
2. ***Purpura (without thrombocytopenia)***:
   a. Vessel wall related disorder:
      I. Age related
      II. Vasculitis
      III. Scurvy
   b. Defective platelet function:
      von Willebrand's disease (vWD)
   c. Coagulopathy.

Clinical manifestations:

1. Due to thrombocytopenia: Spontaneous bleeding
2. Purpura: Reddish, non-blanching spots; palpable (vasculitis)/ non-palpable (non-inflammatory cause)
3. Features of the underlying disease.

Investigations:

1. Clotting profile
2. Investigations to detect the underlying disease.

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Idiopathic thrombocytopenic purpura (ITP)

Disease characterized by immune autoantibody mediated thrombocytopenia.

Types:

ITP is of 2 types:

- Acute ITP: Usually occurs in newborns/ children
- Chronic ITP: Usually occurs in adults.

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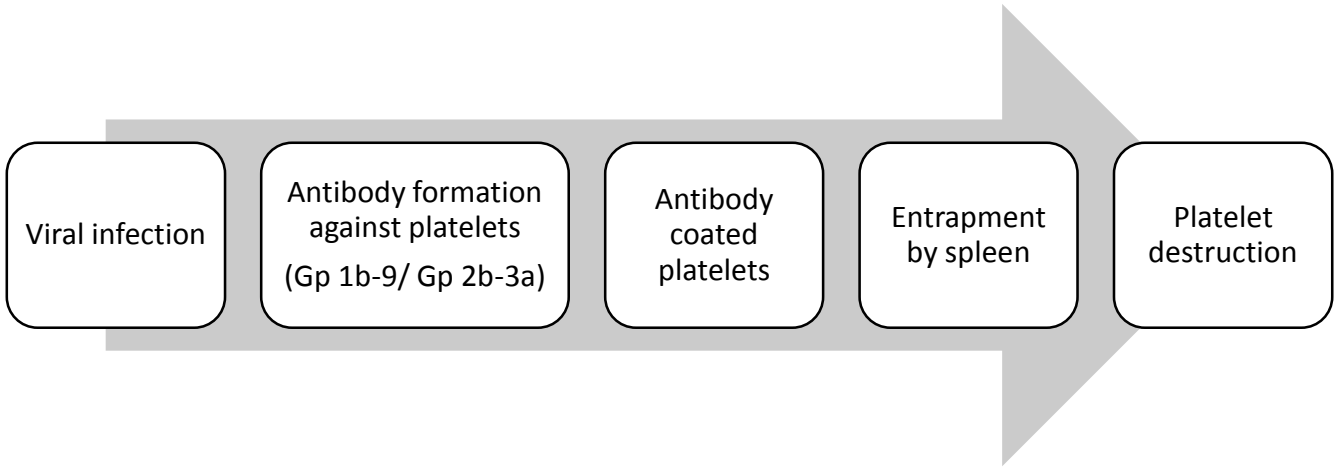
Pathophysiology:



Clinical features:

1. Often asymptomatic
2. Bleeding manifestations: Superficial/ deep
3. ***Splenomegaly is characteristically absent*** (in acute ITP, mild splenomegaly may be present).

Investigations

1. Platelet count: ↓
2. Hb, WBC count: Normal
3. Clotting profile: Usually normal (BT may be ↑)
4. Antiplatelet antibody may be detected.

Treatment

1. Supportive treatment:
   - Often not required in acute ITP
   - If significant bleeding present:
     - ✓ Platelet transfusion
     - ✓ IV IgG therapy.
2. Specific treatment:
   - Long term prednisolone (as ITP is an immune mediated disease)
   - Rituximab
   - Newer drugs (Thrombopoietic receptor agonist):
     These are used when patients don't response to other treatments:
     - ✓ Eltrombopag
     - ✓ Romiplostim.

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- Splenectomy (in case of splenomegaly and also because spleen is the site of antibody production against platelets)

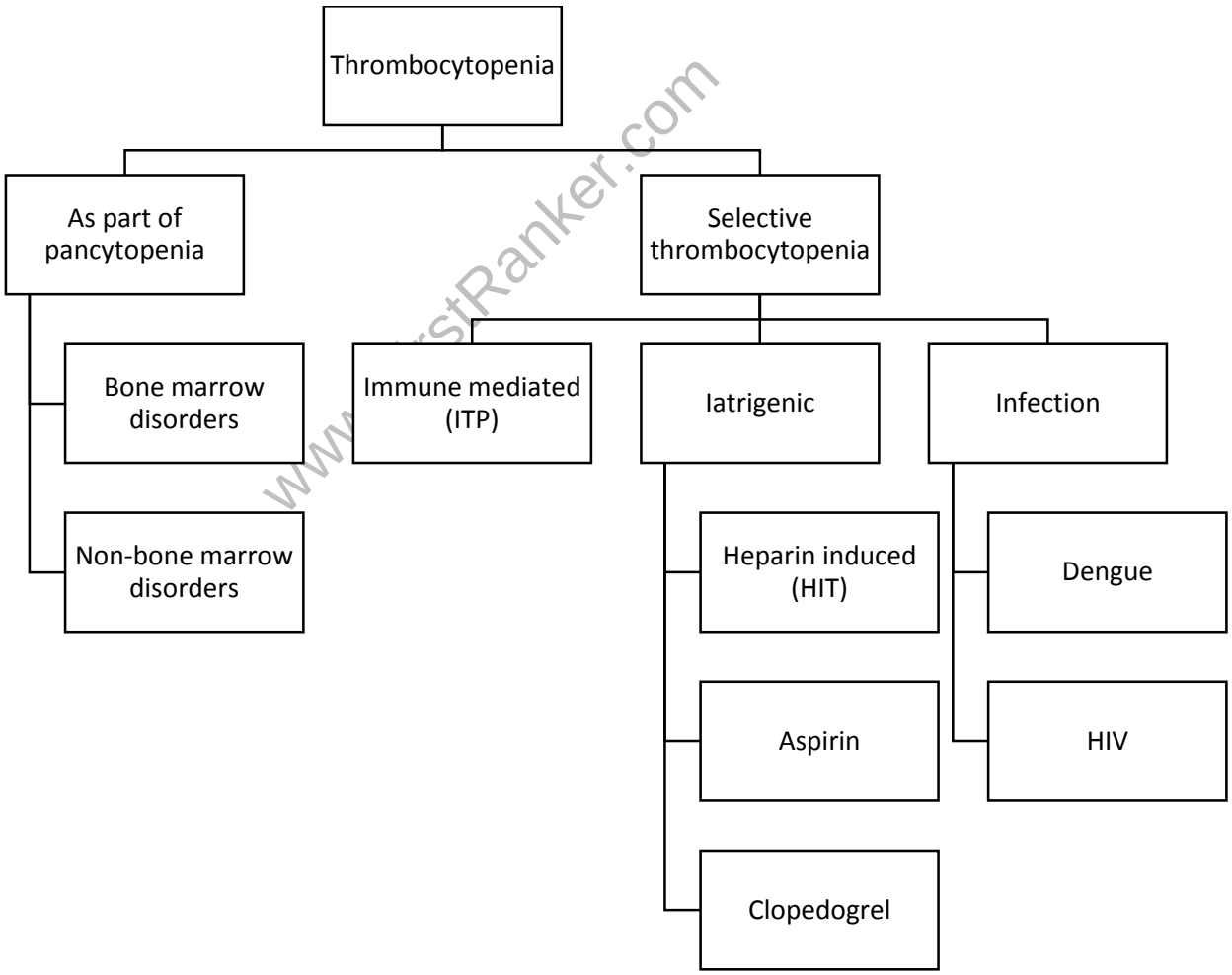
Difference between acute and chronic ITP

Acute ITP	Chronic ITP
Newborns/ infants	Adults
Preceded by an episode of viral infection	Afebrile
Splenomegaly (mild) may present	Usually absent
Often self-limiting	Often needs treatment

Thrombocytopenia

Reduction in the number of platelets <1.5 lakhs/µL (normal level: 1.5-4.5 lakhs/ µL).

Etiology:



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Clinical features:

1. Due to thrombocytopenia:
   a. Asymptomatic
   b. Symptomatic: Spontaneous bleeding manifestations
      Note: Risk of spontaneous bleeding increases significantly when platelet count goes <20000/ µL. A count <10000/ µL is called "critical thrombocytopenia".
2. Features due to underlying disease.

Investigation

1. Platelet count: ↓
2. Hb, WBC count: Normal/ ↓
3. Coagulation profile:
   a. BT: ↑
   b. Other parameters (CT/ PT/ INR/ aPTT) are often normal
4. Investigation(s) to confirm the underlying disease.

Treatment

1. Supportive treatment:
   Platelet transfusion
   Indication:
   a. Significant bleeding
   b. Before any invasive transfusion.
2. Definitive treatment:
   Treatment of the underlying disease.

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Hemophilia

It is a congenital coagulopathy due to deficiency of factor VIII.

Types:

A. Hemophilia A: Deficiency of factor VIII
B. Hemophilia B: Deficiency of factor IX
C. Hemophilia C: Deficiency of factor XI.

Clinical features:

Spontaneous bleeding:

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1. Superficial: Purpura, gum bleeding, epistaxis
2. Deep: ***Hemarthrosis***: May lead to painful swollen joints. Recurrent hemarthrosis in the same joint may lead to joint damage; resulting in restriction of movement.

Investigation

Clotting profile:

- ✓ BT: Normal
- ✓ ***CT:*** ↑
- ✓ PT, INR: Normal
- ✓ ***aPTT:*** ↑ (defect in the intrinsic pathway)
  Note: If aPTT fails to normalize even after mixing patient's serum with a normal serum, then circulating antibody against factor VIII is suspected.
- ✓ Estimation of factor VIII level/ activity.

Treatment

1. Minor bleeding:
   - Desmopressin (stimulates release of any stored factor VIII)
   - Antifibrinolytic agents (prevent degradation of fibrin):
     - Tranexamic acid
     - Aminocaproic acid.
2. Major bleeding:
   Fresh frozen plasma/ factor VIII concentrate.

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von Willebrand's disease (vWD)

It is a bleeding disorder due to congenital deficiency of von Willebrand factor (vWF) which plays an important role in:

1. Platelet aggregation and adhesion
2. Transportation of factor VIII.

Clinical features:

Bleeding manifestations:

1. Prolonged bleeding even after minor injury
   Ex.: After dental extraction/ from wound site/ suture site, the bleeding refuses to stop.
2. Spontaneous bleeding: Superficial/ deep.

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Investigations

1. Platelet count: Normal
2. ***BT:*** ↑
3. CT: Normal
4. PT, INR, aPTT: Normal.
   Note: In severe forms of vWD, aPTT may get prolonged due to reduced functional activity of factor VIII.
5. Confirmation of diagnosis by detecting vWF level/ activity.

Treatment

1. Minor bleeding:
   a. Desmopressin
   b. Antifibrinolytic agents:
      ✓ Tranexamic acid
      ✓ Aminocaproic acid.

Coagulopathy due to chronic liver disease (CLD)

Etiology:

Decreased synthesis of clotting factors in chronic liver disease.

Clinical features:

1. Asymptomatic
2. Symptomatic: Bleeding manifestations: may be superficial/ deep.

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Investigations

1. Platelet count: May be ↓
2. BT: Normal/↑
3. CT: ↑
4. PT, INR, aPTT: ↑
   Note: Usually PT and INR get prolonged before prolongation of aPTT as factor VII has got a very short half-life.
5. Liver function test.

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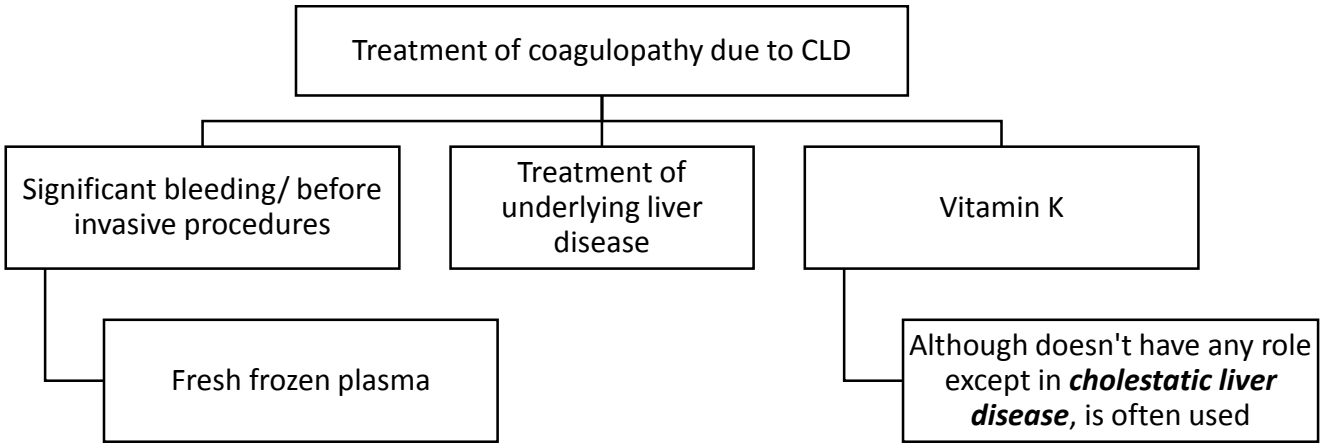
Treatment



Coagulopathy due to vitamin K deficiency

Cause:

Lack of carboxylation of vitamin K dependent factors (factor II, VII, IX, X).

Causes of vitamin K deficiency:

1. Decreased intake
2. Malabsorption
3. Cholestatic liver disease.

Clinical manifestations:

1. Asymptomatic
2. Symptomatic: Bleeding manifestations.

Investigations

Clotting profile:

- BT: Normal
- CT: Normal
- PT, INR, aPTT: ↑
  Note: Often PT and INR only are prolonged as factor VII is the key factor of extrinsic pathway.

Treatment

1. Vitamin K: Oral/IM
2. Treatment of the underlying disease.

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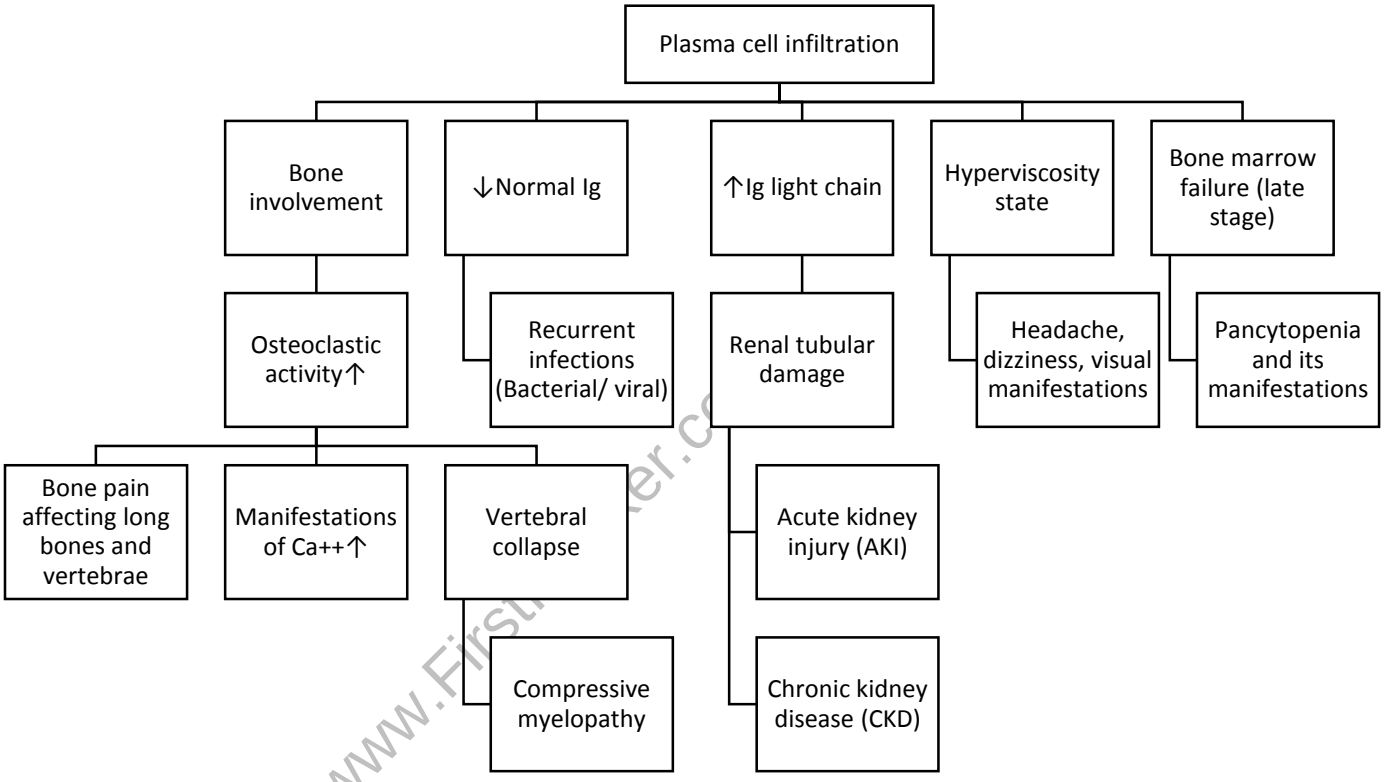
Miscellaneous topics

Multiple myeloma

Malignant transformation of those hematopoietic stem cells which eventually leads to *plasma cells*.

Pathogenesis + Clinical features:



Investigations

1. Blood:
    - CBC: Anemia (normochromic normocytic)
    - WBC and platelet count: Normal (may decrease in late stage due to bone marrow infiltration and failure)
    - ESR: ↑ (due to ↑rouleaux formation from hyperviscosity state)
2. Urea creatinine: ↑
3. Globulin level: ↑
4. Serum Ca++: ↑ when ***ALP level is typically normal***.

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5. Serum protein electrophoresis:
   Monoclonal spike (may be IgG/ IgA/ light chain)
6. Urine:
   Proteinuria (Bence Jones protein: Ig light chain)
7. Urine electrophoresis:
   Monoclonal spike
8. X-Ray:
   Areas of osteolysis: '***punched out lesions***'.

Treatment

1. Supportive treatment:
   a. Emergency treatment of hypercalcemia (IV fluid)
   b. Treatment of CKD
   c. Treatment of vertebral pain by radiotherapy.
2. Definitive treatment:
   a. Chemotherapy: [Bortezomib + Dexamethasone + Lenalidomide]
   b. Bisphosphonate
   c. Bone marrow transplantation (in selected patients).

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Myelodysplastic syndrome

It is a hematopoietic stem cell disorder characterized by combination of *pancytopenia, morphological abnormalities of blood cells* and *hypercellular marrow*.

Clinical features:

1. Due to pancytopenia:
   - Features of anemia
   - Features of thrombocytopenia
   - Features of neutropenia.
2. Due to compensatory extramedullary hematopoiesis:
   Splenomegaly ± Hepatomegaly.

Investigations

1. Blood:
   - Hb: ↓
   - WBC count: ↓
   - Platelet count: ↓

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2. Peripheral film:
    - Regarding RBC: ***Reticulocyte count typically abnormally low (sometimes absent) despite anemia***
    - WBC: Hyposegmented neutrophils, typically ***bilobed nucleus***, also called "***Pelger Huet abnormality***".
    - Platelet: Very small (dwarf) megakaryocytes.
3. Bone marrow:
   Hypercellular marrow showing "***Ring sideroblast***".

Treatment

1. Supportive treatment:
   a. Anemia:
      - ✓ RBC transfusion
      - ✓ Erythropoietin
      - ✓ Lenalidomide.

   b. Neutropenia:
      - ✓ Treatment of infections
      - ✓ G-CSF.

   c. Thrombocytopenia:
      - ✓ Platelet transfusion
      - ✓ Thrombocyte receptor agonist.
2. Definitive treatment:
   a. Myelosuppressive agent:
      Azacytidine.
   b. Bone marrow transplantation.

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Disseminated intravascular coagulation (DIC)

It is a thrombohemorrhagic disease characterized by *spontaneous bleeding* as well as *microvasculature thrombosis*.

Triggering factors:

D. Severe tissue **d**amage (Ex: Burn, head injury)

I. Infection (Septicemia)

C. Cancer (Acute promyelocytic leukemia)

O. Obstetric causes (Ex: IUFD/ Abruptio placentae).

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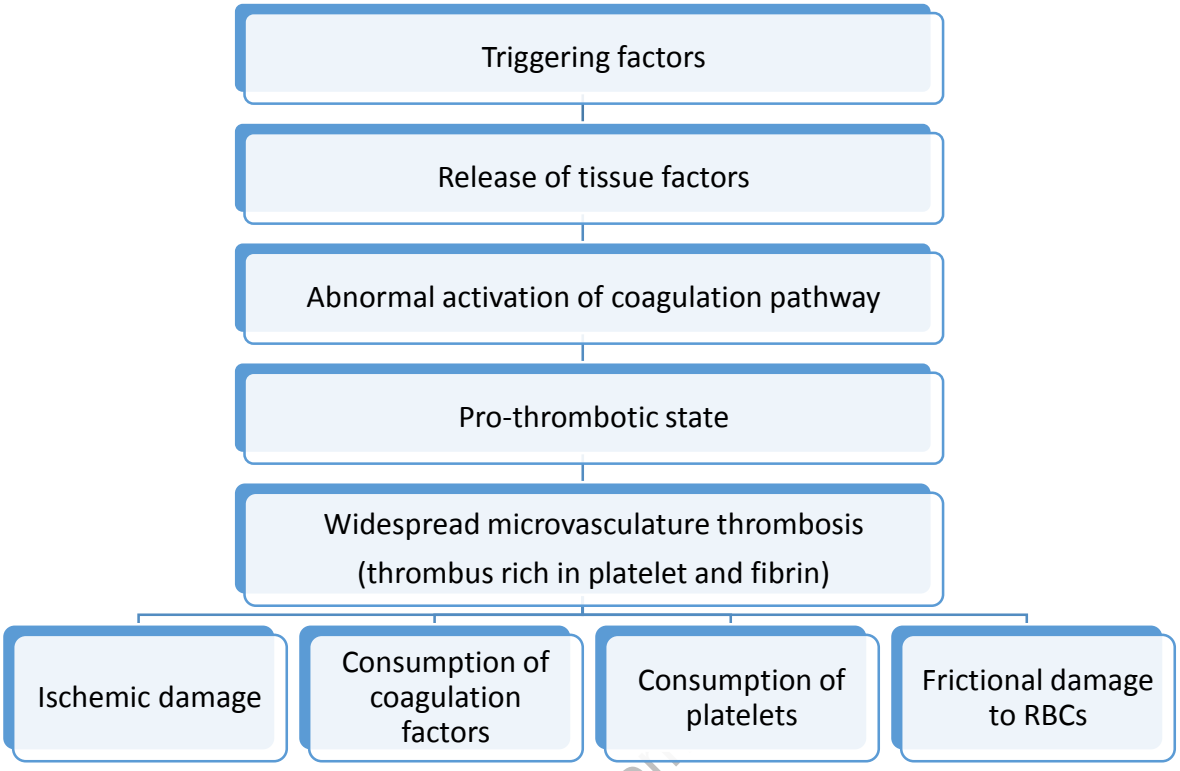
Pathogenesis:



- All these ultimately leads to consumptive coagulopathy.

Clinical features:

1. Features of the underlying disease
2. Patients with intravascular hemolysis are often asymptomatic
3. Ischemic injury to kidney: Acute kidney injury (AKI)
4. Due to consumptive coagulopathy:
   Spontaneous bleeding, starts with superficial bleeding.
   Ex: Oozing of blood from venipuncture surgical site.
   Gum bleeding, epistaxis etc. may occur.

Investigations

1. Platelet: Mild ↓
2. Hb, WBC: Variable (depending upon the underlying disease)
3. Peripheral film: ***Fragmented RBCs (Schistocytes)***
4. Clotting profile: PT, INR, aPTT: ↑

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5. **D-Dimer test:** Fibrin degradation product (FDP): ↑
6. Serum fibrinogen: ↓.

Treatment

1. Treatment of the underlying disease
2. Supportive:
   - Treat bleeding manifestations by Fresh frozen plasma
   - Low dose heparin.

Blood transfusion

Type of blood products:

Blood product	Indications
Packed cell/ packed RBC	Symptomatic anemia (1 unit RBC increases Hb level by 1 gm% and hematocrit by 4%)
Platelet	Thrombocytopenia with significant bleeding/ before any invasive procedure
Fresh frozen plasma	Coagulopathic bleeding

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Complications of blood transfusion:

1. Immediate (within minutes to hours):
   a. ***Hypersensitivity reaction***:
      - Cause: Presence of *antigen in donor plasma*
      - Clinical feature: Urticaria (itch), rash, chill and rigor; lid swelling, bronchospasm, hypotension in severe cases
      - Treatment:
        - Immediately stop the transfusion
        - Anti-allergic: IV Diphenhydramine
        - In severe cases: IV hydrocortisone/ IV adrenaline.

2. Early (within hours to days):
   a. ***Hemolytic transfusion reaction***:
      - Acute hemolytic episode precipitated by mismatch blood transfusion.
      - It is of 2 types:
        I. Early:
           ➢ Within hours of transfusion

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- Major hemolysis
- Cause: ABO incompatibility.

II. Late:

- Occurs 4-5 days after transfusion
- Minor hemolysis
- Cause: Antigenic discrepancy (minor blood group antigens), autoantibodies form in the intervening 4-5 days following transfusion before hemolysis starts.

- Clinical features:

Major hemolysis	○ Acute back pain ○ General uneasiness ○ Cardiovascular collapse ○ Acute kidney injury ○ DIC.
Minor hemolysis	○ Mild jaundice ○ Mild anemia.

- Treatment:
  - Immediately stop transfusion
  - Send/ resend the bag of blood and patient's blood sample for grouping and cross-matching.
  - Aggressive rehydration to prevent AKI.

b. ***Leukoagglutinin reaction***:

- Cause: Due to *antigens on WBC of the donor blood* to which the recipient had already been sensitized during previous transfusion.
- Clinical features:
  Fever with chill and rigor occurs usually 10-12 hours after transfusion.
- Treatment:
  - Immediately stop the transfusion
  - IV Diphenhydramine/ IV Hydrocortisone.

c. Transfusion related acute lung injury (TRALI):

ARDS precipitated by massive transfusion.

3. Late (within weeks to months):
   Blood borne infections:
   a. HIV
   b. HBV
   c. HCV.

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