HEMATOLOGY AND ONCOLOGY

Pediatrics

KKT

Contents

Iron deficiency anemia (IDA)

- The most common form of anemia in childhood

- Daily iron requirement
  - ✓ 6 months-2 years ➢ 15 mg/day
  - ✓ 4-10 years ➢ 10 mg/day
  - ✓ 11-18 years ➢ 18 mg/day

- Causes of iron deficiency
  - ✓ ↓Iron intake
    - ↓Socio-economic status, anorexia, food fads, negligence, ignorance
    - Cow's milk (contains less bioavailable iron and can cause allergic gastroenteritis)
    - Late weaning of breast-milk with late introduction of supplementary diet (breast-milk contains sufficient iron only for the first 6 months of age)

  - ✓ ↓Iron absorption
    - Hypochlorhydria/ achlorhydria – due to chronic gastritis (e.g. atrophic gastritis), gastrectomy
    - Small intestine disease (e.g. celiac disease, malabsorption syndromes)

  - ✓ ↓Iron storage
    - Preterm low birth weight, small for gestational age
    - Early cord clamp, cord and placental hemorrhage
    - Multiple pregnancy, twin-to-twin transfusion syndrome (feto-fetal transfusion)
    - Feto-maternal transfusion

  - ✓ ↑Iron demand
    - Preterm low birth weight (for catch-up growth)
    - Infancy, puberty (periods of rapid growth)
    - Pregnancy

  - ✓ ↑Iron loss
    - From GI tract
      - Hookworm infestation
      - Rectal prolapse, polyposis, portal hypertension
      - Inflammatory bowel disease
      - Meckel's diverticulum, hiatus hernia
    - From genitourinary tract
      - Menorrhagia, hematuria
    - From respiratory tract and others
      - Hemoptysis, epistaxis, gum bleeding
      - Cephalhematoma

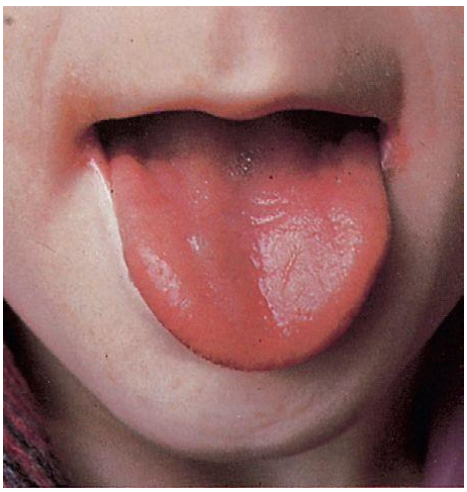
  - ✓ Inborn errors of metabolism

- Clinical features
  - ✓ Features of anemia
    - Pallor
    - Constitutional symptoms – fatigue, weakness, tiredness, palpitation, breathlessness
    - Cardiomyopathy, anemic heart failure (high output heart failure), hemic murmur

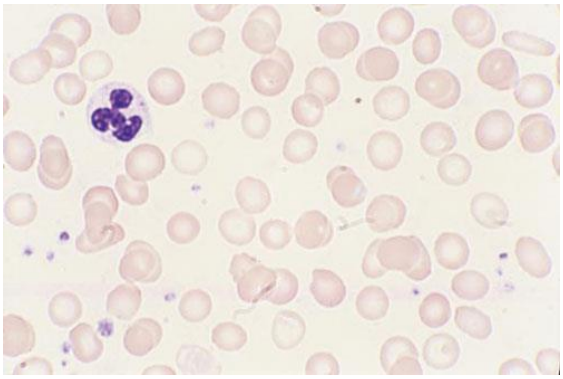
  - ✓ Features of iron deficiency
    - Pica – craving for eating unusual (non-nutritional) things
    - Frequent infections (due to reduced immune status)
    - Epithelial changes
      - Skin – angular stomatitis
      - Hair – brittle hair
      - Nail – koilonychia, longitudinal ridges, brittle nail
      - Tongue – atrophic glossitis (due to atrophy of tongue papillae)
      - Esophagus – dysphagia, esophageal web (post-cricoid web)
      - Intestine – malabsorption due to villous atrophy
    - Growth retardation
    - ↓Mental performance, ↓school performance

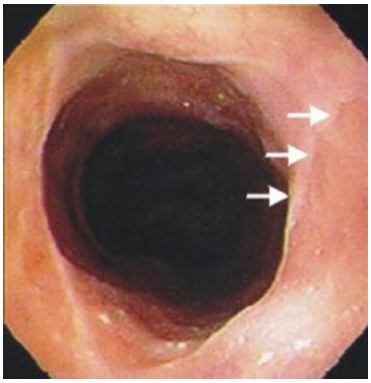
  - ✓ Features of underlying cause
    - Hookworm infestation – passing of worms in the stool, abdominal pain, urticarial rash

- Complications of iron deficiency anemia
  - ❖ Anemic heart failure
  - ❖ Splenomegaly (15%)
  - ❖ Plummer-Vinson syndrome (risk of squamous cell carcinoma, esophagus)
  - ❖ Repeated upper respiratory tract infections



- Investigations
  - ✓ Investigations for disease (iron deficiency anemia)
    - Hemogram
      - Hb↓, retic count ↓
      - MCV↓, MCH↓, MCHC↓
      - WBC – normal, platelet – normal
    - Blood film
      - RBC
        - ➢ Hypochromic microcytic anemia
        - ➢ Mild to moderate degree of anisopoikilocytosis
          - Normocytes and microcytes
          - Pencil-shaped cells, few target cells
      - WBC – normal, platelet – adequate in distribution
    - Bone marrow examination (mostly not necessary)
      - Cell trails, cell fragments – hypercellular
      - Micronormoblastic erythroid hyperplasia
      - Depletion of bone marrow iron (Perl Prussian Blue stain)
    - Biochemical investigations (Iron study)
      - ↓Serum iron, ↑Total iron binding capacity (TIBC)
      - ↓Ferritin, ↓Transferrin saturation
  - ✓ Investigations for etiology
    - For hookworm infestation – stool REME
    - For urinary pathology – UREME, USG (abdomen)
    - For TB – CXR, tuberculin skin test
  - ✓ Investigations for complications
    - For heart failure – CXR, ECG, echocardiogram
    - For infections – infection screen
    - For esophageal web – barium swallow, OGD scopy





- Management

  ❖ **<u>Management of underlying cause is more important than iron replacement therapy.</u>**

  ✓ Management of underlying cause
    - Hookworm infestation – deworming with anthelminthics
    - Rectal prolapse, polyposis – surgery

  ✓ Iron replacement therapy
    - Oral iron therapy
      - Forms – ferrous sulphate, ferrous gluconate, ferrous fumarate, ferrous succinate
      - Dose – elemental iron 3-6 mg/kg/day in 3 divided doses
      - Should be given in empty stomach for better absorption (not after food, not after milk)
      - Advantage – rate of rise in Hb level – 1 g/dl/week
      - Disadvantage – nausea, vomiting, abdominal pain, constipation, black stool
      - Treatment course
        - Oral iron therapy should be continued at least 6-8 weeks even after correction of Hb level (to replenish storage iron)

    - Parenteral iron therapy
      - Indication
        - Intolerance to oral iron therapy
        - Altered bowel habit, GI pathology
      - Forms – dextran iron, non-dextran iron (iron sorbitol, iron sucrose)
      - Dose: Iron (mg) = wt (kg) x Hb deficit (g/dl) x 4
      - Advantage – ↓GI side effects
      - Disadvantage
        - Anaphylaxis (especially with dextran iron)
        - Injection site reaction (pain, discoloration)

    - Blood transfusion
      - Indication
        - Anemic heart failure
        - When rapid correction of Hb level is required
      - Form – packed cell transfusion slowly (with IV Lasix before and mid-transfusion)
      - Advantage – rapid correction of Hb level (rate of rise in Hb level – 1g/dl/unit)
      - Disadvantage – transfusion reactions

- Prevention
  - ✓ Health education about iron-rich food; avoid diet restriction, fortification of food products
  - ✓ Exclusive breastfeeding for 6 months; introduction of supplementary diet at 6 months of age
  - ✓ Standard delivery care, iron supplementation to preterm low birth weight infants
  - ✓ Iron supplementation to adolescent girls and pregnant women
  - ✓ Avoid walking barefoot over the fields to prevent hookworm infestation

Thalassemia syndromes

- Reduced or absent globin chain synthesis resulting in chain imbalance and ineffective erythropoiesis

- Types of thalassemia syndromes in Myanmar
  - ❖ α-thalassemia
  - ❖ β-thalassemia
  - ❖ Thalassemia E

Table 11–3 Clinical and Genetic Classification of Thalassemias

Clinical Syndrome	Genotype	Clinical Features	Molecular Genetics
β-Thalassemias			
β-Thalassemia major	Homozygous β-thalassemia (β^0/β^0, β^+/β^+, β^0/β^+)	Severe anemia; regular blood transfusions required	Mainly point mutations that lead to defects in the transcription, splicing, or translation of β-globin mRNA
β-Thalassemia intermedia	Variable (β^0/β^+, β^+/β^+, β^0/β, β^+/β)	Severe anemia, but regular blood transfusions not required	
β-Thalassemia minor	Heterozygous β-thalassemia (β^0/β, β^+/β)	Asymptomatic with mild or absent anemia; red cell abnormalities seen	
α-Thalassemias			
Silent carrier	$-/\alpha$, α/α	Asymptomatic; no red cell abnormality	Mainly gene deletions
α-Thalassemia trait	$-/-$, α/α (Asian) $-/\alpha$, $-/\alpha$ (black African, Asian)	Asymptomatic, like β-thalassemia minor	
HbH disease	$-/-$, $-/\alpha$	Severe; resembles β-thalassemia intermedia	
Hydrops fetalis	$-/-$, $-/-$	Lethal in utero without transfusions	

		β-TM	β-TI	HBE/β-Thal		HbH
Hb levels		<5 g/dL	~7-10 g/dL	Mild	9-12 g/dL	2.6-13.3 g/dL
				Moderately Severe	6-7 g/dL	
				Severe	4-5 g/dL	
BLOOD SMEAR	Low Hb production	Red cell hypochromia microcytosis, Target cells				
	Haemolysis	Irregularly crenated RBC, increased reticulocytes (5-10%)				
	Ineffective erythropoiesis	Nucleated RBC, Basophilic stippling				
	Specific feautures	+Numerous F-cells/acid elusion	+F- cells/acid elusion	+ DCIP staining (Hb E) + F-cells/acid elusion		HbH inclusion bodies
Hemoglobin study		HbF up to 100% HbA2 ↑	HbF 10-50% (up to 100%) HbA2>4%	HbE (40-60%) HbF (60-40%) ± Hb A (with β^+-thal) HbA2 ↑		Variable HbH (0.8-40%) HbA2 ↓ + the presence of α-varaints i.e. Hb CS, Hb PS etc.

β-thalassemia major (Cooley's anemia)

- ❖ Autosomal recessive disorder
- ❖ Consanguineous marriage of parents
- ❖ Family history of thalassemia
- ❖ Clinical features appear only after 6 months of age

- Clinical features
  - ❖ Clinical features due to disease process
    - ✓ Features due to ineffective erythropoiesis
      - o Persistent progressive severe anemia
      - o Constitutional symptoms (fatigue, weakness, tiredness, palpitation, breathlessness)
      - o Cardiomyopathy, anemic heart failure, hemic murmur
      - o Growth retardation, leg ulcers

    - ✓ Features due to compensatory medullary hemopoiesis
      - o Thalassemic face – frontal bossing, depressed nasal bridge, prominent malar eminence, malformed teeth
      - o Vertebrae and long bones – osteoporosis and pathological fractures

    - ✓ Features due to extramedullary hemopoiesis
      - o Hepatomegaly – abdominal distension
      - o Extramedullary masses (e.g. paravertebral, intra-thoracic or intra-abdominal masses)

    - ✓ Features due to extravascular hemolysis
      - o Massive splenomegaly – abdominal pain, splenic rupture
      - o Hypersplenism – pancytopenia (progressive anemia, repeated infections, bleeding)

    - ✓ Features due to hemolysis
      - o Hemolytic jaundice
      - o Biliary stones (pigment stones)

    - ✓ Features due to iron overload (hemosiderosis and hemochromatosis)
      - o Skin – hyperpigmentation (especially knuckles)
      - o Pancreas
        - ▪ Exocrine pancreas – impaired fat digestion and absorption (fat intolerance, steatorrhea), impaired fat soluble vitamin absorption
        - ▪ Endocrine pancreas – diabetes mellitus (bronze diabetes)
      - o Endocrine insufficiency
        - ▪ Hypopituitarism, hypothyroidism, hypogonadism
        - ▪ Endocrine insufficiency can cause growth retardation, delayed puberty and osteoporosis.
      - o Heart – dilated cardiomyopathy, restrictive cardiomyopathy
      - o Liver – cirrhosis of liver

❖ Clinical features due to treatment
  ✓ Features due to regular blood transfusion
    - Blood transfusion reactions
    - Transfusion-transmitted infections (HIV, HBV, HCV, malaria, syphilis)
    - Iron overload (1 unit of blood contains 200 mg of iron)

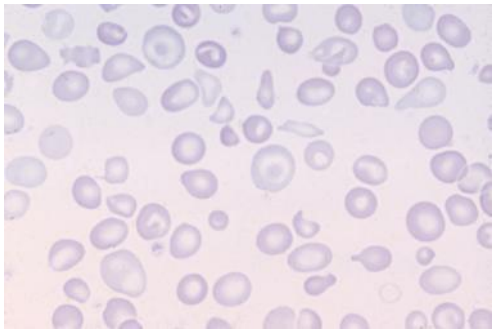
  ✓ Features due to iron chelation therapy
    - Desferrioxamine
      - *Yersinia enterocolitica* infections
      - Visual problems (cataract, retinopathy)
      - Auditory problems (tinnitus, deafness)

  ✓ Features due to splenectomy
    - OPSI (opportunistic post-splenectomy infections) (pneumococcus, meningococcus, *Hemophilus influenzae* type b)
    - Thrombocytosis and thrombosis

- Major causes of death – severe anemia, heart failure, liver failure, infections

- Investigations
  ❖ Investigations for disease (chronic hemolytic anemia)
    ✓ Hematological investigations
      - Hemogram
        - Hb↓, Retic count↑
        - MCV↓, MCH↓, MCHC↓
        - WBC – ↔/↑ (reactive leukocytosis)/↓ (pancytopenia)
        - Platelet – ↔/↑ (reactive thrombocytosis)/↓ (pancytopenia)

      - Blood film
        - Hypochromic microcytic anemia
        - Severe degree of anisopoikilocytosis
          - Microcytes and normocytes
          - Pencil-shaped cells, target cells (many)
        - Features of hemolysis
          - Nucleated RBCs, polychromasia, reticulocytosis, spherocytes, fragmented RBCs
          - Marked basophilic stippling



      - Bone marrow examination (not usually necessary)
        - Cell trails and cell fragments – hypercellular
        - Micronormoblastic erythroid hyperplasia

    ✓ Biochemical investigations for hemolysis
      - Bilirubin↑, LDH↑
      - Haptoglobin↓, hemopexin↓

- ❖ Investigations to exclude DDx (IDA)
  - ✓ Iron study
    - Serum iron ↔/↑
    - Ferritin ↑
    - TIBC ↔/↓
    - Transferrin saturation ↔/↑

- ❖ Investigations for etiology (β-thalassemia major)
  - ✓ Hemoglobin electrophoresis (cellulose acetate electrophoresis)
    - HbA – reduced/absent
    - HbA_2 – raised (5-10%)
    - HbF – raised (90-95%)

  - ✓ Demonstration of HbF
    - HbF is more resistant to acid and alkali than HbA.
      - ➢ Acid elution test (Kleihauer test)
      - ➢ Alkaline denaturation test (Singer's test)

  - ✓ Osmotic fragility test
    - ↓Osmotic fragility to hypotonic saline (↑osmotic resistance)

  - ✓ Genetic tests
    - PCR (polymerase chain reaction), RFLP (restriction fragment length polymorphism)

- ❖ Investigations for complications
  - ✓ Investigations for hemochromatosis
    - o For iron overload – ferritin, transferrin saturation
    - o For endocrine insufficiency – hormonal assays (GH, TFT, sex hormones)
    - o For heart failure – CXR, ECG, echocardiogram
    - o For liver failure – LFT, USG (abdomen)
    - o For pancreatic failure – CT (abdomen) for pancreatitis, RBS for DM

  - ✓ Investigations for bone changes
    - o Skull X-ray
      - Hair-on-end appearance (thinning of outer and inner tables, widening of diploic space, thickening of skull vault)
    - o Vertebral X-ray – cupping
    - o Hand X-ray – lace-like appearance (prominent trabeculae)
    - o DEXA scan for bone mineral density (BMD) and osteoporosis

  - ✓ Investigations for hepatosplenomegaly – USG (abdomen)

  - ✓ Investigations for transfusion-transmitted infections
    - o Infection screening (HIV Ab, HBV serology, anti-HCV Ab, blood for mp, VDRL)

- Management
  - ❖ Management of disease
    - ➢ General management
      - ✓ Blood transfusion
        - Regular life-long blood transfusion is the mainstay treatment.
        - Purpose of blood transfusion
          - To improve anemia
          - To suppress ineffective erythropoiesis
          - To ensure active life and adequate growth
        - Recommended blood products – packed red cells (leuko-reduced)
        - Transfusion regimens
          - Low transfusion regimen – Hb 6-8 g/dl
          - High transfusion regimen – Hb 8-10 g/dl
          - Super-high transfusion regimen – Hb 10-12 g/dl
        - Transfusion methods
          - Packed cell transfusion 10-15 ml/kg
          - IV frusemide 1 mg/kg before and at the mid of transfusion
        - Transfusion interval – every 3-4 weeks (every 1-2 week if cardiac insufficiency)
        - All thalassemic patients should be vaccinated with hepatitis B vaccine before starting vaccination.
      - ✓ Iron chelation therapy
        - Indications for iron chelation therapy
          - Serum ferritin > 1000 ng/ml
          - After 10-20 units of blood transfusion
        - Types of iron chelation therapy
          - Desferrioxamine (DFO) (Desferral)
            - Dose – 25-50 mg/kg/day over a period of 8-12 hours during the night at least 5-6 nights/week
            - Route – continuous subcutaneous infusion using micro infusion pump
            - Disadvantages – *Yersinia enterocolitica* infection, visual problems (cataract, retinopathy), auditory problems (tinnitus, deafness)
          - Deferiprone (DFP) (Kelfer/ Ferriprox)
            - Dose – 75-100 mg/kg/day in 3 divided doses PO
            - Disadvantages – neutropenia/ agranulocytosis, arthralgia, zinc deficiency, GI disturbances

- ✓ Splenectomy
  - Done in children > 6 years of age to prevent post-splenectomy sepsis

  - Indications for splenectomy
    - Symptomatic massive splenomegaly
    - Hypersplenism
    - ↑transfusion requirement
      - 1.5 times normal
      - >250 ml/kg/year of packed red cells
      - >400 ml/kg/year of whole blood

  - Complications of splenectomy
    - OPSI (opportunistic post-splenectomy infections) (pneumococcus, meningococcus, *Hemophilus influenzae* type b)
    - Thrombocytosis and thrombosis

  - Pre-splenectomy prophylaxis
    - Immunoprophylaxis
      - 4-6 weeks prior to splenectomy
      - Pneumococcal conjugate vaccine, meningococcal conjugate vaccine, Hib vaccine

  - Post-splenectomy prophylaxis
    - Immunoprophylaxis
      - Booster dose of pneumococcal conjugate vaccine, annual influenza vaccine
    - Chemoprophylaxis – life-long penicillin prophylaxis
    - Thromboprophylaxis – low dose aspirin for thrombosis

- ➢ Supportive management
  - ✓ Avoid iron-rich food
  - ✓ Folic acid supplementation (1-5 mg/day)
  - ✓ Calcium and vitamin D supplementation

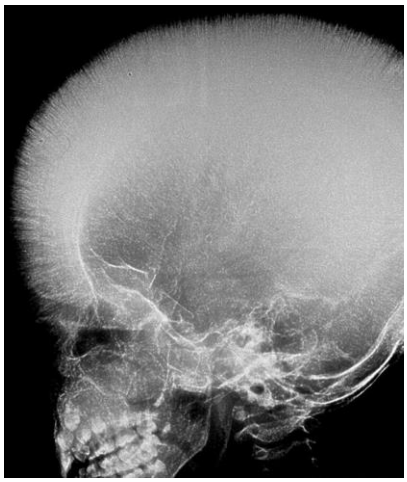
- ➢ New therapeutic approaches
  - ✓ Hemopoietic stem cell transplant (HSCT)
    - Replacement of defective stem cells with normal stem cells to prevent ineffective erythropoiesis and chain imbalance
    - It is only possible if HLA matched sibling donor is available.
    - Thalassemia-free survival – at least 75%

  - ✓ HbF inducers (hydroxyurea, azacytidine, myleran)
    - Promoting ɣ -chain synthesis to form HbF to prevent chain imbalance

  - ✓ Gene therapy – transfer of normal gene in stem cells

- ❖ *Management of complications*
  - ➢ *Management of heart failure*
  - ➢ *Management of liver failure*
  - ➢ *Management of pancreatic insufficiency*
    - ✓ *Replacement of pancreatic enzymes, fat soluble vitamins*
    - ✓ *Insulin therapy for diabetes mellitus*
  - ➢ *Management of endocrine insufficiency*
    - ✓ *Hormone replacement therapy (GH, thyroid hormone, sex hormone)*
    - ✓ *Calcium, vitamin D, bisphosphonates for osteoporosis*
  - ➢ *Management of infections – proper antibiotics*
  - ➢ *Management of biliary stones – surgery*

- Prevention
  - ✓ Genetic counseling
  - ✓ Antenatal diagnosis
    - Chorionic villous sampling
    - Fetal blood sampling



G6PD deficiency

- The most common enzyme disorder worldwide

- Congenital hemolytic anemia especially on exposure to oxidative stress due to accelerated breakdown with or without reduced activity of G6PD enzymes
  - X-linked recessive disorder
  - Male are affected. Female are carriers.
  - Female are affected in Turner syndrome, homozygous condition, lyonization.
  - Family history of G6PD deficiency in males of maternal side

- G6PD variants (over 300 variants)

Classes of G6PD variants	% of enzyme activity	Presentation
Class I	< 10% (severely deficient)	Chronic non-spherocytic hemolytic anemia
Class II	< 10% (severely deficient)	Acute intravascular hemolysis
Class III	10-60% (moderately deficient)	Acute intravascular hemolysis
Class IV	60-150% (normal activity)	Normal
Class V	>150% (increased activity)	Normal

  - Normal variant – G6PD A (in Africa), G6PD B (worldwide)
  - Abnormal variant – G6PD A- (class III), G6PD Mediterranean (class II)

- Clinical presentation
  - Neonatal jaundice and kernicterus
  - Acute intermittent intravascular hemolysis
  - Favism
  - Chronic non-spherocytic hemolytic anemia

- Precipitating factors for hemolysis in G6PD deficiency
  - Drugs
    - ❖ Drugs with definite risk of hemolysis – methylene blue, nitrofurantoin, primaquine, quinolone, rasburicase, sulphonamide, dapsone
    - ❖ Drugs with possible risk of hemolysis – chloroquine, sulphonylurea, aspirin
  - Chemicals – moth balls (naphthalene balls)
  - Food – fava beans (*Vicia faba*)
  - Infection and illness – hepatitis, diabetic ketoacidosis

- Clinical features of acute intravascular hemolysis
  - History of exposure to precipitating drugs or food
  - Sudden onset of pallor, high-colored urine (hemoglobinuria) and back pain
  - Fever with chills and rigor, tachycardia, hypotension, facial flushing
  - Children with hemolysis due to hepatitis have severe jaundice and severe clinical course with high mortality

- Complications – anemic heart failure, acute kidney injury

- Investigations
  - ❖ Investigations for diagnosis (acute intravascular hemolysis)
    - ✓ Hemogram - Hb↓, retic count ↑, WBC↔, platelet↔
    - ✓ Blood film
      - o Features of hemolysis – nucleated RBCs, reticulocytosis, polychromasia, fragmented RBCs, spherocytes
      - o Bite cells, blister cells
      - o Heinz bodies (with supravital stain)

    - ✓ Biochemical investigations for hemolysis
      - o Bilirubin↑, LDH↑
      - o Haptoglobin↓, hemopexin↓
      - o Hemoglobinemia (+), methemalbuminemia (+)
      - o Hemoglobinuria (+), hemosiderinuria (+)

  - ❖ Investigations to exclude DDx
    - ✓ For AIHA – direct Coomb's test
    - ✓ For malaria – blood for mp
    - ✓ For PNH – flow cytometry (CD55, CD59)

  - ❖ Investigations for etiology (G6PD deficiency)
    - ✓ Screening tests
      - o Methemoglobin reduction test
      - o Brilliant cresyl blue dye test
      - o Fluorescent spot test

    - ✓ Definitive tests
      - o Quantitative spectrophotometric analysis (G6PD enzyme assay)
        - ➢ May be normal (false negative) during acute attack because
          - ▪ Old RBCs are destroyed
          - ▪ Young RBCs have normal or near-normal G6PD activity
        - ➢ G6PD enzyme assay should be estimated 6 weeks after acute hemolysis

    - ✓ Genetic tests
      - o Polymerase chain reaction (PCR)
      - o Restriction fragment length polymorphism (RFLP)

  - ❖ Investigations for precipitating factors
    - ✓ For hepatitis – liver function test, serology for viral hepatitis
    - ✓ For DKA – RBS, ketone bodies, ABG

  - ❖ Investigations for complications
    - ✓ For anemic heart failure – CXR, ECG, echocardiogram
    - ✓ For acute kidney injury – UREME, renal function tests

- Management
  - ❖ No specific therapy for G6PD deficiency

  - ❖ Management of acute intravascular hemolysis
    - ✓ Removal of precipitating factors

    - ✓ Supportive therapy
      - o Nutrition
        - ▪ Folic acid, multivitamin supplement
        - ▪ Antioxidant (Vitamin E, selenium)
      - o Hydration – adequate hydration to prevent AKI and to promote perfusion
      - o Fever control – paracetamol, tepid sponging

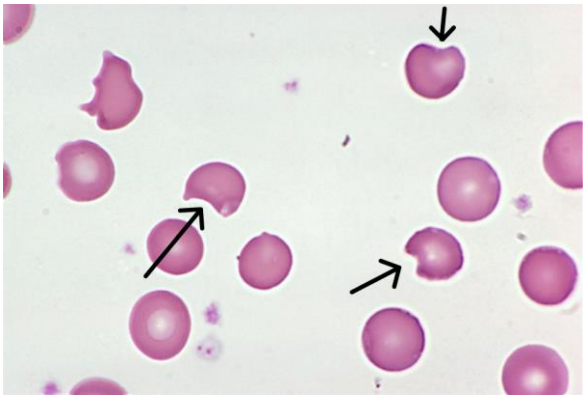
    - ✓ Management of complications
      - o Severe anemia – blood transfusion
      - o AKI – renal replacement therapy

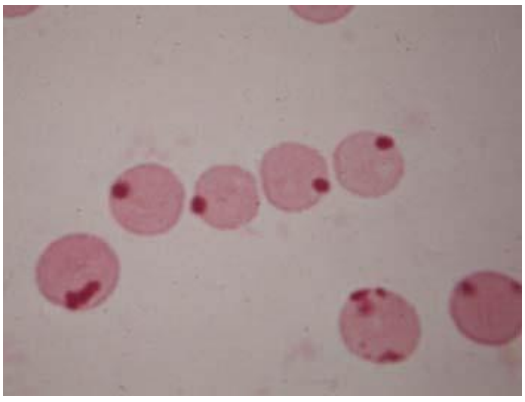
  - ❖ Management of neonatal jaundice
    - ✓ Phototherapy, exchange transfusion

- Prevention
  - ❖ Prevention of G6PD deficiency
    - ✓ Genetic counseling
    - ✓ Antenatal diagnosis

  - ❖ Screening of G6PD deficiency
    - ✓ Neonatal screening for G6PD deficiency
    - ✓ Give known oxidant drugs with caution in male patients in highly prevalent areas of G6PD deficiency
    - ✓ Give known oxidant drugs only after screening of G6PD deficiency

  - ❖ Prevention of acute intravascular hemolysis in G6PD deficient patients
    - ✓ Health education of parents and children about the nature of the disease and checklist of oxidant drugs to avoid





Hypoplastic anemia (Aplastic anemia)

- Bone marrow failure to produce mature blood cells due to suppression of or injury to hemopoietic stem cells resulting in hypoplasia of single cell line or all cell lines

- Causes
  - ❖ Congenital
    - ✓ Fanconi anemia
    - ✓ Diamond-Blackfan anemia

  - ❖ Acquired
    - ✓ 1° – idiopathic
    - ✓ 2°
      - o Drugs
        - ▪ Antibiotics – chloramphenicol, sulphonamide
        - ▪ Anti-epileptics – phenytoin, carbamazepine
        - ▪ Anti-thyroids – carbimazole, thiouracil

      - o Chemicals
        - ▪ Insecticides and fertilizers (aromatic hydrocarbons, benzene, DDT)
        - ▪ Gold, arsenic

      - o Exposure to ionizing radiation
      - o Autoimmune diseases – SLE
      - o Infection – parvovirus B19, post-viral hepatitis, EBV
      - o PNH (25% associated with hypoplastic anemia)

- Classification according to severity (Camitta criteria)
  - ❖ Moderate aplastic anemia
    - ✓ BM cellularity < 30%
    - ✓ Reduction in ≥2 of 3 blood elements below normal range
    - ✓ Absence of severe pancytopenia

  - ❖ Severe aplastic anemia
    - ✓ BM cellularity < 25% normal or
    - ✓ BM cellularity < 50% with < 30% hemopoietic cells
    - ✓ And at least 2 of the following
      - o Retic count < 1% (< 40 x $10^3/mm^3$)
      - o Neutrophil count < 0.5 x $10^3/mm^3$
      - o Platelet count < 20 x $10^3/mm^3$

  - ❖ Very severe aplastic anemia
    - ✓ Criteria for severe aplastic anemia +
    - ✓ Neutrophil count < 0.2 x $10^3/mm^3$

- Clinical features
  - ❖ Symptoms
    - ✓ Anemia
      - o Persistent progressive severe anemia
      - o Pallor, constitutional symptoms
      - o Cardiomyopathy, anemic heart failure, hemic murmur
    - ✓ Bleeding
      - o Skin bleeding – petechiae, purpura, ecchymosis
      - o Mucosal bleeding – epistaxis, gum bleeding, hemoptysis, H&M, bleeding per rectum, hematuria
      - o Internal organ bleeding – ICH (features of ↑ICP) (life-threatening)
    - ✓ Infections
      - o Recurrent infections
      - o Common infections occur more commonly (respiratory tract infections and GI infections)
      - o Opportunistic infections can occur

  - ❖ Signs
      - o Pallor disproportionate to amount of bleeding
      - o Hepatomegaly (-), splenomegaly (-), lymphadenopathy (-)
      - o Bone pain (-), joint pain (-), sternal tenderness (-)

- Investigations
  - ❖ Investigations for disease
    - ✓ Hemogram
      - o Hb↓, Retic count↓
      - o WBC↓, neutrophil↓
      - o Platelet↓
    - ✓ Blood film – normochromic normocytic anemia or macrocytic anemia
    - ✓ Hemostatic parameters
      - o Hess test (+)
      - o Bleeding time – prolonged
      - o Clotting time – normal
    - ✓ Bone marrow examination
      - o Aspiration – blood tap, dry tap
      - o Trephine biopsy – hypocellularity of hemopoietic cells, replaced by fat

  - ❖ Investigations for etiology
      - o For Fanconi anemia – cytogenetics
      - o For infection – infection screen (HIV, HBV, HCV)
      - o For autoimmune disease – ANA, anti-dsDNA
      - o For PNH – flow cytometry (CD55, CD59)

  - ❖ Investigations for complications
      - o For anemic heart failure – CXR, ECG, echocardiogram
      - o For infections – CXR for pneumonia
      - o For ICH – CT (head)

- Management
  - ❖ Supportive management
    - ✓ Prevention and treatment of anemia
      - Packed cell transfusion for
        - Hb < 7 g/dl or
        - Hb > 7 g/dl + fever/ bleeding
      - Iron chelation therapy for patients with serum ferritin > 1000 ng/ml

      - ➢ Routine use of erythropoietin is not recommended

    - ✓ Prevention and treatment of bleeding
      - ➢ Avoid aspirin and anti-platelets
      - ➢ Avoid unnecessary IM injections
      - ➢ Avoid unnecessary skin tests
      - ➢ Use a cloth or soft toothbrush for brushing teeth

      - Platelet transfusion (platelet concentrate/ PRP) for
        - Platelet < 10 x $10^3/mm^3$
        - Platelet < 20 x $10^3/mm^3$ + fever/bleeding
      - Anti-fibrinolytic agent (tranexamic acid) for mucosal bleeding (contraindication – hematuria)

    - ✓ Prevention and treatment of infections
      - Personal hygiene, hand hygiene, dental hygiene, food and water hygiene
      - For neutropenic fever (neutrophil < 0.5 x $10^3/mm^3$ + fever)
        - Full barrier nursing, infection screen and blood culture

        - Empirical antibiotics therapy with broad-spectrum antibiotics
          - ➢ IV ceftriaxone 50mg/kg/dose 12 hourly + IV amikacin 7 mg/kg/dose 12 hourly

            - If still febrile after 4-7 days with anti-bacterial therapy
              - ➢ Anti-fungal therapy with IV amphotericin
            - If oral ulcer or perirectal infections
              - ➢ Add IV metronidazole 7.5 mg/kg 8 hourly
            - If receiving immunosuppressive therapy
              - ➢ Consider prevention and treatment of *Pneumocystis jiroveci* with septrin

        - Specific antibiotics therapy according to C&S results
        - Continue antibiotics therapy until
          - ➢ Afebrile for 3-5 days +
          - ➢ Neutrophils > 0.5 x $10^3/mm^3$

      - ➢ A short course of G-CSF may be considered for severe infections not responding to anti-bacterial and anti-fungal therapy

- ❖ Specific management
  - ✓ Removal of 2° causes (e.g. drugs, chemicals)

  - ✓ Hemopoietic stem cell transplant (HSCT) (60-80% survival rate)
    - HLA-identical sibling HSCT
    - HLA-matched unrelated donor HSCT

  - ✓ Immunosuppressive therapy (if HSCT is unavailable)
    - 1^{st} line therapy
      - Cyclosporine and levamizole (disadvantage – renal toxicity)
      - Danazole (disadvantage – hepatotoxicity)

    - 2^{nd} line therapy
      - Anti-thymocyte globulin (ATG) or anti-lymphocyte globulin (ALG)
      - Cyclophosphamide (disadvantage – hemorrhagic cystitis)

    - Role of steroid – controversial (it can promote bacterial and fungal infections)

- Prevention
  - ❖ Protect children against contact with insecticides and fertilizers
  - ❖ Rational use of antibiotics and anti-epileptics in children

Causes of pancytopenia

- ↓Synthesis by bone marrow
  - BM failure – aplastic anemia
  - BM infiltration
    - ✓ Infection – HIV, disseminated TB
    - ✓ Inflammation – autoimmune diseases (SLE)
    - ✓ Malignancy
      - 1° – acute leukemia, lymphoma, multiple myeloma
      - 2° – bone metastasis
  - BM fibrosis – myelofibrosis
  - BM injury – cytotoxics, radiation
  - Ineffective hemopoiesis – VitB12/folate deficiency

- ↑Destruction by spleen
  - Hypersplenism

Causes of purpura

- Platelet disorders
  - ❖ Quantitative platelet defects (thrombocytopenia)
    - ➢ Congenital
      - ✓ Fanconi anemia
      - ✓ Wiskott-Aldrich syndrome
    - ➢ Acquired
      - ✓ ↓Platelet production by bone marrow
        - o BM failure – aplastic anemia
        - o BM infiltration
          - ▪ Infection – HIV, disseminated TB
          - ▪ Inflammation – autoimmune diseases (SLE)
          - ▪ Malignancy
            - 1° – acute leukemia, lymphoma, multiple myeloma
            - 2° – bone metastasis
        - o BM fibrosis – myelofibrosis
        - o BM injury – cytotoxics, radiation
        - o Ineffective hemopoiesis – VitB12/folate deficiency
      - ✓ ↑Platelet destruction
        - o Hypersplenism
        - o Immune
          - ▪ Immune thrombocytopenic purpura (ITP)
          - ▪ Systemic lupus erythematosus (SLE)
          - ▪ Alloimmune neonatal thrombocytopenia
        - o Thrombotic microangiopathies
          - ▪ Disseminated intravascular coagulation (DIC)
          - ▪ Thrombotic thrombocytopenic purpura (TTP)
          - ▪ Hemolytic uremic syndrome (HUS)
        - o Others
          - ▪ Drugs – heparin
          - ▪ Infections – HIV, Gram-negative bacteria, HCV, dengue, EBV
          - ▪ Dilutional coagulopathy in massive blood transfusion
  - ❖ Qualitative platelet defect (platelet dysfunction)
    - ➢ Congenital – Glanzmann's thrombasthenia
    - ➢ Acquired – uremia
  - ❖ Vascular defects
    - ➢ Congenital – Marfan syndrome, Ehler-Danlos syndrome
    - ➢ Acquired – steroid, vitamin C deficiency (scurvy), uremia, meningococcemia, vasculitis, Henoch-Scholein purpura

Immune thrombocytopenic purpura (ITP)

- Acquired thrombocytopenia due to autoimmune destruction of platelets and suppression of platelet production by bone marrow

- Classification of ITP
  - ✓ Primary ITP – isolated thrombocytopenia with no underlying cause
  - ✓ Secondary ITP – immune-mediated thrombocytopenia with underlying cause

- Phases of ITP
  - ✓ *Newly diagnosed ITP (diagnosis to 3 months)*
  - ✓ *Persistent ITP (3-12 months)*
  - ✓ *Chronic ITP (>12 months)*

  - ❖ Acute ITP
  - ❖ Chronic ITP (persistent thrombocytopenia for >6mths)

- Differences between acute ITP and chronic ITP

	Acute ITP	Chronic ITP
Age	Children	Adults
Sex	M = F	F:M – 3:1
Association	Preceding viral infection	Autoimmune diseases
Resolution	Spontaneous resolution (usually within 2 months)	Not remit within one year

- Clinical features
  - ✓ Symptoms
    - Preceding viral infection
    - Bleeding
      - Spontaneously or after trauma
      - Skin bleeding – petechiae, purpura, ecchymosis
      - Mucosal bleeding – epistaxis, gum bleeding, hemoptysis, hematemesis and melena, bleeding per rectum, hematuria
      - Internal organ bleeding – ICH

  - ✓ Signs
    - Pallor proportionate to bleeding
    - Splenomegaly (+) (in 10% of cases)
    - Hepatomegaly (-), lymphadenopathy (-)
    - Bone pain (-), joint pain (-), sternal tenderness (-)
    - Exclusion of all other causes of thrombocytopenia (diagnosis of exclusion)

Investigations

- ❖ Investigations for diagnosis
  - ✓ Hemogram – Hb↔/↓, WBC↔, platelet↓
  - ✓ Blood film
    - o Normochromic normocytic anemia (acute bleeding)/hypochromic microcytic anemia (chronic bleeding)
    - o WBC – normal
    - o Platelet – scanty in distribution
  - ✓ To assess hemostatic parameters
    - o Hess test (+)
    - o Bleeding time – prolonged
    - o Clotting time – normal
  - ✓ To differentiate between quantitative platelet disorders and qualitative platelet disorders
    - o Platelet count – reduced
    - o Platelet function test – normal
  - ✓ To assess immune-mediated thrombocytopenia
    - o Anti-platelet antibodies (+) in 70-90% of cases
  - ✓ Bone marrow examination (not usually necessary) (only when uncertain diagnosis)
    - o ↑Megakaryocytes (mature and immature forms)
    - o Cytoplasmic vacuolation, poor platelet granulation, poor platelet budding of megakaryocytes
- ❖ Investigations to exclude secondary causes
  - ✓ Viral screen (HIV, HCV)
  - ✓ Autoimmune screen (ANA for SLE)
- ❖ Investigations for complications
  - ✓ ICH – CT (head)

- Management
  - ❖ Management of acute ITP
    - ➢ Most do not need active treatment
    - ➢ Spontaneous resolution within 2 months
    - ➢ Prevention of bleeding
      - ✓ Avoid aspirin and anti-platelets
      - ✓ Avoid unnecessary IM injections
      - ✓ Avoid unnecessary skin tests
      - ✓ Use a cloth or soft toothbrush for brushing teeth

- *Conservative outpatient management (Indications)*
  - ✓ *Definite diagnosis of ITP*
  - ✓ *Clinically well child without active bleeding*
  - ✓ *Good parental supervision and safe home environment*
  - ✓ *Guaranteed follow-up*

- Criteria for hospital admission
  - ✓ Uncertain diagnosis
  - ✓ Active bleeding

- Inpatient management
  - ✓ Steroid
    - Indication for steroid
      - Active bleeding
      - Platelet count < 20 x $10^3/mm^3$
    - Oral prednisolone 2 mg/kg/day x 2 weeks, tapered over 1 week, regardless of response
    - Mechanism of action
      - Inhibit anti-platelet antibody production
      - Prolong platelet survival
      - Improve vascular stability
    - Disadvantages – hypertension, hyperglycemia
    - *(IV dexamethasone 1 mg/kg/day x 4 days for emergency care)*

  - ✓ IV IgG
    - Indication – to rapidly raise platelet count
    - Total dose of 2 g/kg using either protocol:
      - 0.4 g/kg/day x 5 days or
      - 1 g/kg/day x 2 days
    - Mechanism of action
      - Block Fc receptor of splenic macrophage and prevent platelet destruction by the spleen
    - Platelet count rises within 48hrs of infusion.
    - Disadvantages – hypersensitivity reaction, headache, aseptic meningitis

  - ✓ Anti-D (useful only in D positive individuals)
    - Indication – to rapidly raise platelet count
    - Time – 24-48 hours, durability – 3-4 weeks
    - Mechanism of action
      - Form RBC-antibody complex which are then destroyed by splenic macrophages instead of platelets
    - Disadvantages – hemolytic anemia, DIC, renal failure

  - ✓ Fresh blood/platelet transfusion
    - Used only in life-threatening bleeding

- Management of chronic ITP
  - Aim – to maintain hemostatically safe platelet count instead of trying for cure
  - Usually do not need active treatment
  - Regular follow-up, report to hospital after injuries

- Refractory ITP
  - Persistent thrombocytopenia (< $20x10^3/mm^3$) for > 6-12 months and at least minor bleeding manifestations

- Management of chronic and refractory ITP
  - First line therapies
    - ✓ Low dose steroid
      - Oral prednisolone 0.1-0.2 mg/kg/day
      - If no response, 1-2 mg/kg/day not more than 6 months
    - ✓ To rapidly raise platelet count
      - IV IgG
      - Anti-D

  - Second line therapies
    - ✓ Splenectomy
      - *Done in children > 6 years of age to prevent post-splenectomy sepsis*
      - *Complications of splenectomy*
        - *OPSI (opportunistic post-splenectomy infections) (pneumococcus, meningococcus, Hemophilus influenzae type b)*
        - *Thrombocytosis and thrombosis*

      - *Pre-splenectomy prophylaxis*
        - *Immunoprophylaxis*
          - *4-6 weeks prior to splenectomy*
          - *Pneumococcal conjugate vaccine, meningococcal conjugate vaccine, Hib vaccine*

      - *Post-splenectomy prophylaxis*
        - *Immunoprophylaxis – booster dose of pneumococcal conjugate vaccine, annual influenza vaccine*
        - *Chemoprophylaxis – life-long penicillin prophylaxis*

    - ✓ Rituximab (anti-CD20 antibody)
      - Alternative to splenectomy or in patients with failed splenectomy

  - Modifying T cell response – danazol, azathioprine, cyclosporine A

  - Immunosuppressive therapy – CHOP regimen, pulse corticosteroids

Causes of coagulation disorders

- Congenital coagulation disorders
  - Hemophilia
  - von Willebrand disease

- Acquired coagulation disorders
  - Liver disease
  - Vitamin K deficiency
  - Anticoagulants
  - Disseminated intravascular coagulation (DIC)
  - Circulating inhibitors of coagulation

Hemophilia Vs von Willebrand disease

Table 22.3 Investigations in haemophilia A and von Willebrand disease

	Haemophilia A	von Willebrand disease
PT	Normal	Normal
APTT	↑↑	↑ or normal
Factor VIII:C	↓↓	↓ or normal
vWF Antigen	Normal	↓
RiCoF (activity)	Normal	↓
Ristocetin-induced platelet aggregation	Normal	Abnormal
vWF multimers	Normal	Variable

PT, prothrombin time; APTT, activated partial thromboplastin time; RiCoF, ristocetin co-factor, measures vWD activity.

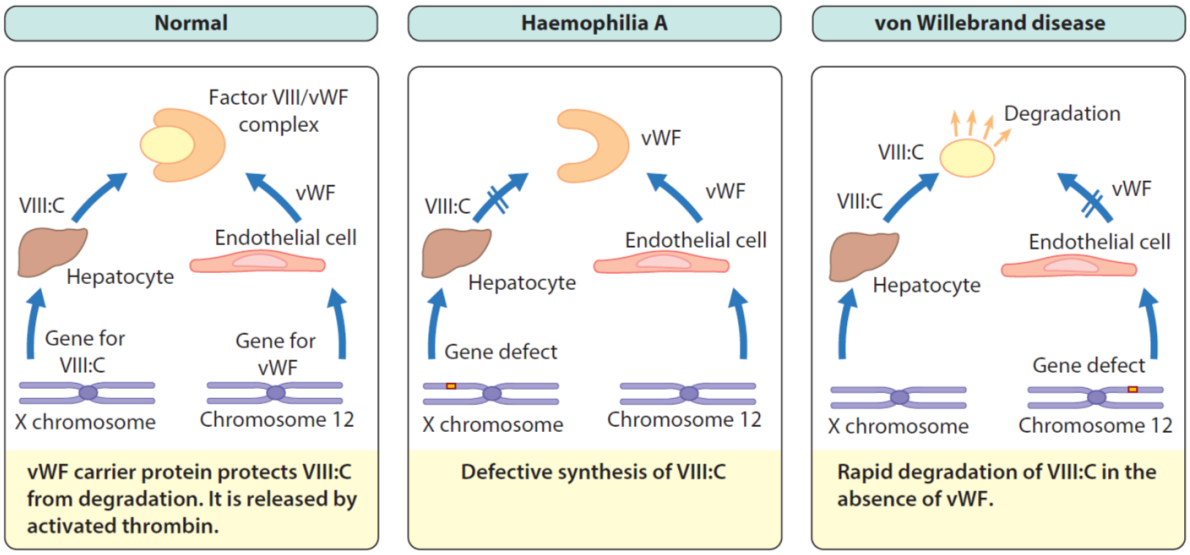


Figure 22.15 Factor VIII synthesis: normal, haemophilia A and von Willebrand disease.

Hemophilia

- The most common congenital clotting disorders due to clotting factor deficiency in intrinsic pathway
  - ❖ X-linked recessive disorder
  - ❖ Male are affected. Female are carriers.
  - ❖ Females are affected in Turner syndrome, homozygous condition, lyonization.
  - ❖ Family history of hemophilia in males of maternal side

- Classification
  - ❖ According to factor deficiency
    - ✓ Hemophilia A – factor VIII deficiency
    - ✓ Hemophilia B – factor IX deficiency (Christmas disease)

  - ❖ According to severity

Severity of hemophilia	% activity of clotting factors	Bleeding manifestation
Mild hemophilia	5-30%	Severe bleeding with major surgery or major trauma
Moderate hemophilia	1-5%	Severe bleeding with minor surgery or minor trauma
Severe hemophilia	< 1%	Spontaneous joint or muscle bleeding

- Clinical features
  - ❖ Severe bleeding after injury in mild and moderate hemophilia

  - ❖ Recurrent spontaneous bleeding in severe hemophilia
    - ✓ During neonatal period,
      - o Severe bleeding from umbilical cord
      - o Prolonged bleeding from heel prick and venipuncture sites
    - ✓ During infanthood,
      - o Bleeding into weight-bearing joints when start to crawl, stand and walk
    - ✓ During childhood,
      - o Severe bleeding post-circumcision
      - o Severe bleeding after dental extraction
      - o Severe bleeding after minor and major surgeries

  - ❖ Types of bleeding
    - o Joint bleeding (hemarthrosis), muscle bleeding (hematoma), wound bleeding
    - o Skin bleeding – bruise
    - o Mucosal bleeding – epistaxis, gum bleeding, hemoptysis, hematemesis and melena, bleeding per rectum, hematuria
    - o Internal organ bleeding – ICH, mediastinal bleeding, retroperitoneal bleeding

  - ❖ Pallor proportionate to bleeding

- Complications
  - ❖ Complications of disease
    - ✓ Pain (the most common and disturbing symptom) (local pain or referred pain)

    - ✓ Pressure effects
      - o Hemarthrosis → arthritis → chronic hemophilic arthropathy → permanent joint damage
      - o Limb hematoma – compartment syndrome, peripheral neuropathy, gangrene
      - o Neck hematoma and tongue hematoma – airway obstruction
      - o ICH, retroperitoneal bleeding – fatal
      - o Mediastinal bleeding – cardiac tamponade, respiratory failure
      - o Intramural intestinal bleeding – intestinal obstruction
      - o Bone bleeding – pseudo-tumor formation

    - ✓ Anemia

  - ❖ Complications of treatment
    - ✓ Due to blood transfusion – transfusion reactions, transfusion-transmitted infections
    - ✓ Due to development of factor inhibitors – resistance to replacement therapy

  - ❖ Psychological and social complications

- Investigations
  - ❖ Investigations for disease and etiology (diagnosis and severity of hemophilia)
    - ✓ Hemogram – Hb↓, WBC↔, platelet↔
    - ✓ Blood film – NNA (acute bleeding)/ HMA (chronic bleeding)

    - ✓ To assess hemostatic parameters
      - o Hess test (-)
      - o Bleeding time – normal
      - o Clotting time – prolonged

    - ✓ To assess clotting pathways
      - o OSPT (for extrinsic pathway) – normal
      - o APTT (for intrinsic pathway) – prolonged
      - o Thrombin time (for final common pathway) – normal

    - ✓ To exclude vWD
      - o vWF assay – normal

    - ✓ To differentiate hemophilia A and hemophilia B
      - o Thromboplastin generation test (TGT)

    - ✓ To assess factor level and coagulant activity
      - o Factor VIII assay for hemophilia A
      - o Factor IX assay for hemophilia B

- ❖ Investigations for complications
  - ✓ For complications of disease
    - To know site of bleeding – endoscopy and imaging (X-ray, USG, CT, MRI)
  - ✓ For complications of treatment
    - For transfusion-transmitted infections – infection screen
    - For factor inhibitors development – factor inhibitors level

- Management
  - ❖ Principles of management
    - ✓ Comprehensive health care by multi-disciplinary team approach
      - Prevention and control of bleeding
      - Treatment of complications and rehabilitation
      - Health education of parents and children for early detection of hemophilia
      - Counseling about benefits of prophylaxis, rehabilitation and prolonged management

  - ❖ General management of hemarthrosis
    - ✓ First aid measures
      - P – Protection of joint (splintage)
      - R – Rest
      - I – Ice compression
      - C – Compression (gentle) (bandaging)
      - E – Elevation of dependent joint to a comfortable position

    - ✓ Pain management
      - Functional training
      - Adequate analgesia (paracetamol, COX-2 inhibitors, opioid analgesia)
      - Orthopedic surgery if persistent and disabling pain

    - ✓ Prevention of joint deformities
      - Physiotherapy and muscle strengthening exercises after acute phase of bleeding

  - ❖ Drug therapy for bleeding episodes
    - ✓ DDAVP (Desmopressin)
      - Mechanism of action – release factor VIII from body stores
      - Indication – muscle or joint bleeding in mild hemophilia

    - ✓ Tranexamic acid
      - Mechanism of action – inhibits fibrinolysis and prevents breakdown of blood clots
      - Indication – oral bleeding, epistaxis
      - Contraindication – hematuria (risk of clot retention and renal failure)

  - ❖ Specific management (Replacement therapy)
    - ✓ Calculation of required amount of clotting factors
      - Factor VIII = weight (kg) x % rise in factor VIII desired x 0.5
      - Factor IX = weight (kg) x % rise in factor IX desired x 1.4

- ✓ Half-lives of clotting factors
  - Half-life of factor VIII – 8 hours
  - Half-life of factor IX – 18-20 hours

- ✓ Blood products for replacement therapy
  - Fresh whole blood (< 8 hours old) – 1 ml contains 1 unit of factor VIII and factor IX
  - Fresh plasma (< 8 hours old) – 1 ml contains 1 unit of factor VIII and factor IX

  - Fresh frozen plasma (contains factor VIII and factor IX) (given within 30 min)
    - Each unit contains about 200 units of factor VIII and factor IX
  - Cryoprecipitate (contains factor VIII, vWF, fibrinogen) (given within 30 min)
    - Each unit contains about 100 units of factor VIII
  - Factor concentrate
    - Pooled – increased risk of infection
    - Recombinant – no risk of infection

- ✓ Home therapy
  - Home infusion of factor concentrate after proper training of parents and children

- ✓ Prophylactic therapy
  - Prophylactic infusions of factor concentrate can convert severe hemophilia to mild or moderate hemophilia, reducing morbidity and mortality of hemophiliac patients

❖ Management of factor inhibitors development
- ✓ Using very high dose of clotting factors
- ✓ Immunosuppressive therapy
- ✓ Factor VIII bypassing agents (activated factor VIIa, activated prothrombinase complex)

- Prevention

❖ Prevention of bleeding
- ✓ Avoid aspirin and anti-platelets
- ✓ Avoid unnecessary IM injections
- ✓ Give vaccinations via subcutaneous route
- ✓ Avoid aspiration of joints

- ✓ For surgical procedure
  - Measure factor level; assess factor inhibitors; ensure adequate factors are available
  - Prophylactic transfusion of clotting factors
    - Major surgery – raise up to 100% of factor VIII and maintain at 30-50% up to 2 weeks
    - Minor surgery – raise up to 50% of factor VIII

❖ Prevention of hemophilia
- ✓ Genetic counseling
- ✓ Antenatal diagnosis
- ✓ Carrier detection – factor VIII C : factor VIII Ag < 0.6 is suggestive of carrier

WBC neoplasms

- Risk factors for WBC neoplasms
  - ✓ Radiation and radiotherapy
  - ✓ Infection
    - EBV, HTLV-1, HIV, HHV-8
    - *H. pylori*
  - ✓ Chemicals (hydrocarbons) and cytotoxic
  - ✓ Hereditary (genetic and chromosomal disorders) (e.g. Down syndrome, Bloom syndrome)

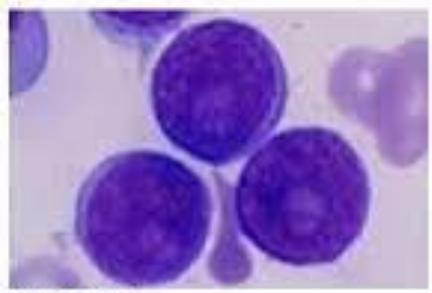
Leukemia

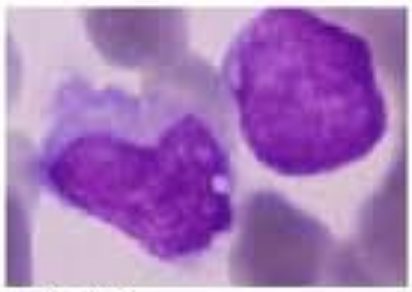
- Accumulation of malignant WBCs in bone marrow and/or blood resulting in bone marrow failure and/or tissue infiltration

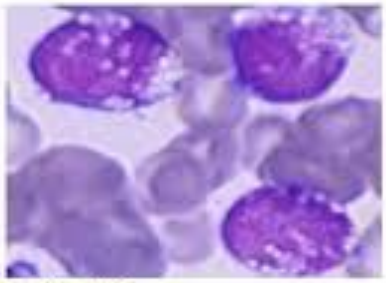
- Classifications of leukemia
  - ✓ Acute leukemia
    - Acute lymphoblastic leukemia (ALL)
    - Acute myeloid leukemka (AML)

  - ✓ Chronic leukemia
    - Chronic lymphocytic leukemia (CLL)
    - Chronic myeloid leukemia (CML)

- Types of leukemia in children
    - Acute lymphoblastic leukemia (ALL)
    - Acute myeloid leukemia (AML)
    - Chronic myeloid leukemia (CML)


ALL-L1


ALL-L2


ALL-L3

Acute lymphoblastic leukemia (ALL)

- Most common malignancy of childhood
- Most common hematological malignancy of childhood

- Major risk factors for ALL
  - ❖ Ionizing radiation
  - ❖ Down syndrome

- Clinical features
  - ❖ Features of disease
    - ➢ Features of bone marrow failure
      - ✓ Anemia
        - o Persistent progressive severe anemia
        - o Pallor, constitutional symptoms
        - o Cardiomyopathy, anemic heart failure, hemic murmur
      - ✓ Bleeding
        - o Skin bleeding – petechiae, purpura, ecchymosis
        - o Mucosal bleeding – epistaxis, gum bleeding, hemoptysis, H&M, bleeding per rectum, hematuria
        - o Internal organ bleeding – ICH (features of ↑ICP) (life-threatening)
      - ✓ Infections
        - o Recurrent infections
        - o Common infections occur more commonly (respiratory tract infection, GI infection)
        - o Opportunistic infections can occur
    - ➢ Features of tissue infiltration
      - ✓ Bone pain, joint pain, sternal tenderness
      - ✓ Lymphadenopathy, hepatosplenomegaly
  - ❖ Features of etiology – features of Down syndrome (facial dysmorphism, congenital heart disease)

- Complications
  - ❖ Emergency complications (hematological emergencies)
    - ➢ Febrile neutropenia
    - ➢ Life-threatening bleeding
    - ➢ Mediastinal obstruction (especially in T lymphoblastic leukemia)
    - ➢ Tumor lysis syndrome
  - ❖ Complications of ALL
    - ➢ Bone marrow relapse
    - ➢ CNS relapse (CNS leukemia – meningism, cranial nerve palsies)
    - ➢ Testicular relapse (painless unilateral/bilateral testicular swelling)

- ❖ Complications of management
  - ➢ Complications of blood transfusion
    - ✓ Transfusion reactions
    - ✓ Transfusion-transmitted infections (HIV, HBV, HCV, malaria, syphilis)

  - ➢ Complications of chemotherapy
    - ✓ General complications
      - o Bone marrow failure (anemia, infections, thrombocytopenia)
      - o Chemotherapy-induced mucositis
      - o Chemotherapy-induced nausea and vomiting

    - ✓ Specific complications
      - o Methotrexate – mucositis, pulmonary fibrosis, cirrhosis
      - o Adriamycin – cardiotoxicity

- Investigations
  - ❖ Investigations for disease (diagnosis and classification of ALL)
    - ➢ Hemogram – Hb↓, WBC↓/↔/↑, platelet↓

    - ➢ Peripheral blood film (Romanovsky stain) (FAB classification of ALL)
      - ▪ L1 – monomorphic, small lymphoblasts, high N:C ratio
      - ▪ L2 – pleomorphic, small and large lymphoblasts, low N:C ratio
      - ▪ L3 – Burkitt's leukemia (basophilic cytoplasm with vacuolation)

    - ➢ Bone marrow examination
      - ▪ Lymphoblasts > 25% (30%)
      - ▪ Erythropoiesis↓, megakaryopoiesis↓

    - ➢ Cytochemical stain
      - ▪ Lymphoblasts – PAS positive

    - ➢ Immunophenotyping
      - ▪ T lymphoblastic leukemia (CD2, CD3, CD5, CD7 – positive)
      - ▪ B lymphoblastic leukemia (CD10, CD19, CD20 – positive)

    - ➢ Cytogenetics
      - ▪ For diagnosis and prognosis
        - o Hyperdiploidy – good prognosis
        - o Philadelphia chromosome (t 9;22) – poor prognosis

  - ❖ Investigations for etiology
    - ➢ For Down's syndrome – chromosomal study (trisomy 21)
    - ➢ For EBV infection – EBV serology

- ❖ Investigations for complications
  - ➢ For complications of ALL
    - o For lymphadenopathy – lymph node biopsy
    - o For hepatosplenomegaly – USG (abdomen)
    - o For CNS leukemia – CSF analysis (CSF leukocytes↑ and/or leukemic cells (+))
  - ➢ For emergency complications
    - o For febrile neutropenia – infection screen, swabs (including ENT), cultures
    - o For ICH – CT (head)
    - o For mediastinal obstruction – CXR, CT (chest)
    - o For tumor lysis syndrome – uric acid↑, K^+↑, phosphate↑, calcium↓, LDH↑
- ❖ Investigations for management
  - o Hemogram, ESR, CRP
  - o CXR, ECG, echocardiogram
  - o Glucose, LFT, RFT, UREME

- Management of ALL
  - ❖ Management of emergency complications
    - ➢ Febrile neutropenia (Neutropenic regimen)
      - o Full barrier nursing, infection screen, blood culture
      - o Empirical antibiotics therapy with broad-spectrum antibacterial ± antifungal followed by
      - o Specific antibiotics therapy according to C&S results until
        - ▪ Afebrile for 3-5 days
        - ▪ Neutrophil count > 0.5 x $10^3/mm^3$
    - ➢ Life-threatening bleeding – blood transfusion
    - ➢ Mediastinal obstruction – radiotherapy
    - ➢ Tumor lysis syndrome – adequate hydration, rasburicase/allopurinol
  - ❖ General management
    - ➢ Prevention of complications of chemotherapy
      - o To prevent or treat bone marrow failure (replacement therapy) – prophylactic/therapeutic transfusion of packed cells and platelets
      - o To prevent *Pneumocystis jiroveci* pneumonia – septrin prophylaxis
      - o To prevent tumor lysis syndrome – adequate hydration, allopurinol
    - ➢ Treatment of complications of chemotherapy
      - o For chemotherapy-induced nausea and vomiting – ondensetron
      - o For chemotherapy-induced mucositis – omit enteral feeding, give parenteral nutrition

- ❖ Supportive management
  - Nutrition – adequate nutrition via enteral and/or parenteral nutrition
  - Hydration – optimal fluid and electrolyte balance
  - Pain and fever control
  - Play and occupational therapy
  - Psychological and social support
  - Hospice care for terminally ill child

- ❖ Specific management
  - ➢ Chemotherapy – mainstay treatment
  - ➢ Allogeneic or autologous bone marrow transplant, immunotherapy
  - ➢ Role of surgery – for lymph node biopsy
  - ➢ Role of radiotherapy – for metastasis (CNS leukemia) and mediastinal obstruction

  - ➢ Chemotherapy
    - ✓ Phases of chemotherapy
      - Remission induction
        - Combination chemotherapy to induce remission
        - Remission – absence of any clinical or laboratory evidence of leukemia) (clinical improvement, absence of abnormal leukemic cells in bone marrow and blood, normal or improving blood count)
      - Consolidation – intensive chemotherapy to reduce or eliminate hidden leukemic cells
      - Maintenance therapy – combination chemotherapy to reduce the risk of relapse
      - CNS-directed therapy (in each phase) – intrathecal methotrexate ± CNS irradiation

    - ✓ Duration of chemotherapy
      - Girls – 2 years
      - Boys – 3 years

- Poor prognostic factors
  - Age – < 1 year, > 10 years
  - Boys, Black, B lymphoblastic leukemia
  - Failure to respond to therapy
  - WBC count at diagnosis – > 50 x $10^3/mm^3$
  - CNS leukemia
  - Cytogenetics – Philadelphia chromosome

- Prevention of ALL
  - ✓ Avoidance of radiation exposure in pregnant women
  - ✓ Protection of children against exposure to dangerous chemicals
  - ✓ Avoidance of unnecessary or repeated radiological investigations in children

Malignant lymphoma

- Malignant proliferation of cells of lymphoid tissue (lymphocytic or histiocytic lineage)
  - Hodgkin lymphoma
  - Non-Hodgkin lymphoma

Non-Hodgkin lymphoma

- *Types common in children and adolescents – lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B cell lymphoma, anaplastic large cell lymphoma*

- Clinical features
  - Can arise in any lymphoid tissue, very rapidly progressive
  - Mainly involving cervical and supraclavicular lymph nodes
  - Nodal spread – localized or generalized lymphadenopathy with painless, rubbery lymph nodes
  - Extranodal spread – hepatosplenomegaly, bone marrow failure
  - Earlier symptoms – cough, sore throat, abdominal pain, vomiting, fever, weight loss, night sweat

- Complications
  - CNS lymphoma – ↑ICP, paraplegia (spinal cord compression)
  - Cervical and Waldeyer ring lymphoma – airway obstruction
  - Intra-thoracic lymphoma – SVC syndrome, cardiac tamponade, pleural effusion
  - Intra-abdominal lymphoma (30-40% of patients) (mainly involve ileum, cecum and appendix) – intestinal obstruction, perforation, bleeding, ascites, IVC obstruction
  - Tumor lysis syndrome, venous thromboembolism

- Staging (St. Jude Children's Research Hospital staging system)
  - Stage I
    - Single tumor (extra-nodal) or single nodal area, excluding mediastinum or abdomen
  - Stage II
    - Single tumor with regional node involvement
    - Two or more tumors or nodal areas on one side of the diaphragm
    - Primary GI tract tumor (resected) with or without regional node involvement
  - Stage III
    - Tumors or lymph node areas on both sides of the diaphragm
    - Any primary intrathoracic or extensive intra-abdominal disease (unresectable)
    - Any primary paraspinal or epidural tumors
  - Stage IV
    - Bone marrow or CNS disease regardless of other sites (marrow involvement defined as 0.5% to 25% malignant cells)

- Investigations
  - For diagnosis – FNAC of lymph nodes, lymph node biopsy

  - For complications
    - For nodal and extranodal spread – imaging (X-ray, USG, CT, MRI)
    - For bone marrow spread – BM biopsy
    - For pancytopenia – hemogram, blood film, infection screen, hemostatic parameters
    - For tumor lysis syndrome – LDH, calcium, phosphate, potassium level
    - For CNS lymphoma – CSF analysis

- Management
  - Management of emergency complications
    - Febrile neutropenia – neutropenic regimen
    - Life-threatening bleeding – blood transfusion
    - Mediastinal obstruction – radiotherapy
    - Tumor lysis syndrome – adequate hydration, rasburicase/ allopurinol

  - General management
    - Prevention of complications of chemotherapy
      - ✓ For BM failure – replacement therapy with blood components
      - ✓ For tumor lysis syndrome – adequate hydration, allopurinol
    - Treatment of complications of chemotherapy
      - ✓ For chemotherapy-induced nausea and vomiting – ondensetron

  - Supportive management
    - Nutrition – adequate nutrition via enteral and/or parenteral nutrition
    - Hydration – optimal fluid and electrolyte balance
    - Pain and fever control
    - Psychological and social support

  - Specific management
    - Role of surgery – for lymph node biopsy, resection of nodal and extranodal areas, for complications (intussusception, intestinal perforation, suspected appendicitis, GI bleeding)
    - Role of radiotherapy – for metastasis (CNS leukemia) and mediastinal obstruction
    - Chemotherapy – mainstay treatment
      - ✓ Choice of protocol depends on histology and stage, duration – 6-18 months
      - ✓ R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone)

  - Management of relapse (extremely poor prognosis) (no uniform approach to rescue therapy)
    - Different/ previously unused chemotherapy
    - Allogeneic or autologous stem cell transplant

- Prognosis
  - Important prognostic factors – tumor burden at presentation and treatment administered
  - Disease free survival for 2 years
    - Nearly 90% in limited stage disease
    - 70% in stage III and IV disease