Session Learning Outcomes

At the end of the session, student should be able to:

- Define and discuss the clinical features, pathophysiology, investigations and management of various myeloproliferative disorders including myelofibrosis, essential thrombocythemia and polycythaemia rubra vera.
- Define and discuss the clinical features, pathophysiology, investigations and management of various bleeding disorders including haemophilia and Von Willebrand’s disease.
- Discuss the clinical features, investigations, and management of disseminated intravascular coagulation.
- Understand the haematological disorders and other factors predisposing to venous thrombosis and management of the same.
Session Plan

- **Myeloproliferative Disorders:**
  - Myelofibrosis
  - Essential thrombocythemia
  - Polycythemia rubra vera

- **Bleeding Disorders:**
  - Disorders of primary haemostasis
  - Coagulation disorders

- **Thrombotic disorders:**
  - Disseminated intravascular coagulation
  - Venous thrombosis
Myeloproliferative Disorders
Myeloproliferative Disorders

Definition: a group of chronic conditions characterized by clonal proliferation of marrow erythroid precursors, megakaryocytes, or myeloid cells.

- Includes conditions like:
  - Myelofibrosis
  - Essential thrombocythaemia
  - Polycythaemia rubra vera
  - Chronic myeloid leukaemia (covered in session 5)

- Aetiology:
  - Genetic mutation on chromosome 9 that codes for JAK-2
Myelofibrosis

- Definition: a rare disease of the bone marrow in which there is excessive collagen fibres build up forming scar tissue inside the marrow cavity. This is due to the uncontrolled growth of fibroblasts and pleuripotent stem cell. It is also known as myeloid metaplasia, leucoerythroblastosis or chronic myelosclerosis.

- Pathophysiology:

Hypercellular bone marrow with an excess of abnormal megakaryocytes → release growth factors → reactive proliferation of fibroblasts → fibrosed bone marrow → blood cell maturation fails → leucoerythroblastic anaemia and giant platelets → extra medullary hematopoiesis
Myelofibrosis

- Clinical features:
  - Fatigue, Pallor, shortness of breath, palpitations
  - Fever, sweating, itching
  - Unexpected bleeding
  - Night sweat, Weight loss
  - Bone pains in the legs
  - Splenomegaly
  - Pain in the left shoulder and upper left portion of the body
Myelofibrosis

- **Diagnosis:**
  - Full blood count
  - Peripheral blood smear
  - Bone marrow biopsy
  - Serum urate and folate
  - Genetic analysis for JAK-2

- **Management:**
  - Red cell transfusions
  - Folic acid supplements
  - Cytotoxic therapy
  - Splenectomy
  - HSCT
  - *JAK-2* inhibitor
Myelofibrosis: Excessive collagen fibres build up forming scar tissue inside the marrow cavity due to the uncontrolled growth of fibroblasts and pleuripotent stem cells. Genetic mutation on chromosome 9 that codes for JAK-2 in 50% cases.

- Uncontrolled/Clonal proliferation of blood cells.
- Hypercellular bone marrow with an excess of abnormal megakaryocytes.
- Release growth factors.
- Reactive proliferation of fibroblasts.
- Fibrosed bone marrow.
- Failure of blood cell maturation.
- Leuoerythroblastic anaemia and giant platelets.
- Extra medullary haematopoiesis.
- Bone pains in the legs.
- Symptoms of Anaemia: Fatigue, Pallor, shortness of breath, palpitations.
- Increased predisposition to infection: Fever, sweating.
- Systemic signs and symptoms: Night sweat, Weight loss.
- Splenomegaly, splenic infarction and perisplenitis, Pain in the left shoulder and upper left portion of the body.

**Diagnosis:**
- FBC
- Peripheral blood smear
- Bone marrow biopsy
- Serum urate and folate
- Genetic analysis for JAK-2

**Management:**
- Red cell transfusions
- Folic acid supplements
- Cytotoxic therapy
- Splenectomy
- HSCT
- JAK-2 inhibitor
Essential Thrombocythaemia

Definition: a disease characterised by malignant proliferation of megakaryocytes that results in a raised level of circulating platelets that are often dysfunctional leading to a tendency of bleeding and thrombotic episodes.

Clinical features:
- Bleeding from GIT, Respiratory tract and skin
- Blood in stools
- Easy bruising
- Dizziness
- Enlarged lymph nodes
- Headaches
- Epistaxis
- Ulcers on the fingers and toes
- Cerebral stroke
Essential Thrombocythaemia

- **Management:**
  - low-dose aspirin
  - Inhibitor of megakaryocyte maturation
  - Intravenous radioactive phosphorus (32P)

- **Complications:**
  - Acute leukaemia
  - Myelofibrosis
Polycythæmia Rubra Vera

- **Definition**: A clonal stem cell disorder in which there is an increase in haemoglobin, PCV and red cell count.

- **Clinical features**:
  - Mainly in patients over the age of 40 years
  - Symptoms of hyper viscosity
  - Symptoms of peripheral arterial disease or a cerebrovascular accident
  - Venous thromboembolism
  - Peptic ulceration
  - Plethora with deep cyanosis
  - Hepatosplenomegaly and gout
  - Aquagenic pruritus
Polycythaemia Rubra Vera

Diagnosis:

- Full blood count
- Genetic analysis for JAK-2
- Absence of causes of a secondary erythrocytosis
- Bone marrow examination

Management:

- Aspirin
- Venesection
- Bone marrow suppression
- Radioactive phosphorus

Complications:

- Cerebrovascular attacks
- Coronary events
- Acute leukaemia
- Myelofibrosis
## Polycythaemia Rubra Vera

<table>
<thead>
<tr>
<th>Cause of a secondary erythrocytosis</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>High erythropoietin due to tissue hypoxia</td>
<td>High altitude Cardiorespiratory disease High-affinity haemoglobins</td>
</tr>
<tr>
<td>Inappropriately increased erythropoietin</td>
<td>Renal disease (hydronephrosis, cysts, carcinoma) Other tumours (hepatoma, bronchogenic carcinoma, uterine fibroids, phaeochromocytoma, cerebellar haemangioblastoma)</td>
</tr>
<tr>
<td>Exogenous erythropoietin administration</td>
<td>Performance-enhancing drug-taking in athletes</td>
</tr>
</tbody>
</table>
Bleeding Disorders
Disorders of Primary Haemostasis

Definition: The failure of initial formation of the platelet plug

○ Aetiology:
  • Vessel wall abnormalities
    – Hereditary haemorrhagic telangiectasia
  • Platelet function disorders
    – Idiopathic thrombocytopenic purpura
    – Thrombotic thrombocytopenic purpura
  • Von Willebrand disease (will be covered under clotting disorders)
Hereditary Haemorrhagic Telangiectasia

Definition: It is an autosomal dominant disease characterised by bleeding from multiple telangiectases which consist of localised collection of non-contractile capillaries.

- Aetiology:
  - Genetic mutations in the genes encoding endoglin and activin receptor-like kinase, which are endothelial cell receptors for transforming growth factor-beta (TGF-β), a potent angiogenic cytokine.
Hereditary Haemorrhagic Telangiectasia

○ Clinical features:
  ○ Recurrent bleeds, particularly epistaxis,
  ○ Haematemesis, haemoptysis or bleeding elsewhere
  ○ Iron deficiency due to occult gastrointestinal bleeding
  ○ Telangiectases and small aneurysms on the fingertips, face and tongue, and in the nasal passages, lung and gastrointestinal tract
  ○ Larger pulmonary arteriovenous malformations leading to arterial hypoxaemia
  ○ Predisposition to paradoxical embolism, resulting in stroke or cerebral abscess.
Hereditary Haemorrhagic Telangiectasia

- Management:
  - No universal treatment
  - Regular iron therapy
  - Local cautery or laser therapy

Idiopathic Thrombocytopenic Purpura

Definition: It is a disease characterised by a severe reduction in the number of circulating platelets due to an autoimmune attack on the platelets, the antibody being IgG type.

- Clinical features:
  - Easy bruising or sometimes epistaxis
  - Menorrhagia in females
  - Spontaneous bleeding
  - Purpuric spots and haemorrhages on skin
  - Iron deficiency anaemia
Idiopathic Thrombocytopenic Purpura

- Management:
  - No treatment required if a platelet count of more than $30 \times 10^9/L$
  - Prednisolone
  - Intravenous immunoglobulin with corticosteroids
  - Platelet transfusion

Foot with acute purpura and petechiae

Grossman, S, Porth, CM 2013, Porth’s pathophysiology, Concepts of Altered Health States, 9th edn, Lippincott Williams & Wilkins
Thrombotic Thrombocytopenic Purpura

- **Definition:** It is a rare disorder that likely results from introduction of platelet-aggregating substances into the circulation leading to abnormal platelet aggregation and adhesion to the endothelium.

- **Clinical features:**
  - Purpura, petechiae,
  - Vaginal bleeding,
  - Neurologic symptoms: headache, seizures, altered consciousness

- **Management:**
  - Plasmapheresis
  - Plasma infusion
Haemophilia A

- Definition: Haemophilia A is an X-linked recessive disorder of factor VIII deficiency that is characterised by a lifelong tendency to excessive haemorrhage and a greatly prolonged coagulation time.

Haemophilia A

Clinical features:

- Superficial injury presents with massive bleeding
- Spontaneous bleeding into skin, muscle and joints
- Typically large joints involved, especially knees, elbows, ankles and hip
- Muscle haematomas, most commonly in the calf and psoas muscles
- Hot, swollen and very painful joint
- Synovial hypertrophy, destruction of the cartilage and secondary osteoarthritis
- Retroperitoneal and intracranial bleeding
Haemophilia A

- **Diagnosis:**
  - Bleeding time (BT)
  - Prothrombin time (PT)
  - Activated Partial Thromboplastin Time (APTT)
  - Von Willebrand Factor (vWF) assays
  - Factor VIII assays

- **Management:**
  - Intravenous infusion of factor VIII concentrate
  - Vasopressin receptor agonist
Haemophilia B

- **Definition:** Hemophilia B, or Christmas disease, is an inherited, X-linked, recessive disorder that results in deficiency of functional plasma coagulation factor IX.

- **Clinical features:**
  - Similar to Haemophilia A

- **Diagnosis:**
  - Factor IX assays

- **Management:**
  - Intravenous infusion of factor IX concentrate
Von Willebrand Disease

- **Definition:** Von Willebrand disease is a relatively common hereditary bleeding disorder characterized by a quantitative or qualitative deficiency of von Willebrand factor (vWF).

- **Clinical features:**
  - Superficial bruising, epistaxis, menorrhagia
  - Gastrointestinal haemorrhage
  - Bleeding episodes much less common than in severe haemophilia
  - Excessive haemorrhage may only be observed after trauma or surgery
Von Willebrand Disease

- **Diagnosis:**
  - Bleeding time (BT)
  - Prothrombin time (PT)
  - Activated Partial Thromboplastin Time (APTT)
  - Von Willebrand Factor (vWF) assays
  - Factor VIII assays

- **Management:**
  - Vasopressin receptor agonist
  - Intravenous infusion of factor VIII with vWF concentrate
Thrombotic disorders
Disseminated Intravascular Coagulation

- **Definition:** It is characterised by systemic activation of the pathways involved in coagulation and its regulation which may result in the generation of intravascular fibrin clots causing multi organ failure, with simultaneous coagulation factor and platelet consumption causing bleeding.

- **Aetiology:**
  - Infection/sepsis
  - Trauma
  - Obstetric conditions
  - Severe liver failure
  - Malignancy
  - Tissue destruction
  - Vascular abnormalities
  - Toxic/immunological
Disseminated Intravascular Coagulation

- Clinical features:
  - Coagulation and formation of microemboli
  - Bleeding: petechiae, purpura, oozing from puncture sites, or severe hemorrhage
  - Tissue hypoxia and necrotic damage to vital organs
  - Renal, circulatory, or respiratory failure
  - Acute bleeding ulcers
  - Convulsions and coma
  - Hemolytic anemia
Disseminated Intravascular Coagulation

Diagnosis:
- International Society for Thrombosis and Haemostasis scoring system for diagnosis:
  - Presence of an associated disorder
  - Fibrin degradation products
  - Prothrombin time
  - Fibrinogen level
  - Platelet count

Management:
- Treatment of underlying cause
- Intensive care
- Blood component therapy
- Heparin
- Antifibrinolytic therapy is contraindicated
Venous Thrombosis

- **Definition:** It is the most common presentation of venous thromboembolic disease.

<table>
<thead>
<tr>
<th>Factors predisposing to venous thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
</tr>
<tr>
<td>Age, coexisting disorders, obesity, patient Hx or FHx of deep vein thrombosis or pulmonary embolism, OCP and HRT</td>
</tr>
<tr>
<td><strong>Surgical conditions</strong></td>
</tr>
<tr>
<td>Abdominal or pelvic surgery, joint replacement or hip fracture surgery.</td>
</tr>
<tr>
<td><strong>Medical conditions</strong></td>
</tr>
<tr>
<td>MI, IBD, pneumonia, Malignancy, Nephrotic syndrome, immobility following a stroke</td>
</tr>
<tr>
<td><strong>Haematological conditions</strong></td>
</tr>
<tr>
<td>PCV, essential thrombocythaemia, myelofibrosis</td>
</tr>
</tbody>
</table>
Venous Thrombosis

○ Management:
  • Elevation and analgesia
  • Thrombolysis
  • Anticoagulation with low molecular weight heparin
  • Coumarin anticoagulant, such as warfarin

○ Complications:
  • Post-thrombotic syndrome:
    – Persistent leg swelling, heaviness and discoloration
    – Ulceration around the medial malleolus.
Reading and Resources

- Crowley LV, 2012, *An Introduction to Human Diseases – Pathology and Pathophysiology Correlations*, 9th edn, Jones and Bartlett Learning
Reading and Resources

- Mosby’s dictionary of medicine, nursing and health professions 2013, 9th edn, Elsevier, St. Louis, MO.
- VanMeter, KC & Hubert, RJ 2014, *Gould's pathophysiology for the health professions*, 5th edn, Elsevier, St Louis, MO.
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