Objectives

- Define oedema, describe the pathophysiology and distinguish between localized and generalized forms
- Define congestion and hyperaemia, explain their mechanisms and make clinical correlations
- Briefly review the mechanism of haemostasis
- Define haemorrhage, and describe the mechanisms and clinical consequences
- Define shock and its various types, explain its mechanisms and clinical consequences
- Define thrombosis, describe the pathophysiology using the Virchow triad and correlate with predisposing factors and clinical consequences
- Define embolism and its various types, and explain its mechanisms and clinical consequences
- Define infarction, describe its morphology and mechanism and make relevant clinical correlations.

Outline

I. Oedema

a. **Definition**
b. **Location:** *Interstitial vs Body cavities*
c. **Mechanisms:** *Pathophysiologic categories of oedema*
d. **Localized vs Generalized oedema**
e. **Morphology**
f. **Clinical complications**

II. Hyperaemia and Congestion

a. **Definition of Hyperaemia vs Congestion**
b. **Localized vs Generalized**
c. **Morphology and Clinical correlation, e.g. congestion in the liver and lungs**

III. Haemostasis

a. **Overview of haemostatic response**
b. **Role of platelets**
c. **Role of coagulation cascade**
d. **Role of endothelium**

IV. Haemorrhage

a. **Types of haemorrhage**
b. **Causes of haemorrhage**
c. **Clinical significance**

V. Shock

a. **Definition**
b. **Types of shock**
c. **Compensatory mechanisms**
d. **Septic shock:** *Background, Pathogenesis and Outcome*
e. **Stages of shock**

f. **Effects on major organs**
g. **Clinical consequences**

VI. Thrombosis

a. **Definition**
b. **Virchow's triad**
c. **Causes:** *Genetic vs Acquired*
d. **Morphology**
e. **Fates of a thrombus**
f. **Clinical features:** *Venous vs Cardiac/ Arterial*
g. **Disseminated intravascular coagulation**

VII. Embolism

a. **Definition**
b. **Pulmonary thromboembolism**
c. **Systemic thromboembolism**
d. **Fat and bone marrow embolism**
e. **Air embolism**
f. **Amniotic fluid embolism**

VIII. Infarction

a. **Definition**
b. **Mechanisms:** *Arterial vs Venous occlusion*
c. **Morphological features:** *Configuration, Colour and Sequelae*
d. **Factors affecting development of infarct**

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. OEDEMA

Definition

- Oedema is the accumulation of excessive extracellular fluid

Location: interstitial vs body cavities

- Fluid accumulation in the interstitial space is called oedema
- Fluid can also collect in the various bodily cavities, e.g. hydrothorax or pleural effusion, hydropericardium or pericardial effusion, peritoneal effusion (ascites)

Mechanisms: Pathophysiologic categories of oedema

- Oedema develops as a result of disturbances in the **Starling's forces**: increased capillary hydrostatic pressure, reduced plasma oncotic or osmotic pressure, increased vascular permeability and/or lymphatic obstruction, generalized sodium and water retention, can all result in oedema
- Oedematous conditions due to **increased hydrostatic pressure**: deep vein thrombosis (DVT) leading to ipsilateral lower limb oedema; pulmonary and peripheral oedema due to congestive heart failure. Do note for latter condition: the secondary sodium and water retention as triggered by the diminished renal blood flow and activation of the renin-angiotension-aldosterone (RAA) system, compounds the oedematous state.
- Oedema due to **reduced plasma oncotic pressure**: protein loss due to nephrotic syndrome, reduced albumin production due to chronic liver disease and protein malnutrition. Similar to the previous point, the activation of the RAA system perpetuates the oedematous state by causing sodium and water retention.
- Oedema due to **increased vascular permeability**: due to inflammatory conditions
- **Lymphatic obstruction** e.g. due to inflammation, neoplastic infiltration or post-surgical/ radiation effect, can also lead to oedema.
- **Conditions causing primary salt and water retention** e.g. excessive salt intake in the setting of kidney disease, aldosterone-producing adrenal cortical tumours, may lead to oedema.

Localized vs Generalized oedema

- Causes of **localized oedema**: DVT leading to oedema of the affected lower limb; localized skin infection and inflammation with oedema in the vicinity
- Causes of **generalized or systemic oedema**: congestive heart failure, hypoproteinaemic states (*vide supra*)

Morphology

- Subcutaneous oedema: typically worse in **gravity-dependent** areas e.g. around ankles when standing or sacrum, when patient mostly recumbent. Also typically pitting in nature.
- Oedema due to hypoproteinaemia: usually more generalized and more pronounced in loose connective tissue e.g. periorbital region
- Pulmonary oedema: results in heavy congested lungs with frothy blood-stained fluid, when sectioned (at autopsy)

- Brain oedema: may be localized (due to e.g. tumour, abscess) or generalized (due to e.g. encephalitis, hypertensive encephalopathy). The latter manifests as a swollen brain with narrowed sulci and broad gyri.

Clinical complications

- Subcutaneous oedema can impair wound healing and predispose to skin/ soft tissue infections
- Pulmonary oedema **impairs gaseous exchange**, and predisposes to respiratory failure or pneumonia
- Brain oedema may lead to raised intracranial pressure and **tonsillar herniation** that could compress brainstem, thereby compromising the cardio-respiratory centres (coning)

II. HYPERAEMIA AND CONGESTION

Definition of hyperaemia vs congestion

- Hyperaemia is due to arteriolar vasodilation resulting in increased blood flow and thence blood volume within the vasculature of the organ.
- Hyperaemia can be **physiological** e.g. increased blood flow to muscles during exercise, or **pathological** e.g. increased blood flow to an area of inflammation
- Congestion is 'passive' in nature and is due to venous outflow obstruction resulting in increased blood volume within the vasculature of the organ (note: congestion that is sufficiently severe and unrelieved may lead to hypoxaemia and necrosis of the affected organ.)

Localized vs generalized forms of congestion

- Localized types of congestion: e.g. DVT resulting in congestion and oedema of the affected lower limb
- Generalized or systemic type of congestion: pulmonary and systemic venous congestion due to congestive heart failure

Morphology and Clinical correlations, e.g. congestion in the lungs and liver

- Grossly, congested organs tend to be enlarged, **heavy** and **cyanotic** (due to increasing deoxyhaemoglobin); in contrast, hyperaemic tissue is typically **red** or erythematous
- In the lungs, acute congestion (e.g. due to left-sided heart failure) leads to interstitial vascular **congestion**, **oedema** and haemorrhage. With chronicity, alveolar **haemosiderophages** ('heart failure cells') appear and interstitial fibrosis may set in ('brown induration' of the lungs)
- In the liver, acute congestion (e.g. due to right-sided heart failure) features central vein and sinusoidal dilatation, and centrilobular hepatocytic degeneration. With chronicity, there is a **'nutmeg liver**' gross appearance correlating microscopically with centrilobular hepatocytic necrosis/hepatocytic drop-out and haemorrhage with associated haemosiderophages. Fibrosis may set in in the long term ('cardiac cirrhosis').

III. HAEMOSTASIS

Overview of haemostatic response

- Immediate and transient arteriolar **vasoconstriction**, mediated primarily by endothelin
- **Platelet** adhesion, activation and aggregation – **primary haemostasis**
- **Coagulation cascade** activation with formation of thrombin and thereafter fibrin. Polymerized fibrin and platelets aggregates constitute **secondary haemostasis**
- Counter-regulatory mechanisms (e.g. via tissue plasminogen activator t-PA) limits the haemostasis to the affected site

Role of platelets

- Platelets **adhere** to extracellular matrix e.g. collagen via von Willebrand factor (vWF)
- Platelet conformational changes encourage fibrin binding and coagulation factor and calcium interactions
- Platelet **release reaction**, e.g. ADP and Thromboxane A2 (T_XA_2)(latter also a vasoconstrictor)
- Platelet **aggregation** facilitated by similar factors e.g. ADP, T_XA_2
- Continued platelet activation with GpIIb-IIIa receptor changes facilitating fibrinogen binding
- RBCs and leukocytes also get caught up and contribute to the haemostatic plug

Role of coagulation cascade

- **Sequential activation** of proenzymes to activated enzymes, ultimately to produce **fibrin** from fibrinogen
- This takes place on the phospholipid-rich surfaces of activated platelets and endothelial cells
- 2 arms: **Intrinsic** pathway, tested by the PTT test and the **Extrinsic** pathway (set off by the release of tissue factor), tested by PT.
- Note varied effects of thrombin apart from mediating the conversion of fibrinogen to fibrin: anticoagulation, platelet activation, pro-inflammatory activity.
- Counter-coagulation mechanisms: localized to sites of exposed phospholipids, dilution of factors by blood flow, endothelial counter-regulatory mechanism, fibrinolyic cascade (plasmin breaks down fibrin*; countered by plasmin inhibitor) (*note: fibrin degradation products or D-dimers is a good laboratory marker of thrombosis).

Role of endothelium

- Intact endothelium is normally inhibitory to platelet activation and coagulation and has fibrinolysis properties. **Injury or activation of endothelium** leads to promotion of coagulation.
- Platelet inhibitory effects: prevents platelet access to ECM; PGI_2 and NO inhibits platelets; degradation of ADP via adenosine diphosphatase
- Anticoagulation effects: thrombomodulin, proteins C and S, heparin-like surface molecules, tissue factor pathway inhibitor
- Tissue plasminogen activator (t-PA) is produced: cleaves plasminogen to plasmin, facilitating fibrinolysis

IV. HAEMORRHAGE

Types of haemorrhage

- Can be spontaneous or traumatic
- Due to abnormalities of platelets, coagulation factors or blood vessel wall

Causes of haemorrhage

- Most common causes of mild haemorrhage are congenital vWF deficiency, aspirin use and renal disease/ uraemia
- Defects in primary haemostasis: quantitative or qualitative **platelet defects.** Manifests as **petechiae** (1-2 mm in size) or slightly larger purpura in skin, mucous membranes or serosal surfaces
- Defects in secondary haemostasis: can be congenital/ genetic or acquired and involve **abnormalities in coagulation factors.** Manifests as bleeding into joints or soft tissue
- Generalized defects involving small blood vessels: most often due to **vasculitis** or vascular fragility e.g. scurvy, resulting 1-2 cm sized **bruises** or **ecchymoses** (if palpable mass – haematoma).

Clinical significance

- Depends on quantity and rate of blood loss: loss of up to 20% of blood volume or slow loss, may have less impact. Greater degree of haemorrhage leads to **hypovolaemic shock**
- Prolonged and slow blood loss can lead to iron deficiency **anaemia**.
- Location is important: skin haemorrhages cause less of an impact. A modest amount of intracranial haemorrhage (with ensuing raised intracranial pressure) or pericardial haemorrhage (causing tamponade) are **potentially fatal.**

V. SHOCK

Definition

- Systemic hypoperfusion and cellular hypoxia as a result of either reduction in cardiac output or effective circulating blood volume.

Types of shock

- **Cardiogenic shock**: common causes include myocardial pump failure due to **myocardial infarction**, arrythmia, pericardial tamponade and outflow obstruction due to massive pulmonary thromboembolism
- **Hypovolaemic shock**: common causes include **severe blood loss** due to trauma, marked fluid loss due to vomiting, diarrhoea and extensive burns
- **Septic shock:** due to marked vasodilation and blood pooling ('distributive' shock) as a result of microbial infection and the haemodynamic effects of the inflammatory-immune responses
- Other **distributive shock** aetiologies: **anaphylaxis** due to severe IgE-mediated allergic reaction, **neurogenic** shock due to central nervous system trauma and ensuing loss of vascular tone

Compensatory mechanisms

- **Neurohumoral responses**: sympathetic nervous system stimulation and effects of catecholamines, leading to vasoconstriction, increased heart rate and myocardial contractility
- Other neurohumoral responses: activation of **renin-angiotensin-aldosterone system** and antidiuretic hormone release, keeping water in the circulatory system
- **Diversion of blood** from cutaneous and splanchnic circulations to critical organs (e.g. brain, heart, kidney)
- **Fluid shift** to the intravascular compartment
- Increased haematopoietic (erythrocytic) cell production by the bone marrow

Septic shock: background, pathogenesis and outcome

- Major cause of death in intensive care units because of ill and often immunocompromised patients and increasing invasive interventions being performed.
- Gram positive and negative **organisms** and fungi are most often responsible
- Superantigens cause T cell activation and **proinflammatory cytokines** to be released
- Initially raised cardiac output, but ultimately systemic **vasodilation**, endothelial cell activation and hypercoagulable state lead to tissue hypoperfusion and multiorgan damage
- **Inflammatory responses**, stimulation of leukocytes (macrophages) and release of inflammatory cytokines and other factors; coagulation cascade and complement activation also contribute to the inflammatory state
- **Endothelial cell (EC) activation** and injury: increased vascular permeability and oedema. EC also releases NO and other mediators leading to vasodilation
- **Promotion of procoagulant state**: EC activation contributes to eventual disseminated intravascular coagulation (DIVC)
- **Metabolic abnormalities** of insulin resistance and hyperglycaemia. Stress hormones e.g. cortisol being released, eventually may culminate in adrenal insufficiency
- **Multiorgan dysfunction / failure** occurs: e.g. myocardial contractility can be reduced, and also adult respiratory distress syndrome (shock lung)
- **Mortality rate is quite high** at 20**%** and dependent on extent and virulence of infection, premorbid state of patient, pattern and degree of inflammatory-immune response, and timeliness of treatment.

Stages of shock

- **Non-progressive phase**: compensatory neurohumoral mechanisms (*vide supra*) maintain perfusion of vital organs
- **Progressive phase**: Increasing **circulatory and metabolic disturbances** arise; lactic acidosis from anaerobic respiration inhibits vasomotor responses resulting in vasodilation
- **Irreversible phase**: **Multiorgan failure** and death is inevitable even though perfusion might be restored by treatment efforts (*vide infra)*

Effects on major organs

- **Kidney shutdown** (**renal tubular necrosis**) occurs resulting in oligo- or anuria with critical electrolyte abnormalities.
- **Ischaemia of intestines** cause the loss of fluids and escape of bacteria into the blood circulation.
- **Myocardial ischaemia** and necrosis, reducing cardiac output
- **Liver necrosis**
- **Acute respiratory distress syndrome** or diffuse alveolar damage (shock lung)
- **Brain ischaemia** and necrosis

Clinical consequences

- Shock is characterized by tachycardia, tachypnoea and cold and clammy skin; except early septic shock typified by warm and reddish complexion due to cutaneous vasodilation.
- **Major organ dysfunctions** as described in preceding section leads to **vicious cycle** and deterioration of the shock
- For survivors of initial complications of shock, there could be renal insufficiency with ensuing **fluid and electrolyte imbalances.**
- Prognosis of shock depends on type of shock, premorbid status of patient and timeliness of appropriate treatment: hypovolaemic shock in the young with aggressive treatment has reasonable survival chances while elderly with **cardiogenic or septic shock have much worse prognosis.**

VI. THROMBOSIS

Definition

- **Inappropriate intravascular blood clotting** without preceding significant vascular injury

Virchow's triad

- Thrombosis occurs due to endothelial injury, alterations in normal blood flow or hypercoagulable state
- **Endothelial injury**: e.g. due to **atherosclerosis**, or other physical or chemical injuries; results in platelets coming into contact with ECM and becoming activated, increased production of procoagulants (e.g. tissue factor) or decreased inhibitors of coagulation (e.g. PGI_2)
- **Altered blood flow: stasis or turbulence**: stasis e.g. in veins, cardiac or aortic aneurysms, atrium during atrial fibrillation) – disrupts laminar blood flow and allows platelets to come into contact with endothelium; turbulence – generates eddy currents and pockets of stasis, and also injures endothelium, resulting in thrombosis.
- **Hypercoagulable states: Inherited** (e.g. Factor V and prothrombin mutations; antithrombin III, proteins C and S deficiency) and **acquired** causes (oestrogen-containing pills, pregnancy, heparin and its adverse effects on platelets, antiphospholipid antibodies)

Morphology

- **Venous thrombi** (e.g. DVT) occur mostly due to stasis, are occlusive and are dark red in colour

- **Aortic or cardiac thrombi** occur often due to endothelial injury and are non-occlusive; smaller arterial thrombi may be occlusive (e.g. coronary thrombosis)
- Arterial and cardiac thrombi may have alternating light and dark-coloured laminations (lines of Zahn)
- Valvular thrombi: main types are vegetations of infective endocarditis, nonbacterial thrombotic endocarditis and Libman-Sacks endocarditis (due to SLE).

Fates of a thrombus

- Propagation
- Embolization (*vide infra*)
- Organization and recanalization
- Microbial infection leading to septic emboli or mycotic aneurysm

Clinical features: Venous, Cardiac and Arterial thrombi

- Thrombi in superficial leg veins predispose to skin infections and **venous ulcers**; DVT give rise to limb swelling, congestion and pain, but most dangerously, possibility of pulmonary embolization.
- Clinical states predisposing to DVT: post-major surgery, **prolonged bed rest**, post-partum state, severe trauma, burns and cancer (with production of pro-coagulants)
- **Cardiac thrombosis** can occur as a consequence of **myocardial infarction** because of endothelial injury and abnormality in intracardiac blood flow; mitral valve disease with scarring and stenosis e.g. due to rheumatic heart disease, also may cause atrial dilatation, and with contribution by atrial fibrillation, may lead to stasis and thrombosis within the atrium.
- Arterial thrombosis most often arise as a consequence of atherosclerosis with plaque rupture and ulceration.
- Cardiac and arterial thrombi can **embolize** to various arteries causing **infarcts** in the brain, kidney, spleen etc.

Disseminated intravascular coagulation (DIVC)

- Formation of **widespread fibrin microthrombi** in the blood circulation
- Triggering conditions include obstetric complications, burns, sepsis and advanced malignancy
- As a result of widespread vascular **thrombotic occlusion,** ischaemic damage to the heart, lungs, liver, kidney, brain can occur.
- The consumption of platelets and coagulation factors and the activation of fibrinolysis can lead to the occurrence of uncontrolled **bleeding**.

VII. EMBOLISM

Definition

- Intravascular solid, liquid or gaseous material carried by the bloodstream to a site distant from its point of origin.
- Most common form is **thromboembolism**; other materials include air bubbles, fat globules, foreign body, tumour fragments, bone marrow, septic/ infective material

- Causes vascular occlusion where it ultimately lodges resulting in ischaemia or infarction; septic emboli leads to abscess formation.

Pulmonary thromboembolism

- Occurs in up to 0.4% of hospitalized patients and accounts for many deaths.
- Most common origin is **DVT**; many smaller thrombi/ thromboemboli are silent or asymptomatic
- Can be single and massive, or showers of smaller emboli.
- Massive main pulmonary arterial trunk or **saddle embolus** (sitting on bifurcation) results in acute right heart failure and **sudden death**
- Embolus lodging in small or medium-sized arterial branches give rise to **pulmonary haemorrhage** or sometimes infarct
- Multiple of repeated smaller emboli occurring over time can result in widespread occlusion of the pulmonary circulation, with ensuing **pulmonary hypertension** and right heart failure

Systemic thromboembolism

- Common origins for such thromboemboli are the ventricular cavity adjacent to myocardial infarction, from left atrium that is dilated or undergoing fibrillation, vegetations of infective endocarditis and venous thromboemboli crossing from the right heart to the left, via septal defects (paradoxical embolism)
- Arterial origins of thromboemboli are most often from atheromatous plaques or aortic aneurysms.
- Outcome of such systemic thromboembolisms depend on degree of collateral blood supply, tissue vulnerability to ischaemia, prior presence of anaemia or heart failure, and calibre of vessel. Critical organ infarcts are the dreaded outcome.
- Cerebral infarct and lower limb ischaemia and gangrene are the most common affected target sites; embolism to the kidneys, intestines, spleen and upper limbs also occur but are less frequent.

Fat and marrow embolism

- Typically occurs a few days after **bone fractures** or other musculoskeletal injuries, when bone marrow or fat globules gain access to the blood stream; often asymptomatic
- Patients present with petechial haemorrhages, drowsiness, seizures, cough or breathlessness as a result of fat **emboli to the skin, brain and lungs**; condition may be fatal
- Released fatty acids are toxic to the endothelium, and together with free radicals and chemical mediators released from leukocytes, cause further tissue damage, haemorrhage and oedema; platelet activation and RBC aggregation occur and may form microthrombi

Air embolism

- Occurs when air bubbles get access or form in the blood circulation; causes include incidents during head and neck, thoracic or gynaecological surgery
- Classically occurs as diving accident – **decompression disease** – when diving in deep waters, air is dissolved in the blood; whereupon on rapid surfacing, **air bubbles form in the blood stream** and embolize to the muscles and bone (causing pain - ***bends***), pulmonary circulation (breathlessness, cough - ***chokes***) and cerebral circulation (drowsiness, disorientation - ***staggers***).

- Caisson disease a rare cause of avascular necrosis of the femoral head due to chronic decompression disease

Amniotic fluid embolism

- Very rare obstetric complication (1:40000 births) where amniotic fluid and its content enters the uterine veins and embolize; very high reported fatality
- Leads to embolization to the pulmonary circulation and **sudden cardiac collapse**; if patient survives, diffuse alveolar damage and **DIVC** may develop because of release of injurious fatty acids and thrombogenic substances present in the amniotic fluid
- Autopsy and microscopic examination may show hair, mucin and fetal squames in pulmonary capillaries

VIII. INFARCTION

Definition

- **Infarction** is **ischaemic necrosis** of tissue or organs most often as a result of vascular occlusion

Mechanisms: arterial vs venous occlusion

- Arterial occlusion is most often due to **thrombosis** or **thromboembolism**, vasospasm or extrinsic compression
- Venous occlusion resulting in infarct occurs most often when there is only a single venous outflow from the affected organ, when the venous flow is compromised e.g. testicular or ovarian torsion.

Morphological features: configuration, colour and sequelae

- Infarcts are often wedge-shaped with the apex directed at the occluding feeding artery and fanning out at the peripheral aspect
- Red infarcts are due to haemorrhage in the area
- Causes of red infarcts include infarcts due to venous occlusion and prior congestion, loosely-textured organs (e.g. lung), organs with dual blood supply (e.g. liver and lung), perfusion being restored at a later time after infarction has occurred.
- White or bland infarcts typically occur in solid-textured organs e.g. spleen and kidney, with tissue supplied by end arteries/ arterioles with minimal collateral circulation.
- Coagulative necrosis is typified by myocardial infarct and liquefactive necrosis occurs in brain infarcts. Myocardial infarct heals by fibrous scarring while brain infarct is replaced eventually by gliosis.

Factors affecting development of infarct

- **Anatomy of arterial blood supply**: Organs with dual and overlapping blood supply e.g. lung, liver, and brain regions supplied by circle of Willis, are relatively protected from ischaemia when one route is obstructed.
- **Rate of development of vascular occlusion**: a slowly developing occlusion allows time for collateral blood supply to occur, e.g. coronary arterial circulation, and lowering the risk of infarct. In the face

of gradually evolving ischaemia, some organs may avoid infarction but may undergo atrophy instead.

- **Tissue vulnerability:** brain can only tolerate ischaemia for a few minutes, the myocardium for few dozen minutes while fibroblasts can stay alive even after hours of ischaemia
- **Prior hypoxaemia/ hypoxia** e.g. severe anaemia, congestive heart failure, may lead to earlier occurrence of infarct in the face of a partial vascular occlusion