PATH VIVAS

APOPTOSIS

Definition
Programmed cell death

Pathology
Highly regulated intracellular sequence of events
Activation of enzymes with **degradation** of intracellular **nucleic acid** and **organelles**
Cell **membrane remains intact** but may **bleb** to form **apoptotic bodies**
Targetted for **phagocytosis** – usually my **macrophages**
No cell contents leaks out, so there is **no surrounding inflammation**

Initiators

Extrinsic: TNF receptors + FAS receptor activation → caspase activation

Intrinsic: mitochondrial breakdown → release of pro-apoptotic mediators into cytoplasm → activation of caspases

Caspases act as final common pathway → **proteolysis and cleavage of nucleic acid**.

Causes
Physiological:
Programmed cell death during **embryogenesis**
Apoptosis of lymphocytes that show **self-reactivity** (i.e. central tolerance)
Death of cells that have **served their purpose** (e.g. neutrophils)

Pathological:
Death of **mutated cells** / cells that have accumulated DNA abnormalities
Death of infected (**virus**) cells by interaction with NK cells / cytotoxic T cells
Viral hepatitis

Cellular changes
Cell shrinkage
Chromatin condensation
Formation of cytoplasmic blebs and apoptotic bodies
Phagocytosis by macrophages

ATROPHY

Definition
Decrease in organ/tissue size due to an decrease in both cell size and number
Can be physiological / pathological

Causes
Decreased workload
Decreased innervation
Decreased blood supply
Decreased nutrition
Loss of endocrine stimulation (e.g. endometrial atrophy)
Aging

Mechanism
Decreased protein / organelle synthesis
Increased protein degradation and autophagy

PATHOLOGICAL CALCIFICATION

2 types:
Dystrophic calcification: normal levels of calcium, but deposited in areas of abnormal tissue.
E.g deposition of calcium in atheromatous lesions
E.g. calcific AS

Metastatic calcification: abnormally high levels of calcium, deposited in normal tissue
E.g. Multiple myeloma → calcification of gastric mucosa / nephrocalcinosis / pulmonary calcinosis

Causes of hypercalcaemia

Elevated PTH:
Hyperparathyroidism, PTH secreting tumours

Destruction of bone:
Multiple myeloma, boney mets

Vit D related disorders:
Excess vitamin D
Granulomatous disorders (e.g. sarcoid)

Renal dysfunction
Secondary / tertiary hyperPTH
High phosphate

MECHANISMS OF CELLULAR INJURY

What happens inside cells when they are injured
Mitochondrial dysfunction
⇓ATP due to ⇓Ox phos
⇓Na-K pump → Na influx, K efflux → cell swelling
Ca influx / release from intracellular stores → activation of proteolytic enzymes and enzymes that degrade nucleic acid
Cell membrane damage and loss of intracellular contents into interstitium
Accumulation of ROS

What is a free radical
Chemical species with a single unpaired electron in its outer orbit
E.g. superoxide
E.g. hydrogen peroxide

Pathological effects of a free radical
Can culminate in <u>necrosis / apoptosis</u>
Lipid peroxidation (→ membrane damage)
Protein oxidation (→ effects enzyme structure)
DNA lesions (→ breaks / cross-linkages)

HYPERPLASIA

Definition
Increase in the number of cells in a tissue/organ, to increase its size or to replace tissue that has been lost

Mechanisms
- ⇑Local production of growth factors
- ⇑Growth factor receptors on cells
- ⇑Intracellular signaling → ⇑transcription and translation of DNA into proteins, increased movement through the cell cycle

Types of hyperplasia
Physiological:
- Endocrine:
    - Uterus during pregnancy
    - Breast tissue during puberty
- Compensatory:
    - Replacement of liver following liver injury / partial hepatectomy

Pathological:
- Tumour formation (benign / malignant)
- Viral infection – e.g. HPV
- Excess hormones – e.g. BPH, e.g. endometrial hyperplasia → abnormal uterine bleeding

HYPERTROPHY

Definition
Increase in size of tissue / organ due to an increase in cell size
⇑cellular contents and organelles, ⇑ protein synthesis
Can occur in both dividing and non-dividing cells

Triggers
Stimulation by hormones / growth factors
⇑Functional demand

Types
Physiological
- Lactating breast
- Uterus in pregnancy
- Increasingly used skeletal / cardiac muscle

Pathological:
- Heart in chronic HTN
- BPH

ISCHAEMIC INJURY

2 stages
Reversible
Irreversible

Sequence of events in reversible cell injury
Mitochondrial dysfunction + swelling
⇓ATP due to ⇓Ox phos
⇓Na-K pump → Na influx, K efflux → cell swelling
⇑intracellular Ca due to increase influx + release from intracellular stores → activation of enzymes that degrade proteins + DNA
Change in cytoskeletal architecture → membrane blebbing
Change in membrane permeability
⇓intracellular pH due to accumulation of lactic acid
Ribosome detatchment from RER

1) ATP
2) Loss of cell membrane integrity
3) Defects in protein synthesis / ⇑protein degradation
4) DNA damage
5) Cytoskeletal damage

Irreversible injury
- Severe mitochondrial swelling
- Severe cell membrane disruption
- Lyosomal swelling, rupture, and autodigestion
- Nuclear: pyknosis → karyohexxis → karyolysis
- → Necrosis / apoptosis

Reperfusion injury
Increase in cellular injury once perfusion is restablished
Formation of reactive oxygen + nitrogen species
⇑⇑⇑Ca in cell
Activation of inflammation + compliment cascades

Proteins release in cell injury:
Cardiac: troponin, CK-MB
Liver: ALP, transaminases

METAPLASIA

Definition
Replacement of one cell type with a different cell type
Is usually reactive to a change in environment / stimulus – theoretically the new cell type is better able to cope with the stressors of the new stimuli
May be physiological / pathological

Mechanism
Due to reprogramming of stem cells / undifferentiated cells
Due to changes in signaling from GFs / cytokines / extracellular matric proteins

Examples:
Barrets Oesophagus – change in SS of oesophagus to columnar gastric/intestinal mucosa
Smoking / Vit A defic – change of ciliated columnar resp epith of resp tract → SS
Myositis ossificicans – muscle → bone

Outcomes
Perisitence of new cell type
Reversal
Metaplasia – dysplasia – malignant transformation

NECROSIS

Cellular changes in necrosis
Irreversible injury
Cells swelling
Membrane blebbing
Disruption of membrane integrity
Myelin figures (whorls of cell membrane fragments)
Nuclear changes: karyohexis, pyknosis, karyolysis
Surrounding inflammation

Different types of tissue necrosis
Coagulative – architecture preserved due to enzymatic denaturation
Liquifactive – loss of tissue architecture due to enzymatic digestion → lquid mass
Caesous
Fibrinoid – Ab-Ag immune complex mediated
Fat necrosis

STEATOSIS

Definition
Abnormal accumulation of **triglycerides** in parenchymal cells

Organs commonly involved
Liver
Heart
Kidneys

Causes
Alcohol abuse
DM
Protein energy malnutrition (kwashiorkor)
Toxins

In the liver it results from any of the stages in lipid handling from fatty acid entry, to esterification to form TAG, to metabolism within the liver or packaging for exportation from liver.

ACUTE INFLAMMATION

Vascular changes in acute inflammation
- **Transient vasoconstriction**
- **Vasodilation** – opening of arterioles and capillary beds, histamine, NO action of vasc SM
- **Increased vascular permeability** – mainly post-capillary venules
- **Stasis/congestion** – due to extrusion of fluid and plasma protein → increased viscosity
- ⇑Expression of vascular adhesion molecules on endothelial cells for leukocytes

Mechanism of increased vascular permeability
- **Endothelial contraction/retraction**
    - Gaps between endothelial cells in post-capillary venules
    - Immediate transient response
    - Mediated by: histamine, LTs
- Direct endothelial injury
    - Rapid, long-lasting
    - E.g. burns, bacterial toxins
- Transcytosis
    - ⇑transport of fluid + protein through endothelial cells
    - VEGF ⇑number of transport proteins (by stringing together vacuoles)
- New blood vessel formation
    - Formation of new leaky blood vessels by VEGF mediated angiogenesis

Characteristics of acute inflammation
- Relatively rapid onset, duration of hours-days
- Vasodilation
- Increased vascular permeability
- Loss of fluid + plasma protein into interstitial space
- Rolling, arrest, diapedesis of leukocytes (esp neutrophils) and movement along chemotactant gradient towards site of inflammation
- Pain
- Activation of complement cascade

Compliment
- Cascade of >20 proteins which are activated by classical, alternative, lectin pathway
- Common pathway is activation of C3 convertase
- C3a + C5a – anaphylatoxin, degranulation of mast cells, chemoattractant
- C5b-C9 – MAC
- C3a – opsonisation, ⇑phagocytosis

Croup
- Acute laryngotracheobronchitis
- Imflammation + spasm → narrowing of airway
- Barking cough + inspiratory stridor
- Predominantly viral aetiology: parainfluenza, influenza, adenovirus

INFLAMMATORY MEDIATORS

Triggers for release of inflammatory mediators

- Mechanical irritation
- Microbial products
- Cell injury / necrosis

Mediators of acute inflammation + actions

Histamine: vasodilation, inc vasc perm, endoth activation
PG: vasodilation, inc vasc perm
Leukotrienes: inc vasc perm, chemotaxis, WC adhesion & activation
PAF: vasodil, inc vasc perm, chemotaxis, WC adhesion, degran
Complement: WC chemo and activation, vasodilat
Cytokines (TNF, IL-1): endo activation (adhesion), fever, pain, hypotension, dec vasc resist
Chemokines: chemotaxis, WC activation
Kinins: inc vasc perm, vasodil, pain, sm m contraction

Histamine
Bradykinin
Serotonin
LTs
PAF
PGs
Lipoxins
Compliment
ROS
NO
Cytokines – IL-1, TNFα

ACUTE INFLAMMATION

3 main components of acute inflammation

1) Vasodilation – increased blood flow
2) Increased vascular permeability – esp post-capillary venules, allowing plasma proteins + leukocytes to leave the circulation
3) Emigration of leukocytes to the site of injury: initially neutrophils (first 24hrs), monocytes/macrophages in more prolonged inflammation (after 24hrs)

3 processes by which leukocytes move to site of injury

Multistep process, mediated by chemokines and adhesion molecules

1) Margination
    - Leukocytes take peripheral position in BVs
    - Rolling: along endothelium due to transient binding via selectins
    - Arrest: binding to endothelium via integrins
    - Examples of adhesion molecules: PCAM, selectins, integrins, CD31

2) Transmigration / diapedesis
    - Movement through interendothelial spaces of post-capillary venules
    - Secretion of collagenases which allow movement through the BM

3) Chemotaxis
    - Movement of leukocyte down a chemoattractant gradient
    - Movement mediated by actin-myosin cytoskeleton of the leukocyte

Followed by leukocyte activation: e.g. neutrophil phagocytosis and enzyme release

Examples of chemoattractants

- Endogenous:
    - Compliment (C3a, C5a)
    - Leukotrienes
    - Cytokines, interleukins
    - Complement
    - Histamine
- Exogenous:
    - Bacterial products, e.g. LPS

Which chemical mediators are responsible for pain, fever, tissue damage:

- Fever: IL-1, TNFα, acting at OVLT in brain to induce PG production
- Pain: histamine, bradykinin, CGRP, substance P
- Tissue damage: lysosomal enzymes, ROS, NO

Cell types in different kinds of inflammation

- Neutrophils: acute inflammation (first 24hrs) may persist for 4 days in pseudomonal infections
- Monocytes / macrophages: >24hrs
- Lymphocytes: viral
- Eosinophils: hypersensitivity

Why do neutrophils predominate in acute inflammation?

- More numerous in blood
- Greater response to chemokines
- Greater affinity for adhesion molecules
- Shorter ½ life

What is the role of leukocytes in acute inflammation?

- **Receptor mediated recognition** of target materials – opsonins, PAMPS
- **Phagocytosis** (neutrophils, macrophages)
- **Induction of apoptosis** / killing of infected cells (NK, CD8 T) – ROS / NO / Fas-Caspases / lysosomal enzymes
- **Induction of humoral response** / activation of B cells to produce Ab

INFLAMMATION

Different morphological types of acute inflammation

- **Serous**:
    - Thin fluid from plasma or mesothelial lining cells
    - E.g. burns
    - E.g. effusions
- **Fibrinous:**
    - Severe inflammation with greater vascular permeability allow exudation of larger proteins like fibrin
    - E.g. pericardial, pleural, meninges
- **Suppurative / purulent:**
    - Purulent exudate, with neutrophils, necrosis + oedema
    - E.g. staph OM / SA
    - E.g. appendicitis
- **Ulceration:**
    - Local defect in mucosal surface
    - E.g. acute stress ulceration of gastric mucosa

Possible outcomes of acute inflammation

- Resolution +/- scarring
- Chronic inflammation
- Abscess formation
- Fibrosis

CHRONIC INFLAMMATION

Characteristics of chronic inflammation

- Inflammation for prolonged period (>1 week)
- Macrophage is the hallmark cell
- Also lymphocytes + plasma cells
- Simultaneous processes of:
    - Active inflammation → tissue destruction
    - Attempts at tissue repair (angiogenesis + fibrosis)

Cells present in chronic inflammation

- Monocytes / macrophages
- Granuloma: epilelioid cells / multinucleate giant cells
- Plasma cells
- Th lymphocytes (CD4 + CD8)
- Eosinophils
- Neutrophils (sparse)

What mediates ongoing inflammation

- Ongoing expression of adhesion molecules + chemotactic factors leading to **continued recruitment** of macrophages. E.g. macrophage activating factor
- Local proliferation of macrophages
- Immobilisation of macrophages at the site of inflammation

Causes of chronic inflammation

- **Persistent infection:**
    - TB
    - OM
- **Prolonged exposture to irritant:**
    - Foreign body
    - Silica → silicosis
    - Endogenous: lipid in atheroma
- **Autoimmune**:
    - RA
    - SLE

Products released by macrophages in chronic inflammation

- Products causing **tissue damage**:
    - ROS
    - NO
    - Proteases (elastases, collagenases)
    - AA metabolites (PG, LT, TxA2)
- Products causing **fibrosis**:
    - TGF-β
    - FGF
    - VEGF

COMPLEMENT

What is the complement system

- Plasma proteins involved in immune response
- Complement proteins 1-9 present in plasma in active form
- Role in defending the body from microbes

Modes of activation

- Alternate pathway: complement activation by exposure to microbial cell wall components (e.g. LPS)
- Classical pathway: complement activation by exposure to immune complex (Ag + Ab)
- Lectin pathway: activation by microbial carbohydrates, recognized plasma mannose-binding lectin

Final common pathway is activation of C3 convertase which cleaves C3

How does complement mediate inflammation

- C3a + C5a (anaphylatoxins):
    - Vascular:
        - Mast cell degranulation + histamine release
        - Vasodilation
        - Increased vascular permeability
    - Leukocyte:
        - Activation + chemoatractants
- 35b:
    - MAC
    - C5b-C9 inserts pore into cell membrane → lysis
- C3b:
    - Opsonisation: allows recognition and activation by professional phagocytes

Arthus reaction

- T3 hypersensitivity reaction
- Mediated by localized excess of Ab → immune complex formation
- Can precipitate, resulting in vasculitis

IMMUNE MEDIATORS

Which mediators of inflammation are derived from cells?

- Preformed:
    - Vasoactive amines
        - Histamine (mast cells)
        - Serotonin (platelets)
- Newly synthesized:
    - AA metabolites:
        - PGs
        - TXA2
        - LTs
        - Lipoxins
        - PAF
    - ROS, NO
    - Cytokines (IL1, TNFα)

Which cells release histamine?

- Mast cells
- Basophils
- Platelets

Effects of histamine?

- Vasodilation arterioles
- Increased vascular permeability

ANGIOGENESIS

What is angiogenesis?

- Process of new blood vessel formation
- 2 mechanisms:
    - Branching and extension of preexisting vessels
    - Recruitment of endothelial progenitor cells (EPCs)
- EPCs are present in:
    - Bone marrow
    - Pre-existing vessels

Examples of angiogenesis
- Wound healing
- Fracture healing
- Tumour growth
- Embryogenesis

Steps in angiogenesis
- Vasodilation
- Proteolytic degradation of BM of parent vessel, allows formation of capillary sprout
- EPCs cells migrate to angiogenic stimulus
- Proliferation of endothelial cells
- Maturation of EPCs and linkage with preexisting vessel endothelial cells
- Capillary formation with lumen
- Recruitment of periendothelial cells for support (pericytes, smooth muscle cells)

Factors involved
- VEGF
- Angioproteins 1 + 2
- TGFβ

Inhibitors of angiogenesis
- Endostatin, produced by proteinases, inhibits endothelial proliferation + angiogenesis

FIBROSIS

Pathogenesis of fibrosis

- **Excess deposition of collagen + ECM**

- **Trigger:**
  - **Chronic inflammation**
  - **Persistent stimulus** – infection / FB / autoimmune

- **Cells which secrete mediators:**
  - **Macrophages**
  - Lymphocytes
  - Platelets
  - Endothelium

- **Mediators** released
  - **FGF**
  - **PDGF**
  - **TGFβ**
  - **Cytokines (IL1, TNFα)**

- Result:
  - **<u>Recruitment + proliferation of fibroblasts</u>**
  - **Lay down collagen + ECM, and inhibit their breakdown**

- TGFβ is always involved
  - Attract monocytes / macrophages
  - Fibroblast activation and proliferation
  - Increased collagen + fibornectin synthesis
  - Inhibition of matrix metalloproteinases

Examples

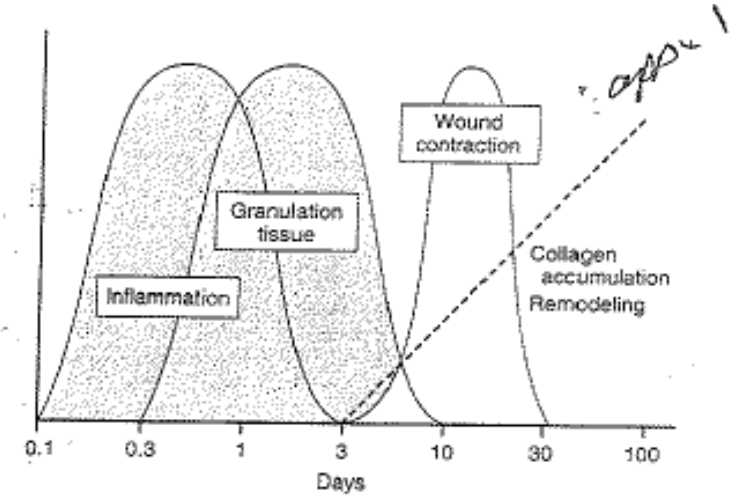
- Cirrhosis
- Pulmonary fibrosis
- Glomerulonephritis
- Chronic pancreatitis

SCAR FORMATION

Process of scar formation

1) **Haematoma (<24hrs)**
2) **Inflammation (<24hrs)**
3) **Proliferation → granulation tissue (first week)**
4) **Maturation (weeks)**

- **Haematoma**
- **Inflammation**
  - Infiltration in inflammatory cells which removed damaged and dead tissue
  - Neutrophils (<24hr) → macrophages (by day 3)
- **Re-epithelialisation**
  - Invasion of epithelial spurs from wound edges towards the midline
- **Granulation issue**
  - **Fibroblasts**
    - Migration + proliferation of parenchymal + CT cells : e.g. fibroblasts
  - **Synthesis of ECM + collaged deposition**
    - Collagen III → Collagen I
    - Elastic tissue
- **Angiogenesis**
  - Blood vessels initially leaky → oedema
  - Angiogenesis regresses over coming weeks
- **Tissue remodeling**
  - Alteration in cellularity
  - Reduced vascularity
  - Breakdown of ECM by MMPs
- **Would contraction**
  - Myofibroblasts
- Acquisition of **wound strength** (crosslinking collagen etc)



How do wounds recover tensile strength?

- Collagen III → 1

- Collagen formation > degradation
- Structural modification: crosslinking of collagen + increased fibre size

Timeframe of recovery of tensile strength

- 1 week: 10% tensile strength
- 3 months: 70%
- No significant improvement after this

Factors influencing scar formation

- Local:
    - Type of tissue
    - Extent of tissue damage / loss
    - Blood supply
    - Presence of FB
    - Presence of infection
    - Movement of wound edges
- Systemic:
    - Systemic disease: diabetes, steroids
    - Systemic infection
    - Systemic hypoperfusion / anaemia
    - Nutrition (vit C, protein, copper, zinc)
    - Genetics: e.g. keloid
    - Age

Wound contraction

- Usually in large surface wounds
- Mediated by myofibroblasts
- Helps being dermal edges together
- ⇓wound SA
- Can restrict joint movement

Role of platelet-derived growth factor (PDGF) in wound healing

- Monocyte chemotaxis
- Fibroblast migration and proliferation
- Collagen synthesis
- Collagenase secretion (remodeling)

COAGULATION CASCADE

What is coagulation cascade?

- Integral to heamostasis
- Series of reactions which convert inactive pro-enzymes into active enzymes
- Culminates in the activation of thrombin, which cleaves fibrinogen → fibrin
- Fibrin is an insoluble fibrillar protein responsible for clot formation
- Activation of this series of reaction is via either extrinsic (tissue factor activated) or intrinsic pathways.
- Extrinsic: activated by TF exposed at site of injury
- Intrinsic: activated by F12
- Pathways converge on activation of F10 (common pathway = F1,2,5,10 + calcium)

What mechanisms restrict activation of coag cascade?

- Restriction of activation of cascade to areas of exposed phospholipids

- Natural anticoagulants:
    - Protein C / S
        - Inhibit F5 + 8
        - Vitamin K dependent
    - Thrombomodulin
        - Coverts thrombin from pro-coagulant to anticoagulant by making it activate protein C
    - Antithrombin III
        - Inactivates F 9,10,11,12
        - ATIII is activated by binding endogenous (endothelium) or exogenous heparin
    - Plasmin:
        - From inactive plasminogen by action of F12 or t-PA
        - Breaks down fibrin → FDPs
        - FDPs have their own weak anticoagulant activity
    - Tissue-factor pathway inhibitor

Endogenous antiplatelet mechanisms

- Intact endothelium
- PGI2
- NO
- ADPase

Endogenous factors preventing clot formation

- Antiplatelet
- Anticoagulant
- Fibrinolytic

DIC

Triggers for DIC

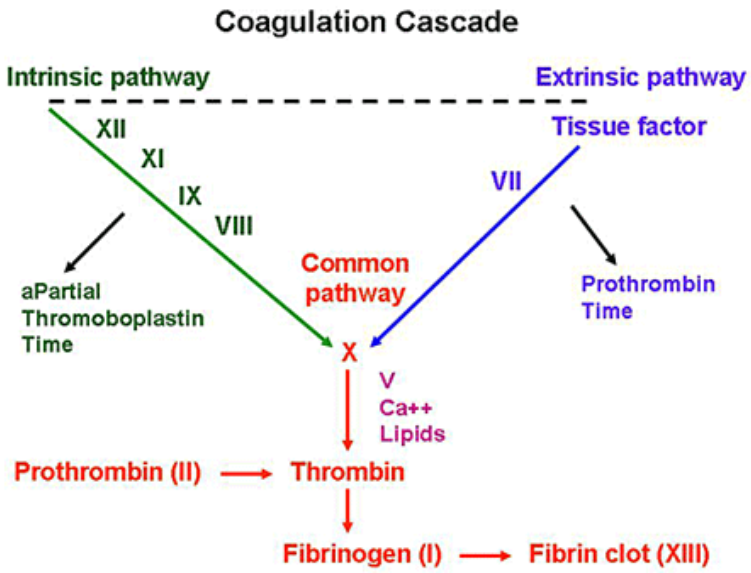
- **Sepsis** (endotoxin gram –ve, meningococcal sepsis, rickettsia)
- **Trauma**
- **Obstetric complication** (e.g. amniotic fluid embolism, retained dead fetus)
- **Burns**
- **Malignancy** (e.g. APML)
- **Toxins** (e.g. snake envenomation)

How does endothelial injury initiate DIC

- Exposure of subendothelial matrix →
  - Platelet activation
  - Coagulation cascade
- Direct trauma to endothelium by:
  - Immune complex
  - Microorganisms
- Cytokine mediated endothelial dysfunction
  - TNF → ⇑expression of tissue factor and release into the circulation
  - TNF → ⇑endothelial adhesion molecules → ⇑leukocyte attachment → ⇑endothelial damage

Pathological process

- **2 triggers:**
  - **Widespread endothelial injury**
  - **Systemic release of tissue factor / thromboplastic substances**
- Widespread activation of platelets and both arms of the coagulation cascade
- Results in **consumptive coagulopathy → deficiency of factors + platelet + fibrinogen →** bleeding diathesis
- **Fibrin deposition in the microcirculation** → thrombi → **ischaemia**
- Simultaneous activation of fibrinolytic system → **bleeding**
- **MAHA** secondary to thrombi in the microcirculation
- Consequence: **ischaemia + bleeding**



Presentation of DIC on FBC + blood film:

- ⇓**Platelet**
- ⇓**Fibrinogen**
- ⇑**Fibrin degradation products**
- ⇑**Bleeding time,** ⇑**PT,** ⇑**APTT**
- **MAHA with schistocytes**

EMBOLISM

What is an embolus?

Detached **intravascular** mass
Carried in blood from **site of origin** to **distant site**, with impaction at this distant site
Can be solid, liquid, gas

Different types of embolus

- Thrombus / clot
- Tumour
- Amniotic fluid
- Cholesterol
- Gas (decompression sickness / iatrogenic)

Can be systemic or pulmonary

What is a systemic thromboembolism
- Embolus consisting of thrombus in the systemic arterial circulation

Sources of systemic thromboembolism
- Intracardiac mural thrombus (80%)
    - 2/3 LV
    - ¼ LA
- Thrombus from vascular artheroma (carotid / AA)
- Vegetations on cardiac valves
- VTE via PFO (paradoxical embolus)

Difference in lodgement of venous vs. arterial emboli

- Venous: usually impacts in pulmonary vascular bed
- Arterial: multiple sites of distal impaction:
    - Lower limb (75%)
    - Brain (10%)
    - UL + other viscera

Pathology of infarcts arising from emboli
- Ischaemic coagulative necrosis (except brain, liquefactive necrosis)
- White infarct:
    - Solid / dense organs
    - End arterial circulation
- Factors affecting infarction:
    - Degree of collareralisation
    - Speed of onset of occlusion
    - Degree of vessel occlusion
    - Sensitivity of tissue to hypoxia
    - O2 content of blood

VENOUS THROMBOEMBOLISM

From where do pulmonary emboli derive

- Vast majority (95%) are deep veins of legs, normally above the knee
- Pass to RA, RV, pulmonary circulation
- Size will determine site of distal impaction

Risk factors for PE

- Intrinsic thrombophilia:
    - Genetic: F5 leiden
    - Acquired: e.g. malignancy, SLE
- Vessel trauma / endothelial disruption
- Immobility
- FHx (genetic component)
- Personal Hx
- Hormone (OCP, HRT)

Or

- **Primary: genetic thrombophilia**
- **Secondary: everything else**

Clinical outcomes of PE

- Most are clinically silent (60-80%)
- SOB, tachycardia, fever
- Haemoptysis
- Collapse
- Arrest
- PAH + cor pulmonale

Fat embolism

- Associated with long bone fractures (very occasionally soft tissue injuries)
- 90% of major fractures
- 10% are symptomatic
- <10% of which are fatal
- Occurs 1-3 days after injury
- Fat embolism syndrome (symptomatic)
    - Pulmonary insufficiency (desats, ⇑RR)
    - Neurological symptoms (restlessness, irritability, coma)
    - Anaemia (haemolysis, MAHA)
    - Thrombocytopaenia (aggregation → consumption → petechial rash)

HAEMOSTASIS

Haemostasis:

1. **Vasoconstriction**
2. **Primary haemostasis (platelet plug)**
3. **Secondary haemostasis (fibrin clot)**
4. **Balance between clot formation (thrombin) and dissolution (plasmin)**

1. **Vasoconstriction**
    - Arteriolar
    - Neurological: reflex neurogenic
    - Humoral: endothelin
2. **Primary haemostasis (platelet plug)**
    - Subendothelial ECM exposed → adhesion + secretion + aggregation
3. **Secondary haemostasis (fibrin clot)**
    - TF activation of extrinsic pathway via F7 → fibrin clot
4. **Balance between clot formation (thrombin) and dissolution (plasmin)**
    - tPA + thrombomodulin regulate

Polymerised fibrin + platelet combine to form mature clot

Formation of primary haemostatic plug

Role of platelets in haemostasis:

- **Primary haemostatic plug**
- **Privides a surface to recruit + concentrate activated coagulation factors**

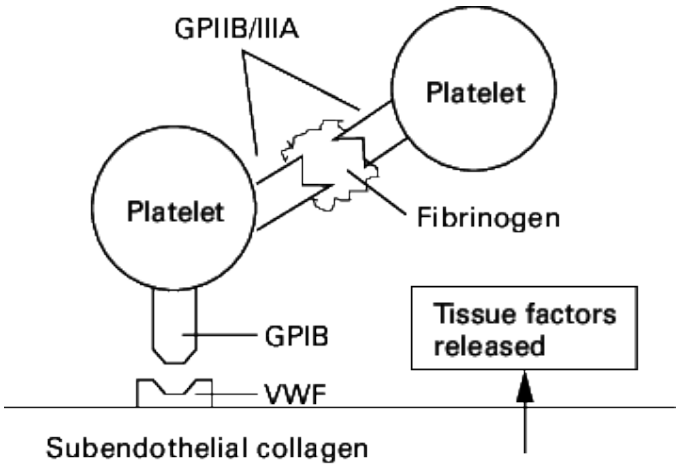
Formation of primary haemostatic plug

- Primary haemostasis is formation of platelet plug
- Phases of platelet involvement:
    1. **Adhesion** (shape change)
    2. **Secretion** (release reaction)
    3. **Aggregation**

- Endothelial damage exposes underlying ECM:
    - Collagen
    - vWF
- Platelets **adhere** to subendothelial ECM:
    - GP1b – vWF (on collagen)
- **Activation** of platelet:
    - Shape change (more round)
    - Exposure of –ve charged phospholipids on platelet surface, essential for Ca binding and activation of intrinsic pathway of coagulation
    - Secretion (preformed granules):
        - ADP
        - TxA2
        - Ca

        - -vely charge phospholipid
    - ADP binds ADP-R (P2Y12) → positive feedback activation of platelets
- Platelet **aggregation**:
    - Stimulated by TXA2 + ADP
    - GP2b3a – fibrinogen
    - Initial aggregation is reversible
    - Platelet contraction + thrombin conversion of fibrinogen→fibrin forms the irreversible secondary haemostatic plug.

Platelet granules:
- **Alpha granules** (fibrinogen, factors V and VIII, platelet factor 4, PDGF, TGFβ)
- **Delta granules / dense bodies** (ADP and ATP, ionised calcium, TXA2, histamine, serotonin, adrenaline).



Conversion of primary haemostatic plug → secondary haemostatic plug:
- Thrombin binds to platelets expressing ADP + TXA2
- Fibrin formation which locks platelets into clot via GP2b3a receptors
- Platelet contraction

Initial adhesion
- vWF bridges subendothelial collagen and platelet surface receptor Gp1b
- Also collagen binds directly to platelet collagen receptors

Activation of coagulation cascade (secondary haemostasis)
- **Triggers:**
    - **Endothelial injury**
    - **Exposure of subendothelial tissue factor / thromboplastic substances**
- Acitvation of intrinsic (F12) + extrinsic (F7) clotting cascade
- Series of amplifying enzymatic reactions converting pro-enzyme to active enzyme
- Final common pathway is 10, 5, 2, 1
- Result is activation of thrombin and conversion of fibrinogen → fibrin

- Fibrin polymerises forms a network – fibrin clot

What does PT measure
- Extrinsic pathway + common pathway
- Factors 7 → 10, 5, 2, 1
- Extrinsic is Vit K dependent

What does APPT measure
- Intrinsic pathway + common pathway
- Factors 12, 11, 9, 8 → 10, 5, 2, 1

1 = Fribrinogen
2 = Prothrombin
3 = Tissue factor
4 = Calcium
12 = Hageman factor

Tell me about the final common pathway:
- I + E pathways converge on activation of F10
- Using Ca + activated F5 as cofactors, F10 activates prothrombin → thrombin
- This occurs on the surface of damaged endothelium or activated platelets
- Thrombin (2a) converts fibrinogen (1) → fibrin (1a) in presence of Ca
- Thrombin also activates F13 → crosslinking of fibrin

Fibrinolysis

- Plasminogen → plasmin
- Plasmin degrades fibrin → FDPs (e.g. D-dimer)
- Plasminogen activated by:
    - t-PA
    - F12a

- t-PA
    - Derived from endothelial cells
    - Most active when bound to fibrin
    - Urokinase is like t-PA, circulating serine protease

- α2-plasmin inhibitor
    - Inactivates free plasmin

INFARCTION

Define infarction

- Ischaemic necrosis caused by arterial, or venous, occlusion

Mechanisms leading to infarction

- Arterial thrombosis (e.g. from atherosclerotic plaque rupture)
- Embolus
- Arterial vasospasm
- Extrinsic vascular compression
- Torsion of vessel
- Venous obstruction and congestion

Factors effecting infarct development

- Nature of blood supply (dual vs. end-arterial)
- Degree of collateralisation
- Speed of onset of occlusion
- Degree of vessel occlusion
- Sensitivity of tissue to hypoxia
- O2 content of blood

ISCHAEMIC INJURY AT A CELLULAR LEVEL

What constitutes irreversible ischaemic injury

- Irreparable structural + intracellular damage
- → Necrosis / apoptosis
- At a cellular level, consistent changes are:
    - Severe distruption of cell membrane with loss of integrity
    - Mitochondrial swelling with inability to generate ATP via ox phos
    - Lysosomal swelling

- Other features of cell injury
    - Cellular swelling
    - Failure of Na-K ATPase
    - Nucelar changes: pyknosis → karyohexxis → karyolysis
    - Myelin figures

Mechanism of hypoxic cell injury

- Hypoxia → ⇓mitochondrial ox phos → ⇓ATP
- Failure of Na-K pump
- Failure of glycogen + protein synthesis
- Accumilation of intracellular Ca → activation of proteases and degrading enzymes
- Disruption of cytoskeleton
- Loss of cell membrane integrity, cell surface blebs, myelin figures
- Swelling of intracellular organelles
- Seperation of ribosomes from ER
- Irreversible changes:
    - Swollen mitochondria
    - Severe cell membrane disruption
    - Lyosomal swelling, rupture, and autodigestion
    - Nuclear: pyknosis → karyohexxis → karyolysis

Ischaemic vs. hypoxic cell injury

- Ischaemic – no provision of O2, substrates, no removal of waste products
    - Anaerobic resp not possible
- Hypoxic – continued provision of substrates and removal of waste
    - Anaerobic resp still possible
- Therefore ischaemic often more damaging than hypoxic

OEDEMA

Definition

- **Increased interstitial fluid**

Causes

- **Inflammatory – exudative:**
  - **Infection**
  - **Immune**
  - **Necrosis**
  - **FB**
  - **Traumatic**
- **Non-inflammatory – transudative, Starling's law:**
  - **⇑Hydrostatic pressure:**
    - **Generalised:**
      - **CCF / restrictive pericarditis**
      - **Hypervolaemia – fluid overload**
      - **Na + water retention: renal insufficiency / ⇑R-A-A**
    - **Localised venous:**
      - **Venous obstruction e.g. DVT**
    - **Localised arteriole:**
      - **Heat**
    - **Lymphatic obstruction**
  - **⇓Oncotic pressure**
    - **Nephrotic syndrome**
    - **Liver failure**
    - **Protein malnutrition**
    - **Protein losing enteropathy**

Exudate vs. transudate

- **Inflammatory → exudate:**
  - **High protein**
  - **High LDH**
- **Non-inflammatory → transudate:**
  - **Low protein**
- **Defined by Light's criteria**

What factors determine movement of fluid between vascular + interstitial spaces?

- **Starling's forces**

$$J_V = K_f [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where:

J_V	Net fluid flux
K_f	Filtration coefficient
P_c	Capillary hydrostatic pressure
P_i	Interstitial hydrostatic pressure
σ	Reflection coefficient
π_c	Capillary oncotic pressure
π_i	Interstitial oncotic pressure

- Hydrostatic pressure
- Colloid osmotic pressure (oncotic pressure)
- Permeability of capillary walls
- Net balance is normally quite neutral:
    - Out at arteriolar end
    - In at venous end
    - Small amount returned to circulation via lymphatics

Clinical features of heart failure:

- Lung:
    - OPN
    - PND
    - Dyspnoea with ⇓ET
    - Pulmonary oedema / pleural effusions
- Cardiac:
    - Displaced apex
    - 3rd HS
    - JVP elevation
    - Murmurs
- Renal:
    - Fluid retention
    - AKI
- Liver:
    - Hepatic congestion
    - Cirrhosis
    - Ascites
- Brain:
    - Confusion secondary to hypoxia

Pathogenesis of cardiogenic oedema

- ⇓CO
- → ⇓Renal perfusion + ⇑sympathetic drive
- → ⇑R-A-A (secondary hyperaldosteronism)
- → ⇑Blood volume
- → ⇑Venous pressure

PLATELETS

Role of platelets in haemostasis:

- **Primary haemostatic plug**
- **Privides a surface to recruit + concentrate activated coagulation factors**

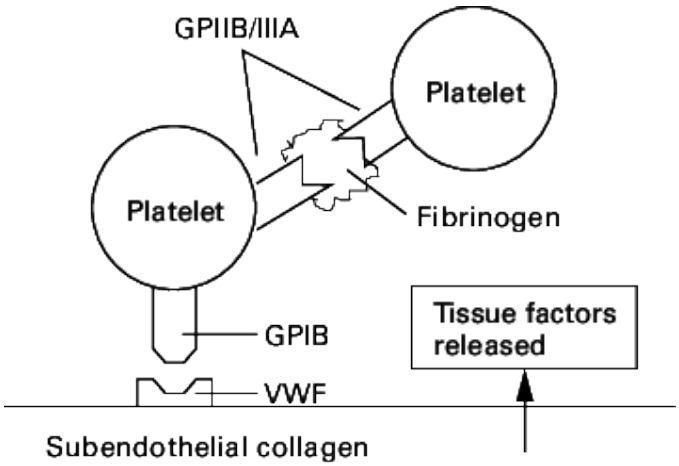
Formation of primary haemostatic plug

- Primary haemostasis is formation of platelet plug
- Phases of platelet involvement:
    4. **Adhesion** (shape change)
    5. **Secretion** (release reaction)
    6. **Aggregation**

- Endothelial damage exposes underlying ECM:
    - Collagen
    - vWF
- Platelets **adhere** to subendothelial ECM:
    - GP1b – vWF (on collagen)
- **Activation** of platelet:
    - Shape change (more round)
    - Exposure of –ve charged phospholipids on platelet surface, essential for Ca binding and activation of intrinsic pathway of coagulation
    - Secretion (preformed granules):
        - Essential for aggregation:
            - ADP
            - TxA2
        - Essential for coagulation:
            - Ca
            - -vely charge phospholipid
    - ADP binds ADP-R (P2Y12) → positive feedback activation of platelets
- Platelet **aggregation**:
    - Stimulated by TXA2 + ADP
    - GP2b3a – fibrinogen
    - Initial aggregation is reversible
    - Platelet contraction + thrombin conversion of fibrinogen→fibrin forms the irreversible secondary haemostatic plug.

Platelet granules:

- **Alpha granules** (fibrinogen, factors V and VIII, platelet factor 4, PDGF, TGFβ)
- **Delta granules / dense bodies** (ADP and ATP, ionised calcium, TXA2, histamine, serotonin, adrenaline).



Conversion of primary haemostatic plug → secondary haemostatic plug:

- Thrombin binds to platelets expressing ADP + TXA2
- Fibrin formation which locks platelets into clot via GP2b3a receptors
- Platelet contraction

REPERFUSION INJURY

Definition

- Death of additional cells caused by reperfusion of ischaemic tissue, in addition to those damaged by ischaemic itself

Mechanisms of injury

Reactive oxygen / nitrogen species	Incomplete reduction of incoming O2 Due to damaged mitochrondria In parenchymal + endothelial cells Action of oxidases → superoxide anions
Inflammation	Ischaemic cells → ⇑expression of adhesion molecules + cytokines ⇑Recruitment of inflammatory cells (neutrophils)
Complement cascade	Deposition of IgM in ischaemic tissues → activation of complement cascade (classical pathway) → cell damage
Mitochondrial dysfunction	Damage to mitochondrial membranes → **mitochondrial permeability transition** → release of cytotoxic factors from mitochondria, and failure of ATP production

SHOCK

Definition

- Impaired tissue perfusion and consequent cellular hypoxia
- Consequent to failure of perfusion pressure (hypotension) due to:
    - Reduced CO
    - Reduced effective circulating volume

Categories of shock

Cardiogenic	AMI / arrhythmia
Hypovolaemic	Haemorrhage / burns
Sepsis / SIRS	Infection, pancreatitis
Distributive	Anaphylaxis, Addisonian crisis
Obstructive	Tension pneumo, tamponade, PE
Neurogenic	Spinal injury

Stages of shock

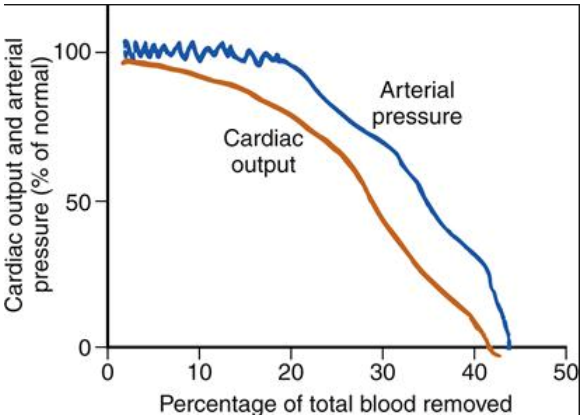
- Non-progressive:
    - Reflex physiological mechanisms support vital organ perfusion
        - Baroreceptor
        - ⇑Symp drive → ⇑HR, vaso+venoconstriction
        - ⇑R-A-A
        - ⇑ADH
        - Renal conservation of fluid with ⇓UO
        - Thirst
- Progressive:
    - Tissue hypoperfusion + metabolic disturbance (e.g. lactic acidosis)
        - Anaerobic metabolism → lactate
        - ⇓Vasomotor response → peripheral blood pooling
        - Hypoxic cell injury
        - DIC
        - Organ failure
- Irreversible:
    - Non-reversible tissue + cellular injury
        - Even if tissue perfusion is restored, survival not possible due to extend of irreversible cell injury
    - At cellular + tissue level:
        - Lyosomal enzyme release
        - NO → ⇓myocardial contractility
        - ATN → AKI
        - Ischaemic gut
        - Arrest + death

Clinical features of shock:

- ⇑RR
- ⇑HR
- ⇓BP, ⇓pulse pressure
- Cool peripheries, ⇑CRT

- ⇓UO
- Altered mental state

Blood loss vs. CO



Steep fall at 20% blood loss
Death at 45% blood loss

GRAM NEGATIVE SEPSIS

Mechanisms
- **Direct microbial injury**
- Activation of **host inflammatory** responses in response to **endotoxin**

- **Endotoxin binds to LPS binding protein in serum**
- **Complex does the following:**

Direct endothelial injury + activation	
Innate immune system activation	Endotoxin – TOLL-like R Neutrophils Monocytes, macrophages
Inflammatory mediator release	IL1, 2 TNFα NO, PAF Reactive O2 species
Activation of **complement** cascade	
Activation of **coagulation** cascade	
Metabolic abnormalities	⇑glucose, insulin resistance
Immune suppression (counter reg)	Anti-inflammatory mediators Leukocyte apoptosis

- Low dose endotoxin:
  - ⇑Inflammation → ⇑clearance of bacteria
- Moderate dose:
  - Fever, procoagulant
- High dose:
  - Septic shock

    - Systemic vasodilation
    - ⇓CO (⇓contractility)
    - Widespread endothelial injury → DIC, ARDS

Outcomes of septic shock

- Hypotension
- End organ failure:
    - Cardiomyopathy
    - AKI
    - ARDS
- DIC
- Death

What factors affect extent + severity of shock

- Extent of infection
- Virulence of infection
- Host immune status
- Host comorbidities

DIC in shock

Pathological process

- **2 triggers:**
    - **Widespread endothelial injury**
    - **Systemic release of tissue factor / thromboplastic substances**
- Widespread activation of platelets and both arms of the coagulation cascade
- Results in consumptive coagulopathy → deficiency of factors + platelet + fibrinogen → bleeding diathesis
- Fibrin deposition in the microcirculation → thrombi → ischaemia
- Simultaneous activation of fibrinolytic system → bleeding
- MAHA secondary to thrombi in the microcirculation
- Consequence: ischaemia + bleeding
- Compounded by stasis

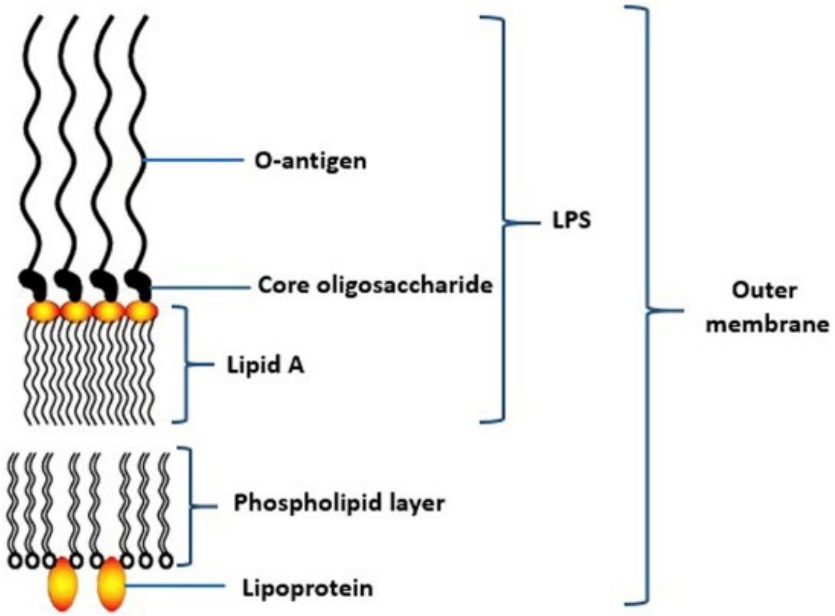
- Altered levels of:
    - Thrombomodulin
    - Protein C
- ⇓Fibrinolysis via plasminogen activator inhibitor

Vascular <u>endothelial cell activation</u> during shock:

1. Vasodilation	
2. Increased permeability	**Endothelial contraction/retraction** ○ Gaps between endothelial cells in post-capillary venules ○ Immediate transient response ○ Mediated by: histamine, LTs - Direct endothelial injury ○ Rapid, long-lasting ○ E.g. burns, bacterial toxins
3. Activation of coagulation cascade + thrombosis	**DIC = consumptive coagulopathy** • ⇑Tissue factor production • ⇓Fibrinolysis • Stasis

What is bacterial endotoxin

- Component of outer cell wall of gram –ve bacteria
- Lipopolysaccharide
- Normally gram –ve bacilli
- Generic fatty acid core + specific polysaccharide coat



Effect of septic shock on organ systems:

- Heart - ⇓contractility, ⇓CO
- Large BVs – vaso+venodilation
- Capillaries – endothelial dysfunction, ⇑permeability, leukocyte accumilation
- Blood – DIC
- Lungs – ARDS
- Renal – AKI (ATN)
- Liver – failure
- Brain – hypoxic brain injury

Chemical mediators involved in shock

Complement cascade	
Coagulation cascade	
Kallikrien-kininogen	Bradykinin
Arachidonic acid / eicosanoid	LTs, PAF, TXA2, PGs
Inflammatory cytokines	TNF, ILs
Vasoactive	Histamine, serotonin
Lysosomal enzymes	Proteases
Free radicals	Oxygen, nitrogen

VENOUS THROMBOSIS

Contributors to venous thrombosis

- **Virchow's triad**
  - **Endothelial injury / dysfunction**
    - Most important, may alone result in thrombosis, especially in areas of high flow
    - Alters dynamic balance between pro- and anti-thrombotic effects
  - **Abdnormal blood flow / stasis**
    - Turbulence / stasis
    - Brings platelets into contact with endothelium
    - Turbulance can cause endothelial injury
    - Prevents inflow of anticoagulant factors
  - **Hypercoaguability**
    - Congenital vs. acquired

Risk factors of venous thrombosis

Congenital	Antithrombin deficiency Prothrombin mutation Homocyteinaemia (MTHFR mutation) Protein C / S deficiency Factor V leiden Fibrinolysis defects
Acquired	Hypercoaguability: • APLS • Malignancy • Hormonal (OCP) • Pregnancy / post-partum • DIC • Nephrotic syndrome Stasis: • Venous compression (e.g. pelvic mass, May-Thurner's) • Lack of mobility • Hyperviscosity states (PCRV) Endothelial injury: • Venous catheterization (e.g. central line) • Smoking • Burns / fractures / trauma

Possible outcomes of venous thrombosis

- Dissolution (fibrinolysis)
- Organisation (inflammation → fibrosis)
- Recanalization
- Propogation → vessel occlusion
- Embolism

B CELLS

Where a B cells located?

- Bone marrow
- LNs
- Spleen
- Circulating
- MALT

How do B cells respond to antigenic stimulus?

- Receptors for complement / Ig
- Conversion to plasma cells with assistance of Th2 cells
- Production of Ig

How are B cells stimulated in GvHD?

- Activation of Th2 T helper cells
- Production of IL4,5
- Differentiation of B cells to plasma cells and class switching
- Production of antibodies

HOST DEFENCES

GIT	Gastric acid Lytic pancreatic enzymes Bile detergents Mucosal barrier Secreted IgA Clearance by defecation
Resp	Nasal turbinates + mucous Coughing Ciliated epithelium – mucociliary escalator Secreted IgA Alveolar macrophages

What can disrupt the protective mechanisms of the resp tract?

- Congenital: Cystic fibrosis / Kartageners / Primary ciliary dyskinesia
- Smoking
- Aspiration
- Intubation
- Airway trauma / burns
- Airway infection

LYMPHOCYTES

Major subdivisions
- B cells
- T cells:
    - CD4+ Th1
    - CD4+ Th2
    - CD8+ cytotoxic T cell
    - Treg
- NK cells

Roles of lymphocytes
- Adaptive immunity
- Circulate widely
- Respond to antigens
- Can form effector or memory cells in response to antigen

T cells	Ag binds to TCR on T cells, CD3 co-receptor Ag needs to be presented on MHC1 (unprocessed) or MHC2 (processed) Costimulation with CD4 / CD8, CD40L, CD28 Th – respond to antigen presented on MHC2 by APCs Tc – respond to antigen presented on MHC1 by all nucleated cells
Th1	Secrete IL2 + IFNgamma → activation of macrophages
Th2	Secrete IL4 → activation of B cells and class switching of plasma cells
Tc cells	Cytotoxic – e.g. Fas-FasL, perforin + granzyme
B cells	Recognise Ag via surface BCR (IgM / IgD) Differentiation into plasma cells – Ig secretion (humoral immunity) Effector or memory cells
NK cells	Innate immunity Kills infected cells without prior antigen exposure

Type 1 HS

- **Rapid immunological reaction, interplay of IgE, antigen, and mast cells**
- **In a previously sensitized individual**
- **Examples: anaphylaxis, atopic asthma**

- Exposure to antigen
- Uptake of antigen by dendritic cells (APCs)
- Presentation of processed antigen on MHC2 by dendritic cells
- Activation of Th2 cells by combination with TCR-CD3 complex
- Secretion of IL-4 by Th2 cells → activation and class switching of B cells into IgE producing plasma cells.
- IgE binds to mast cells (Fc receptors)
- Repeat exposure to allergen antigen → crosslinking of IgE → mast cell degranulation
    - Primary and secondary mediators – vasoactive amines + lipid mediators
- End result:
    - Vasodilation

- Increased vascular permeability
- Smooth muscle spasm
- Inflammatory cell infiltration

Primary mediators (immediate)	**Bioactive amines: Histamine** **Enzyme** (tryptase, chymase, acid hydrolase) **Proteoglycans:** Heparin Eosinophil chemotactic factor Neutrophil chemotactic factor Adenosine
Secondary mediators (late phase)	PAF PGD2 Leukotrienes Cytokines

Phase 1 reaction:

- Vasodilation
- Vascular leakage
- Smooth muscle spasm
- Glandular secretion
- Starts 5-30 mins, subsides within 1 hr
- Mediators:
    - Biogenic amines
    - Enzymes
    - Proteoglycans

Late phase reaction:

- Ongoing inflammatory reaction without additional exposure to triggering antigen
- Infiltration of tissues with inflammatory cells: eosinophils, neutrophils, basophils, monocytes, T cells.
- Mucosal cell epithelial damage
- Time course – 2-24 hrs later

Clinical presentation of anaphylaxis

- Skin
- Resp
- GIT
- Cardiovascular

Type 2 HS

- Immunological hypersensitivity characterized by antibodies directed at self antigens
- Antigens can be:
    - Endogenous: present on cell surface or ECM
    - Exogenous: e.g. drug metabolite

- Consequence of Ab binding to Ag:

Opsonisation + **phagocytosis**	IgG Abs opsonize cells Activates complement → C3b Fc / complement recognized by phagocytes Phagocytosis of opsonized cell *Transfusion reaction / HLDNB* *Autoimmune haemolytic anaemia*
Complement + Fc mediated **inflammation**	Ab binds to fixed tissue Ag Activates compliment → C5a + C3a ⇑Vascular permeability, mast cell degranulation, inflammatory cell infiltrate PMNs activated by C3a + Fc → release inflammatory mediators (PGs, lyosomal enzymes, ROS) *RF* *Goodpastures, GN*
Ab-dependent cellular **cytotoxicity** (ADCC)	IgG coats cells, cell then destroyed by monocytes, neutrophils, NK cells – without phagocytosis
Ab-mediated cellular **dysfunction**	Abs directed against cell surface receptors Cause cellular dysfunction without causing cell injury or dysfunction *Graves, MG, pernicious anaemia*

OCCD:
Opsonisation → phagocytosis
Complement → inflammation
Cytotoxicity
Dysfunction

Type 3 HS

Hypersensitivity mediated by immune complex formation, with or without complement activation.

- 3 phases:
    1. **Ab-Ag (immune complex) formation** in circulation
        - IgG / IgM antibodies
    2. **Deposition** of IC in tissues
    3. IC-mediated **inflammation** at site of deposition → tissue damage
        - @ approx 10 days
        - Fc of Ab binds to leukocyte receptors
        - IC → activation of classical pathway of complement cascade

Complement	C3b – opsonisation C5a, C3a – anaphylatoxins C5b-C9 - MAC
Inflammatory cells (neuts, macro)	Lysosomal enzymes ROS / RNS PGs PAF Histamine
Hageman factor **Kinins**	Coagulation cascade Kinogens

        - Deposition + consumption of complement (⇓C3 levels)

- Common sites of IC deposition (think of manifestations of autoimmune disease)
    - Renal glomeruli
    - Joints
    - Skin
    - Small blood vessels
    - Serosa
    - Heart

Examples of T3HS

- **Serum sickness**
- **SLE**
- **Arthus reaction**
- **Post-strep GN**

Examples of antigens:

Exogenous	Foreign protein (serum sickness) Bacterial (post-strep GN) Viurses (PAN)
Endogenous	DNA (SLE)

Clinical presentation

- Arthritis
- Skin lesions
- Vasculitis
- Nephritis / proteinuria
- Fever

Type 4 hypersensitivity

- **Antigen sensitizes**
  - **CD4 +ve T cells**
  - **CD8 +ve T cells**
- **Results in cellular injury:**
  - **Cytokine mediated**
    - CD4 Th1
    - TH17 cells
    - → release of inflammatory mediators (IL2, IFy, TNFα)
    - → inflammatory cell infiltration (macrogphage, mono, neut)
  - **Direct cell-mediated**
    - CD8 cytotoxic T cells
    - Fas-FasL, granzyme-perforin

- Tissue changes:
  - **Perivascular** cell infiltrate
  - ⇑Microvascular **permeability**
  - Tissue **oedema**
  - **Fibrin** deposition
  - **Granuloma** formation
  - Cellular **necrosis**

- Examples:
  - DMT1
  - MS
  - RA
  - TB
  - Contact sensitivity dermatitis
  - Inflammatory bowel disease

- **Tuberculin skin reaction**
  - Mediated by **differentiated effector T cells**
    - Th1: IL2, IFgamma, TNFα → macrophage activation
    - Th17: IL17 → recruit neutrophils + monocytes
  - Starts 8-12hrs
  - Peaks 24-72hrs
  - Tissue changes:
    - Perivascular cell infiltrate (perivascular cuffing)
    - ⇑Vascular permeability
    - Tissue oedema
    - Granuloma formation with epithelioid cells
    - Fibrin deposition

- Cellular necrosis

How does it differ in a naïve individual?	In naïve individual, **CD4+T cells** differentiate into T_H 1cells after recognising antigen presented on APCs in association with class II MHC molecules. **T_H1cells** can enter the circulation and remain in the **memory** pool of T cells for long periods (years)

NEOPLASM

Define neoplasm:
- Abnormal growth of tissue
- Growth exceeds that of, and is uncoordinated with, original tissue
- Growth continues in the absence of stimulus which evoked the change

How can malignancy affect host?
- Direct local effects:
  - Mass effect / pressure
  - Haemorrhage
  - Ulceration
- Systemic:
  - Cachexia
  - Paraneoplastic

TUMOUR INVASION + METASTASIS

Predecing clonal expansion + growth + angiogenesis

Detatchment	Breaking on intercellular bonds, tumour cells separate from one another Downreg of E-cadherin
Attachment	Attachment to ECM via laminin + fibronectin receptors
Degradation	Breakdown of ECM & BM: T4 collagenase MMP Plasminogen activator
Migration	Migration of tumour cell +/- haemoatogenous dissemination Tumour cell embolus (aggregate of tumour cells) Arrest + extravasation at distant sites Growth and angiogenesis

Importance of matrix metalloproteinases
- Collagenases produced by tumour cells or surrounding stromal cells
- Cleave collagen IV of BMs (epithelial / endothelial)
- Breakdown products are generated which facilitate:
  - Angiogenesis
  - Tumor growth
  - Tumor motility

What influences the distribution of metastasis?

Tumour cell adhesion molecules	Ligands for these molecules are preferentially expressed on target organ cells
Chemokines	*For* target tissues
Chemoattractants	*From* target tissues
Permissive environment?	Some tissues, e.g. skeletal muscle, not permissive environment

PARANEOPLASTIC SYNDROMES

- Complex of symptoms
- Cannot be readily explained by local or distant spread of tumor
- Not caused by elaboration of hormones native to the tissue in which the tumor arose

Endocrine	Cushings (ACTH) – small cell lung SIADH – small cell lung, intracranial ⇑Ca (PTHRP) – squamous lung Carcinoid (5HT, bradykinin) – lung, pancreas, GIT Polycythaemia (EPO) – Renal / ovarian
Nerve / muscle	MG L-E
Derm	Acanthosis nigricans Dermatomyositis
Bone	HPOA Clubbing
Haem	Polycythaemia Thombophlebitis (Trosseau's – pancreatic Ca)

Cancer cachexia

- Unclear mechanism
- Anorexia
- Cytokines - TNFα
- ⇑BMR

CANDIDA

Clinical spectrum

Benign commensal	Asymptomatic
Superficial mucosal	Mouth, oesophagus, vagina
Superficial cutaneous	Intertrigo, balantitis, paronychia
Invasive / disseminated	Candidaemia Myocardial / endocarditis Meningitis Abscess – brain / lung / liver / renal Endopthalmitis

Virulence features

Phenotypic switching	Rapid adaptation to host environment
Enzymes	Degrade ECM
Adhesion	To host cells, via adhesins
Adeonsine	Blocks neutrophil degranulation

Candida: <u>PEA</u>

CLOSTRIDIA

- Gram +ve, anaerobic, spore forming rod

Perfringens	Gas gangrene
Difficile	Diarrhoea + pseudomembranous colitis
Tetani	Spastic paralysis
Botulinum	Flaccid paralysis

Mechanism of action of C. Botulinum

- Oral ingestion
- Cholinergic terminal cytoplasm, A-toxin cleaves synaptobrevin
- Failure of release of ACh vesicles into the NMJ
- Flaccid paralysis

Mechanism of action of C. Perfringens

- **Enzymes:** collagenase, hyaluronidase
- **Toxin (α-toxin): phospholipase C**
    - Lyses RBCs, WBCs, endothelial cells
    - ⇑Vessel permeability
    - Release of phospholipid derivatives: PGs
    - Dysregulation of cell metabolism + death

CROUP

- Acute laryngotracheobronchitis
- Causes inflammatory narrowing of airway
- Barking cough, insp stridor
- Viral:
    - Parainfluenza
    - RSV

Characteristics of acute inflammation

- Rapid onset, hours→days
- Vasodilation → ⇑blood flow
- ⇑Vascular permeability → oedema
- Neutrophil emigration & accumulation

E. COLI

- Gram –ve rod
- Facultive anaerobe

Infections caused by E.coli

- UTI / prostatitis / epididymoorchitis
- Peritonitis
- Cholecystitis

Endotoxin vs. exotoxin

- Endotoxin:
    - LPS from outer cell wall of gram –ve
    - Cause injury via host cell response
- Exotoxin:
    - Secreted by bacterium
    - Causes direct cell injury

E. coli enteritis

Enterotoxic	Travellers diarrhea Heat labile toxin: like cholera toxin (AC, cAMP, CFTR, Cl) Heat stable toxin: (GC, cGMP)
Enterohaemorrhagic O157	Ground beef Shigella-like toxin Bloody diarrhea + HUS MAHA + AKI + TTP
Enteroinvasive	No toxins, invades mucosa Colitis
Enteroaggregative	Adheres via fimbriae Non-bloody diarrhoea

EBV

- dsDNA virus belonging to HHV class of viruses (HHV4)

Pathogenesis of glandular fever

- Saliva transmission
- Enveloped glycoprotein binds to B cells
- Invasion of nasopharyngeal submucosal lymphoid tissue
- Fate of infected B cells:
    - Lysis + virion release
    - Latent infection
- Host immune response:
    - CD8 Tc cells, NK cells
    - Atypical lymphocytes
    - Reactive T cell proliferation → lymphadenopathy + splenomegaly
    - IgM → IgG to viral capsid Ag
- Can cause B-cell lymphoma

Clinical features of glandular fever:

- Pharyngitis
- Fever
- Tender lymphadenopathy
- Hepatosplenomegaly, prone to rupture
- Rash
- Chronic fatigue

Outcome of glandular fever:

- Most resolve at approx. 1 month
- Some have chronic fatigue
- Liver: jaundice, deranged LFTs
- Splenic rupture
- Malignant transformation (lymphoma)

HERPES SIMPLEX VIRUS

Clinical:

- Cold sore
- Gingivostomatitis / oesophagitis
- Herpetic whitlow
- Genital herpes
- Keratitis
- Encephalitis
- Pneumonia

Mechanism of reactivation:

- Virion travels from mucocutaneous site → sensory nerve nucleus in the dorsal root ganglion

- Latency: **mRNA transcription but not translation**
- Ractivation: **avoidance of immune recognition + antidromic movement along sensory neurone**
    - Inhibition of MHC1
    - Fc binding proteins to inactivate Ig
    - Complement binding proteins to inactivate complement

HERPES ZOSTER

Pathogenesis

- Previous exposure to VZV
- Infects sensory neurons in DRG
- Latency in DRG
- Reactivation in elderly / immunocomprimised
- Antidromic movement along sensory neurone to cause vascular eruption along dermatomal distribution (radiculoneuritis)
- Can cause nerve dysfunction

HIV

- Initial invasion of APCs
- Subsequent invasion of CD4+ Th cells:
    - GP120 ←→ CD4
    - CXCR4, CCR5 costimulation
- CD4 depletion
- Immunosupression
- Outcomes:
    - Opportunistic infections
    - Neoplasms
    - Wasting disease
    - Neurological manifestations

AIDS in USA

- **Homosexual males 50%,**
- Heterosexual contacts 33%
- IV drug users 25%,
- Recipients of blood transfusions 1%
- Haemophilliacs 0.5%
- Vertical transmission
- Breast milk
- Needlestick (0.3%)

INFLUENZA

Structure of virus

- ssRNA
- Orthomyxoviridae
- Bound by nucleoprotein that determines its A / B / C classification
- Spherical capsule
- Envelope with 2 predominant proteins:
    - Haemagluttinin
    - Neuraminidase

Subtypes of influenza virus:

- A, B, C – determined by nucleoprotein
- H – haemagglutinin
- N – neuraminidase

- B/C – children, don't cause epidemics as no antigenic shift/drift

What causes pandemics / epedemics

- Antigenic drift – epedemics
    - Mutation in H/N
- Antigenic shift – pandemics
    - Antigenic change due to **recombination** of viral RNA with animal host RNA
- Influenza B/C don't show antigenic drift/shift

Host clearance of influenza

- CD8+ Tc cells
    - Respond to infected host cells expressing viral antigen on MHC1
- Macrophages
    - IFN induced production of **anti-influenza Mx1** in macrophages
- Immunity:
    - Ab to H + N

How does influenza cause pneumonia

- Attachment to URT epithelium
- Necrosis of cells → inflammatory response
- Interstitial inflammation with outpouring of fluid into the alveoli
- Secondary infection – staph / strep

MALARIA

What causes malaria?

- Protozoa – plasmodium
- Intracellular parasite
- 4 main species:
    - Falciparum
    - Vivax
    - Ovale
    - Malariae

Life cycle:

- Sporozoite in saliva of female anopheles mosquito
- Sporozoites enter blood and travel to liver, invade hepatocytes
- Multiply rapidly in liver to form schizonts (and hyponozoits)
- Schizozony (with rupture of hepatocyte) → release of merozoites into blood
- Merozoite binds to surface of RBCs and enters RBCs in a vacuole
- Merozoites → trophozoites → schizont formation in RBCs
- Rupture of RBCs with release of merozoites
- Some merozoites → gametes in bloods
- Taken up by mosquito bite – fusion of gametes → zygote → sporozoites

Clinical presentation of P falciparum:

- Fever
- Anaemia
- Cerebral malaria
- Pul oedema
- DIC
- AKI

- Congestion of spleen → splenomegaly
- Cerebral malaria: clumping of parasitosed RBCs → small vessel obstruction → ischaemia, local hypoxia, inflammation
- AKI: Hb casts
- Cytokine release → DIC / fever

Plasmodium falciparum

- Infects RBCs of any age – severe parasitaemia
- Clumping of paraistosed RBCs
- ⇑**Cytokines**
- →
    - Anaemia
    - AKI
    - Cerebral
    - Pulmonary oedema

What causes resistance to malaria

- Inherited RBCs – HbS, HbC
- Repeated stimulus → immune response: T cells, Abs

- HLA subgroups

MEASELS

- ssRNA
- Paramyxovirus
- Only one strain of virus so amenable to vaccination
- Spread by respiratory droplets

Pathogenesis

- Respiratory droplet spread
- Multiplies in URT epithelial cells
- Moves to lymphoid tissue where it multiplies in mononuclear cells
- Haematogenous spread
- Preventable by vaccination as only single strain
- Epidemics in unvaccinated

Clinical presentation of measles

- Rash, conjunctivitis, coryza, fever, Koplik's spots
- Viral pneumonia
- Acute measles encephalitis
- SSPE
- Croup
- Immunosuppression

Immune response

- **T cell** mediated immunity: **controls infection**
- Hypersensitivity to viral antigens → rash
- **Future immunity** mediated by **Ab**

Host cell receptors for measles virus

- CD46 – present on all nucleated cells, binds haemagluttinin
- SLAM – present on immune cells, binds haemagluttinin

NEISSERIA MENINGITIDIS

- Gram negative cocci
- Aerobic
- 13 serotypes
- Grow on chocolate blood agar

Pathogenesis

- Colonises oropharynx – 10% pop are carriers at any one time

- Colonisation can last for months
- Spread by resp droplets
- Most people develop immune response and clear it - future immunity to this serotype but 13 serotypes
- New serotypes can cause invasive disease
- Invades resp epithelium → haematogenous spread
- Encapsulated – evades immune response: prevents oposonisation / complement destruction
- Mortality approx. 10%

Clinical presentation of meningococcus

- Meningitis
- Sensorineural hearing loss
- Seizures
- Sepsis
- Death

Other causes of meningitis

- Viral
    - Enterovirus
    - Measals
- Fungal
    - Cryptococcus
- Bacterial:
    - Pneumococcus
    - Haemophilus
    - Listeria
    - GBS
    - E. coli
    - TB

STAPH AUREUS

- Aerobic gram +ve cocci

Virulence factors

Capsule	Attachment to host cells (e.g. receptors for fibronectin) Evasion of host immune system
Surface proteins	Attachment to host cells
Secreted enzmes: lipase	Lipase degrades skin lipids allowing abscess formation
Secreted toxins: **Haemolytic toxin (α)**	Membrane damage
Enterotoxin	Food poisoning
Exfoliative toxin (A+B)	SSS
Superantigen	TSS

Toxic shock syndrome

- RFs:
    - Tampon use
    - Nasal packs
    - Post-op wound infection
    - Post-natal infections
    - Staph skin infections

- Clinical features:
    - Rash
    - Shock
    - AKI
    - DIC
    - Resp failure

Other diseases of staph aureus:

- Impetigo
- Cellulitis
- Folliculitis
- Skin abscess
- Scalded skin syndrome

- Pneumonia
- Osteomyelitis
- Septic arthritis
- IE

Other staphylococci bacteria

- Aureus
- Epidermidis – opportunistic, e.g. prosthetic valves
- Saprophiticus – UTI

Skin infections

- Staph aureus
- Strep pyogenes
- Clostridium perfringens
- Clostridium tetani
- Pseudomonas

STREPTOCOCCUS

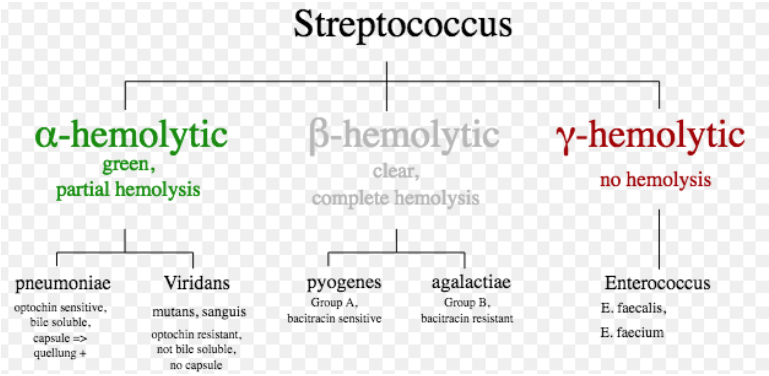
- Gram +ve aerobe, in chains or pairs

- Suppurative infections
- Immune-mediated sequalae

Strep infections
- Skin – erysipelas, scarlet fever
- Throat
- Ear
- Pneumonia
- Meningitis
- Endocarditis

Usually cause **acute suppurative infections**

GAS	β-haemolytic	Suppurative infection
GBS	β-haemolytic	Neonatal sepsis Female genital
	α-haemolytic	Pneumoniae Viridans
	Y-haemolytic	Enterococcus



Post-strep sequalae:

- RF (T2HS)
- GN (T3HS)
- Erythema nodosum
- Neuropsychiatric / tics (PANDAS)

Strep virulence factors

Capsule	Attachement to host cell Evade immune system
M protein	Prevents phagocytosis
Enzyme	Compliment C5a peptidase
Toxins	Pyrogenic toxin – rash + fever Pneumolysin – lyses target cells (S. pneumonia)
HMW glucans	Aggregation of platelets

VARICELLA ZOSTER VIRUS

- HHV
- dsDNA

- Causes chicken pox + shingles

Pathogenesis
- Aerosol / direct contact spread
- Haematogenous dissemination
- Vesicular skin lesions
    - 2 weeks after aerosol exposure
    - Initially macular → vesicular
    - Central location → peripheral in waves
    - Vesicles rupture, crust, heal
    - Skin + mucous membranes
- Virus dormant in DRG, reactivation if immunosuppressed

Tissues involved in primary VZV infection
- Skin
- Mucous membrane
- Neurones

Shingles:
- Reactivation of latent virus in DRG
- Evades immune response
- Antidromic movement along sensory nerves → skin lesion
- Complications:
    - Interstitial pneumonia
    - Visceral / GI lesions
    - Encephalitis

Complications of VZV
- Pneumonia (interstitial)
- Meningitis / encephalitis / transverse myelitis
- Shingles +/- bacterial superinfeciton
- GI: necrotizing GI lesions

AAA

- Local dilatation of aorta
- Normally inferior to the renal arteries
- Usually contains atheromatous plaque +/- mural thrombi

Risk factors for AAA

- HTN

- Smoking
- Diabetes
- Male
- Age > 60
- Atherosclerosis

Primary
- CT disorder
- Infection e.g. syphilis
- Trauma
- Immunological

Pathogenesis

- **Atherosclerotic plaque** in the intima → compresses the media
- → **Cystic medial degeneration** → weakness of the wall
- → **Local inflammation**
- → **Proteolytic enzymes / MMPs** → collagen degradation
- **Loss of vascular smooth muscle cells** + elastic fibres

Consequences of AAA

- **Rupture → haemorrhage (retroperitoneal / intraperitoneal)**
- **Obstruction of branch vessel**
- **Mass effect (e.g. on ureter)**
- **Thrombus + embolus**

Risk of rupture

- <4cm – minimal
- 4-5cm – 1% year
- 5-6cm – 11% year
- >6cm – 25% year

5cm is the watershed of risk

AORTIC DISSECTION

Pathogenesis
- **Intimal tear into the media** in a vessel with **weakness of the media**
- Seperation of the media either proximally or distally creating a false lumen
- I.e. **strips along laminar plane between middle and outer thirds of media**
- **Weakness of the media due to:**
    - HTN
    - CT disorder

- Trauma / arterial cannulation
- Cystic degeneration

Classification
- By location
- Stanford (A vs. B)
- Debakey (I, II, III – B.A.D)

Consequences
- Rupture into pericardium / pleural / peritoneum
- Loss of vascular branches → ischaemia (e.g. spinal cord)
- Tamponade
- AVR
- MI

AORTIC VALVE STENOSIS

Consequences of aortic stenosis

- LVOO → ⇑Afterload → concentric LVH
- CCF (systolic / diastolic)
- Myocardial ischaemia (angina / MI)
- Syncope
- Endocarditis

Causes of AS
- Senile calcification
- Congenital bicuspid valve (calcification)
- Rheumatic (often more than one valve, may also include AR) – post-inflammatory scarring

Calcific AS
- **Wear + tear** → calcification
- **Heaped up calcified masses within cusps**
- 80s + 90s in normal valve
- Earlier in congenital bicuspid

RFs:
- Age
- Bicuspid
- RF
- Atherosclerotic RFs

Complications of congenital bicuspid valve
- Calcification
- Stenosis
- Regurg
- IE

ATHEROSCLEROSIS

Local factors:

- Endothelial dysfunction
    - Haemodynamic disturbance (e.g. turbulence)
    - Hypercholesterolaemia
- Inflammation
    - HTN
    - Hyperlipidaemia
    - Cigarette toxins
    - Pro-inflammatory cytokines (TNF)

Pathogenesis:

Endothelial injury / dysfunction	
LDL accumulation + oxidation	
Inflammatory cell infiltrate	Monocytes infiltration into **intima** → Macrophage + foam cells
Smooth muscle	Movement of SMCs from media → intima, proliferation
Lipid	Accumulation of lipid in core of intimal lesion, intracellular + extracellular

Sudden events at an atherosclerotic plaque

Thrombosis	• Rupture / fissuring of intimal surface Or Erosion / ulceration to subendothelial BM • → Exposure of thrombogenic ECM → thrombosis • Can cause occlusion
Intra-plaque haemorrhage	• Bleeding into plaque from thin-walled neovascularization
Embolism	• Atheroembolism of plaque thrombus
Aneurysm	• Pressure/ischaemic atrophy of underlying media + loss of elastic tissue • Cystic medial degeneration

Major complications:

- Occlusion:
    - Thrombosis
    - Critical plaque size
- Embolism
- Aneurysm

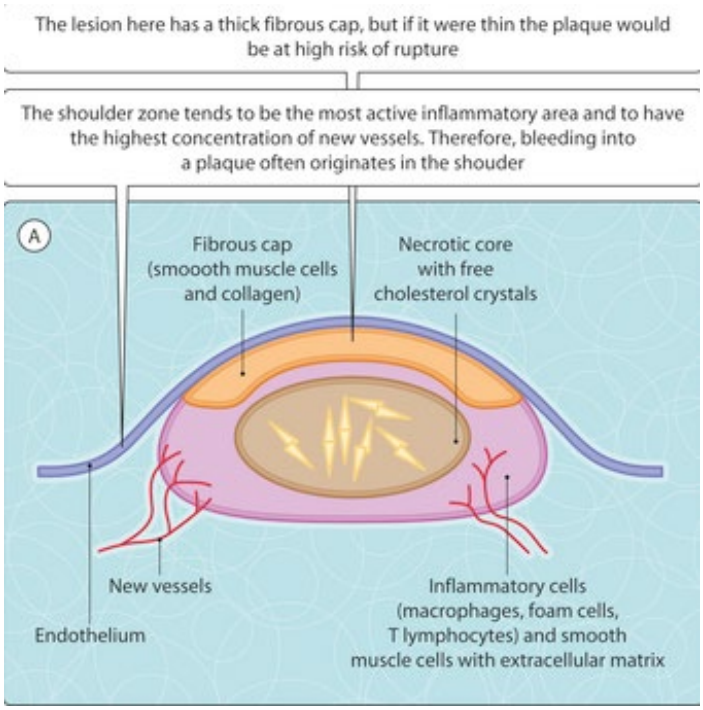
Stable vs. unstable plaque

Stable	Thick fibrous cap (dense collagen) **Minimal inflammation** Small necrotic core
Unstable	Thin fibrous cap ⇑**Inflammation** Large necrotic lipid core

Vessels most affected

- Abdominal aorta
- Coronaries
- Popliteal
- ICA + COW

Draw an atherosclerotic plaque



Fibrous cap	Collagen SMCs Calcification
Cellular layer	Inflammatory cells – Macros, foam, T cells SMCs Fibroblasts ECM
Necrotic / lipid core	Free cholesterol Foam cells

Angiogenesis	Most pronounced at shoulder zones

CARDIOMYOPATHY

Definition

- Heterogeneous
- Primary pathology of the myocardium
- A/w mechanical or electrical dysfunction
- Usually a/w inappropriate LV hypertrophy or dilatation
- Congenital or acquired

- Can get a similar picture from myocardial involvement in a systemic disorder (e.g. LVH secondary to HTN) – *secondary cardiomyopathy*

Types of cardiomyopathy

Hypertrophic (+/- outflow obstruction)	Genetic
Dilated	Genetic ETOH Pregnancy Vitamin deficiency Drugs Myocarditis Infection (e.g. chagas) Autoimmune
Restrictive	Infiltrative (e.g. amyloid, sarcoid) Scleroderma
ARVD	

Consequences of CM

- Valve dysfunction (regurg, IE)
- Mural thrombus
- Arrhytmia
- CCF
- SCD

Dilated vs. hypertrophic

Dilated	Hypertrophic
Systolic dysfunction (⇓EF) Enlarged chambers	Diastolic dysfunction, normal/⇑ EF Impaired compliance

Features of HCM

- Myocardial hypertrophy without dilatation
- Asymmetrical septal wall thickening
- Diastolic dysfunction
- May be a/w LVOO

- Microscopic:
    - Myocyte hypertrophy
    - Helter-skelter myocyte disarray
    - Interstital fibrosis

COR PULMONALE

- RHF
- **Not secondary to L sided HF**
- Secondary to **pulmonary HTN**
- Acute or chronic

Causes of cor pulmonale

Pulmonary HTN secondary to…

Parenchymal disease	COPD / bronchiectasis / fibrosis
Vessel disease	Primary pul HTN, PE, vasculitis
Chronic hypoxia	Altitude, OSA
Chest wall restriction	Obesity / kyphoscoliosis / neuromusc

Features of cor pulmonale

- RVH / dilatation
- Congestion of **systemic** / **portal** system (not pulmonary)
- Peripheral oedema
- Congestive hepatomegaly, centrilobar necrosis
- Ascites

INFECTIVE ENDOCARDITIS

What predisposes to IE

Cardiac	Damaged valves • MVP • Bicuspid AV • Rheumatic HD Prosthetic valves
Extra-cardiac	Bacteraemia Candidaemia IVDU Immunodeficiency Indwelling vascular catheters Malignancy

Organisms

- Strep viridans
- Staph aureus
- Staph epidermidis
- HACEK (haemophilus, actinobacillus, cardiobacterium, eikenella, kingella)
- Fungal

Complications of IE

- Cardiac:
    - Abscess
    - Valvular failure
    - CCF
    - Aortic root abscess → heart block
    - SCD
- Systemic:
    - Systemic sepsis
    - Septic emboli – Oslers nodes
    - Mycotic aneurysms
    - Immunological sequalae – GN, JW lesions

HEART FAILURE

Definition

- Cardiac function is impaired or unable to maintain sufficient CO to meet the metabolic demands of the tissues, at normal filling pressures.

Classification

- Systolic vs. diastolic
- LHF vs. RHF

- High-output vs. low-output
- Acute vs. chronic

Systolic	Dilated CM Ischaemic Myocarditis Valvulopathy Arrhythmia
Diastolic	Hypertrophic CM Restrictive CM Tamponade

Main ones they want:

- **HTN**
- **IHD**
- **Valvular HD**

Clinical features:

- Heart:
  - 3rd HS, gallop
  - Tachycardia
  - Displaced apex, heave
  - JVP
- Lungs:
  - Pulmonary oedema
  - ⇑RR, ⇓SO2
  - OPN, PND
- Renal:
  - RAA
  - AKI
- Brain:
  - Hypoxia → confusion
- Hepatic:
  - Congestive hepatomegaly, cirrhosis
  - Ascites

Cardiac pathological changes in HF:

- **Ischaemia** / infarction
- **Hypertrophy**
- **Calcification**
- Interstitial **fibrosis**

Liver pathological changes in HF:

- **Nutmeg** liver
- **Centrilobular necrosis**
- Centrilobular **fibrosis**
- Cardiac **cirrhosis**

HYPERTENSION

Classification

- **Primary (essential)**
- **Secondary**

Secondary hypertension

Renal	Renovascular – RAS, vasculitis GN / PKD
CVS	Coarctation PAN
Endocrine	⇑Adrenocortical function (Cushing's, Conn's, CAH) ⇑Catecholamines (phaeo) Acromegally ⇑Thyroid Exogenous hormones / sympathomimetics
CNS	⇑ICP

Primary HTN

Genetics	Multi-gene interaction Monogenic – affecting Na resorption
Vasoconstrictive	Vasoconstriction / structural change to vessel walls → ⇑TPR
Environmental	Stress / obesity / smoking / lack of exercise / salt in diet

Consequences of HTN

- Atherosclerosis
    - MI
    - PVD
- CVA
- Dissection
- Aneurysm
- CKD
- CCF
- Multi-infarct dementia
- Retinopathy

Malignant HTN

- SBP > 200, DBP > 120
- End organ damage:
    - Retinal
    - Renal
    - Encephalopathy
    - CCF
- Usually superimposed on pre-existing HTN
- Occurs in <5% HTN patients

- High mortality untreated

Hypertensive heart disease

Criteria
- Systemic HTN
- LVH
- Absence of another cause

Macroscopic features of HTN heart disease
- LV wall thickening → ⇑weight of heart
- No LV dilatation
- LA enlargement

Consequences
- Diastolic dysfunction
- HF
- SCD
- AF/Aflut

ACUTE CORONARY SYNDROME

Pathophys of ACS secondary to atherosclerosis

Acute plaque change	Rupture / fissure Erosion / ulceration Haemorrhage into atheroma
Thrombosis	Exposure of thrombogenic subendothelial ECM → activation of coagulation Platelet adhesion + aggregration Platelet release of mediators causing vasospasm
Vasoconstriction	Local: from platelets Local: perivascular inflammatory cell release (endothelin, serotonin, NPY) Local endothelial dysfunction: ⇓NO Systemic: adrenergic agonists
Cumilates in vessel occlusion: ⇓Myocardial perfusion → Ischaemic necrosis	

1. **Acute plaque change**
2. **Thrombosis (1^{o} + 2^{o} haemostasis)**
3. **Vasoconstriction**
   → **ISCHAEMIC NECROSIS**

Complications of AMI

- Contractile dysfunction: cardiogenic shock
- Arrhythmias
- Myocardial rupture (free wall / septum)
- Ventricular aneurysm
- Pericarditis (Dressler's)
- Pericardial effusion / tamponade
- Mural thrombus
- Papillary muscle rupture → acute regurgitation

Consequences of cardiac rupture

- Free wall → tamponade (commonest, occurs days 1-10)
- Septal → VSD (L->R shunt)
- Papillary → MR

Ventricular modeling post-MI

- Hypertrophy + dilatation
- → ⇑O2 demand → ischaemic & ⇓cardiac function
- Fibrosis → scarring → stiffening

Systemic factors affecting infarct healing

- **Nutritional**: protein, vit C
- **Metabolic**: diabetes
- **Circulatory**: sufficiency of reperfusion
- **Hormonal**: glucocorticoids

Time-course of changes

- **Reversible + irreversible changes**
- **Anaerobic metabolism begins immediately**
- **Cell death after 30mins**
- **Extensive necrosis after 2 hrs**

1) Loss of contractility occurs in <2min
2) Onset of adenosine triphosphate (ATP) depletion occurs in seconds
   ATP reduced to 50% of normal in 10min
   ATP 10% of normal in 40min
3) Irreversible cell injury occurs in 20-40min
4) Microvascular injury occurs >1hr
5) Gross features of a myocardial infarction are present at 4-12hrs.
6) <24hrs – early coagulative necrosis
7) 3-7 days: disintegration of myofibres
8) 2-8 days: collagen deposition and fibrotic scarring

Consequences of reperfusion

- Early: nil
- Late:
    - Haemorrhage
    - Accelleration of disintegration of **damaged** myocytes
    - **New injury** due to O2 free radicals

PERICARDITIS

Clinical features:

- Chest pain (positional, pleuritic)
- Fever
- Pericardial rub
- Muffled heart sounds
- Congestive failure

Pericarditis:

- Infectious:
    - Viral
    - Bacterial
    - TB
    - Fungal
- Immune mediated:
    - RF
    - SLE
    - Scleroderma
    - RA
- Metabolic:
    - Uraemia
- Post-MI – Dressler's
- Trauma
- Drug induced
- Radiation induced

Types of pericardial effusion

Serous	Usually non-infectious, inflammatory
Fibrinous / serofibrinous	Commonest Post-MI, trauma, infectious, inflammatory
Purulent	Bacterial infection
Haemorrhagic	Malignant
Caseous	TB

ARDS

Pathogenesis

1. **Acute inflammatory** response (neutrophils)
2. Injury to **alveolar capillary endothelium**
3. ⇑**Vascular permeability**
4. Alveolar **flooding** + **fibrin** deposition
5. Formation **hyaline membranes**
6. Damage to T2 pneumocytes → widespread **surfactant abnormalities**
7. Organisation + scarring

Conditions causing ARDS

- Infection (sepsis, gastric aspiration)
- Trauma / burns
- Inhaled irritants (smoke, O2 toxicity)
- Chemic injury (heroin, salicylate poisoning)
- Haematological (DIC)
- Pancreatitis
- Uraemia

Outcome of ARDS

- Death
- Survival with organization + scarring

ASTHMA

- Disease of conducting airways
- Due to airway hypersensitivity
- Episodic bronchoconstriction
- Inflammation of bronchial walls with excess mucous secretion

Types of asthma

Atopic	Most common T1HS Th2 mediated IgE production in response to allergen, re-exposure → crosslinking of IgE and mast cell degranulation Immediate (bronchoconstriction), late phase (inflammation) Th2 – IL4, IL5
Non-atopic	Hyperirritability of bronchial tree No allergen sensitivity ? Viral induced Skin test negative

Drug induced	Aspirin B-blocker
Occupational	

Triggers

Atopic	Environmental (dust, pollen, animal dander, food) +ve family Hx
Non-atopic	Viral (rhinovirus, RSV) Exercise Cold Air polluntants

Early phase of acute atopic asthma

- Th2 mediated IgE production in response to allergen, re-exposure → crosslinking of IgE and mast cell degranulation →
    - Vasodilation
    - ⇑Vascular permeability → oedema
    - Bronchoconstriction
    - Mucous production
- Opening of gap junctions between epithelial cells →
    - Antigen can enter mucosa
    - Further acute inflammatory response
- Some **direct action via vagal reflexes**

Late phase:

- Recruitment of **leukocytes**
    - Neutrophils
    - Eosinophils (major basic protein)
    - Basophils
    - Lymphocytes
    - Monocytes
- Inflammatory mediator release
- **Epithelial damage**

Inflammatory mediators

- Histamin
- Bradykinin

- Leukotrienes
- PGs
- PAF

- ACh

- Cytokines: IL, TNF

Cells involved

- **Mast cells**
- **Eosinophils**
- **Basophils**
- **Lymphocytes**
- **Macrophages**
- **Neutrophils**

BRONCHIECTASIS

- Permanent DILATION of bronchi + bronchioles
- Due to destruction of muscle + elastic tissue, with scarring
- Resulting from, or associated with, chronic necrotizing infections

Causes:
- Idiopathic
- Infection
- Obstruction
- ABPA
- Congenital:
    - CF
    - PCD / Kartageners
    - Young's

FAT EMBOLISM SYNDROME

Causes:
- Microscopic fat globules travelling in the circulation
- Long bone fracture
- Occurs in 90% of skeletal injury, but only 10% symptomatic

Pathophys:

Mechanical obstruction	▪ Mechanical obstruction of microvasculature in: o Lungs o Brain ▪ Due to: o Fat globules o Aggregated platelets + RBCs
Biochemical injury	▪ FFA → endothelial injury + platelet activation

Consequences:
- Resp: respiratory distress, hypoxia
- Neuro: confusion, seizures

- Haem: TCP, anaemia
- Asymptomatic
- Death

PULMONARY EMBOLISM (PE)

Pathogenesis

- DVT (95% in lower limb)
- Through to RV → pulmonary arterial tree
- Main pulmonary arteries or any downstream vessels

Clinical

- Asymptomatic
- Symptoms:
    - CP
    - Resp distress
    - Syncope
    - Arrest
    - Haemoptysis
- Signs:
    - ⇑HR
    - ⇑RR
    - ⇓SO2
    - ⇓BP
    - Acute RHF
    - Pulmonary HTN

RFs for PE:

- See DVT RFs

Determinants of severity

- Extent of pulmonary artery flow obstruction
- Size of vessel occluded
- Number of emboli
- Overall CVS + resp status (baseline)

EMPHYSEMA

- Chronic lung condition
- Irreversible enlargement of airways distal to terminal bronchiole
- Due to destruction of alveolar walls
- Without fibrosis

Pathogenesis

- Fundamental: **imbalance between destructive protease and protective anti-protease activity.**

Inflammation	▪ **Exposure to toxic substances** such as cigarette smoke ▪ → **inflammation** ▪ Neutrophil / macro / lymphocyte infiltration → ⇑**cytokines, oxidants, elastase** ▪ → **Epithelial cell death + ECM proteolysis** ▪ **Elastin degradation products** mediate further inflammation
Protease vs. Antiprotease	▪ Smoking ⇑elastase activity in neutrophils + macrophages ▪ Free radicals ⇓antiprotease activity, ⇑neutrophil elastase ▪ **1% of patients have low antiprotease activity due to α-1-antitrypsin deficiency (PiZZ variant)**
Oxidant vs. anti-oxidant	▪ Cigarette smoke → ⇑⇑⇑ROS, depletes antioxidant activity

Clinical presentation COPD

Emphysema = pink puffer	Chronic bronchitis = blue bloater
Barrel chest Dyspnoeic Prolonged expiration Hyperventilation to maintain normal gas exchange	Recurrent chest infections with purulent sputum Less dyspnea, ⇓resp drive Hypoxic + cyanotic Cor pulmonale

Complications of emphysema

- Obstructive lung disease
- Hypoxia
- Resp failure
- Pul HTN → cor pulmonale
- Pneumothorax
- Infection

Anatomical types of emphysema

Centriacinar	Smoking Central/proximal part of respiratory unit Distal alveoli spared

	UL > LL
Panacinar	α1-AT defic Uniform destruction of acinus LL > UL
Paraseptal	⇑Risk pneumothorax
Irregular	

LUNG CANCER

Risk factors

Environmental	Tobacco smoke Asbestos Air pollution Occupational (arsenic)
Genetic	Dominant oncogenes: c-MYC, k-RAS Loss of tumour suppressor: P53, RB
Precursors	Squamous dysplasia Atypical adenomatous hyperplasia

Histological classification
- Adenocarcinoma – commonest
- Squamous cell
- Small cell
- Large cell
- Carcinoid

Routes of metastasis
- Lymphatic
- Haematological
- Direct seeding
- Local invasion

Clinical
- Cough
- Haemoptysis
- Weight loss
- Dyspnoea
- Chest pain

Paraneoplastic:
- Small cell: ACTH, SIADH
- Squamous: PTHRP
- Carcinoid: 5HT / bradykinin → flushing, diarrhea, bronchospasm
- HPOA
- Lambert-Eaton syndrome

Effects of local spread

- Collapse, consolidation, bronchiectasis
- SVC obstruction
- Osophageal obstruction → dysphagia
- Pleural effusion
- Pericardial effusion
- Invasion of RLN → hoarseness
- Invasion of phrenic N → diaphragmatic paralysis
- Horner's

MALIGNANT MESOTHELIOMA

- ⇑Risk in those with heavy exposure to asbestos
- Up to 10% lifetime risk
- Asbestos bodies found in the lungs
- Long latent period
- Smoking does not ⇑ risk of mesothelioma, but asbestos ⇑ risk of lung cancer in smokers

Sites of malignant mesothelioma

- Pleura
- Peritoneum
- Pericardium
- Genital tract
- Tunica vaginalis

PNEUMONIA

- Bacterial causes:
    - Strep penumoniae
    - Haemophilis influenzae
    - Morexella catarrhalis
    - Chlamydia
    - Legionella
    - Mycoplasma
    - Klebsiella
    - Staph Aureus

- RFs:
    - Extremes of age
    - Underlying lung disease, e.g. COPD
    - Underlying systemic disease: DM, CCF
    - Immunodeficiency
    - Asplenia
    - Recent / concurrent viral infection

Aspiration pneumonia

- Aspiration of gastric contents
- In patient unable to protect their airway
    - ⇓LOC
    - Stroke / abnormal gag reflex
    - Persistent vomiting
- Chemical +/- bacterial pneumonitis
- GI bacteria, can be multiple, predominantly aerobic, e.g. E.coli
- Necrotising, abscess formation

Contrast aspiration pneumonia to CAP

- CAP:
    - Viral / bacterial
    - Name bacteria
    - Variable response depending on host and infectious agent
    - Abs improve clinical course
    - Lower mortality
    - Complications:
        - Abscess
        - Empyema
        - Pericarditis, myocarditis, endocarditis
        - Meningitis
        - Septic emboli

Atypical pneumonia

- Interstitial rather than alveolar infiltration
- No consolidation
- Patchy inflammatory changes
- Moderate elevation WCC
- Different clinical symptoms
    - ⇓Cough / sputum
    - ⇑ fever, headache, myalgia
- Different organisms
- Lower mortality

Organisms:

- Virus (e.g. influenza, parainfluenza, RSV)
- Bacterial: mycoplasma, chalmydia, legionella, coxiella

Legionella

- Artificial aquatic environment
- Inhalation of aerosolized droplets
- Or aspiration of contaminated water

Dx Legionella

- Urinary antigen
- Sputum fluorescent Ab test
- Culture
- PCR

TB

Natural Hx of TB

Primary TB	Primary complex of localized caeseous necrosis + mediastinal LNs May heal (organisms not viable) or result in latent infection
Latent period	
OR Primary progressive	Rapid spread of TB including haemotogenously → miliary TB
Secondary TB	Reactivation of latent MTB, or reinfection Destructive caeseating lesions which may remain localized to the lungs or may be progressive and systemic (miliary TB)

Pathogenesis

- Aerborne droplet spread
- MTB enters alveoli macs and replicates
- Blocks phagosome-lysosome fusion so intracellular MTB not killed
- T4HS (T-cell mediated, delayed hypersensitivity) – death of macrophage and granuloma formation. Th1 cells, via MHC expressed antigen, release IFN + TNF which activate macs.
- Granuloma formed by recruitment of monocytes which become epithelioid histiocytes.
- Granuloma contains the MTB in anaerobic conditions
- Reinfection / reactivation → heightened immune reaction → tissue destruction

Virulence factors of MTB
- Escape macrophages
- Avoid death inside macrophages by inhibiting phagosome-lysosome fusion
- Induce T4HS at approx. 3 weeks → epithelioid cell granulomas
- Cord factor, LAM, complement activation

Secondary TB
- May directly follow primary infection, or follow a period of latency
- Caused by:
    - Reactivation
      Or
      - Reinfection

- Pulmonary features of secondary TB
    - **Apex** of upper lobe
    - **Inflammation** + granuloma + multinucleate giant cells
    - **Caesous necrosis**
    - **Cavitation**
    - Healing with **fibrosis + calcification**
    - Complications:

- Haemorrhage due to erosion of BVs
- Miliary spread
- Pleural effusion
- Empyema
- Meningitis

Diagnosis of TB

- **Clinical** features
- Apical lung lesion on **CXR**
- **Tuberculin skin test**
- **Microbiological**:
  - Acid-fast smears + cultures
  - PCR

ANAEMIA

Classification

Blood loss	Acute vs. chronic
⇑RBC destruction	Inherited: • Membrane: HS • Enzyme/metabolism: G6PD • Hb: sickle, thalassaemia Acquired: • Immune: autoimmune, alloimmune • Drug: dapsone • Infection: malaria • MAHA: DIC, valve, TTP • Toxic: envenomation
⇓RBC production	Inherited • Fanconi's aplastic anaemia Acquired • Infiltrative – leukaemia, myelofibrosis • Nutritional – B12 / folate • EPO deficit – renal disease • Drug induced aplasic anaemia

Fe Defic Anaemia

- Causes: **⇓intake, ⇓absorption, ⇑requirement, ⇑blood loss**
  - Chronic blood loss – menstrual / GI / hookworm
  - Poor PO intake – dietary
  - Poor absorption – coeliac, gastrectomy
  - Increased requirement – pregnancy, puberty
- Fe stores are depleted:
  - Ferritin

    - Haemosiderin
- Then serum iron + transferrin decreases
- Erythroid activity increases, RBCs become hypochromic + microcytic

Symptoms of Fe Defic anaemia

- Symptoms of anaemia
- Symptoms of blood loss
- Specific clinical signs:
    - Koilonychia
    - Alopecia
    - Glossitis
    - Oesophageal webs
    - Pica

Fe defic anaemia bloods

- Microcytic hypochromic anaemia
- ⇓Fe
- ⇓Ferritin
- ⇓Transferrin sat
- ⇑TIBC

Ethnic anaemias

HS	Northern Europe
Sickle	African
Thal	Mediterranean
Pernicious	Caucasian

Haemolytic anaemia classification

- Intravascular vs. extravascular
- Hereditary vs. acquired

Features of haemolytic anaemia

- ⇓RBC life span due to premature destruction (<120 days)
- ⇑EPO + erythropoiesis → reticulocytosis
- Accumilation of products of Hb breakdown (bilirubin)

INTRAvascular haemolysis

Mechanical injury	MAHA - Valves, TTP, DIC
Ig + complement fixation	ABO mismatched blood transfusion
Infectious	Malaria (intracellular parasitosis)
Toxins	Clostridia

Consequence of intravascular haemolysis

- Anaemia
- Haemoglobinaemia
- Haemoglobinuria
- Unconjugated hyperbilirubinaemia from catab of haem in phagocytes
- Haemosiderinuria + renal haemosiderosis
- ⇓Haptoglobin
- ⇑MetHb
- Reticulocytosis

PERNICIOUS ANAEMIA

Pathogenesis of PA

- Immune-mediated destruction of gastric mucosa
- → Chronic atrophic gastritis
- T-cell + autoantibody mediated
- ⇓Parietal cells → ⇓IF → ⇓B12 absorption in terminal ileum
- 3 types of Ab:
    - T1 – blocks B12 binding to IF
    - T2 – blocks B12-IF complex binding to ileal receptors
    - T3 – proton pump Ab

Clinical

- Slow as large stores of B12 in body
- Megaloblastic anaemia → symptoms of anaemia
- Leukopaenia, thrombocytopaenia
- Neurological: SCD, spastic paraparesis, optic atrophy
- Atrophic glossitis

HAEMOPHILIA A

- ⇓Factor 8
- Cofactor for F9 in activation of F10
- X-linked recessive
- Males + homozygous females
- 30% de novo mutation without FHx

Causes of bleeding

- Factor 8 part of intrinsic pathway
- Co-factor for F9 in activation of F10
- Causes inappropriate coagulation, and also inappropriate fibrinolysis
    - Failure to produce thrombin → ⇓TAFI (thombin activatable fibrinolysis inhibitor) → ⇑fibrinolysis.

<1%	Severe
2-5%	Moderate

6-50%	Mild

SICKLE CELL ANAEMIA

- Hereditary haemoglobinopathy
- Autosomal recessive
- Glumatic acid → valine on Ch 11
- ⇓Solubility of Hb → sickling when doxygenated

Pathological presentation:
- **Haemolytic** anaemia
- **Microvascular occlusion** → ischaemia
    - Painful crises
    - Tissue infarction
- Splenomegally + splenic infarct → **autosplenectomy**
- ⇑Susceptibility to infection by **encapsulated bacteria**

- Heterozygous – asymptomatic unless severe hypoxia
- Homozygous – most Hb is HbS, leads to alteration of Hb when deoxygenated → sickling and membrane changes

Sickling triggers:
- Hypoxia
- Acidosis
- Dehydration

THROMBOCYTOPAENIA

⇓Platelet production	• Congenital • Aplastic anaemia • Infiltrative BM disorders • Ineffective: megaloblastic • Drugs (ETOH) • Viral (measles, HIV)
⇑Platelet destruction	• Consumptive – DIC, TTP • Immune – ITP • Infective – HIV, CMV • Sequestration - splenomegally • Drugs - heparin • Dilutional - massive blood transfusion

Immune thrombocytopaenia
- **Primary: acute vs. chronic**
- **Secondary (e.g. heparin)**

Chronic ITP – adult females
- Formation of Abs against platelet membrane glycoproteins (2b-3a, or 1b-9)
- Opsonised platelets removed by phagocytes (mononuclear)

- Spleen major site of removal
- 80% improve after splenectomy (both site of destruction + site of auto-Ab synthesis)

Acute ATP – children

- Follows viral illness
- Abrupt onset
- Antiplatelet Abs
- Usually self-limiting with resolution in 6 months

VON WILLEBRAND DISEASE

Inherited bleeding disorder
Compound defect in platelet function + coagulation pathway (vWF + F8 complex)

Haem effects

- ⇑Bleeding time
- ⇑APTT (⇓F8 due to normal complex with vWF)
- ⇓Riscocetin cofactor activity

Clinical features

- Spontaneous bleeding from mucous membranes
- Wound bleeding
- Menorrhagia
- Bleeding into joints rare, severe types only

Types

T1	⇓ circulating vWF T1 – AD, common, mild
T3	⇓ circulating vWF T3 – AR, severe
T2	Defective vWF AD, mild

Why does it affect APTT

- vWF + F8 complex extends HL of F8 from 2.5 → 12hrs

BOWEL OBSTRUCTION

Causes of bowel obstruction:

- SBO:
    - Adhesions
    - Hernia
    - Intersussception
    - Strictures
- LBO:
    - Volvulus
    - CRC

Consequences of bowel obstruction

- Perforation
- Peritonitis
- Sepsis
- Bowel ischaemia
- Electrolyte disturbance
- Death

How does hernia cause bowel obstruction

- Hernia is a projection of a viscera through the walls of its containing cavity into an anatomically abnormal location
- **Weakness / defect in abdominal wall**
- **Protrusion of serosa-lined pouch of peritoneum** through defect (hernia sac)
- **Visceral protrusion** through sac
- **Entrapment** of hernia sac in narrow neck
- Venous stasis → oedema → incarceration + stangulation

CHOLERA

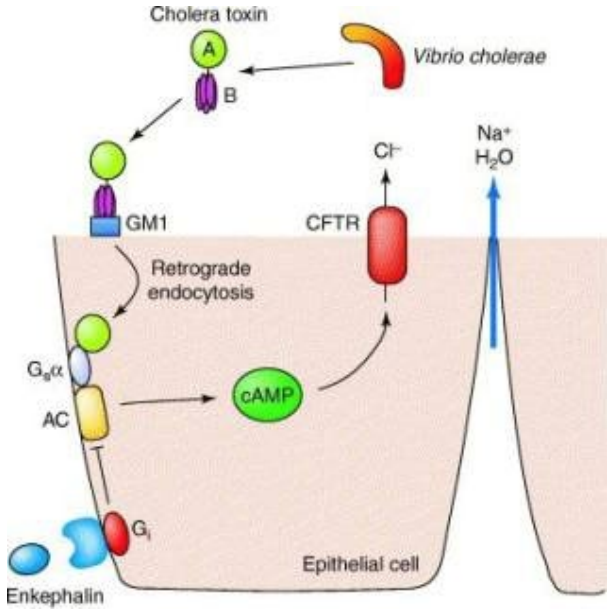
- Vibrio cholera
- Gram –ve
- Comma-shaped / flagellate

Pathogenesis of cholera

- Non-invasive
- Flagella proteins for attachment + colonization
- Cholera enterotoxin (exotoxin):
    - 5 x B subunits
    - 1 x A subunits

B subunit	Binds to intestinal epithelial cells Facilitates retrograde endocytosis
A subunit	In cytoplasm, activated Gs protein Adenyl cyclase → ⇑cAMP → opens CFTR Release of Cl^- into lumen, with secretion of HCO3, Na, H2O

	Massive secretory diarrhea which overwhelms colonic absorption **Rice water diarrhoea**



CHRONIC GASTRITIS

Causes of chronic gastritis

- H. pylori
- NSAIDS
- ETOH
- Autoimmune
- Radiation
- Stress

H. pylori induced gastritis

- Most common cause
- Gastric antrum
- Generates ammonia
- Distruption of mucosal defence mechanisms
- ⇑Gastric acid, ⇓gastrin

Complications of gastric ulcer

- Bleeding
- Perforation
- Obstruction
- Adenocarcinoma

H. PYLORI + PUD

- H. pylori secretes:
    - **Urease** – generates free ammonia
    - **Protease** – breaks down glycoproteins in gastric mucosa
    - **Phospholipases** – damages mucosal epithelial cells
    - **Bacterial platelet activating factor** – capillary thrombosis
- Damage of epithelium → leakage of tissue nutrients to sustain H. pylori
- ⇑**Gastric acid secretion,** ⇓**bicarbonate** secretions
- Induce **immune response** – T + B cell response

Complications of PUD

- Bleeding
- Perforation
- Obstruction: oedema / scarring, in pylorus, intractable vomitting

CROHNS

- Transmural inflammation of bowel
- Granulomatous (non-caseating)
- Anywhere mouth → anus
- Skip lesions
- Ulceration + fissures + fistulae

Complications of Crohns:

- Perforation
- Peritonitis
- Abscess / collection
- Stricture
- Fistula
- Malabsorption
- Neoplasia
- Extra-GI

Extra-intestinal features of Crohns

Joints	Polyarthropathy Ank spond Clubbing
Skin	EN, pyoderma gangrenosum
Eyes	Uveitis
Biliary	Sclerosing cholangitis
Systemic	Amyloidosis

ULCERATIVE COLITIS

Path features

- One of two pathologies that compose IBD
- Severe, ulcerating, inflammatory disease
- Confined to colon + rectum (backwash ileitis)
- Continuous (no skip lesion)
- Only involves mucosa + submucosa (not transmural)

- Superficial, broad-based ulcers
- Psudopolyps
- Crypt abscesses
- Megacolon
- Dysplasia → malignant potential

Extraintestinal manifestations (as for CD)

Features of carcinoma secondary to UC

- Multi-focal
- Infiltrative without exophytic masses

INFECTIVE GASTROENTERITIS

Viral	Norovirus Rotavirus Adenovirus
Bacterial	Preformed toxin: staph aureus, clostridium perfringens Toxic: cholera, enetrotoxic E.coli Invasive: enteroinvasive E.coli, shigella, salmonella
Parasites	Giardia, amoebiasis Helminths Cryptosporidium

Pseudomembranous colitis

- Overgrowth of C.diff
- A/w antibiotic use – distruption of normal bowel flora (normally 3rd gen cephalo)
- Toxins:
    - Disruption of epithelial cytoskeleton
    - Tight junction barrier loss
    - Cytokine release
    - Apoptosis
- Denudation of epithelium
- Dense inflammatory infiltration of lamina propria
- Mucopurulent exudate
- Pseudomembrane: adherent layer of inflammatory cells + debris at site of mucosal injury

- RFs:
    - Age
    - Abx treatment
    - Hospitalisation
    - Exposure

- Clinical features:
    - 30% hospitalized patients colonized, most asymptomatic
    - Watery diarrhoea
    - Fever + leukocytosis
    - Abdominal pain
    - Dehydration
- Dx: detection of toxin
- Rx: metronidazole + vanc

BOWEL ISCHAEMIA

What can cause bowel infarction?
- **Arterial obstruction**:
    - Atherosclerosis
    - Embolus
    - Aortic dissection / aneurysm → obstruction branch artery
    - Volvulus / hernia → mechanic compression
- **Venous occlusion**
    - Hypercoaguable state
    - Neoplasm
    - Abdominal mass
- **Non-occlusive ischaemia**:
    - Shock
    - High dose vasopressors
- **Vasculitis**
    - HSP
    - Wegeners

Acute transmural infarction
- Congestion
- Oedema + haemorrhage in wall
- Mucosal necrosis
- Gangrene
- Third spacing of fluid into lumen
- CVS: shock
- Metabolic: acidosis, electrolyte disturbance
- Perforation
- Death

Chronic bowel ischaemia
- Segmental, patchy, mucosal degeneration

- Strictures

Clinical presentation of infarction
- Severe **pain**
- Peritonitic abdomen
- Bloody diarrhea
- Raised lactate
- Sepsis
- Shock

Part of bowel must vulnerable to ischaemia
- **Watershed zones**
    - Splenic flexure
    - Sigmoid
- Located at end of arterial supply / transition area
- At epithelial level, villi more vulnerable than crypts as capillaries run upwards to villi

SALMONELLA

- Gram –ve bacillus
- Flagellated
- Eneterobactericea
- Food + water borne

Typhoid fever pathogenesis

- Caused by:
    - Salmonella typhi (endemic)
    - Salmonella paratyphi (travellers)
- Invades GI M-cells, then phagocytosed by macrophages
- Terminal ileum + colon
- I.e. invasive
- Reactive hyperplasia of GI lymphoid tissue
- Neural reflex pathway
- Haematogenous dissemination

Clinical:

- **Fever + rash + bloody diarrhea**
- Vomitting
- Anorexia
- Flu-like symptoms

ALCOHOLIC LIVER DISEASE

Path features

Hepatic steatosis	Fatty change Perivenular fibrosis
Hepatitis	Hepatocyte necrosis Inflammatory **Mallory bodies**
Cirrhosis	Fibrosis Hyperplastic nodules Nodular disruption of liver architecture
HCC	

- Steatosis + hepatitis are reversible

Acute alcoholic hepatitis
- Hepatocyte swelling + necrosis
- Mallory bodies: eosinophilic cytoplasmic inclusions
- Neutrophilic reaction
- Fibrosis: stimulation of sinusoidal stellate cells → fibroblastic change

Cirrhosis

Diffuse, largely irreversible	
Parenchymal nodules of regenerating hepatocytes	
Fibrous septa	Dense bands of fibrous tissue Laid down by sinusoidal stellate cells (activated by cytokines from Kuppfer cells, → shift to myofibroblast phenotype) Collagen 1 + 3
Global disorganization of liver architecture	
P-S shunting	Reorganisation of vascular architecture → portosystemic shunting

Sequalae of cirrhosis:
- Failure of synthetic function: ⇓albumin, ⇓clotting factors
- Portal HTN: varicies, ascites, GI bleed
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Encephalopathy / coma
- Infection

CIRRHOSIS

Causes of cirrhosis

- Alcoholic
- Infectious: HBV, HCV
- Biliary disease: PBC, PSC
- Autoimmune
- Metabolic: Wilson's, HH, α1-AT defic
- Drug induced: α-methyldopa
- CCF → congestive cirrhosis

CHOLECYSTITIS

Pathogenesis of acute calculous cholecystitis

- **Chemical irritation of obstructed GB**
- Protective glycoprotein layer lost
- Obstruction by stone → dysmotility → stasis
- Damage to membrane by:
    - Bile salts detergent action
    - Toxic lysolethicins
    - Activation of hydrolases
    - PGs → inflammation
- ⇓ Mucosal blood flow (due to distension + ⇑intraluminal pressure)

Acalculous (10%)

- Rarer, slower/more insidious, may have no GB symptoms
- Ischaemia of end artery
- Stasis, local inflammation, distension
- Predisposing:
    - Major surgery
    - Sepsis
    - Shock
    - Trauma
    - Immunosupression

Clinical pres:

- RUQ pain
- Fever
- Vomitting
- Anorexia
- Features of sepsis: tachy, sweating

Complications of cholecystitis

- **Bacterial infection → cholangitis / sepsis**
- Empyema

- Perforation + collection/abscess
- Biliary fistula
- Porcelain gallbladder

GALLSTONES

RFs for cholesterol stones
- Age
- Gender – W>M
- OCP / Pregnancy:
    - ⇑Hepatic lipoprotein receptors → ⇑cholesterol uptake
    - ⇑HMG-CoA reductase → ⇑cholesterol synthesis
- Acquired disorders → gallbladder stasis
- Genetic disorders: ABC transporters

Pathogenesis of cholesterol stone formation
- Requires simultaneous conditions:

Bile supersaturated with cholesterol	
GB hypomotility	
Cholesterol crystal nucleation	
Hypersecretion of mucus	Traps cholesterol crystals → aggregation into stones

HEPATITIS A

- ssRNA
- Picornavirus
- Unenveloped
- Icosahedral capsid

- Faeco-oral spread

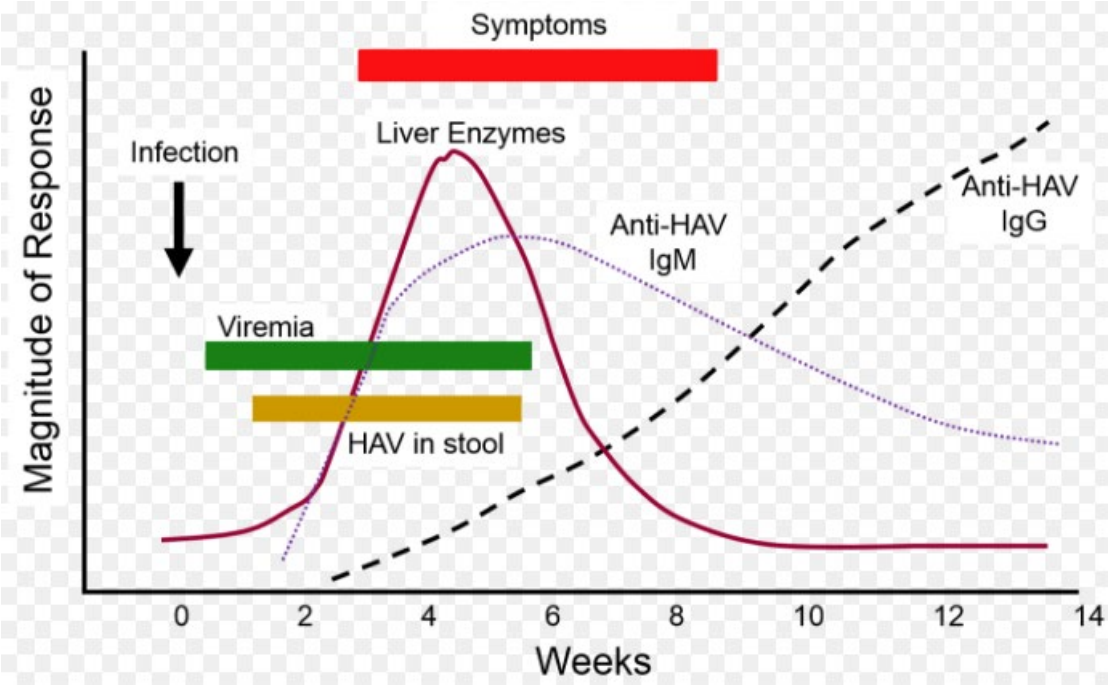
Clinical differences to HBV
- **Self-limiting**
- **No carrier** state
- **No chronic** state
- **No cirrhosis / HCC**
- Small incidence of fulminant hepatitis – 0.1% fatality

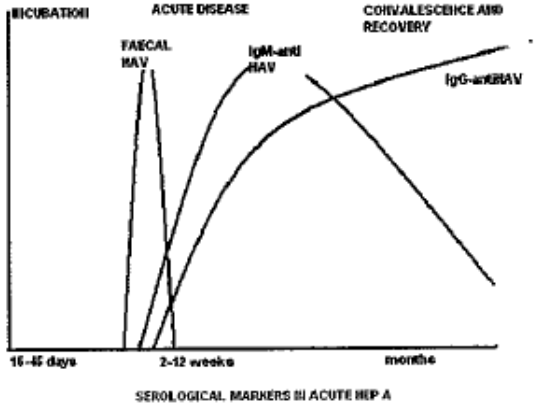
Natural Hx
- Faecal-oral transmission
- **Incubation** period **2-6 weeks**
- More likely to be **asymptomatic** in children
- **Prodrome (pre-ictal)**:
    - N&V
    - Diarrhoea
    - Malaise
    - Fever

- **Jaundice (ictal)**:
    - After 1-2 weeks
    - Hepatomegaly (± splenomegaly)
    - Dark urine, pale stools
- Small incidence of **fulminant hepatitis** – 0.1% fatality
- No chronic or carrier state

Serological diagnosis

- Incubation 2-6 weeks
- Acute rise in fecal HAV shedding – 2-12 weeks
- Acute: IgM anti-HAV
    - As IgM titre rises, fecal shedding stops
- Chronic: IgG anti-HAV
    - Begins to appear shortly after IgM
    - Elevates over months, lasts years





SEROLOGICAL MARKERS IN ACUTE HEP A

They like a graph

HEPATITIS B

dsDNA
Enveloped
Hepadnarviridae

Serology

HBsAg positive – indicates current infection.
Anti-HBc total positive – exposure to HBV. IgM anti-HBc negative – exposure not acute or recent.
Anti-HBs negative – no current immunity to HBV. Diagnosis: Chronic Hepatitis B.

Acute Hep B serology

- **HBsAg**
- **HBeAg**
- HBV DNA
- **Anti-HBcAg IgM**
- *NOT anti-HBsAg*

Chronic Hep B serology

- HBsAg > 6months
- Active replication: HBeAg, HBV DNA
- Anti-HBcAg
- *NOT anti-HBsAg*

Transmission

- Congential – vertical transmission
- Parentral blood:
    - Blood products
    - IVDU
    - Needlestick
- Sexual
- Unknown

Outcomes:

65% acute is subclinical – complete recovery
25% acute symptomatic (<1% fulminant)
10% healthy carrier
10% will become chronic
    - 70% of chronic will recover
    - 30% of chronic will cirrhosis
    - 3% of chronic will HCC

HEPATITIS C

- ssRNA
- Enveloped
- Flaviviridae

Risk factors

- **IVDU**
- **Multiple sex partners**
- Surgery
- Needle stick
- Multiple contact with HCV infected person
- Vertical
- Unknown

Natural Hx:

- Incubation: **2-26 weeks**
- Acute infection asymptomatic in 85%
    - Otherwise usually mild acute disease
    - Rare fulminant hepatitis
    - 15% complete resolution without chronic infection
- HCV RNA detectable at 1-3 weeks
- Persistent infection → chronic hepatitis: >80%
    - Cirrhosis – 30%
    - HCC

Serology

- **HCV RNA**
    - **Appears at 1-3 weeks**
    - Coincides with transaminitis
- IgM then IgG anti-HCV Abs
    - Only 50% have Abs detectable during acute infection

Features making vaccination difficult

Antigenic variability	Highly stable core, extremely **variable envelope**
Genetic variability	Multiple quasispecies due to **RNA pol** mutation

- HCV also able to inhibit IFN-mediated cellular response

HEPATITIS D

- ssRNA
- **Must always be in conjunction with Hep B infection**
    - HBsAg provides a capsule
- Complete virion consists of:
    - HBsAg outer coat
    - Internal HD Ag polypeptide + circular ssRNA

Acute infection	Exposure to both HBV + HDV Indistinguishable from acute HBV infection HBV must establish first to provide HBsAg needed for development of complete HDV virions
Superinfection	Chronic HBV carrier exposed to new inoculation of HDV Disease develops approx. 1 month later

Manifestation of superinfection

- Severe acute hepatitis in previously unrecognized HBV carrier
  Or
- Exacerbation of previously mild chronic HepB

- 90% of HDV superinfection goes to chronic infection

HDV diagnosis

- **HDV RNA**
    - Appears early
- **IgM anti-HDV**
    - Most reliable marker of recent infection
    - But appears late and is short-lived
- Co-infection: IgG against both HDAg + HBcAg

INFECTIVE ACUTE HEPATITIS

Clinical picture:

- **Acute asymptomatic with recovery**

- **Acute symptomatic:**
    1. Incubation
    2. Symptomatic pre-icteric
    3. Symptomatic icteric
    4. Convalescence

    - Symptomatic pre-icteric:
        - Constitutional – fever, myalgia
        - Liver symptoms (tender hepatomegaly)
        - **Serum sickness** 10%

    - Symptomatic icteric:
        - **Conjugated** hyperbilirubinaemia

- Recovery
    - Weeks – months
    - T-cell response (CD4, CD8)

- **Fulminant hepatitis:**
    - Over 2-3 weeks
    - **Encephalopathy**
    - **Coagulopathy**
    - **ARDS**
    - **Hepatorenal failure**
    - Usually HAV / HBV
    - No stigmata of chronic liver disease

- **Chronic hepatitis:**
    - **> 6 months** of:
        - Symptoms
        - Biochemical
        - Serological
    - Variable course to:
        - Cirrhosis
        - Liver failure
        - HCC

Path of acute hepatitis:

1) Inflammation + necrosis/apoptosis
- **Enlarged red liver**
- **Ballooning** degeneration
- Hepatocellular **necrosis**
- **Bridging necrosis**
- **Cholestasis**

2) **Regeneration**
- Hepatocyte proliferation
- Monocyte infiltration, **Kuppfer cell uptake of debris**

JAUNDICE

Unconjugated	⇑ Bilirubin • Haemolysis ⇓Hepatic uptake of bilirubin • Drug interference • Gilbert's ⇓Conjugation (⇓UGTA1 activity) • Gilbert's • Crigler-Najar • Physiological jaundice of newborn • Hepatitis • Cirrhosis
Conjugated	⇓Canalicular membrane transporters • Rotor syndrome • Dubin-Johnson ⇓Bile flow • Intrahepatic / extrahepatic biliary duct obstruction

Features of liver failure

- Jaundice
- Pruritis
- Ascites
- Bruising
- Spider nevi
- Gynaecomastia
- Hypogonadism
- Palmar erythema
- Caput medusa
- Hepatorenal, hepatopulmonary

Bilirubin metabolism:

- Catabolism of haem from senescent RBCs
- Transported to liver bound to serum albumin
- Hepatocellular uptake
- Glucuronidation (UGTA1) – bilirubin digluconuride excreted in bile
- Gut deconjugation → colourless urobilinogens → excreted in faeces
- 20% GI urobilinogen is reabsorbed in the ileum + colon + returned to the liver, some of which is then excreted in urine

ACUTE LIVER FAILURE

Causes of acute liver failure

- Infection (mainly A + B)
- Toxins
    - Paracetamol
    - Halothane
    - Rifampicin
    - Mushrooms

Hepatorenal failure

- Renal failure in a person with severe liver failure
- No intrinsic reason of renal failure
- Characterised by:
    - Renal vasoconstriction
    - ⇓Renal perfusion + GFR
    - Na retention
    - Impaired water excretion
- Reversible but represents poor prognosis

PANCREATITIS

Causes

- Gallstones
- ETOH
    - These 2 represent 80% of acute pancreatitis
- ⇑Ca
- ⇑Lipids
- Drugs (e.g. azathioprine)
- Poisons
- Trauma
- Shock
- Infectious (e.g. mumps)
- Iatrogenic (ERCP)

Pathogenesis of acute pancreatitis

- Autodigestion of pancreatic parenchyma
- By inappropriately activated pancreatic enzymes
- Trypsin activation is integral
    - Subsequently activates proelastin, prokallikrien, Hageman factor
- →
    - Interstitial **inflammation**
    - **Oedema**
    - **Haemorrhage**
    - **Fat necrosis**

Causes of inappropriate activation of digestive enzymes

Pancreatic duct obstruction	Accumilation of lipase in interstitium Local fat necrosis Release of proinflammatory cytokines Acute inflammation + ischaemia
Primary acinar cell injury	Drugs / toxins / ischaemia
Defective transport of proenzymes in acinar cells	Release of activated enzymes

Cellular morphology

- **Inflammation** + microvascular leakage
- **Oedema**
- **Necrosis**
- **Haemorrhage**
- **Lipolysis**
- **Proteolysis of parenchyma**
- **FFA + Ca → salts → precipitate**
- **Fat necrosis**

- Peritoneal fluid
- Extra-pancreatic fat necrosis (e.g. omentum)

Consequences

- Third space losses
- Shock
- Multi-organ failure
    - ARDS
    - Acute renal tubular necrosis
    - DIC

Lab findings acute pancreatitis

- ⇑Amylase, first 24hrs
- ⇑Lipase, first 3-4 days
- Glycosuria
- ⇓Ca (poor prognosis)
- Leukocytosis
- AKI

CHRONIC PANCREATITIS

Morphological features

- Parenchymal **fibrosis**
- **Calcification**
- **⇓Size + number of acini → ⇓exocrine secretions**
- Relative sparing of **islets** of Langerhans, but may ⇓ in late disease
- **Dilation +/- blockage of pancreatic ducts**

Clinical

- **Irreversible** impairment of pancreatic function
- **Endocrine**: diabetes
- **Exocrine**:
    - Steatorrhoea
    - ⇓ADEK
    - Malabsorption
- **Pseudocyst** formation
- Chronic **pain**
- Poor long-term prognosis

PORTAL HYPERTENSION

Prehepatic	Portal vein thrombosis
Hepatic	Cirrhosis Massive steatosis Schistosomiasis Granulomatous disease
Post-hepatic	Budd-Chiari Severe RHF Constrictive pericarditis

Consequences of portal HTN

- Ascites
- SBP
- Porto-systemic shunting: varicies, haemorrhoids
- Congestive splenomegaly: TCP / pancytopaenia
- Hepatic encephalopathy

Mechanism of ascites

- Starling's forces in sinusoids:
    - ⇑Hydrostatic pressure
    - ⇓Albumin
- ⇑ Formation of hepatic lymph
    - Exceeds capacity of thoracic duct so percolates into peritoneum
- Secondary hyperaldosteronism → ⇑renal conservation of Na + H2O

ACUTE KIDNEY INJURY (AKI)

- Acute ⇓ **renal function**
- Normally **reversible**
- Usually due to **tubular injury**

Causes

Pre-renal	⇓Perfusion

Intrinsic renal	• **ATN**
	  ○ **Ischaemic**
	  ▪ Systemic: shock, thrombosis (HUS, TTP, DIC)
	  ▪ Intrarenal: vasculitis
	  ▪ Intracapsular tamponade
	  ○ **Toxic**:
	  ▪ Myoglobin
	  ▪ Drugs / contrast
	  ▪ Crystals
	• **Acute TIN**
	  ○ Hypersensitivity reaction to drugs

Post-renal	• **Post-renal obstruction:** ○ Tumour, clot, stones

Phases of AKI

Initiation (<36hr)	⇓UO ⇑Urea
Maintenance	⇓UO Na + H2O retention ⇑Urea ⇑K Metabolic acidosis
Recovery	⇑UO Na + H2O loss ⇓K ⇑Risk of infection

RENAL FUNCTION

***Renal blood flow (RBF) = 1200 ml/min (25% of CO)**
***Glomerular filtration rate (GFR) = 125 ml/min (10% of renal perfusion)**
***Filtration fraction = 0.16-0.20**
***Urine flow = 1.5 ml/min**
***Max H2O resoprtion – 99.7% of filtered load**
***Max urine osmolarity – 1400mosm**
***Maximal urine flow is 16mL/min (normal 1.5ml/min)**

GFR is ⇓ by:

- **AT2**
- **Vasopressin**
- **Noradrenaline**
- **Hypotension**

GFR is ⇑ by:

- **Dopamine**
- **ACh**
- **ANP**
- **Bradykinin**
- **High protein diet**

NEPHROTIC SYNDROME

Features

- Massive proteinuria (>3.5g/day)
- Hypoalbuminaemia (plasma protein < 30g/L)
- Generalised oedema
- Hyperlipidaemia + lipiduria
- Hypercoaguability
- ⇑Susceptibility to infection

Mechanisms:

- Alteration in **glomerular capillary** / **epithelial walls**:
  - **Structural** damage vs. **physiochemical** changes
  - → ⇑**permeability** to protein
- **Hypoalbuminaemia**, due to:
  - Renal protein loss
  - ⇑Renal protein catabolism
  - ⇓Hepatic synthesis
- **Oedema**, due to:
  - Loss of colloid osmotic pressure (Starling's law)
  - ⇑Na + H20 retention due to activation of RAAS
- ⇑**Serum lipids**
  - ⇑Synthesis
  - ⇓Catabolism

Mechanism of oedema

- **Starling's Forces**
  - ⇓Serum albumin → ⇓colloid osmotic pressure
- **Accumulation of Na + H2O in tissues**
  - Due to activation of R-A-A by:
    - Hypovolaemia
    - ⇑ADH
    - ⇑Sympathetic drive

Causes of nephrotic syndrome

Primary glomerular nephritis (GN) (95% children, 60% adults)	Children: minimal change Adults: membranous, FSGS
Systemic (mostly adults)	DM Amyloid SLE Drugs (NSAIDs, heroin) Infection (e.g. hepatitis viruses)

POST-STEPTOCOCCAL GN

Pathogenesis

- GAS (β-haemolytic) – types 12, 4, 1 (with cell wall M protein)
- Post pharyngeal / skin infection (impetigo / scarlet fever)
- Immunologically mediated, T3HS
- Ab-Ag complex forms over 1-4 weeks
- Granular immune deposits in the glomeruli (IgG + C3) – esp GBM
- Complement activation
- → **Acute proliferative GN**
- ⇑Titres of antistreptococcal Ab

Post-step GN is an **acute proliferative GN**

Clinical

- **1-2 weeks post** streptococcal infection
- Constitutional symptoms: **malaise, fever**
- **Nephritic** picture
    - Haematuria
    - Red cell casts
    - Mild proteinuria
    - Periorbital oedema
    - HTN
- 95% recover within 3 weeks
- 4% chronic
- 1% severe acute renal failure (rapidly progressive GN)

- **In adults the clinical course is less benign – 60% full recover (vs. 95%)**
- In the remainder:
    - Slow resolution
    - Chronic GN
    - Rapidly progressive GN

Bloods:
- Depleted C3
- Strep Ags

PRE-ECLAMPSIA

Path
- **Placental ischaemia**
- Endothelial dysfunction
- Vasoconstriction
    - ⇓PGI2, PGE2
    - ⇑Renin-AT
    - ⇑TXA2
- ⇑Vascular permeability → proteinuria + oedema
- Systemic HTN + DIC

Clinical course
- Has to be >20/40, normally >32/40
- Oedema + proteinuria
- Headache + visual changes
- Exclampsia: convulsions + coma

Changes at a placental level
- **Villous hypovascularity**
- **Villous ischaemia**
- **Placental infarcts**
- Fibrinoid necrosis
- Retroplacental haematoma
- Prominent syncytial knots
- Thickened trophoblastic BM

PYELONEPHRITIS

Organisms

- Gram –ve bacillus
    - E. coli
    - Proteus
    - Klebsiella
    - Enterobacter
    - Strep faecalis
- Other:
    - Staph
    - Fungal

Ascending infection of urinary tract

- Colonisation of distal urethra
- Entry into bladder
- Urinary tract obstruction / stasis of urine
- Vesicoureteric reflux
- Intrarenal reflux

Predisposing factors to acute pyelonephritis

- Females < 50
- Males > 50yrs
- DM / immunosuppression
- Pregnancy
- Urinary tract obstruction
- Instrumentation
- Vesico-ureteric reflux

Chronic pyelonephritis

- Chronic **reflux** or **obstruction** → pelvocalyceal damage
- Recurrent infection → recurrent renal inflammation → scarring

URINARY TRACT OBSTRUCTION

Congenital	PUJ narrowing Urethral strictures Bladder neck narrowing
Acquired	Calculi Tumours (TCC) Blood clots Prostatic enlargement Inflammation: urethritis, prostatitis Retroperitoneal fibrosis Sloughed papilla Gynae: uterine prolapse Functional: neurogenic bladder

Consequences

- **⇓GFR**
- Progressive dilation upstream of obstruction: ureter, pelvis, calyces (hydronephrosis)
- Blunting of the apices of the pyramids
- Enlargement of kidney
- Renal parenchymal atrophy
- End result: large, thin-walled, non-function cystic kidney.

Acute obstruction

- Pain:
    - Distension
    - Sx of underlying pathology (e.g. calculi)
- LUTS: polyuria, nocturia, dribbling
- Asymptomatic
- AKI (bilateral obstruction)

Clinical consequences of acute obstruction

- Infection
- Stone formation
- Hydronephrosis → obstructive nephropathy → renal failure
- Complications of renal failure

RENAL STONES

Types

Ca oxalate	70%
Ca phosphate	
Struvite (triple phosphate)	20%
Uric acid	
Cysteine	
Xanthine	

Calcium oxalate

- **Idiopathic hypercalcuria**
- **Secondary hypercalcaemia + hypercalcuria**
    - ⇑PTH
    - Bone disease
    - Sarcoid
- **Hyperoxaluria**
    - Primary
    - Enteric

Magnesium, ammonium phosphate (struvite)

- Urea splitting organisms (e.g. proteus) → alkaline urine

Urate

- ⇑Cellular turnover

What conditions favour stone formation

- ⇑Ca (e.g. loop diuretic)
- Acid or alkaline
- Bacteria
- ⇓Urine volume
- Anatomic variants: e.g. horseshoe kidney, polycystic
- Metabolic conditions; inherited or acquired

Complications

- Obstructive nephropathy
- Infection
- Pain
- Haematuria

DIABETES

Complications of diabetes

Macrovascular	Atherosclerosis CAD, PVD, RAS Aneurysm Stroke Hyaline arteriosclerosis → stroke
Microvascular	Nephropathy Neuropathy Retinopathy, cateracts, glaucoma Cerebral small vessel disease (Thickened BM, ⇑permeability of vessles to plasma proteins)
Metabolic	DKA HHS Hypoglycaemia
Cutaneous	Ulcers Necrobiosis lipoidica
Infections	⇑susceptibility to infections

Pancreatic changes:

- Loss of islet cells
- Amyloid infiltrates

Renal changes:

- BM thickening
- Mesangial sclerosis
- Glomerulosclerosis
- Nodular = Kimmelsteil-Wilson nodules
- Nephrotic syndrome
- RAS
- Pyelonephritis

Occular:

- Proliferative vs. non-proliferative
- Microaneurysms
- Exudates
- Neovascularisation → retinal + vitreous haemorrhage
- Detatchment
- Cataracts

- Glaucoma

T1 vs. T2DM

DMT1	DMT2
Childhood / young adulthood	Adult
Not overweight	Overweight
⇓Insulin	⇑/N/⇓ insulin
Islet Abs	No Abs
T4HS	T2HS
Polyuria, polydipsia, DKA	HHS
HLA-linked	Stronger genetic, but not HLA
Abrupt onset, exhaustion of B cell reserve (may be ppt by infection ⇑demand on panc)	More insidious onset

Pathogenesis DKA

- Insulin deficiency + glucagon excess
- → ⇑gluconeogenesis, ⇓peripheral utilization of glucose
- → severe hyperglycaemia

- Hyperglycaemia → osmotic diuresis → dehydration

- ⇓Insulin → ⇑lipolysis → FFA
- FFA → ketone bodies in liver
- Rate of ketone production > ketone utilization → ketonaemia
- ⇑Ketones → metabolic acidosis

Aetiology of DMT1
- Genetic predisposition (HLA-linked)
- Precipitating event
- Autoimmune destruction of islet cells
    - T-cell mediated + auto-antibodies
    - Possible molecular mimicracy
- B cell destruction → ⇓cell mass, ⇓insulin
- Hyperglycaemia
- Subclinical → overt DM

Environmental factors contributing to DMT1
- Infection: EBV, mumps, measles
    - May induce inflammation and release of islet antibodies
    - OR molecular mimicracy
- ? Cows milk exposure < 4 months old
- Drugs - pentamidine

Genetics of T1DM
- **MHC 2 (HLA)** – HLA-DR3, DR4
- **DQB1*0302 allele**
- **Insulin gene mutations**

Pathogenesis of T2DM

1. **Insulin resistance**
2. **Quantative + qualitative B cell dysfunction**

- **Insulin resistance**
  - ⇓Response of peripheral tissues to secreted insulin
  - ⇓Receptors or ⇓post-receptor downstream signalling
  - Genetic predisposition + lifestyle (obesity)

- **Quantitative + qualitative B cell dysfunction**
  - Initial B cell hyperplasia → ⇑inslin → compensation for resistance
  - Subsequent failure of sufficient insulin secretion → inadequate insulin secretion in context of resistance
  - Genetic predisposition to β cell failure
  - Mechanism: ⇓glucose sensing, cellular overstimulation

RFs for T2DM

- **Strong genetic but not HLA**, 80% concordance
- **Obesity**

Complications of sustained hyperglycaemia

- Osmotic diuresis:
  - Dehydration
  - Hypercoaguability
- Electrolyte disturbance
  - Na, K, Phos
- Hyperosmolarity
  - Altered LOC

GRAVE'S DISEASE

Clinical

- Hyperthyroidism
- Goitre
- Infiltrative eye disease
- Infiltrative dermopathy

Pathogenesis

- Auto-immune:
  - TSH-receptor stimulating Abs
  - IgG mimics TSH
  - Anti-TPO, anti-thyroglobulin

T2HS – PIC'D: phagocytosis, inflammation, cytotoxicity, dysfunction

THYROTOXICOSIS

- **Hypermetabolic state** caused by ⇑T4, ⇑T3

Cardiac	Tachycardia Arrhythmia Angina High output cardiac failure
Neuromusc	Proximal myopathy, tremor
Occular	Proptosis, lid lag
CNS	Anxiety, insomnia Heat intolerance
Skin	Warm, flushed, ⇑sweating
Thyroid storm	Fever, tachycardia, arrhythmia Can be fatal

- **Causes of thyrotoxicosis**
  - **Graves**
  - **TMNG**
  - **Toxic adenoma / carcinoma**
  - **Neonatal from maternal Graves**

PITUITARY ADENOMAs

Types
- Classified according to hormone type
- Basophils: FSH, LH, ACTH, TSH
- Acidophils: GH, Prolactin
- Functioning vs. non-functioning adenomas

Clinical syndromes

Prolactin	Galactorrhoea Amenorrhoea Infertility Loss of libido
Somatotroph	Giantism Acromegally
ACTH	Cushing's
Gonadotroph	Hypogonadism (lethargy, loss of libido)

General**:**
- **Mass effect**
  - Headache
  - Bitemporal hemianopia
  - Diplopia
- **Pituitary apoplexy**

FRACTURE HEALING

Classification of fractures

- Complete / incomplete
- Open / closed
- Comminuted
- Diplaced
- Angulated
- NV compromised
- Pathologic

Fracture healing

Haematoma	*Immediate – hours* Fills fracture gap Provides fibrin mesh framework
Influx	*Days* Inflammatory cells Fibroblasts Osteoprogenitor cells Angiogenesis
Procallus	Haematoma organizing → procallus
Fibrocartilaginous callus	Mesenchymal cells + cartilage cells along fracture line
Ossification	*2-3 weeks* Activation of osteoprogenitor cells Procallus → boney callus (woven bone)
Remodelling	*6 weeks* Callus matures, remodelling

Remodelling:

- Initial large volume of callus
- Portions not physically stressed are resorbed, reducing callus size

Factors impeding fracture healing

- Inadequate immobilization
- Inadequate alignment
- Vascular insufficiency
- Infection
- FB
- Systemic factors:
    - Smoking
    - DM
    - Nutritional

GOUT

Hyperuricaemia

Primary gout 90%	Usually idiopathic Overproduction – diet, unknown enzyme deficiencies Reduced excretion / filtration
Secondary gout 10%	Increased cell turnover: leukaemia, TLS Psoriasis Inborn errors of metabolism (⇑production) ▪ HGPRT deficiency ▪ Lesch-Nyhan syndrome CKD (⇓excretion)

Pathogenesis of gout

- Purine metabolism → urate
- Hyperuricaemia
- PPT of urate crystals into joints – synovium, cartilage
- Release of crystals into the synovial fluid (? following trauma precipitant)
- Supersaturation of urate in synovial fluid
- Intense inflammatory response
    - Phagocytosis of crystals by macs / neuts
    - Release of inflammatory by macs + neuts
    - → further chemotactic stimuli for inflammatory cells
    - Mediators:
        - ILs
        - Lysosomal enzymes
        - LTs
        - PGs
        - O2 free rads
- Acute arthritis:
    - Intense acute inflammation
    - Cartilage + joint damage

Causes for hyperuricaemia → primary gout

- Age
- Genetic predisposition
- ETOH
- Obesity
- Drugs e.g. thiazides
- Duration of hypercalcuria

Path features of gout

- **Acute** arthritis – *see description of pathogenesis above*
- **Chronic** arthritis
- **Tophi** in synovial membrane and periarticular tissue
- **Nephropathy** (deposition of urate crystals in kidney)
- Urate **stones**

OSTEOARTHRITIS

RFs

Genetic + mechanical

- Age
- Gender
- Obesity, DM
- Joint:
    - Congenitally abnormal joints
    - Injury

Pathogenesis

Chondrocyte injury	
Chondrocyte proliferation **Secretion of ECM** **Secretion of inflammatory mediators**	Inflammatory mediators Collagens Proteoglycans Proteases
Loss of chondrocytes & loss of cartilage	Chronic inflammation / ongoing injury → chondrocyte drop-out Dislodged cartilage into joint space
Loss of proteoglycans	
Subchondral bone change	Fibrillation, subchondral cysts Eburnation Osteophytes

Clinical

- Deep achey pain, morning stiffness, worse with use, crepitus, ⇓ROM
- Oligoarthritis in 95%
- Women: hands and knees
- Men: hips
- Osteophytes @ spinal foramina → radiculopathy → pain, neuro symptoms, atrophy

OSTEOMYELITIS

Pathogenesis acute OM

- Haematogenous spread of organism to bone
- Extension from contiguous site
- Local bone injury with direct organism entry

- **Acute inflammation** (neutrophils)
- **Abscess** (subperiosteal vs. surrounding soft tissue)
- **Necrosis** (dead bone forms **sequestrum**)
    - May be a draining sinus from sequestrum
- **Regeneration** (**involecrum** forms from stripped periosteum by reactive bone deposition, around the sequestrum)

- XR: lytic focus surrounded by zone of necrosis → lifting of periosteum

Organisms

- **Staph aureus (>80%)**
- **E. coli**
- **Salmonella**
- Klebsiella
- Pseudomonas
- GBS (neonates)
- Fungal

Outcomes
- **Resolution**
- **Deformity + bone destruction**
- **Chronic inflammation** (25%)
    - Acute fair ups
    - Pathological fractures
    - Septic emboli – e.g. SBE
    - Sepsis
    - Amyloidosis
    - SCC in draining sinus tracts
    - Sarcoma of bone

RFs
- Immunosupression:
    - HIV
    - DMs
    - Steroids
- Trauma
- Joint surgery / prosthesis
- IVDU

RHEUMATOID ARTHRITIS

Pathogenesis

- Exposure of genetically susceptible host to an antigen resulting in chronic inflammation
- Autoimmune, T4HS
- Mediated by Th cells + inflammatory mediators
- → Progressive joint disruption

Genetic susceptibility	HLA-DRB1
Environomental arthritogens	? Microbial
Autoimmunity	Autoimmune T4HS Th-cell mediated

Morphology of joint lesion

- **Hyperplasia of synovium** → pannus formation
- Perivascular inflammatory cell infiltrate:
  - Neutrophils
  - Macrophages
  - CD4 Th cells
  - Plasma cells
- Angiogenesis
- Pannus invades the joint cartilage
- Osteoclastic action → juxta-articular boney erosions
- Pannus spans the joint space → fibrous ankylosis
- Ossification of panus → boney ankylosis

Extra-articular manifestations

- **Rheumatoid nodules**
  - 25% - often forearm / elbow
- **Fibrinoid necrosis**
  - Epitheloid cells, macrophages
- **Vasculitis**
  - Mononeuritis multiplex
  - Digital ulcers / nail bed infarcts
- **Dermatological** - PG
- **CKD**
- **Felty's syndrome – splenomegaly + neutropaenia**

Long term

- Joint destruction
- CKD
- ⇑CVS

BERRY ANEURYSMS

Location

- **90% near major arterial branch points**
- **Ant cerebral artery**
- **Acom**
- Multiple in 20-30%

Morphology

- Thickened hyalinised intima
- Thinned media
- Normal adventitia

RFs for rupture

- **Size (>1cm = 50% rupture / year)**
- ⇑**ICP** (straining, orgasm)

Natural Hx of SAH

- Thunderclap headache, +/- LOC
- **Up to 50% mortality at time of bleed**
- **Re-bleeding**
- **Vasospasm** → secondary ischaemic injury
- **Hydrocephalus** (communicating vs. non-communicating)

Sequalae of SAH

- Vasospasm → ischaemic stroke
- Fibrosis + scarring → communicating / non-commuicating hydrocephalus
- Death

CEREBRAL INFARCTION

Causes of infarction

- **Global** cerebral ischemia – general ⇓ cerebral perfusion e.g. shock
- **Focal** cerebral ischemia (localized):
    - Arterial **thrombosis** (usually secondary to atherosclerosis)
    - **Arteriosclerosis** → lacunar infarcts
    - **Embolic** (thrombus / fat / air – name sites of thromboembolism)
    - **Vasculitis** (e.g. PAN, giant cell, infectious vasculitis [CMV, syphilis])
    - **Dissection**
    - **Vasospasm** (e.g. amphetamine / cocaine)
    - **Venous obstruction** (e.g. hanging)

Arterial obstruction

- **Atherosclerosis**
- **Thrombosis**
- **Embolism**

Venous obstruction

Other:

- **Dissection**
- **Aneurysm**
- **Vasculitis**
- **External compression**

Sources of arterial thromboembolism

- L atrium
- L ventricle
- Valvular vegitations
- Carotids (bifurcation)
- Venous system via PFO (paradoxical embolus)

Place of embolism impaction

- Lodges in **MCA**
- Usually impacts at **branch point**
- Causes ischaemia

Haemorrhagic vs. non-haemorrhagic ischaemia

Haemorrhagic	Non-haemorrhagic
Red Normally follows **embolic** events Multiple **petechial haemorrhages** which can be confluent Due to **reperfusion**	**Pale** Usually a/w **thrombosis**

Thrombolysis

- Attempts to **reverse injury in ischaemic penumbra**
- Earlier treatment leads to better outcome and less risk of haemorrhagic transformation
- Complications of thrombolysis higher with embolic / haemorrhagic CVAs

Effects of HTN in the brain:

1. **Lacunar** infarcts
2. **Slit haemorrhages**
3. Massive **ICH** (deep)
4. **HTN encephalopathy**

CEREBRAL OEDEMA

Vasogenic	BBB disruption → ⇑ vascular permeability Fluid shift intravascular → interstitial Generalised vs. localised
Cytotoxic	⇑ Intracellular fluid due to cellular injury Neuronal / glial cell injury E.g. generalized hypoxic / ischaemic insult
Hydrocephalus / interstitial	Interstitial oedema around lateral ventricles with hydrocephalus due to ⇑ hydrostatic pressure

Generalised cerebral oedema

- Flattened gyri
- Narrowing of sulci
- Compression of ventricles
- Herniation syndromes

Herniation syndromes

Subfalcine	Displacement of cingulate gyrus under the falx cerebri
Transtentorial / uncal	Medial aspect of temporal lobe over free margin of tentorium
Tonsillar	Cerebellar tonsils through foramen magnum

DEMENTIA

Causes of dementia

- AD (commonest)
- Multi-infarct
- FTD
- LBD
- CJD (Prion)
- Infectious: neurosyphilis, HIV

Pathogenesis of AD

- **Lysis** of transmembrane **Amyloid Precursor Protein (APP)** - involved in cell signaling and transcription regulation
- Aβ amyloid aggregrates into **amyloid fibrils** which can be directly **neurotoxic**
- Also accumulation of **neurofibrillary tangles** of **hyperphosphorylated protein TAU**
- Severity of AD is related to **loss of synapses**

INTRACEREBRAL HAEMORRHAGE

Causes

- **HTN**
- **Cerebral amyloid**
- Vascular malformations
- Neoplasia
- Bleeding disorders
- Vasculitis

Areas of brain

- HTN – deep – **putamen** (most common), thalamus, pons
- Amyloid – more superficial

Cerebral amyloid angiopathy

- **Deposition of amyloidogenic peptides** in the walls of…
    - **medium + small** caliber
    - **meningeal + cortical** vessels
- Deposition of amyloid weakens the vessel wall

INTRACRANIAL BLEED

- Extradural
- Subdural
- SAH
- Intraventricular
- Intraparenchymal

Extradural

- Dural artery – usually MMA @ level of pterion – is torn by skull fracture
- Haematoma strips dura off of skull
- May be lucid period before ⇓LOC

Concussion

- **Altered LOC** secondary to **head injury**
- Transient **neurological dysfunction**
- Transient **respiratory arrest**
- Transient loss **of reflexes**
- Unclear pathogenesis – may be **dysregulation of RAS**

- Clinical features of concussion:
    - Headache
    - N&V
    - Amnesia
    - Concentraion + memory issues
    - Irritability / behavior changes

MENINGITIS

CSF features of bacterial meningitis

- ⇑CSF pressure
- Turbid
- ⇓Glucose, ⇑Protein
- Pleocytosis with neutrophil predominance
- (Bacteria on gram stain)

CSF features viral meningitis

- Moderately ⇑protein
- Normal glucose
- Lymphocytes

Neonates	GBS E. coli Listeria
Infants	Haemophilus Strep pneumoniae
Adults	Meningococcus Strep pneumoniae
Elderly	Listeria Strep pneumoniae

Other causes of meningitis

- Viral
- Fungal
- TB

- Chemical / drug induced
- Carcinomatous

Other classification

Acute pyogenic	Bacterial
Aseptic	Viral / chemical
Chronic	TB, carcinomatous

Viral

- Enteroviruses:
  - Cocksackie
  - Echovirus
  - Poliovirus

MULTIPLE SCLEROSIS

- Neruological deficits, or imaging evidence of demyelinating lesions of the CNS, distinctly separated in time and space
- Cause by autoimmune demyelination
- Unilateral optic neuritis is common
- Also brainstem + cord lesions

Pathogenesis

- **Autoimmune, demyelinating** disorder of CNS
- White matter lesions separated in time and space
- Likey **T-cell mediated** T4HS attack of oligodendrocyte (myelin) self-antigens
- Aetiology unclear
- **Genetic + environmental** (microorganism trigger?)
- CD4+ Th1 cells react against viral trigger, release IL2 + IFN, active macrophages against self antigen
- Inflammatory cells create **plaques**

CSF in MS:

- ⇑Protein (mild)
- ⇑ Gammaglobulin – oligoclonal bands
- Pleocytosis

PARKINSON'S DISEASE

Clinical

- 3-5Hz pinrolling tremor
- Rigidity
- Bradykinesia
- Slow, festinent gait
- ⇓Facial expression
- Micrographia

Pathogenesis

- Loss of dopaminergic neurons in the nigrostriatal pathway
    - Idiopathic PD
    - Secondary:
        - MSA
        - PSP
        - Drugs – DA antags / toxins (MPTP)
        - Head injury (dementia pugalistica)
        - Post-encephalitis

Parkinsons <u>disease</u>

- Unclear pathogenesis
- **Damage to DA neurons** from toxins/drugs/AI
- **α-synuclean aggregation** → stress response
- **⇓Ubiquitin – proteasome** activity
- **Altered mitochondrial function** (loss of PINK1)

α-synuclean
⇓Ubiquitin-proteasome
Mitochondrial dysfunction
DA neurone dysfunction

PERIPHERAL NERVE REPAIR

- Death of neurone distal to site of injury (**Wallerian degeneration**)
- Axonal cone growth of **1-2mm / day**
- Growth **through schwann cell column**
- Regeneratic clusters

SPINAL CORD INJURY

Changes occurring in spinal cord after acute injury

Acute	**Haemorrhage** **Necrosis** **Axonal swelling** in surrounding white matter
Late	Area of neuronal destruction: cystic + gliotic Wallerian degeneration of long white-matter tracts Liquefactive necrosis in CNS

Acute clinical features of cervical spinal cord injury

- **Complete vs. incomplete**
  - Incomplete syndromes: anterior, central, posterior, Brown-Sequard
- **Spinal shock**:
  - Quadraplegia
  - Flacid paralysis
  - Areflexia
  - Total anaesthesia below level
- If above C4:
  - **Diaphramatic paralysis → resp failure**
- **Neurogenic shock:**
  - ⇓HR, ⇓BP

SAH

Causes:

- **Rupture of a berry aneurysm**
- AVM
- Trauma
- Tumour

Location of saccular aneurysms

- Most at major **arterial branch points** of COW
- Preponderance for anterior system - **Acom**
- MCA next most common

Genetic RFs for saccular aneurysm

- **PKD**
- **Marfans**
- **Elhers-Danlos T4**
- **NFM** T1
- **Fibromuscular dysplasia**
- **Aortic coarctation**

Non genetic RFs:
- HTN
- Smoking

Consequences of SAH

Early	Vasospasm → ischaemic injury ⇑ICP Herniation syndromes
Later	Meningeal fibrosis + scarring CSF obstruction → communicating / non-communicating hydrocephalus

SUBDURAL HAEMATOMA

- Damage to **bridging veins** across subarachnoid space between brain and dural venous sinus
- Often due to **shearing forces** during trauma / accell-decell injuries
- **Blood between dura & arachnoid**

Risks
- **Elderly** more at risk as cerebral atropy → veins are stretch across the subdural space with more room for brain to move and create sheering forces
- **Infants** have thin-walled bridging veins

DIFFUSE AXONAL INJURY

- **Microscopic** injury to **axons** – deep brain white matter
- Axonal **swelling** + focal **haemorrhagic** lesions
- Damage to integrity of axons at **Node of Ranvier → alterations in axoplasmic flow**
- Can lead to **immediate death / coma**