HAEMATOLOGY AND IMMUNOLOGY PHYSIOLOGY AND PHARMACOLOGY

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HAEMATOLOGY, TRANSFUSION MEDICINE, AND ONCOLOGY

Describe the physiological consequences of acute and chronic anaemia

- Anaemia = reduction in Hb due to quantitative or qualitative impairment in red cell production
  - Normal adult Hb: 135-165 (males), 115-165g/l (females
- Clinical features of haemolytic anaemia
  - Pallor
  - Jaundice
  - Splenomegaly
  - Gallstones
- Laboratory features of haemolytic anaemia
  - Anaemia
  - Various RBC changes e.g. spherocytes, poikilocytes, polychromasia
  - Reticulocutes
  - WBC + platelets often normal
  - Raised bilirubin (indirect)
  - Raised LDH
  - Low haptoglobin

Outline the major haemoglobinopathies and their clinical significance

Haemoglobin:

- haem incorporated into α, β, y globulin chains → tetramer of these chains forms Hb molecule
- HbA = α2β2 = 98% adult Hb
- HbA2 = α2delta2 = 2% adult Hb
- HbF = α2y2 = foetal type Hb → disappears by 6 months
  - No binding sites for 2,3DPG which binds on β chain

Normal adult Hb (HBA) consists of 2 alpha and 2 beta chains composing a tetramer

- each chain surrounds a porphyrin ring and Fe ion
- An O2 molecule can coordinate with each Fe ion → inducing a conformational change in the tetramer from its tense (T, deoxy) to relaxed (R, oxy) state
  - requires the breakage of salt links within each chain and extrusion of 2,3DPG (2,3 bisphosphoglycerate) from a site where it binds both beta chains
  - 2,3,DPG has a major effect on the affinity of Hb for O2. It is present within erythrocytes at ~the same molar concentration as Hb. It is a highly negatively charged molecule :
    - which in the tense state of Hb occupies a site in the center of the tetramer where it binds 3 positively charged sites on each B chain.
    - This binding must be broken when Hb binds O2
    - This greatly ↓s the affinity of Hb for O2
    - In the complete absence of 2,3DPG, Hb is 50% saturated at 1mmHg PO2 instead of at 26mmHg

Alpha Thalassemias

- Defect in all 4 genes = hydrops foetalus
- Defect in 3 genes: HbH disease, thalassaemia intermedia
- Defect in 1-2 genes = hypochromic microcytic blood film + HbH bodies on incubation with dye

Beta thalassaemias

- Beta thalassemia major
  - Clinical features
    - Severe anaemia
    - Ineffective erythropoiesis
    - Extramedullary haemapoiesis
    - Enlarged liver and spleen, flat bones of face, skull
    - Spontaneous fractures, Iron overload, Reduced growth, Endocrinopathy, Delayed puberty
  - Lab features
    - Anaemia
    - Hypochromic cells, target cells, NRBCs
    - Marrow: red cell hyperplasia, increased iron
    - Most of Hb is HBF on EPG
  - Treatment
    - Long term infusions
    - Iron chelation therapy (SCIL desgerrioxamine, oral: deferasirox)
    - Allogeneic marrow transplantation
    - MRI of liver + heart for iron content
- Beta thalassemia intermedia
  - Clinical diagnosis
  - Numerous genotupes e.g. HbE/B thal
  - Less severe clinical course than major
  - Splenectomy in selected cases
- Beta thalassemia minor
  - Single gene defect (heterozygous)
  - Hyprochromic microcytic blood film
  - High RBC count
  - Raised HbA2 on electrophoresis

Sickle cell anaemia

- Commonest of severe structural Hb variants - Diagnosed from Hb electrophoresis + DNA analysis by RFPL
- Substitution of valine for glutamic in 6th position of beta chain - Single base change: GAG to GTG
- HbS insoluble at low O2 tensions + tends to crystallise - RBCs become sickled
- Pathophysiology: the abnormal sickle Hb polymerised when deoxygenated, deforming the RBC + damaging the cell cytoskeleton – the rigid cells can obstruct or slow blood flow

- RBC adhesion in sickle cell – the abnormally increased adhesion of sickle RBCs can be mediated by multiple molecular interactions – these can bind the RBC to the endothelium, to subendothelial basement membrane, + to other blood cells
- Clinical features
  - Pain – due to vaso-occlusion
  - Infection – pneumonia, osteomyelitis, septic arthritis, parovirus B19
  - Resp – acute chest syndrome, pulmonary HT
  - CNS – stroke
  - Renal – haematuria, proliferative glomerulopathy, nephrotic syndrome, renal failure
  - Leg ulcers
  - Priapism
- Treatment
  - Comprehensive care approach, transfusion, allogeneic transplantation (selected pts)

Describe the physiology of haemostasis, including: • Coagulation • The role of platelets • Fibrinolysis

Haemostasis

- collective term for the mechanisms that stop blood loss
- balance of pro-coagulant + anticoagulant systems
  a. procoagulants system: promotes coagulation → bioamplification system involving activation of clotting cascade
  b. anticoagulant system → regulates or inhibits coagulation

*3 main **components** involved in haemostasis **(Virchows triad)***

- platelets
- endothelium
  a. when damaged → rapidly initiates haemostatic response
  b. normal function = prevent haemostasis + promote blood flow
     - inhibition of platelet adhesion:
       - NO + prostacyclin (PGI2)
       - production of adenosine diphosphate (degrades ADP)
     - anticoagulant effects:
       - due to 2 endothelial membrane bound proteins:
       - heparin sulphate (activates ATIII → inactivates thrombin + FXa)
       - thrombomodulin: directly binds thrombin + activates protein C (inactivates FVa + VIIIa)
     - Fibrinolytic effects
       - Secretes tissue plasminogen activator (t-PA) → cleaves proenzyme plasminogen → form plasmin → degrades fibrin clots from endothelial cell surface (fibrinolysis)
- coagulation proteins

Steps involved in haemostasis

- **Initiation of haemostasis.** Damaged vessel → plasma exposed to:
  a. Von willebrand factor (vWF): binds platelets to sub-endothelial collagen fibres
  b. Collagen fibres: platelets bind to collagen + become activated
  c. Tissue factor (TF): activates plasma coagulation proteins through extrinsic pathway → thrombin
- **Clot formation**: 3 key steps:
  a. Vasoconstriction
     - ↓blood flow → ↓platelet plug washed away + ↓blood loss

  b. Platelet aggregation
     - **Adhesion**: vessel damage exposes TF, collagen, vWF → platelet GPIb-V-IX binds to subendothelial collagen via vWF
     - **Activation**: metabolic process; adhesion triggers GPIb/IIIa activation → irreversible binding to matrix ligands; change shape + activation. Activation results in:
       - **Exocytosis of granules**: contain: 5-HT, TXA2, ADP, PAF, vWF, fibrinogen, thrombin, Ca2+, PDGF
         - **Dense granules**: release ADP, adrenaline, 5-HT → reinforce platelet activation
         - **αgranules:** release fibrinogen, βthromboglobulin, PAF-4, FV, vWF, PDGF, thrombospondin → mediate + reinforce platelet aggregation + adnesion
       - **Activation of phospholipase A2 to form TXA2**
       - **Deformation from disc to sphere with long projections**
       - **Promotion of coagulation cascade**
       - **Platelet contraction** (with clot contraction)
     - **Aggregation**: activated GPIIb/IIIa mediated aggregation via fibrinogen + vWF
     - **Haemostatic plug**: plug of degranulated platelets, fibrin mesh, leukocytes, entrapped RBCs

  c. Coagulation
     - coagulation cascade = biological amplification system involving plasma proteins → formation of thrombin
     - **Classical model: intrinsic + extrinsic** → common pathway
       - reflects in vitro lab tests but not in vivo haemostasis
       - Exrinsic pathway: activated by TF → FVII → FIIa → activates FX → start of common pathway
       - Intrinsic pathway: activated by contact with -vely charged substances e.g. subendothelial collagen
       - Final common pathway: FXa → converts prothrombin (FII) to thrombin (FIIa) → thrombin
     - **New model: cell based**
       - Better represents in vivo mechanism of coagulation
       - *Initiation* phase: coagulation triggered by vessel damage → exposes plasma to TF → FV + FVII activated → activate other nearby clotting factors → formation of thrombin
       - *Amplification*: further activation of clotting factors + platelets
       - *Propagation*: occurs on surface of activated platelet → catalyses formation of thrombin+++
     - Thrombin:
       - acts on fibrinogen mesh within platelet plug → hydrolyses soluble fibrinogen → produce insoluble fibrin strands
       - Activation of FXIII: forms covalent crossbridges between fibrin strands in platelet plug → stable clot
       - +ve feedback loop: activates FV + FVIII → feed into cascade to produce more thrombin
       - activation of protein C by thrombin-thrombomodulin complex: inhibitor of coagulation → deactivates FVa and VIIIa

Fibrinolysis

- Physiological mechanism in which the fibrin within blood clots is slowly dissolved
- Normal part of wound healing + important mechanism to keep small vessels patent
- Key points:
    a. Plasminogen is a b-globulin (proenzyme synthesised by the liver) → becomes interwoven into the fibrin clot as it is formed → converted to plasmin (serum protease)
    b. Main physiological activator of plasminogen is t-PA, expressed by endothelial cells – helps to keep the endothelial cell surface free of fibrin deposits
    c. Fibrin cleaved by plasmin → produces fibrin degradation products (FDPs)
        - One of the FDPs is the d-dimer – cleavage product of cross-linked fibrin

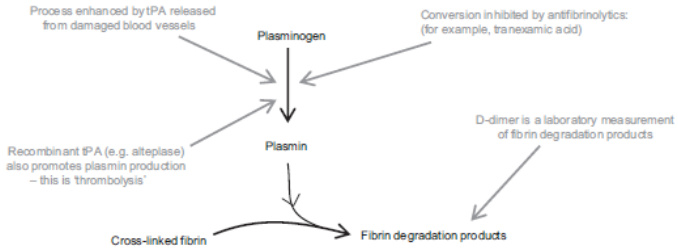
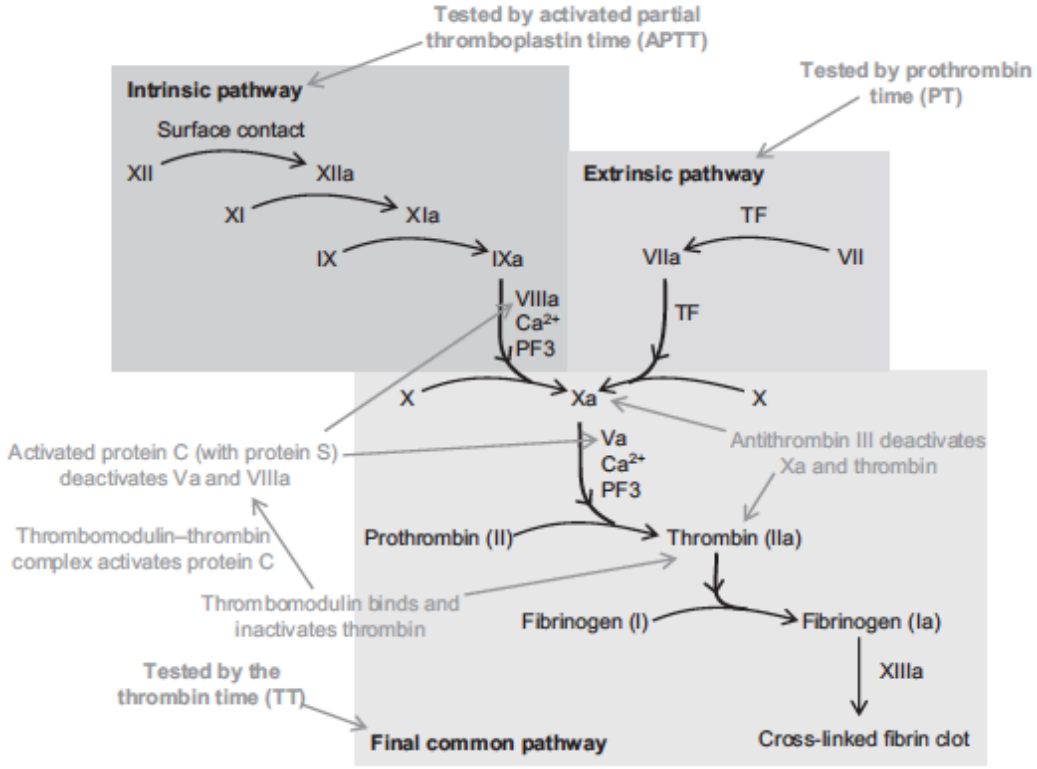


Figure 67.4 Fibrinolysis.

- Fibrinolysis pathway can be manipulated:
    a. Thrombolysis eg streptokinase promotes conversion of plasminogen to plasmin → ↑fibrinolysis
    b. Inhibition of fibrinolysis: eg tranexamic acid inhibits activation of plasminogen



Explain the main difference between the intrinsic and extrinsic pathway of coagulation: PAST QUESTION

Coagulation = bioamplification system in which a few initial substance activate a proteolytic cascade of precursor enzymes

Intrinsic pathway:

- activates on contact with –vely charged certain surfaces (e.g. subendothelial collagen)
- initial reaction results in activation of FXII → activates FXI → Xia activates FIX
- reaction that requires platelet factor 3 → Ca2+ + FVII, IXa converts FX to Xa

Extrinsic pathway

- tissue injury also exposes tissue thromboplastin (tissue factor) in subendothelium → combines with activates FVII → activates FX
- FVIIa tissue factor complex also activates FIX

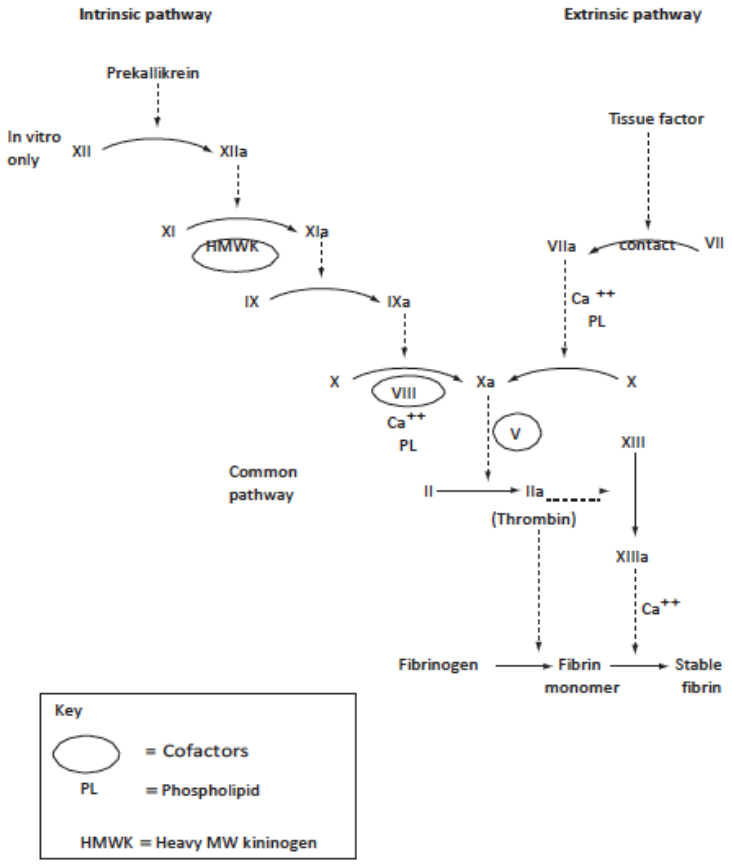
Final common pathway

- Activated FX converts prothrombin to thrombin. Reaction also requires:
    a. Ca2+
    b. FV
    c. Platelet factor 3 ("platelet thromboplastin or phospholipid)

Comparison

	Intrinsic	Extrinsic
Speed	Slow (APTT 25-40s) Tested by prewaming tube to 37o and adding citrate plasma, kaolin, cephalin, and calcium	Fast (PT 12-15s) Tested by prewarming tube to 37o and adding citrated plasma, tissue thromboplastin, and calcium Expressed as ratio (INR) to a standardised result
Importance of deficiencies	VIII and IX (haemophilia A and B) ↑↑ bleeding XII + XI not clinically significant	VII ↑↑ bleeding II and X (common pathway) ↑↑ bleeding
Blood products	FFP – all factors Cryoprecipitate: rich in VIII, fibrinogen, also has vWF, XIII Recombinant VIII, IX	Recombinant VIIa

Anticoagulants	Heparin Reversibly binds to antithrombin III At low doses inhibits factor Xa at high doses it inhibits thrombin, XIIa, Xia, IXa, as well as platelet aggregation	Warfarin Competitively inhibits Vit K epoxide reductase preventing production of FII, VII, IX, X, protein C and S



Outline the role of platelets in haemostasis: PAST QUESTION

Haemostasis

- physiological process that prevents minimises blood bloss from damaged vessels, whilst maintaining fluidity of circulating blood.
- 3 stages: vasoconstriction → primary haemostasis: formation of platelet plug → secondary haemostasis = coagulation

Platelet

- small, granulated cellular fragments derived from megakaryocytes important in haemostasis
- size: 2-3microm diameter
- 150-300 x 10^9/L
- lifespan = 7-10days

Role in haemostasis

1. **vasoconstriction**
   - platelet role in production/ release of vasoconstrictor agents: TXA2 (produced on platelet surface), 5-HT (dense granules)
   - during vascular healing: PDGF (α granule) stimulates smooth muscles to multiply → promotes vascular healing)
2. **primary haemostasis/ platelet plug formation**
   - **Adhesion**: vessel damage exposes TF, collagen, vWF → platelet GPIb-V-IX binds to subendothelial collagen via vWF
   - **Activation**: metabolic process; adhesion triggers GPIb/IIIa activation → irreversible binding to matrix ligands; change shape + activation. Activation results in:
     - **Exocytosis of granules**: contain: 5-HT, TXA2, ADP, PAF, vWF, fibrinogen, thrombin, Ca2+, PDGF
       - **Dense granules**: release ADP, adrenaline, 5-HT → reinforce platelet activation
       - **αgranules:** release fibrinogen, βthromboglobulin, PAF-4, FV, vWF, PDGF, thrombospondin → mediate + reinforce platelet aggregation + adnesion
     - **Activation of phospholipase A2 to form TXA2**
     - **Deformation from disc to sphere with long projections**
     - **Promotion of coagulation cascade**
     - **Platelet contraction** (with clot contraction)
   - **Aggregation**:
     - activated GPIIb/IIIa mediated aggregation via fibrinogen + vWF → enhanced by mediators above
   - **Haemostatic plug**: plug of degranulated platelets, fibrin mesh, leukocytes, entrapped RBCs
3. **secondary haemostasis**
   - initiation, amplification, propagation
   - procoagulants activity
     - platelet factor 3 → formation of Xa + thrombin → propagation
   - Anticoagulant activity: prevents disseminated coagulation
     - Platelet activation/ aggregation opposed by endothelial prostacyclin production (via PLA2 + COX1) → degree of plug formation dependent on balance of prostacyclin: TXA2
     - Activated protein C → bind to platelet surface → inactivate Va, VIIIa, inhibitors of TPA → ↑fibrinolysis

Describe the physiological mechanisms of limiting and preventing thrombosis

- Thrombosis = the process of clot formation
- Haemostasis
  - Physiological mechanism where blood is prevented from being lost from damaged vessels whilst allowing blood to remain fluid in the virculation
    - Balance of pro-coagulation system and anticoagulation system
    - Coagulation system = bioampligication system → activation of few substances triggers cascade of precursor enzymes → ultimately converting soluble fibrinogen to insoluble fibrin → contributes to forming a haemstatic plug
- Regulation
  - Important that haemostatic response is controlled + localised to area of vessel damage
  - Widespread coagulation could: prevent blood flow, damage RBCs (microangiopathic haemolytic anaemia); or DIC (paradoxical bleeding due to depletion of clotting factors

Explain the mechanisms that prevent blood clotting in intact blood vessels, do not draw the clotting cascade: PAST QUESTION

- balance of pro-coagulant + anticoagulant systems
  - procoagulants system: promotes coagulation → bioamplification system involving activation of clotting cascade
  - anticoagulant system → regulates or inhibits coagulation, prevents platelet aggregation → prevents clots from developing in uninjured vessels → maintain blood in fluid state

Factors affecting coagulation can be considered in regards to <u>Virchows triad</u>

1. **vessel wall: endothelial surface factors**
   - Stucture
     - Undamaged vessels → no exposure o subendothelial contact factors which stimulate platelet adhesion/ coagulation cascade
       - Collagen: stimulates intrinsic pathway, platelet adhesion
       - no binding site for vWF → no platelet adhesion
       - no exposure of tissue factor → extrinsic pathway (activation of FVII)
     - Glycocalyx coating:
       - endothelium smooth → laminar flow
       - repels platelets + clotting factors
   - Substances produced by endothelial cells
     - Thrombomodulin: binds thrombin → activates protein C → inactivates Va VIIIa → stimulates fibrinolysis
     - PGI2 (prostacyclin): inhibits platelet aggregation by ↑cAMP; smooth muscle relaxation → vasodilation → ↓vascular resistance → ↑flow
     - NO: inactivates platelet aggregation + local vasodilation
     - Heparin sulphate: natural heparin → ↑ATIII activity → inhibits IIa (thrombin) + Xa
     - Tissue plasminogen activator (TPA): converts plasminogen to plasmin → fibrinolytic
2. **Blood flow factors**
   - Laminar flow: ↓contact time of platelets with endothelium (axial streaming)
   - Coagulant factors diluted + removed by RES
   - Shear stress detaches weakly adherent platelets
3. **Blood constituent factors**
   - Coagulation factors
     - Circulate as inactive factors and generally require vessel wall damage to initiate coagulation cascade
   - Anticoagulants
     - Antithrombin III: circulating protease inhibitor → inhibits FIIa, Xa (and IXa, Xia, XIIa); facilitated by heparin; 70% capacity to limit coagulation
     - Protein C+S: vit K dependent; protein S, thrombomodulin-htombin → activates protein C → adheres to platelet → inactivates FVa and VIIIa + TPA → ↑TPA → ↑plasmin → fibrinolysis
     - $\alpha 2$ macroglobulin: inhibits IIa and contact factors
     - $\alpha 2$ antiplasmin + $\alpha 1$ antitrypsin: inhibit circulating serine proteases
   - Fibrinolytic system
     - Plasmin: cleaves fibrin + fibrinogen into fibrin degradation products → breaks fown fibrin clot
     - Activated protein C: inactivates inhibitors of TPA

Outline the methods for assessing coagulation, platelet function and fibrinolysis

Assessment of coagulation

PT

- Test of extrinsic pathway
- Involves adding TF to sample of plasma + measuring the time of clot formation
- INR is the ratio of a patients PT compared with the average PT of the control model.
- Mainly assesses FVII of the extrinsic pathway + FII, X, fibrinogen of common pathway
- Prolonged by:
  - ↓hepatic synthesis of vit K dependent clotting factors: II, VII, IX, and X → can be due to warfarin therapy
  - Vit K deficiency (eg fat malabsorption) or liver disease
  - DIC due to consumption of clotting factors

APTT

- Test of intrinsic pathway
- Involves adding phospholipid + activator to a plasma sample → then measuring time taken to clot
- Mainly assesses: FVIII, IX, XI, XII of intrinsic pathway + FII, X, fibrinogen of common pathway
- Prolonged by
  - Unfractionated heparin: activation of ATIII → inactivates FXa + thrombin
  - NB LMWH too small to activate ATIII effectively → instead inactivate FXa directly – APTT usually then not prolonged
  - Haemophilia (FVIII deficiency), FIX deficiency, and vWD
  - DIC: due to consumption of clotting factors

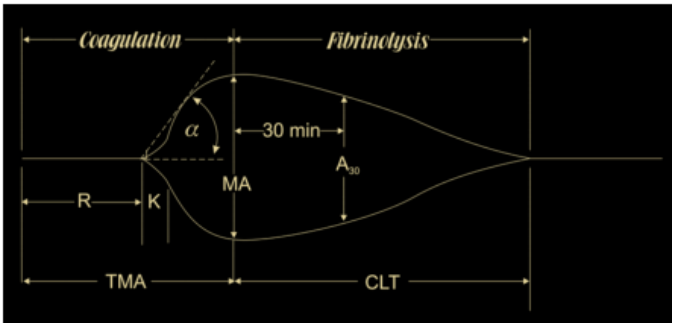
Thrombin time (TT)

- Test of final common pathway
- Thrombin added to plasma + clotting time measured
- Tests interaction between thrombin + fibrinogen

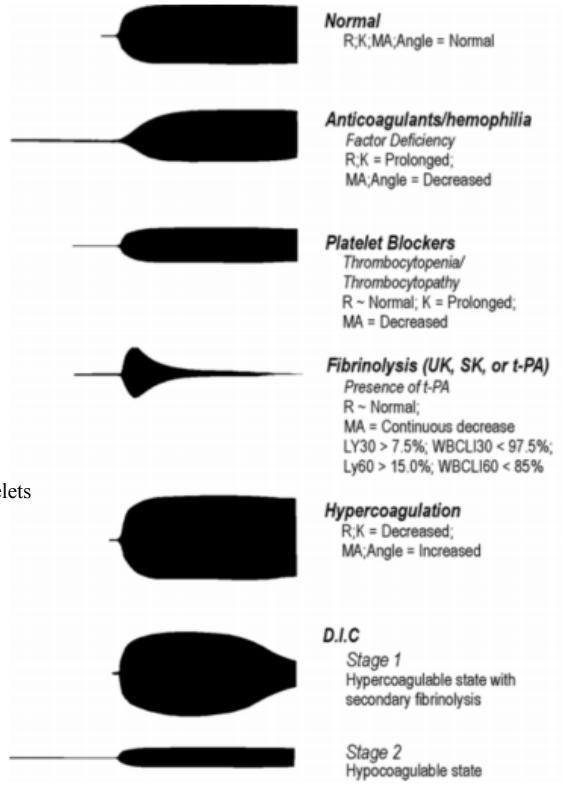
- Prolonged by:
  - Fibrinogen deficiency eg DIC

TEG (thromboelastography)

- Measures the physical property of whole blood as it coagulates
- Tests whole haemostatic process - assess platelet function + coagulation + fibrinolysis in single test
- Faster than lab based tests + better representative of in vivo haemostasis
- Based on the cell based model of coagulation: initiation, amplification, propagation
- **Procedure**
  - Sample of whole blood is added to a slowly rotating cuvette → the low shear environment mimics sluggish venous flow
  - A plastic pin attached to a torsion wire is lowerd into the cuvette
  - As blood clots → fibrin strands form between cuvette and pin i.e. ↑viscosity → ↑torson transmitted → ↑pin movement
  - The speed and strength of clot formation are calculated from the Δtorsion of wire → cigar-shaped graph



-
- **Interpretation**
  - Gross abnormalities of haemostasis can be quickly assessed from the shape
  - More detailed analysis of haemostasis can be made by analysing various pa
  - Plot of time in seconds (x axis) against milimeters of deviation representin
    - **R** = reaction time (s): time from start of test to initial fibrin forn
    - **K** = kinetics (s): time to achieve a certain level of clot strength
    - **α angle** = slope between R and K: measures the speed at which of clot formation i.e. ***thrombin burst***
    - **TMA** = time to maximal amplitude (s)
    - **MA** = maximal amplitude : represents the ultimate strength of t
    - **A30 or LY30** = amplitude at 30mins; %↓in amplitude at 30mir
    - **CLT** = clot lysis time (s)
- Clinical implications
  - ↑R time → lack factors → need FFP
  - ↓α angle → lack fibrinogen → need cryo
  - ↓MA (in isolation) → platelet deficiency or antiplatelet meds → need platelets
  - fibrinolysis → consider TxA
- Disadvantages
  - Availability of equipment
  - Need whole blood samples
  - Inter-operator variability
  - No standardised testing protocol → makes comparing results difficult
  - Needs daily calibration



Echis

Describe blood groups and methods of cross matching blood

Outline the physiology of blood groupings that allows O negative packed cells to be safely transfused to most patients: PAST QUESTION

Blood groups

- Genetically determined surface antiens on RBC membrane + any antibody in plasma
- Most common antigen systems = ABO, rhesus, kell (other: duffy, lewis)

ABO system

- Complex CHO based antigen series: A or B antigen; pts may express one, both, or neither → 4 blood groups (A, B, AB, O)
- Antigens:
  - H-antigen (fructose residue) expressed on nearly all RBC membrane
  - A antigen= N-acetylgalactosamine residue
  - B antigen = D-galactose residue
-
- Individuals express IgM antibody to foreign blood groups → develops within 6 months of birth likely 2` environmental exposure to similar antigens
- Hypersensitivity reaction is ABO-mismatch occurs

Group	RBC	Plasma
A	A antigen	B antibody
B	B antigen	A antibody
O	-	A antibody B antibody
AB	A antigen B antiven	-

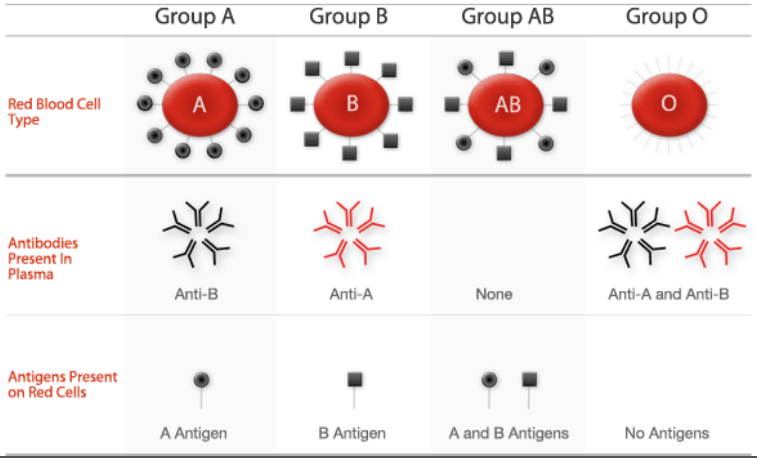
- Universal donor: O-ve
  - No ABO surface antigens → no reaction with recipient plasma antibodies
  - No RhD surface antigen – no reaction with RhD antibodies
  - Contains minimal donor plasma (contains both anti-A and antiB) → would not trigger significant reaction with recipient RBC surgace antigen
  - May not be completely safe because:
    - May contain minor antigen systems (e.g. Kell) → may sensitive patient → furter haemolytic reactions with other blood products
    - Not compatible with rare Bombay blood group (i.e. RBC surface doesn't express H antigen and there are antiH antibodies in plasma)
- Other notes from examiners comments
  - Necessity for prior exposure for development of Rh ab and implications fo rowmen of childbearing age
  - Blood reserved for uncrossmatched blood transfusion has low antigencitity – screened for minor blood groupings
  - Problems with subsequent crossmatching after uncrossmatched O-ve blood is transfused

Rhesus
- Consists of 50 differeent antigens, most important is D → rhesus status is expressed as D+ve or –ve
- Rhesus ab does not naturally occur in Rh-ve individuals. Can occur with: incompatible transfusion, foetal-maternal haemorrhage

Cross matching

- Blood transfusion involves the infusion of safe + compatible blood (or its components) froma donor to a recipient
- Testing completed prior to transfusion: ensure compatibility between donor RBC antigens + recipients plasma antibodies to avoid haemolytic reactions

3 step process
- **1. GROUP: Blood typing (ABO + Rh):**
  - ABO:
    - ABO = complex polysaccharide antigen present on surface of RBC (+ tissue cells liver, kidney, lung, heart)
    - Serum naturally has antibody (IgM) to RBC antigen not present on own RBCs
  - Rh:
    - D only clinically relevant
    - Only present on RBC
    - Nil naturally occurring antibody
  - To establish blood type: recipients **RBCs** mixed with plasma of known groups containing IgM antibody (anti-A, anti-B, anti-AB) + IgG for RhD+ve → observed for agglutination (indicates blood type / Rh+ve)
- **2. SCREEN: Antibody screen:**
  - recipients **serum** mixed with RBC containing known antigen (e.g. ABO, Rh, Kell, Dffy) and monitored for agglutination
  - testing for presence of minor antibodies to other RBC antigen → agglutination indicates presence of minor antibody
- **3. CROSS MATCH:**
  - demonstration of serological compatability between recipients serum + donors RBCs
  - 1. saline test:
    - RBC suspended in saline + mixed with antibodies at room temp,
    - Detects IgM antibody → monitoring for agglutination → re-confirms ABO type
  - 2. Incubation:
    - Incubated to 37o in albumin or low ionic strength salt solution → causes in vitro sensitisation + aids detection of incomplete antibodies (e.g. Rh, Kell, Kidd, Duffy)
  - 3. Indirect Coombs test/ antiglobulin
    - only if recipient serum positive for atypical antibody
    - test for unexpected anti-RBC antibodies → usually IgG antibodies
    - donors RBC washed with saline + antiglobulin (IgG antibody/ coombs reagent) then added
    - + test: agglutination → antiglobulin binds 2 IgG molecules (which are bound to RBCs) i.e. donors RBC are coated with recipients serum abs
    - –ve test: no agglutination (IgG not bound to RBC)



Outline the composition, indications and risks of use of the following blood components and products: • Packed red cells • Fresh frozen plasma • Cryoprecipitate • Platelets • Factor VIIa

RBCs

Indications	- Clinically sig anaemia; symptomatic deficit of O2 carrying capacity - Traumatic/ surgical blood loss

Contraindications	- Consider iron, vit B12, EPO
Presentation	- 250-350ml/unit
Storage:	- 42 days at 2-6° in temp regulated fridge
Compatability testing	- ABO compatability - Rh (D)
Compatible fluids:	- NS, 4% alb, ABO-compatible plasma
Incompatabilities	- Electrolyte + colloid solutions eg gelofusine, hartmanns → can cause clotting in infusion line - 5% glucose can cause RBC to haemolyse
Administration	- Must be commenced <30mins of collection - Must be completed <4hrs - Typically over 1-3hrs

Platelets

Indications	- Platelet function disorders: bleeding secondary to severely low platelets or functionally abnormal platelets - Platelet consumption or dilutional thrombocytopaenia - Bone marrow failure: prophylaxis in pts with counts <10 x10⁹/L - Selected cases pre/post op <50 - Massive haemorrhage/ transfusion
Contraindications	- Do not use in pts with destruction of endogenous and exogenous platelets eg ITP, TTP, HIT unless life-threatening haemorrhage
Presentation	- 50mls
Storage:	- 5 days at 20-24o - Must be agitated continuously in single later
Compatability testing	- ABO compatability - Rh (D)
Compatible fluids:	- NS, 4% alb, ABO-compatible plasma
Incompatabilities	- Electrolyte + colloid solutions eg gelofusine, hartmanns → can cause clotting in infusion line
Administration	- Must be commenced <30mins of collection - Must be completed <4hrs - Typically 15-30mins - One dose of platelets may raise platelet count 10-20points

FFP/ cryo

	FFP	Cryo
Contains	- Plasma separated from cellular component - Contains clotting factors of plasma + complement	- thawing FFP and recovering precipitate → cold-insoluble precipitate is refrozen - contains: FVIII, vWF, fibrinogen, FXIII, fibronectin
Indications	- Single factor deficiencies; no specific factor available - Warfarin + life-threatening bleeding. + vit K and/or prothrombin. NB prothrombinex better for rapid warfarin reversal - Following massive transfusion or cardiac bypass - Liver disease + bleeding + coagulopathy - Acute DIC - TTP	- fibrinogen deficiency / dysfibrinogenaemia + bleeding, invasive procedure, trauma, or DIC - Most common = massive transfusion where fibrinogen <1g/L
Contraindications	- INR <1.5 - If can use specific therapy: vit K, cryp, FVIII - blood vol can be safely replaced with crystalloids	- Not for haemophilia, vWD, FXIII, or fibrinonectin
Doseage	- 10-15ml/kg	-
Presentation	- Vol 150-300ml	- 30-40mls/unit
Storage:	- 12 months at -25o - Once thawed, can be stored for up to 24hrs at 2-6o	
Compatability testing	- ABO → Rh not necessary	
Compatible fluids:	- NS, 4% alb, ABO-compatible plasma	
Incompatabilities	- Electrolyte + colloid solutions eg gelofusine, hartmanns → can cause clotting in infusion line	
Administration	- Typically stat-30mins - Must be completed <4hrs	
Monitoring	- PT and aPTT	-

Albumin

	4% albumin	20% albumin
Indications	- Hypovolaemia or shock - Systemic capillary leak syndrome - Plasma exchange as replacement fluid esp when vol exchanged >20ml/kg	- Hypoproteinaemia - Burns
Contraindications	-	-
Presentation	-	-
Storage:	-	
Compatability testing	-	
Compatible fluids:	-	
Incompatabilities	-	
Administration	-	

IVIG

Indications	*IVIg 6%* Intragam P for replacement IgG therapy - Primary immunodeficiency - Myeloma and CLL with severe secondary hypogammaglobulinaemia + recurrent infections - Congenital or acquired immune deficiency syndromes Intragam P for immunomodulatory therapy in:

	- ITP - Allogeneic BMT - Kawasaki disease - GBS IVIg 10% - Replacement: as above - Therapy in: ITP, GBS, kawasaki, CIDP, multifocal motor neuropathy, MG exacerbations, lambert-eaton myasthenic syndrome; stiff person
Contraindications	- Anaphylaxis
Presentation	- 10, 50, 200ml vials containing 0.6, 3, 12g of IgG and 1,5,20g of maltose
Storage:	- 2-8o - Use <3months once removed from fridge
Compatability testing	-
Compatible fluids:	-
Incompatabilities	- Administer separately from other IV fluids or meds
Administration	- Infuse undiluted; can dilute with up to 2 parts NS of 5% glucose if needed - Adult infusion rate: 60ml/hr (1ml/min) for 15mins → 2ml/min for 15 mins → 3ml/min for 15mins → 4ml/min until complete
Adverse effects	- Usually related to rate of infusion - Symptoms: abdo pain, malaise, headache, chest tightness, flushing/ pallor, urticarial skin rash, cutaneous vasculitis, itching, swelling, nausea/ vomiting - Minor reactions: infusion can be restarted at slower rate - Headache most common symptom - Delayed reactions can develop <24hours: nausea/ vomiting, chest pain, rigors, dizziness, aching legs, arthralgia

Prothrombinex

Indications	- Rx + periop prophylaxis of bleeding in acquired deficiency of PTx factors eg warfarin – when rapid correction required - Rx FIX, II, X when specific factors not available
Contraindications	- Hypersensitivity including allergy to heparin or HIT - Pts with active thrombosis or DIC
Presentation	- Vials containing 500IU FIX, 500 IU FII, and 500IU FX
Storage:	- Store 2-8o for <6 months; protect from light
Administration	- Give slowly at 3ml/min IV
Adverse effects	- Rare: can include anaphylactic reactions, hypercoagulability, vasodilation, DIC, injection site reactions, dyspnoea, vomiting -

FVIII

Indications	- Rx of bleeding in pts with VWD when DDAVP ineffective or CI - Rx + prophylaxis of bleeding associated with FVIII deficiency due to haemophilia A
Contraindications	- Hypersensitivity
Presentation	- Freeze-dried powder dissolved with water for injection
Storage:	- Store 2-8o - Can be stored <25 degrees for <6 months; protect from light
Administration	- Give slowly within 5 mins IV - Do not add or mix to other fluids, including whole blood
Adverse effects	- Allergic reactions or fever are raraely observed - For minor reactions – slow infusion

FIX

Indications	- Haemorrhages or prophylaxis in pts with haemophilia B - Not indicated for rx of FII, VII, or X deficiencies because it doesn't contain therapeutic levels of these coag factors
Contraindications	- Nil
Storage:	- 2-8 degrees; protect from light
Administration	- Give slowly; 3ml/min IVI
Adverse effects	- Allergic reactions or fever are raraely observed - For minor reactions – slow infusion

Transfusion reactions

PRBC (adult leukodepleted)
- content: vol = ~260ml; Hb 50g/unit (190g/L); WCC 0.3
- additive: citrate, phosphate, saline, adenine, glucose, mannitol
- shelf life 42 days at 2-6oC
- inappropriate PRBC transfusion → ↑mortality + morbidity

Transfusion reactions

Haemolytic transfusion reaction
- Will occur if the recipients plasma contains abs that are reactive against the donors RBC antigens
- Recipients abs coat the donor RBCs → the antibody-antigen complex activates complement → haemolysis of donor RBCs
- Can be considered based on time: immediate vs. delayed; or immune vs. non immune

Time based:
- Immediate haemolytic transfusion reaction
  - ABO incompatability → rapid intravascular haemolysis
  - Severity depends on ab titre
  - Urticarial, flushing, chest pain, dyspnoea, jaundice, tachycardia, shock, haemoglobinuria, DIC can occur
  - Transfusion of RhD incompatible blood tends to result in extravascular haemolysis (usually less severe than intravascular haemolysis)
- Delayed haemolytic transfusion reaction
  - Minor RhD antigens + minor blood group systems → may cause delayed haemolytic transfusion reaction
  - Can occur 7-21 days following transfusion
  - Difficult to prevent
  - Following prior exposure to blood antigen → pts develop low titre of ab (too low for lab detection) → when incompatible blood is

transfused, a secondary immune response occurs → takes time for new IgG antibodies to be produced → delay before haemolysis is evident

Immune vs. non-immune

- Immune
  - mild transfusion reactions: urticaria, fever 1:20
  - ABO incompatibility 1:40k
  - Non-ABO incompatibility
  - Anaphylaxis 1:30k
  - Transfusion related immune modulation
  - TRALI 1:10k
  - Graft vs. host disease
  - Blood born infection: malaria, HBV (1:500k), HCV (1:1mill), HIV (1:1mill), CJD (theoretical)
- Non immune
  - Iron overload
  - Microaggregates
  - TACO
  - Tansfusion associated sepsis
  - Massive transfusion adverse effects
    - Citrate toxicity: ↓ionised Ca2+, Mg → arrhythmias
    - Hyperkalaemia
    - Acidosis
    - Hypothermia
    - Dilutional coagulopathy

Describe the changes that occur during blood storage and their clinical implications

Whole blood

- Contains
  - plasma – electrolytes, gases, proteins (albumin, coagulation factors, immunoglobulins)
  - cells – RBC + WBC
  - additives: anticoagulatns (citrate), nutrients (adenine, glucose), buffer (PO4) → aim to ↑shelf life + ↓degradation
- Storage conditions: 4oC to:
  - ↓metabolic activity of cells
  - ↓bacterial colonoisation and growth
  - prevent freezing + cell lysis
  - max storage time 28 days → survival of 70% RBC after transfusion
- **Changes with storage**
  - **Cellular changes**
    - RBC:
      - Cellular integrity: failure of Na/K ATPase → RBC spherical + fragile + ↑rigidity → lysis
      - 30% lysed at 28 days → release freeHb and other cell contents → saturates all haptoglobin
    - WBC
      - Loses phagocytic and bacteriovidal activity
      - Retains antigenic properties
    - Platelets
      - Become non functional <48hrs at 4oC → need to be stored at body temperature
  - **Biochemical changes**
    - ↑[K]: failure of Na/K ATPase + cell lysis: K ~30mmol at 28 days
    - ↑[lactate]: cellular anaerobic metabolism
    - ↓pH: cellular metabolism
    - ↓ATP
    - ↓dissolved O2 and ↑dissolved CO2
    - almost zero inodsed [Ca2+]: complexed by citrate
    - ↓2,3DPG: almost completely depleted at 28 days → ↓ATP and 2,3DPG → transfused blood therefore has a ↑O2 binding affinity than native blood and thys O2 offloading to the tissues is impaired.
    - ↓clotting factors esp. ↓FV and FVIII

Packed RBCs

- Donated whole blood is spun in centrifuge and plasma removed → RBCs are suspended → Hct >75%
- Citrate, adenine, glucose added and mixture stored at 4o
- Shelf life of 42 days

Preservative

- citrate: complexes Ca2+ inhibits clotting
- adenine + glucose: energy substrate for RBC → prevents RBC lysis + prolongs shelf life
- phosphate: buffers ↓pH due to cellular metabolism → prevent lysis

Haematology – other

Describe the production and function of red blood cells: PAST QUESTION

Production of RBC

- foetus <7 months: erythropoiesis mainl in liver
- foetus >7 months to adult: erythropoiesis mainly in bone marrow from haemopoietic pluripotent stem cells
- pluripotent stem cell → myeloid stem cells → actions of BFUE and CFUE → proerythroblast → erythroblast → normoblast → extrusion of nucleus → reticulocyte → leave BM → matures into RBC
- mature RBC lacks nucleus + mitochondira → undergoes anaerobic metabolism
- erythropoietin (synthesised in kidney 90% and liver 10%) → stimulate proerythroblast proliferation and maturation

Function of RBC

- Package for Hb
  - Hb contains 1 globin chain comprised of 4 polypeptide subunits arranged in pairs (2α2β) → each subunit conjugated to haem moiety (modified protoporphyrin ring with Fe2+ core – able to bind 1 molecule of O2)
  - Protects Hb from glomerular filtration
- O2 carriage
  - Normally >95% O2 carried in blood bound to Hb
  - Hb binds tightly to O2 in lungs, loosely in tissues in presence of ↑PCO2
  - Bohr effect: ↓pH, ↑2,3DPG, and ↑temp → ↑delivery of O2 to tissues
- CO2 carriage
  - Direct carriage via carbaminoHb compounds
  - Indirect carriage via buffering H+ formed from CO2 reaction with Hb or H2O (Haldane effect)
- pH buffer of ECF
  - Hb contains 38 histidine residues pKa to act as buffer
  - ↑quantity of Hb → therefore ↑buffer capacity
  - ΔECF pH → H+ + CO2 diffuse into RBC → bufferd by Hb

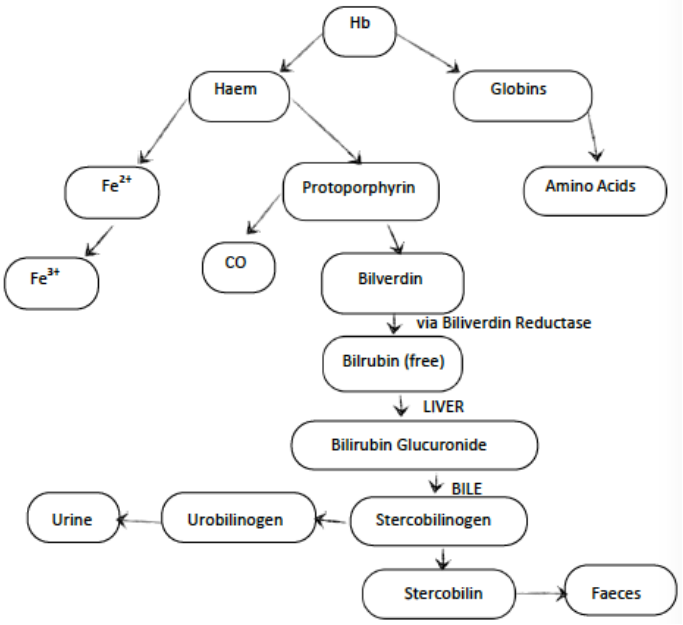
Describe the breakdown of haemoglobin after red cell lysis: PAST QUESTION (17% pass rate)

Background

- RBC produced in bone marrow in adult; in foetus 1o production in liver
- After maturation RBC lifespan = ~120 days
- Haem is incorporated into α, β, y globulin chains → tetramer of these chains forms Hb molecule
- Destruction of RBC
  - As RBC ages → ↓ATP formation → unable to maintain cell integrity
  - Old RBCs are sequestered and lysed in RES, esp. spleen
  - Hb key component of RBC: metalloprotein broken down into 3 constituents: globin protein, protoporphyrin, ionic iron

Fate of 3 constituents

- Globin protein:
  - Broken down by liver/ plasma proteases → amino acids → recycled in synthesis of globin or other proteins
- Protoporphyrin
  - Broken down to bilaverdin + carbon monoxide in spleen
  - Biliverdin → *biliverdin reductase* → bilirubin → bound to alb → transported in liver → conjugated *glucuoronidation* → excreted in bile
  - Conjugated Br metabolised by GIT bacteria → urobilinogen → reabsorbed in enterohepatic circulation → may be excreted in rine
  - Urobilinogen further metabolised to stercobilinogen/stercobilin → may be excreted in faeces
- Iron
  - May be bound to transferrin → transferred to BM for Hb resynthesis
  - May be bound to apoferritin → ferritin → stored in hepatocytes, GI mucosal cells, RES → reused later



Outline the complications of massive transfusion: MAKEUP

Massive transfusion = transfusion of a vol of stored blood > recipients blood vol <24 hours

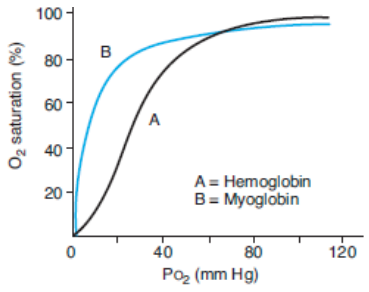
Complications

- **citrate toxicity/ ↓Ca2+**
  - citrate chelates Ca2+
  - ↓Ca2+ → involuntary muscle tremor; ↓HR; wide ST segment; prolonged QT
  - Rx if ECG Δs → CaCl2
- **Hyperkalaemia**
  - RBC in storage loses cell integrity → ↓function of Na/K ATPase → ↑extracellular K
  - K up to 30mmol/L at 28 days
  - Na/K ATPase function regained after transfusion → K diffuses into RBC

- **Acidosis**
  - pH blood at 2 weeks storage → 6.5 – 6.8
  - may exacerbate existing acidosis in pt
  - citrate metabolised in liver on transfusion → HCO3
  - lactate → Emden-Myerhoff glycolytic pathway → emtabolised to pyruvate in Cori cycle
- **Hypothermia**
  - Blood stored at 4oC
  - If transfused rapidly → ↓temp by 1oC for each unit at 4oC
  - <28oC → VF; L shift OHDC (Bohr effect); aggravation ↑K/citrate toxicity
- **2,3DPG deficiency**
  - 2,3,DPG depleted during storage (almost 0 at 4 weeks): L shift OHDC → ↓O2 delivery to tissues
  - rapidly replenished by 24hours post transfusion
  - CPD-adenine preservative minimises this
- **Dilutional coagulopathy**
  - Stored blood has low levels FV, VIII, XI
  - Dilution of pt coagulation factors occurs if total body blood vol replaced >2 in 24hours
  - Platelets in stored blood dysfunctional at 48hours storage
- **TRALI**
  - Acute onset of non-cardiogenic pulmonary oedema <6hours of transfusion
  - Incidence 1:5000 (US); mortality 9% → 1o transfusion related death in USA
  - Typically associated with FFP; can occur in RBC 2o residual plasma in unit
  - May be immune mediated
    - Abs against HLA or HNA (human neutrophil antigen) → sensitisation from previous transfusion/ transplant
    - 2 hit hypothesis:
      - 1st hit: existing pulmonary pathology → localisation of neutrophils in pulmonary vasculature
      - 2nd hit: antigen laden blood transfused → attach to neutrophils → degranulation → release of vasoactive substances
  - non immune mediated: accumulation of bioactive lipids in stored components with neutrophil priming capabilities
- **Other**
  - Microaggregates: clumps of fibrin, pleteles, leucotyes formed in stored blood → lodged in microvasculature → release lysosomes → ARDS
  - Vol overload
  - Haemosiderosis
  - Blood borne infection
  - DIC
  - ↓Mg2+

Outline the similarities and differences between myoglobin and adult haemoglobin, explaining the physiological relevance of the differences: 24% PAST QUESTION

	Myoglobin	**Adult haemoglobin**
Location	Haem containing pigment protein found in skeletal + cardiac muscle Only found in blood stream when released following muscle injury e.g. rhabdo Large amounts can cause renal failure	Large concentrations in RBC that circulate through circulation
Structure	Globular protein; single chain Contain single haem moiety which binds O2 No cooperative binding of O2 since doesn't exist in tetramer formation → in dissociation curve is rectangular hyperbola cf sigmoid Contains 4-5% total body iron	Globular protein; 4 subunits Contain haem moiety made up of 4 subunits, each containing haem moiety conjugated to polypeptide Polypeptide = globin: 2 pairs 2α2β → 4 haem moieties Protoporphyrin ring derivative with central Fe2+ molecule - binds O2 MW 65000 Daltons Contains 70% total body iron
Function	O2 storage → for exercising muscle	O2 carriage → lungs to tissues, CO2 carriage, acid-base buffer
Carriage of O2	Myoglobin content greatest in muscles specialised for sustained contraction	Sigmoid shaped dissociation curve P50 26.6mmHg



PHARMACOLOGY OF HAEMATOLOGY, TRANSFUSION MEDICINE AND ONCOLOGY

Describe the pharmacology of warfarin and other anticoagulant drugs

Anticoagulants = drugs which inhibit/ prevent the activation or propagation of the coagulation cascade

	Warfarin	**Dabigatran**	**Rivaroxaban**	**Apixaban**
Chem	Coumarin derivative Racemic mix	Benzamidine based thrombin inhibitor	Oxazolidinones derivative	Oxazolidinones derivative
Uses	Anticoagulation AF/ prosthetic heart valves Prophylaxis + rx of DVT/ PE	Primary prevention of VTE	VTE prevention	
Pres	Tablets 0.5-5mg racemix mixture warfarin sodium	Tablets 75/119mg dabigatran etexilate	Tablets 10mg	
Action	**Competitive antagonist of hepatic vit K epoxide reductase (VKOR)** → blocks conversion of oxidized vit K to reduced vit K → ↓synthesis of vit K dependent coagulation factors: (II, VII, IX, X) + protein C/S	**Competitive, reversible direct thrombin inhibitor** Pro-drug → plasma + hepatic esterase catalyzed hydrolysis to dabigatran → direct thrombin inhibitor → prevents cleavage of fibrinogen to fibrin Also inhibits: free thrombin, fibrin bound thrombin, thrombin induced platelet aggregation	**Direct factor Xa inhibitor** → interruption of intrinsic + extrinsic coagulation pathways Does not inhibit thrombin / platelet function	**FXa inhibitor** → prevents thrombin generation
CVS	Anticoagulant	Anticoagulant Inhibits platelet aggregation	No affect on platelet function	
Monitor	INR / PT	TT/ Ecarin clotting time (directly assay activity of thrombin) APTT ↑ in high dose (i.e. OD)		↑PT ↑APTT TT normal Anti factor Xa
Reversal	Vit K: 1-10mg FFP: up to 15ml/kg PTX: 25-50IU/kg FVII	FFP, PTx, May be removed by dialysis	PTX, FVIIa → max effect of 50% Too heavily PB for dialysis	PTx 25-50IU/kg Tranexamic acid FVIIa
Route	PO 3-9mg/day titrated to INR	110-220mg daily	PO 10mg	
Onset	8-12hrs (peak 72hr)	Cmax 90-180mins	Cmax 2-4hrs	Cmax 90-200min
Duration	3-5days			
A	Bioavailability 100%	Bioavailability 100%	Bioavailability 80-100%	Rapidly absorbed; Bioavailability 50%
D	99% PB (albumin) VD 0.1L/kg	35% PB (albumin) VD 60-70L	95% PB VD 50L/kg	85% PB VD 0.3L/kg
M	Liver Oxidation + reduction → metabolites conjugated with glucuronide	Liver Conjugation to **active** acylglcuronide → <10% total drug in plasma	Liver : 2/3 oxidative degradation + hydrolysis	Liver Inactive sulfate conjugates
E	**Urine** + faeces Clearance 3.5ml/min/kg Elimination ½ life 40hrs (↓renal impairment) T1/2β 40hr	80% unchanged in **urine**: rate ∝ GFR 20% biliary excretion of acylglucouronides Terminal elimination ½ life 12-14hrs	50% renal; 50% faeces terminal elimination ½ life 5hrs systemic clearance 10L/hr	33% Renal unchanged 33% biliary unchanged ½ life 12hrs
Special points	Spinal + epidural CI in pts on warfarin	Dose ↓ in renal impairment, pts on amiodarone	No dose adjustment in mild-moderate renal impairment	
Advantages	Easily reversed Cheap Familiar Easy to monitor Unaffected even by severe renal failure	Rapid onset + offset No food interactions Wide therapeutic window Convenient – no need to monitor Lower risk of bleeding complications than warfarin	Rapid onset + offset No food interactions / med interactions Wide therapeutic window Convenient – no need to monitor Lower risk of bleeding complications than warfarin	Rapid onset + offset No food interactions / not many med interactions Wide therapeutic window Convenient – no need to monitor Lower risk of bleeding complications than warfarin
Disadvantages	Narrow therapeutic window Patients vary considerably in dose response Many interactions with drugs ad diet Interacts basically with everything	CI in renal failure Difficult to monitor Rapid ↓ of efficacy with missed doses Expensive / No immediate antidote	CI renal failure + severe liver failure Difficult to monitor Rapid ↓ of efficacy with missed doses Expensive / Without immediate antidote	Difficult to monitor Rapid ↓efficacy with missed doses Expensive No immediate antidote

	Unfractionated heparin	**LMWH e.g. enoxaparin**
Chem	Anionic mucopolysaccharide organic acid derived from bovine lung or porcine intestine 5000-25000Da	Depolymerized heparin (chemical or enzymatic degradation) MW: 2000-8000Da
Uses	IVI: DVT, PE, unstable angina, peripheral artery occlusion, ACS SC: DVT prophylaxis	
Pres	Na or Ca2+ salt 1000-25000IU/ml	
Action	Reversibly binds to ATIII → conformational change of ATIII molecule → 1000x↑ATIII activity → inactivation of FXa at low conc + inactivation of FIXa, FXIa, and FXIIa as conc ↑s ATIII inhibits effect of thrombin by binding it + forming inactive complex (ATIII-thrombin complex) ↓platelet aggregation prevention of propagation of thrombus inhibition of fibrin formation	↑action of ATIII on Xa but no effect on rate of binding with thrombin No binding on other plasma proteins ↓platelet aggregation prevention of propagation of thrombus inhibition of fibrin formation
CNS	Does not cross BBB/ placenta	
CVS	↓MAP post rapid IV administration	
Toxicity/ SE	Narrow TI Haemorrhage Hypotension following rapid IV administration OP after prolonged use (binds OC and OBs) Skin necrosis, ↑K, alopecia HITTS (↑risk cf LMWH 2o affinity for PF4)	Haemorrhage HITTS
Monitor	APTT	Xa level (not routine)
Reversal	Protamine	Limited with protamine
Route/ dose	IVI: titrated to APTT 1.5-2x control SC: 5000 bd/tds	SC: 1-1.5mg/kg once daily dosing
Onset	20-60mins	
Duration	4-6hours	12-24hrs
A	Nil PO bioavailability ↓lipid solubility + ↑MW → doesn't cross BBB and placenta	
D	Highly PB → variation of [plasma]; unpredictable anticoagulant activity	↑PB (less than UFH)
M	Heparinases in liver, kidney, RES	Heparinases in liver, kidney, RES
E	Small amount unchanged in urine Clearance 0.5-2ml/kg/min	Renal ½ life 4.5hrs
T1/2β	90mins	
Special points		

Describe the mechanism of the anticoagulant effect of coumarin derivatives and what determines the onset and offset of action: PAST QUESTION

Most commonly used derivative = warfarin

MoA:

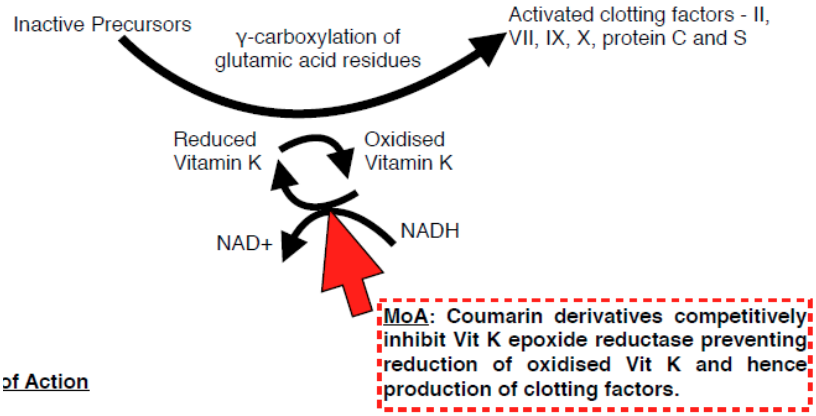
- **Competitive antagonist of hepatic vit K epoxide reductase (VKOR)**
- VKOR catalyses recycling of oxidized vit K back to reduced form
- Reduced vit K involved in gamma-carboxylation of glutamine residues of FII, VII, IX, X (necessary in producing active forms) + protein C/S

Onset of action

- Peak plasma concentration 4-8hrs
- NB inhibits synthesis of new clotting factors without inhibiting action of those already formed → onset of action determined by biological ½ lives of clotting factors
- Protein C has short ½ life: 8hrs
- FII (2-3 days) and X (1-2 days) → initial hypercoagulable state before anticoagulation
- Factors affecting onset:
  - Vit K store (malnutrition/ post op)
  - Circulating factors (liver failure)
  - Warfarin dose
  - Drug interactions
  - Protein binding
  - Protein level

Offset of action

- Metabolised by liver
- Factors affecting offset:
  - vit K level
  - clotting factor level: FFP



of Action

How does warfarin exert its anticoagulant effect what methods can be used to reverse the effects of warfarin prior to surgery? PAST QUESTION

Warfarin

- oral anticoagulant used for treatment + prophylaxis of patients with: AF, VTE, prosthetic heart valves

Mechanism of action

- Exists as 2 enantiomers → S-warfarin 3x more potent than R-warfarin
- Competitively inhibits vitK epoxide reductase (VKORC1)
- VKORC1 converts vit K from oxidised to reduced form
- Vit K in reduced form → gamma carboxylate glutamate residues of clotting factors II, VII, IX, X, protein C + S → activation
- Warfarin →
  - ↓active form of FII, VII, IX, X → anticoagulant effect
  - ↓active form of protein C + S → initial hypercoagulable state
  - NB only disrupts the production of new clotting factors; has no effect on circulating clotting factors
  - Peak effect occurs when sig ↓in concentrations of FII, X (~5-7days)

Reversal

Can be used alone or in combination

1. **Stopping warfarin**
   - S-warfarin is eliminated via oxidation predominantly by CYP2C9 (+ lesser extent CYP3A4 and 1A2) → inactivates metbaolites
   - Elimination ½ life S-warfarin is 29hrs → therefore in pts with normal hepatic metabolic + synthetic functions → take 4-5 days for INR to normalise
2. **Vit K**
   - PO/ IM/ IV (bioavailability 100%)
   - Low dose (1-2.5mg) → slow ↓INR over 24 hours; will often not result in complete reversal and not significantly affect re-establishment of anticoagulation with warfarin
   - High dose vit K (10mg) will slowly ↓INR over 12 hours → therefore often given together with clotting factors (e.g. FFP)
3. **FFP**
   - Plasma from donated blood, which contains all clotting factors → therefore immediately reverses coagulopathy
   - However, short DoA (24-48hrs) → therefore reserved for active bleeding
   - Dose 2-4 units depending on INR + bleeding risk
   - Disadvantages: large fluid vol, possible transfusion reactions e.g. immune, TRALI, infection
4. **Prothrombinex**
   - Human plasma derivative containing concentrates of FII, IX, X → therefore immediately reverses coagulopathy
   - Dose 25-50IU/kg
   - Advantages: reliable reversal, smaller fluid vol, avoids transfusion complications associated with FFP

- Disadvantages = expensive

5. **Recombinant activated FVII**
   - Controversial
   - Indication: life threatening bleed + ↑↑↑INR
   - Given with vit K + FFP
   - Disadvantage: thromboembolic complications

Outline the important pharmacological considerations when stopping warfarin and commencing prophylactic (low dose) LMWH in the peri-operative period: PAST QUESTIONS

Background

- management of anticoagulant during the perioperative period governed by balance between risk of bleeding vs. risk of thromboembolism
  - surgicalb bleeding risk high + VTE risk low → usually cease warfarin
  - surgical bleeding risk low + high VTE → usually continue warfarin
  - surgical bleeding risk high + high VTE risk → consider ceasing warfarin + bridging with LMWH

Considerations for stopping warfarin

- Slow onset long-acting anticoagulant
- MoA: competitively inhibits vit K epoxide reductase → inhibits y-carboxylation of clotting factors → ↓production of FII, VII, IX, X, protein C+S
- Monitored with PT and INR
- Most high bleeding risk surgery require INR <1.5
- Pharmacokinetics
  - Metabolised in liver; low clearance; T1/2 = 40hrs → thus clearance of warfarin + resynthesis of new factors II, VII, IX, X required for offset
  - Anticoagulation effect lasts 3-5 days → need to plan ahead of surgery
- Factors prolonging offset: need to cease warfarin for longer period
  - ↓warfarin metabolism/ liver enzyme inhibition: liver impairment, cytochrome inhibition e.g. amiodarone, fluconazole, metronidazole
  - ↓synthesis of clotting factors: liver impairment, vit K deficiency, cephalosporins
  - Vitamin K deficiency
- Reversal
  - Vit K: 1mg can reverse, but potential problems with warfarin effect post op
  - FFP: NB risk with blood products
  - PTX
  - Activated FVII concentrate
- Restarting warfarin post-operatively → takes 3-5 days for INR to reach steady state → initial phase of hypercoagulability due to ↓protein C and S levels before ↓FII levels

Considerations for starting LMWH

- LMWH = mucopolysaccharides; fast onset + short acting
- MoA: enhance action of ATIII in the inactivation of FXa → inhibit the final common pathway
- Dose: 1mg/kg BD (dose ↓in renal impairment) or 1.5mf/kg daily up to 100mg; subcut
- Commence 2-3 days after warfarin ceased
- Onset:
  - Monitored with anti-Xa assay
  - Onset usually 1hr after subcut injection
  - Peak effect 4hrs
  - DoA: >12 hours (depends on renal function)
  - Usually started when INR below therapeutic range
- Usually ceased 12hrs preop + before any neuraxial blocks assuming normal renal function

Describe the side effects and complications of heparin: PAST QUESTION

Background

- heparin = anionic mycopolysaccharide, commonly used as anticoagulant
- 2 common preparations: unfractionated: MW 5-25kDa or LMWH: MW4-8kDa
- Side effect = unwanted harmful actions of a drug

Side effects: related to dose + duration of therapy

1. **haemorrhage**
   - Ieg ICH, GI; 2o excessive dose
   - mechanism: UH binds ATIII → ↑inactivation of FXa, IIa + FXIIa, Xia, IXa + platelet aggregation
   - UH unpredictable + narrow therapeutic window therefore need to titrate slowly + monitor with APTT → reversed with protamine
   - LMWH more predictable; not reliably reversed with protamine
2. **Heparin induced thrombocytopenia and thrombosis syndrome (HITTS)**
   - Type 1:
     - 30-40% with UH
     - non immune mediated
     - <4 d of starting UH
     - usually not associated with thrombosis
     - self limiting
   - Type II
     - 5% with UH
     - IgG mediated (forming IgG PF4 heparin complexes)
     - Usually 5-14d after starting UH
     - Marked thrombocytopenia <50
     - Associated with thrombosis
3. **Hypotension:** 2o rapid IV administration → direct vaso + venodilation
4. **OP**: prolonged UH admin
5. **Alopecia**: prolonged UH admin
6. **Anaphylaxis** (esp. bovine preparations)

Describe the mode of action of protamine and potential adverse reactions

Protamine sulphate is a basic protein specifically used for the reversal of unfractionated heparin

Mechanism

- basic cationic binding protein combining with an acidic anionic compound to form stable salt complex: protatime = +vely charged → electrostatically binds to –vely charged heparin → forms stable inactive protamine-heparin salt complex → prevents heparin binding to ATIII → complex cleared by RES
- more effective reversal of anti-IIa effect than anti-Xa effect → therefore less effective at reversing LMWH

Dose

- 1mg protamine IV → reverse 100 units IV heparin
- reversal <5 mins

Side effects

- **CVS**:
  - Histamine release → vasodilation, flushing, SOB, hypotension, bradycardia
  - direct myocardial depressant
  - ↓SY outflow from SNS via complement activation + leukotriene release
- **Resp**
  - Thromboxane + 5HT → pulmonary vasoconstriction, HTN, oedema, bronchoconstriction
  - Complement + thromboxane → pulmonary HTN
  - Non cardiogenic pulmonary oedema: thromboxane mediated
  - Bronchospasm
- **Immune**
  - Anaphylactoid/ anaphylaxis: possible cross reactivity with protamine containing insulin
- **Blood**
  - Anticoagulation: if dose given in excess of reversal
  - Heparin rebound phenomenon due to rapid clearance of complexes by RES
- **Drug interactions**
  - Incompatibility with certain antibiotics (inc cephalosporins/ penicillins)
  - May ↑duration of NDNMB

Describe methods to reverse the effect of warfarin

See above

Classify and describe the pharmacology of anti-platelet drugs

Antiplatelets = drugs which impair platelet adhesion/ activation/ aggregation

Classification of antiplatelet agents

- COX inhibitors: aspirin; NSAIDs
- ADP R inhibitors: clopidogrel, prasugrel, ticegralor
- GPIIb/IIIa inhibitors: abciximab, tirofiban
- Phosphodiesterase inhibitors: dipyridamole
- Other agents: dextrans, heparin

	Irreversible COX inhibitor	**Reversible COX inhibitor**	**ADP receptor inhibitor**	**GPIIb/IIIa**	**PDE inhibitor**
Example	Aspirin	Diclofenac	Clopidogrel	Abciximab	Dipyridamole (asasantin)
Chem	Aromatic ester of acetic acid	Phenylacetic acid derivative	Thienopyridine		
Uses	Analgesic / anti-inflammatory /antipyretic Prevention post MI Prevention of graft occlusion post CABG Rx pre-eclampsia DVT prophylaxis in ortho	Analgesic, anti-inflammatory, antipyretic RA, OA, MSK disorders/ Ank spond / gout Renal/ biliary colic Minor post-surgical pain	ACS, recent MI, CVA, TIA PVD Revascularization procedures		
Pres	75/100/300/600mg tablets	25-100mg tablets/ suppositories ampoules 25mg/ml or 75mg/ml Diclofenac sodium for IV slow release available	75/300mg tablets		
Action	**Irreverisbly inhibits platelet TXA2** As platelets anucleic → unable to regenerate TXA2 → ↓platelet aggregation + ↓adhesion	**Non specific reversible COX inhibitor** → thus preventing formation of PGs, thromboxanes, prostacyclin - COX converts arachadonic acid to cyclic endoperoxidases - PGs involved in sensitization to peripheral pain Rs May also inhibit lipo-oxygenase pathway by action on hydroperoxy FA peroxidase	Pro-drug → activated by liver → **irreversibly block ADP platelet Rs** → prevents ADP mediated activation of GPIIb/IIIa complex → ↓platelet aggregation	Tightly complexes GPIIb/IIIa R → block fibrinogen, fibronectin, vWF binding → ↓platelet aggregation **(final common pathway)**	Inhibits PDE → ↑cAMP → ↓[Ca2+] within platelet → block plt aggregation response to ADP
CNS	Antipyretic: inhibition of PG synthesis				
CVS	↓risk MI/ CVA ↑bleeding		Nil		Vasodilation, ↓BP Coronary steal
Resp	↑O2 consumption + CO2 production by uncoupling oxidative phosphorylation	Bronchoconstriction + eosinophilia in asthmatics	Nil		Bronchospasm
AS	↑gastric acid production	Less GI damage than aspirin or indomethacin	Nil		
Other	Reye's syndrome: mitochondrial damage, hepatic failure, cerebral oedema, encephalopathy in children <12	Interfers with neutrophil function			
Toxicity/ SE	Related to non-specific blockade of COX1 and COX2 → ↓PG synthesis ***GIT***: ↑gastric acid, ↓mucosal barrier → PUD/ GI upset ***Renal***: ↓PG dependent renal artery dilation → AKI/ failure in susceptible; papillary necrosis (in chronic) ***Resp:*** ↑O2 consumption/ CO2 production at therapeutic doses → uncouples oxidative phosphorylation ***OD***: ↑RR → resp alkalosis 2o direct stimulation of resp centre, metabolic acidosis 2o nature of drug	COX 1 effects: dyspepsia, nausea, PUD, diarrhoea Disease exacerbation in crohns/ UC	Bleeding Neutropenia	Bleeding; ↓platelet; hypersensitivity; anaphylaxis	↓BP
Route/ dose	PO: 100mg daily (300mg loading)	PO 70-150mg/day IV: 25-75mg to max 150mg/day	75mg daily for ACS: 300mg loading dose		
Onset					
Duration	7-10 days (until formation of new platelets)	4-8hrs	7-10 days (until formation of new platelets)	48hrs; residual effect up to 15days	24hrs
A	Bioavailability 70%; extensive 1st pass metabolism	Bioavailability 60%	Bioavailability 50%		
D	80% PB Vd 10L/kg PkA3: unionized	99.5% PB (1o albumin) VD 0.1L/kg	98% PB VD data incomplete		

	Limited ability to cross BBB				
M	**Liver** 50% to salicylurate 20% to salicylphenolic glucuronide Non linear kinetics 2o presence of 2 saturable pathways: dose dependent elimination	Hepatic hydroxylation + conjugation to inactive metabolites	Extensively metabolised in liver → rapid hydrolysis to carboxylic acid derivative (active) CYP450 pathway	Rapid metabolism by plasma proteases	Hepatic metabolism
E	**Renal**	Renal 65% urine + bile 35% <1% unchanged clearance 263ml/min elimination ½ life 1-2hrs	50% urine; 45% faeces single dose ½ life 6hrs; ½ life active metabolite 8hrs		Biliary excretion
Special points	Use in children is associated with **Reyes** syndrome May ↑effects of co-administered oral anticoagulants + sulfonylureas due to displacement from plasma proteins	No effect on bleeding time, PT, plasma fibrinogen, FV, VII, XIII			

Dextran:

- plasma vol expanders → polysaccharides (bacterial fermentation)
- MoA: specific inhibitor of vWF → ↓platelet adhesion
- Adverse effects: fluid overload, allergy/ anaphylaxis
- Metabolised

Prostacyclin (PGI2)

- MoA: inhibits platelet adhesion/ aggregation 2o ↑asenylyl cyclase activity: ↑cAMP → ↓Ca2+ intracellular → ↓release reactions / ↓TXA2 from arachadonic acid
- Adverse effects: 2o vasodilation → ↓MAP, reflex ↑HR, flushing, headache
-

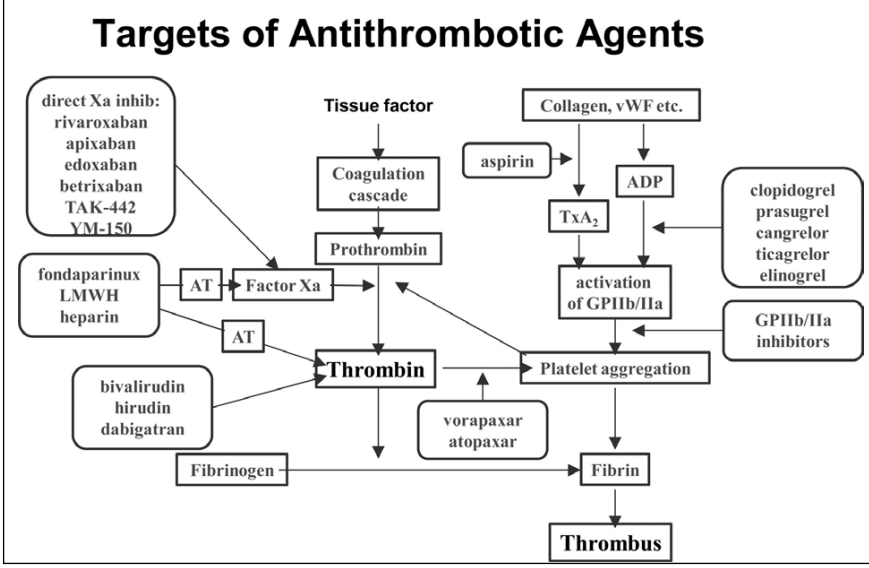
List the drugs used clinically as anti-coagulants and anti-thrombotics. Write short notes on the mechanisms of their actions: PAST QUESTION

Anticoagulants are drugs that delay or prevent clotting of blood by direct or indirect actions on the coagulation system. No effect on thrombus after it is formed

- Heparin: reversibly binds to ATIII + potentiates its effect. At low doses this inhibits FXa and high doses it inhibits thrombin, XIIa, Xia, IXa + platelet aggregation
- LMWH: binds to ATIII + preferentially inhibits Xa compared to thrombin
- Warfarin: competitively inhibits vit K epoxide reductase → preventing oxidised vit K to return to its reduced form which is necessary for the gamma-carboxylation of glutamic acid residues of the inactive precursors to become FII, VII, IX, X, protein C/S
- Dabigatran: competitive reversible non-peptide antagonist of thrombin (PO heparin)
- Rivaroxaban: competitive reversible antagonist of activated FXa (PO LMWH)
- Apixaban:

Antithrombotics: influence the formation of thrombus by interfering with the normal adhesive and aggregation activity of platelets

- Aspirin: irreversible inhibition of platelet COX preventing formation of thromboxane A2 which is a potent vasoconstrictor and platelet aggregator
- Clopidogrel: irreversible inhibition of platelet ADP Rs → inhibits platelet activation, aggregation, degranulation
- Dipyramidole: inhibits adenosine uptake + phosphodiesterases → ↑cAMP + ↑cGMP, ↓Ca2+ → inhibiting platelet adhesion + aggregation
- Abciximab: monoclonal ab, an antagonist to the GPIIb, IIIa R which is final common pathway of platelet aggregation
- Tirofiban: nonpeptide
- Dextran: inhibits vWF + provides protective coat over endothelium, platelets, and RBCs
- Epoprostenol: stimulates adenylate cyclase, ↑cAMP, ↓Ca2_



Outline the pharmacology of thrombolytic agents

Outline the pharmacology of antifibrinolytic agents in particular tranexamic acid and aprotinin

	Tranexamic acid	**Aprotinin**
Chem	Synthetic analogue of amino acid lysine	Polypeptide derived from bovine lung tissue
Uses	Trauma, cardiac surgery, obstetric, menorrhagia	Major cardia/ hepatic surgery
Pres	Tablets, syrup, CCS for IV	10 million units/ml
Action	Reversibly inhibits the lysine binding sites on plasminogen → inhibits activation of plasminogen to plasmin → prevents plasmin binding to + degrading fibrin + preserves fibrins matrix structure	Competitive inhibitor of serine proteases (esp. trypsin, chymotrypsin, plasmin, kallikrein) Inhibits trypsin and related proteolytic enzymes → slows down fibrinolysis Inhibition of kallikrein → inhibition of formation of FXIIa → intrinsic pathway + fibrinolysis inhibited
Toxicity/ SE	Nausea, vomiting, allergic dermatitis	Anaphylaxis 1:200 first time use Thrombosis
Route/ dose	IV, PO 1g slow IV	Test dose 10 000 units → load 2 million units then 500 000 units/hr IVI
Onset		
Duration	3hr	
A	Bioavailability 50%	Rapid
D	3% PB VD 9-12L	Renal phagolysosomes and extracellular space
M	Minimal hepatic	Slowly metabolised by lysosomal enzymes
E	Renal 95% ½ life 2-11hr clearance 110ml/min	Renal 25-40% ½ life 3-10hrs

Outline the pharmacology of cancer chemotherapeutic agents with particular reference to problems that such agents may cause during the perioperative period

Chemotherapeutic agents

1. **alkylating agents**
   - nitrogen mustards: cyclophosphamide
   - alkyl sulfonates: bisulfan
   - nitroureas: carmustine
   - SE: D-D bone marrow suppression; GIT mucosal effect; acquired PChE deficiency
2. **Antimetabolites**
   - Folic acid: MTX → SE: GIT, BM suppression, pulmonary toxicity, non cardiogenic pulmonary oedema
   - Pyrimidine analogues: fluouracil → SE: MI
   - Purine analogues: azathioprine → SE: alopecia, GI effects
3. **Plant alkaloids**
   - Vincristine → SE: BM suppression, peripheral neuropathy, SIADH
4. **Antibiotics**
   - Bleomycin → SE: mucocutaneous reactions, minimal BM suppression; D-D pulmonary toxicity
   - Doxorubicin → SE: D-D cardiomyopathy
5. **Others**
   - Enzymes
     - Aspariginase → SE: min BM suppression; D-D neurotoxicity (2o NH3 accumulation)
   - Synthetics
     - Cisplatin → SE: renal toxicity, ototoxicity, peripheral neuropathy, dysrhythmias
   - Hormones
     - Corticosteroids
     - Progestins
     - Anti-oestrogens
     - Anti-androgens

Pharmacology of haematology – other

Outline the importance of vitamin K and the factors determining its uptake: PAST QUESTION

- vit K = fat soluble vitamin
- Reduced form = essential cofactor for gamma carboxylation of precursors to allow the ability to bind Ca2+

Required in:

- FII, VII, IX, X produced in liver.
  - Important for coagulation; deficiency of vit K or warfarin → ↑PT + bleeding
- Protein C/ S: antithrombotic activity by inhibiting Va/ VIIIa
- Osteocalcin produced by osteoblasts which participate in process of bone mineralisation → deficiency → OP
- Deficiency in newborns → bleeding

Factors determining uptake

- dietary intake of vit K1 (green leafy veggies)
- Production of vit K2 by gram +ve bacteria in GIT; can be inhibited by abx
- Impaired GI absorption: obstruction; disease of terminal ileum; use of cholestyramine (↓fat absorption); ↓transit time 2o drugs
- Vit K stores in liver, spleen, lungs → ↓stores → ↑absorption

IMMUNOLOGY

Explain how the body defends against infection

Write brief notes on innate and acquired immunity: PAST QUESTION

	Innate immunity	**Acquired immunity**
Characteristics	Natural immunity Non specific – no memory Not more efficient on repeat exposures	Adaptive immunity Specific, memory present ↑efficiency after subsequent exposure
Role	1st line of defence	2nd line of defence
Activity	Always present	Normally silent
Response + potentcy	Immediate but limited ↓[potenc	Slower response (days – weeks) ↑potency
Mechanisms	1. Physico-chemical barrier - prevent pathogen access to body - skin: antibacterial substances (lactic + FA) in sweat sebaceous secretions - mucous: traps pathogens → removed by ciliary actions - Hcl: bacteriocidal 2. Humoral defence: soluble factors - Complement cascade: opsonisation + lysis of pathogens; link innate + acquired immunity by activating B lymphocytes - Acute phase proteins, interferon, cytokines, inflammation → opsonisation + regulation of immune response - Proteolytic enzymes (lysozyme) → bacteriocidal 3. Cellular defence: granulocytes - Neutrophils, monocytes, basophils, eosinophils - Attracted toward infection by cytokines + C5a (chemotaxis) - Phagocytosis of pathogen → antigen presentation on MHC class 2 receptors to T cells - Natural killer cells (B cell lineage) → recognise host cells invaded by pathogens – display foreign peptide on MHC class 1R → cell death	**Cell mediated** 1. T lymphocytes: cell mediated immunity - Maturation in thymus - T helper cells (CD4) ○ TH1: secrete pro-inflammatory cytokines + activate macrophages ○ TH2: secrete cytokines + present antigen to B cells ○ Bind MHCII on APCs - T cytotoxic cells (CD8) ○ Directly kill pthogens ○ Bind MHCI on APC - T regulator cells ○ Regulate immune response 2. B lymphocytes: humoral/ antibody mediated immunity - Maturation in bone marrow - Plasma cells → produce specific antibodies to proteins or polypeptides - Activate complement cascade 3. Immunoglobulins: - Produced by plasma cells - 2 light chains + 2 heavy chains (determines function) - IgA: αheavy chains: mucosal surfaces - IgD: βheavy chains: unknown - IgG: gamma heavy chains: plasma immunoglobulins, crosses placenta (passive immunity) - IgM: mu heavy chains: early response during infection → activates complement

Describe the complement system: PAST QUESTION

Definition

- Proteolytic enzyme amplification cascade system; forms part of innate + acquired immune response
- Components circulate as inactive precursors
- Activation amplifies as a cascade; regulated by regulator proteins e.g. C1 esterase inhibitor
- Proteins produced by liver

Main functions

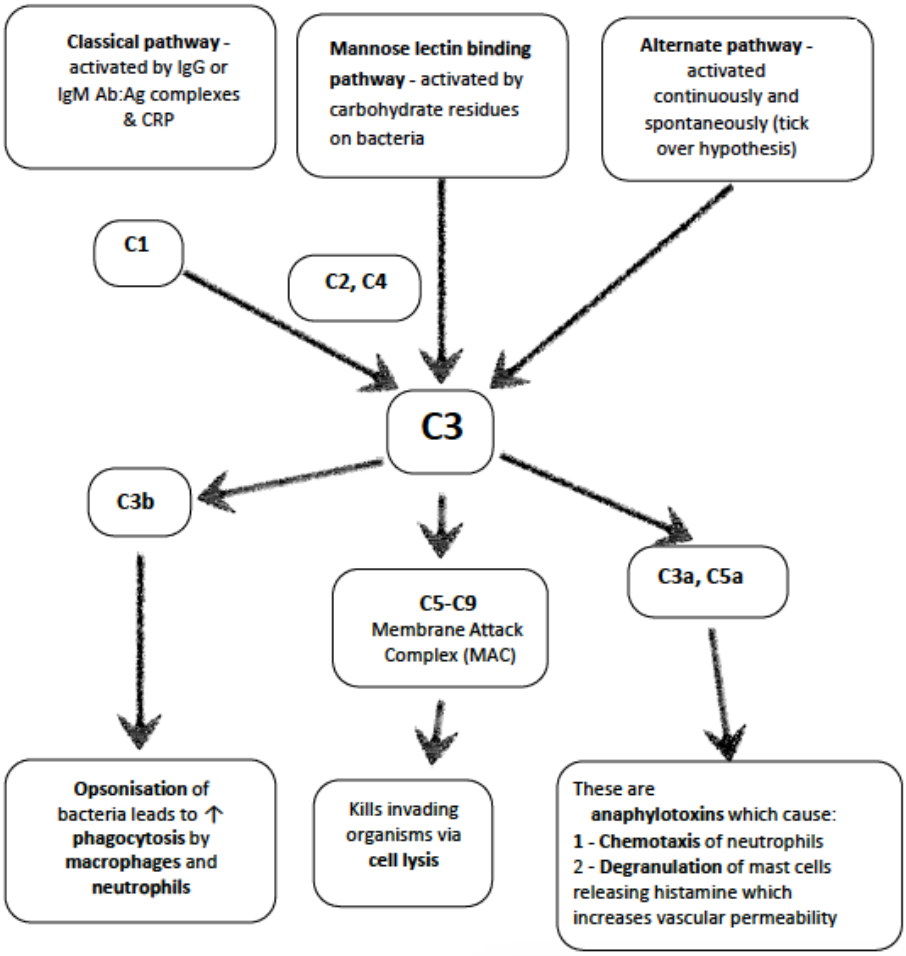
- cell lysis of bacteria (MAC)
- opsonisation → ↑phagocytosis
- release of mediators via mast cell degranulation
- local vasodilation
- neutrophil aggregation
- chemotaxis

Pathways

1. **classical – activation by Ag-Ab complex**
   - system of 11 enzymes
   - pathway activated by formation of Ag-ab complexes, CRP, aggregated Ig (IgM or certain IgG)
   - activates C1 → reactions involving C4+C2 → formation of enzymatic complex C4b-C2a → cleaves C3a and C3b → common pathway
2. **alternate – activation by lipopolysaccharides**
   - C3 undergoes slow, spontaneous conversion to hydrolysed C3
   - Multiple steps leading to complex ith C5 convertase → activation of common pathway
   - Nil ab required
3. **lectin – activation by mannose on surface of parasites, candida, viruses etc**

mechanism

- following activation → triggers final common pathway → C3 activation → C3b acts as C5 convertase → C5b binds C6-C9 → forms membrane attack complex → inserted into target cell membrane → leakage of cellular material → cell lysis + destruction



Describe how white blood cells defend the body against infection: PAST QUESTION

Immunity = capacity of the body to resist infectious microbes, disease, or unwanted biological invasions. Consists of innate + acquired defense systems

WBC consist of 2 groups

- **phagocytoes**
  - granulocytes (neutrophils, eosinophils, basophils) and monocytes
  - form part of innate immunity: natural defence without prior exposure; no specificity or memory
  - derived from pluripotent haemopoietic stem cells
  - cell mediated
    - mast cells
      - chemotaxis + inflammation → degranulation → inflammatory soup
    - neutrophils
      - engulf + digest invading organisms
      - move by chemotaxis (directed movement of cells along gradient of ↑concentration of attracting molecule
    - macrophages
      - ↑cytokines release, engulf debris
      - include: glial cells, medangial cells, kuppfer cells
      - phagocytosis + antigen presentation
      - important against intracellular pathogens
    - natural killer (NK) cells
      - recognition of antigens on target cells (tumour cells or virus infected cells) + antibody dependent cytotoxicity
      - NK cells attack host cells → release cytotoxic granules inducing apoptosis
      - Contain viral infetions while adaptive immune response generates antigen specific cytotoxic T cells to clear infection
- **Immunocytes**
  - B+T lymphocytes, precursor cells, plasma cells
  - Part of acquired immunity: requires pre-exposure to pathogen + characterised by immunological memory + specificity to pathogen

Antigen presentation

- macrophages + B cells act as APCs
- foreign Ag ingested by APC + coupled with MHC → these peptides are expressed on APCs cell surface
  - Ag: MHC1 activates killer T cells (CD8)
  - Ag: MHC2 activates helper T cells (CD4)

Cell mediated immunity (viruses, fungi, cancer) → mediated by cytotoxic T cells

- starts with B cell expression of Ag: HC1 (CD8)
- binding helped by CD8 co-R and helper T cell interactions
- binding activates cytotoxic T cell
- cytotoxic Y cell searches body for cells bearing a given Ag complex that activated it → insertion of perforins (creates ion channel leak via osmosis) + granulysin (protease that digests intracellular elements)

Humoral immunity (kills bacteria) → mediated by B cells + helper T cells (CD4)
- Ag: MHC2 attracts helper T cells that release lymphocykines that ↑B cell activity
- B cell divides producing plasma cells that are responsible for the production of all Abs in the body
- Ab binds to pathogen expressing Ag and earmarks it for destruction via complement system (MAC, opsonisation, chemotaxis, and degranulation) or via phagocytosis

Outline the effects of anaesthesia and surgery on immune function

Describe the immunological basis and pathophysiological effects of hypersensitivity

Hypersensitivity reaction = inappropriate or exaggerated immune response to foreign agent produced by a normal immune system
4 main types of hypersensitivity reactions

Type	Mechanism	Example
Type 1	**IgE mediated** - Initial exposure sensitises + produces IgE - IgE binds onto surface of mast cells - Subsequent exposure cause **mast cells** to release vasoactive substances (**histamine**, **kinins**, NO)	**Anaphylaxis** **Allergic** reaction
Type II	**Antibody** mediated - exposure to foreign agent → produce **immunoglobulins** (IgG, IgM) → activates **immune cascade**	**ABO incompatibility**
Type III	**Immune complex deposition** - exposure to foreign agent → activation of **complement cascade** → deposition of **complement** in capillary	Lupus nephritis **Serum sickness**
Type IV	**Cellular** - exposure to foreign agent → **antigen presentation** on cell → subsequent exposure activate **T cells**	**Mantoux test** Contact dermatitis

Outline the pathology of acute anaphylactic reactions with reference to the mediators released and their effects. Outline the role of epinephrine and its mechanism of action in treating anaphylaxis: PAST QUESTION

Anaphylaxis:
- acute severe type I hypersensitivity reaction affecting multiple organ systems
- most common triggers in anaesthesia:
  - Drugs: antibiotics, muscle relaxants
  - Haptens e.g. p-aminobenzoate
  - Iodine contrast
  - Chlorhexidine
  - Latex

Pathophysiology
- Multiple exposures to target allergen
- 1st exposure: allergen presented by T helper cells to B cells → B cells produce specific IgE to target allergen
- Circulating IgE attach to mast cells → ***sensitization***
- Subsequent exposure to allergen → allergen binds specific IgE on mast cells → mast cell ***degranulation*** → release of allergenic mediators
- Mediators trigger disseminated vasodilation + ↑vascular permeability +/- bronchospasm → ***anaphylaxis***
  - Histamine: Localised release → urticaria; Systemic release → H1 + H2 → vasodilation, ↑vascular permeability → ↓MAP
  - Bradykinin: ↑production PGI2, NO → vasodilation, ↑vascular permeability → ↓MAP
  - Prostaglandins: PGID2 → vasodilation, ↑vascular permeability, bronchoconstriction, chemotactic for neutrophils + activates eosinophils
  - Leukotrienes: LTE B4: chemotactic agent; LTE D4 + E4: angioedema, clotting/ thrombolysis/ DIC
  - Tryptase: activates complement, coagulation, kallikrein-kinin pathways → ↓BP, angioedema, clotting/ thrombolysis/ DIC
  - TNF-a: cytokine → propagates anaphylactic reaction
  - NO: vasodilates
  - Serotonin: vasodilation, bronchoconstriction, aplatelet activation
  - Platelet activating factor: acts at PAF Rs

Clinical effects
- Circulatory collapse: profound vasoplegia → distributive shock
- Airway obstruction: angioedema, bronchospasm,

Adrenaline
- CCS 1:1000 and 1:10 000
- Dose in anaphylaxis: IM 300-500microg; IV 50-100microg titrated; neb 1mg
- MoA: agonist at α1 and β-adrenergic Rs
  - α1: vasoconstriction + venoconstriction → counteracts vasodilation + ↑vascular permeability
  - β1: ↑inotropy → ↑CO → counteracts hypotension
  - β2: bronchodilation → counteracts bronchospasm
  - β2: mast cell stabilization → counteracts mast cell degranulation + mediator release
- side effects
  - α1: peripheral ischaemia
  - β1: ↑MAP, ↑HR, ↑inotropy → ↑myocardial o2 demand → ischaemia/ infarction, haemorrhagic stroke
  - β1: tachyarrhythmias

Outline the principles of tissue/organ transplantation and the mechanisms of rejection of allogeneic organs

Immunology – other

Outline the important features of the lymphatic circulation: PAST QUESTION

Lymphatic circulation consists of the lymphatic capillaries which arise in the tissues and drain lymph through the lymph nodes

Structure/ anatomy:

- lymphatic capillaries present in almost all tissues except cartilage, bone marrow, and CNS
- flow driven by intrinsic (smooth muscle in walls and valves) extrinsic (external pressure – muscular contractions and pulsations from neighbouring arterial vessels) factors
- flow unidirectional due to valves. Prevents return into interstitium
- lymph vessels travel with arteries/ veins
- nearly all lymph vessels pass through lymph nodes and return to circulation via thoracic duct (drains into circulation via the junction of L subclavian and internal jugular vein) + right lymphatic fuct
- 83% returns via thoracic duct

Composition

- lymph: interstitial fluid that enters lymphatic circulation
- protein: low cf plasma; same as ISF; 20g/L (hepatic lymph 60g/L)
- all coagulation factors
- low levels of fibrinogen due to lawge MW (difficult to cross capillary membrane)
- fat
- lymphocytes
- macrophages line sinusoids of lymph nodes of RES
- 3L/day producted: ↑with exercise

Functions

- return protein to circulation: maintain oncotic pressure gradient across capillary membrane
- transport of fat: 90% fat absorbed from GIT extruded from bowel epithelial cells into the ISF → passes into the central lacteal vessels in the villi. Fat forms chylomicrons → transported to the circulation via thoracic duct and do not pass through liver in the portal blood
- immunological
    - filtration + removal of bacteria: sinusoids of LN lined by macrophages of RES → phagocytose bacteria or cellular debri in lymph
    - lymphocyte circulation through blood + lymph
    - presentation of APCs to LNs
- formation of concentrated urine: removing protein rich ISF in medulla → water enters vasa rectaallowing maintenance of osmotic gradient

Factors that ↑lymph formation

- exercise
- peristalsis
- elevated capillary filtration e.g. venous HTN, ↑cap permeability

Outline the direct effects of endogenously released histamine: PAST QUESTION

General

- histamine = endogenous amine; stored in granulated vesicles in mast cells + basophils
- high concentrations in skin, lung, GIT
- non mast cell histamine in brain = NT
- mast cells degranulates in response to IgE and non-IgE mediated action
    - type 1 hypersensitivity reaction → allergy
    - non allergic e.g. cold/ pressure

Histamine receptors

- **H1:**
    - GPCR → phospholipase C → IP3, DAG → ↑Ca2+
    - CNS: post synaptic excitatory
    - CVS: ↓conduction AV node, Cor vasoconstriction
    - Vessels: vasodilation 2o ↑NO, ↑permeability, ↑prostacyclin production (vasodilation, ↓platelet aggregation, ↑airways resistance)
    - Resp tract: ↑bronchial smooth muscle tone; ↑mucous
    - Skin: stimulation of cutaneous nerve endings → pruritis
- **H2**
    - GPCR → ↑AC → ↑cAMP
    - CNS: post synaptic inhibitory
    - CVS: Cor vasodilation, +ve inotrope/ chronotrope
    - GIT: ↑gastric acid production (parietal cells)
- **H3** (only in research)

Brief notes on latex allergy: PAST QUESTION

General

- Prolific naturally occurring plant sap used extensively in medical + non medical settings
- Latex allergy manifests as type 1 or type 4 hypersensitivity reactions
- Cross sensitivity: bananas, avocado, kiwi

Type 1 hypersensitivity

- immediate hypersensitivity reaction
- occurs within sec to min post exposure
- IgE mediated
- Not related to dose: i.e. all or nothing
- Mechanism
    - 1st exposure doesn't call reaction → latex presented byhelper T cells to B cells → IgE ab produced + attached to mast cells "sensitisation"
    - 2nd exposure: arrival of antigen to sensitised mast cells → Ag attaches to IgE → mast cell degranulation → release of mediators: histamine, PAF, bradykinin, 5HT
- causes: vasodilation (erythema + wheal), ↑vascular permeability (angioedema, ↓circulating vol), bronchoconstriction, GIT pain, ↑secretions
- Ix: mast cell tryptase at 1 and 6 hours post exposure; skin prick; RAST
- rx: adrenaline + IV fluids

Type 4 hypersensitivity

- "delayed hypersensitivity" can occur 24hrs post
- Mechanism
    - 2o to Ag presentation to T cells → release of cytokines (IL2, IL4, INF-yamma) → activate macrophages locally → local release of inflammatory mediators
- causes: contact dermatitis
- ↑risk with atopy
- Ix: skin patch testing
- rx: avoidance, prophylactic H blockers / steroids have mixed evidence

IMMUNOLOGY RELATED PHARMACOLOGY

Outline the pharmacology of antimicrobial drugs and their interactions with other drugs used during the perioperative period

Classify antimicrobial agents by mechanism of action: PAST QUESTION

- antimicrobial: kills or suppresses growth of microorganisms
- antibiotic: specifically refers to chemical substances that is produced by microorganisms and has the capacity to kill or inhibit the growth of another microorganism

Antimicrobials

Antibiotics

1. **inhibit cell wall synthesis (bacteriocidal)**
   - Act on bacteria that have a cell wall consisting of lattice work of murein
   - Prevent cross linkage of molecules that make up the lattice
   - Includes:
     - B-lactams
       - Penicillins: thiazolidine rings
         - Contain beta-lactam ring → anti-transpeptidase activity
         - Action against: gram positive + GNC
       - Cephalosporins: hydrothiazine ring
         - 1st gen: cephalexin; cephazolin → boad spectrum; activity mainly against GM +ve
         - 2nd gen: cefuroxime → broader spectrum; includes GM -ve
         - 3rd gen: cefotaxime, ceftriaxone, ceftazidime → ↑GM –ve activity; penetrate CNS
         - 4th gen: cefepime → pseudomonas cover
         - 5th gen: ceftaroline → MRSA
       - Carbapenems: imipenem/ meropenem
         - Very broad spectrum; good GM+ve, GM-ve, anaerobic cover
         - Not active against MRSA and some enterococcal species
         - Beta-lactamase resistant → few options for treating ESBL
       - B lactam ring binds to proteins, preventing peptidoglycan cross linkage → cell lysis
     - Glycopeptides
       - Vancomycin → inhibits glycopeptidase synthesis → interfers with cell wall synthesis
2. **Inhibit protein synthesis (bacteriostatic/ bacteriocidal)**
   - **Macrolides**:
     - Azithromycin/ roxithromycin / erythromycin
     - blocks 50s ribosomal subunit → blocks translation of RNA
     - active against atypical bacteria (mycoplasma, chlamydia), MSSA, streptococci
   - **Lincosamides**
     - Clindamycin, Lincomycin
     - blocks 50s ribosomal subunit
     - mixed + anaerobic infections resistant to penicillins
     - Anti-exotoxin effect → necrotising soft tissue infections
   - **Aminoglycosides**
     - Tobramycin, Gentamicin
       - bind 30R ribosomal subunit → blocks transcription RNA;
       - not active against anaerobes because O2 is needed for uptake into the bacterial cell
       - synergistic with beta-lactams
     - Amikacin
     - GM –ve activity, enterococcus, stephylococcis, MRSA
   - **Fusidanes**
     - Fusidic acid
     - inhibits protein synthesis by complexing with elongation factor and GTP
     - Adjunct in invasive staphylococcal infections esp. joints + bone
     - GM-ve, atypicals, strep
     - Propensity to select for MRSA and clostridium difficile
3. **Inhibit DNA replication → bacteriocidal**
   - Quinolones:
     - Ciprofloxacin, norfloxacin, moxifloxacin
     - inhibits part of DNA supergyrase → blocks coiling of bacterial DNA
   - Rifamycins:
     - Rifampicin
     - binds DNA dependen RNA polymerase → blocks transcription RNA. GM+ve and GM –ve
     - GM+ve, MRSA
   - Nitroimidazoles:
     - Metronidazole
     - breaks DNA strands
     - anaerobic + protozoal infections

Antifungals

- Amphotericin: reacts with ergosterol in fungal cell membrane → creates pores → lysis
- Fluconazole → ↓ergosterol synthesis

Antivirals

- Aciclovir: blocks nucleic acid synthesis
- Zidovudine: reverse transcriptase inhibitor (retroviruses → HIV)
- Ritonavir: protease inhibit → results in product immature, non-infectious particles

Antimicrobial drugs and organisms they act on: MAKEUP

- b lactams
  - penicillins
    - narrow spectrum e.g. benzylpenicillin → gram +ve
    - narrow spectrum resistant to staph β-lactamase e.g. fluclox
    - moderate spectrum e.g. ampicillin, amoxicillin → gm +e, some gm –ve
    - broad spectrum resistant to staph β-lactamase: e.g. augmentin
    - antipseudomonal e.g. piptaz
  - cephalosporins
    - 1st gen: cephalothin
    - 2nd gen e.g. cefuroxime
    - 3rd gen: e.g. ceftriaxone
    - 4th gen: cefopran
  - carbapenems
    - gm +ve, gm-ve, aerobes, anaerobes
    - e.g. imipenem, mero
  - monobactams
    - gm-ve aerobies
    - e.g. aztreonam
- glycopeptides: gm+ve, MRSA e.g. vanc
- macrolites: gm+ve cocci, gm-ve cocci, anaerobes e.g. azithromycin
- lincosamines: gm +ve aerobes, most anaerobes, MRSA e.g. lincomycin, clinda
- aminoglycosides: gm-ve e.g. gent
- tetracyclinces: gm+ve, Gm-ve e.g. doxy
- quinolones: gm-ve e.g. cipro
- nitroimidazoles: anaerobes, protozoa e.g. metronidazole
- sulphonamides: e.g. sulphamethoxazole
- pyrimidine derivatives e.g. trimethoprim
- rifamycins: gm –ve, mycobacteria e.g. rifampicin
- fusidanes: narrow spectrum, s aureus e.g. fusidic acid

Explain the principles of antibiotic prophylaxis

Using cephazolin as an example in joint replacement surgery, outline the principles of antibiotic chemoprophylaxis for surgical site infections: PAST QUESTION

Background

- surgical chemoprophylaxis = use of antibiotics to prevent infection at the surgical site
- chemoprophylactic agents should:
  - be used with aim of preventing infection not treating established infection
  - be used for shortest possible duration in order to ↓risk of resistance
  - ↑therapeutic index – minimal side effects
  - be cost effective
  - be repeated if surgery is prolonged
- Choice depends on:
  - Surgical factors
    - Clean vs. clean-contaminated vs. contaminated
    - Clean surgery normally does not require chemoprophylaxis
    - Joint replacement → insertion of prosthesis, which ↑risk and morbidity associated with surgical site infection → chemoprophylaxis
    - Contaminated surgery – may need to cover gram –ve +/- anaerobes
  - Patient factors
    - Allergies
    - Skin flora: e.g. MRSA

Cephazolin

- 1st generation cephalosporin
- contains beta lactam ring → disrupts bacterial cell wall synthesis → bactericidal
- narrow spectrum (therefore less resistance), high therapeutic ratio, minimal side effects/ toxicity; cheap
- coverage:
  - Gram +ve organisms
  - Good for common skin flora: staph + strep
  - Appropriate choice for joint replacement if pt does not have MRSA
- Timing: >15mins <60mins before skin incision and tourniquet inflation
- Duration: 4-6hrs (renal elimination) → repeat dose in prolonged; renal dose adjustment
- Dose: 1g for adult; 2g if 70-120kg; 3g if >120kg

Outline the pharmacology of antiseptics and disinfectants, their clinical use and associated risks

Antiseptics

- Ethanol: bactericidal → denatures proteins and dissolves lipids → cell lysis
- Chlorhexidine: bactericidal → alters cell wall permeability → cell lysis
- Povidone iodine: continuous release of iodine penetrates cell walls and alters or discontinues protein synthesis

Immunology/ micro – other

For each microbe listed, list the most appropriate antibiotics for treatment of infection resulting from these organisms: MAKEUP

- Candida glabrata → voriconazole/ caspofungin/ amphotericin B
- Clostridium perfringes → penicillin / meropenem/ metronidazole
- Listeria monocytoenes → penicillin / ampicillin
- Neisseria meningitides → ceftriaxone / penicillin (high dose)

- Multi resistant acinetobacter → amikacin/ polymixins
- Nocardia → sulphonamides
- Penicillin intermediate pneumococcus → ceftriaxone / vancomycin
- Vancomycin-resistant enterococcus → linezolid/ daptomycin

Post antibiotic effect: MAKEUP

- Persistence of antibiotic effect observed long after the serum concentration has falled below the MIC
- Seen in antibiotics which inhibit some life-sustaining enzyme, or which bind tightly to cell wall components
- ***Strong post antibiotic effect***
  - mainly seen in drugs which have concentration-dependent kill characteristics
  - benefit from large intermittent doses; high peak concentrations translate into better post-antibiotic effects
  - Drugs:
    - aminoglycosides
    - clindamycin
    - macrolides
    - tetracyclines
    - rifampicin
- ***Moderate post antibiotic effect***
  - seen in drugs that have time dependent kill characteristics
  - includes:
    - carbapenem
    - fluoroquinolonges
    - glycopeptides
    - linezolid
- ***Weak or absent post-antibiotic effect***
  - usually a feature of drugs which act at some critical point in the bacterial reproductive cycle
  - drug must therefore be present in the over MIC concentration at that critical point
  - includes:
    - βlactams
    - cephalosporins
    - monobactams

MIC: MAKEUP

- Minimum inhibitory concentration – primary measure of antibiotic activity
- the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation
- usually reported as ug/ml
- lower MIC = ↑effective abx
- Disadvantages:
  - Minor variations in methodology → large variations of MIC
  - Interlab variation in technique
  - MIC = inhibition of *visible* growth → microorganisms weren't necessarily killed
  - May not be related to in vivo efficacy; abx with low MIC may have no effect if it doesn't penetrate into infected tissue and abx with ↑MIC will still be effective if it happens t be concentrated in the infected tissue (i.e. gent in urine)

Killing characteristics of antibiotics: MAKEUP

- Time dependent killing: according to time spent over MIC
  - Antibiotics that kill bacteria most effectively when the bacteria are about to divide
  - E.g: b lactams, carbapenems, monobactams, linezolid, clindamycin, macrolides
  - If even 50% time spent over MIC = killing efficacy approaches max
- Concentration dependent killing: according to highest peak of concentration
  - Property of antibiotics which disable a crucial step in bacterial metabolism or protein synthesis → the higher the concentration eached, the more synthetic enzyme molecules are inhibited
  - E.g.: aminoglycosides, metronidazole, fluoroquinolones
- Time + concentration dependent killing
  - Property of drugs that inhibit steps in DNA synthesis or replication, or other bacterial components crucial to cellular division
  - Fluoroquinolones, azithromycin, tetrazyclines, vancomycin, linezolid

ESCAPPM organisms: MAKEUP

- induceable cephalosporinase: i.e. might occasionally appear to be sensitive to β-lactam abx, but who develop resistance rapidly due to expression of induceable chromosomal ampC cephalosporinase/β-lactamase enzymes
- AmcC β-lactamase
  - Chromosomal mediated enzyme
  - In given population of ESCAPPM organism, there are mutants which express this → during the course of rx this clone proliferates
  - Not inhibited by clavulanic acid → some inhibited by tazobactam (variable sensitivity to tazocin)
- ESCAPPM:
  - Enterobacter
  - Serratia
  - Citrobacter
  - Acinetobacter + aeromonas
  - Proteus
  - Providencia
  - Morganella

Resistant nosocomial infections: MAKEUP

MRSA

- fluclox (not methicillin) resistance defines the organism in hospital practice

- s aureus resistance = carried on MEC-A gene → codes for low affinity penicillin binding protein (2A) in the cell wall → confers resistance to all beta lactam antibiotics
- Infection
  - Can be asymptomatic carriage in anterior nares, axilla, perineum, imbilicus
  - wound infection, bacteraemia, VAP
- Risk factors
  - NH / previous hospitalisation
  - IDC, surgical wounds, burns, critical care stay
- Prevention
  - Appropriate antibiotic prophylaxis for surgical procedures
  - Barrier precautions / isolating carriers
  - Rapid screening of patients
  - Tracking of old MRSA cases
  - Use of penicillins or cephalosporins to treat skin infections in pts with previous MRSA (risk factor for MRSA bacteraemia)

VRE

- enterococcus (e faecalis / e faecium) = GM +ve gamma haemolytic cocci
- normal flora of intestine, female genital tract, urinary tract → intrinsic low pathogenicity byt high resistance to abx
- arrises in enterococcal populations in pts previously exposed to vancomycin, teicoplanin, and aminoglycosides
- at risk patients: transplant recipients, immunosuppressed, ICU patients, elderly, NG feed
- prevention + infection control:
  - restricted use of vanc/ glycopeptides
  - precautions
- treatment
  - linezolid,

Pseudomonas aeruginosa

- non-fermenting GM-ve bacillus
- treatment: aminoglycosides e.g. gentamicin, tazocin; mero; cefepime + ceftazidime combined with 2nd agent

ESBL

- infections: urosepsis, intraabdo + wound infections, VAP, bacteraemia
- carbapenems, nitrofurantoin in uncomplicated UTI

Name that microbe: MAKEUP

Gram positive organisms		Gram –ve organisms	
Obligate aerobes		***Obligate aerobes***	
Cocci	Bacilli	Cocci	Bacilli
coag –ve staph (staph epidermidis s. aureus strep pneumonia s. pyogenes	Cornebacterium diphtheriae Nocardia asteroids Bacillus anthracis	Moraxella catarrhalis Neisseria gonorrhoea Neisseria menigitidis	Pseudomonas aeruginosa H. influenzae Serratia marcescens Bordetella pertussis Burkholderia cepacia Legionella pneumophila Stenotrophomoas maltophila Acinetobacter Vibrio cholera
Facultative anaerobes		***Facultative anaerobes***	
Enterococcus faecalis Enterococcus faecium	Listeria monocytogenes		E coli Citrobacter Enterobacter cloacae Enterobacter aerogenes Klebsiella oxytoca Klebsiella pneumophila Morganella morganii Proteus mirabilis Salmonella typhi Shigella dysenteriae Yersinia pestis
Obligate anaerobces		***Obligate anaerobes***	
	Clostridium difficile Clostridium perfringens Clostridium botulinum Clostridium tetani		Campylobacter jejuni H pylori Bacteroides fragilis
Non gram stained organisms			
Mycobacterium avium Mycobacterium tubervulosis Mycoplasma pneumoniae Chlamydia pneumonia, trachomatis, psittaci			
Yeasts + fungi			
Candida albicans Candida non albicans Crytptococcus neoformans Pneumocystis jirovecci Aspergillus fumigatus			