Primary Cast Episode 30 - Pathology of Fluids, Haemodynamics & Haematology

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1. **Shock (general and hypovlaemic/haemorrhagic)**
   What is the definition of shock?

   A reduction in cardiac output or the effective circulating blood volume, resulting in hypotension, impaired tissue perfusion and cellular hypoxia

   What are the major categories of shock? Please give examples

   - Cardiogenic - AMI, cardiotoxins, arrhythmias
   - Obstructive - tension pneumothorax, cardiac tamponade, massive PE
   - Hypovolaemic - haemorrhagic, burns, GI losses
   - Distributive - anaphylaxis, adrenal crisis
   - Neurogenic - spinal injury , spinal anaesthetic
   - *Some people add in an additional category of Septic shock or systemic inflammation but this can also be considered a form of distributive shock - sepsis, pancreatitis, trauma (independent of haemorrhage)*

   Charlotte note: this is just one way to define them and you might see different categories from different sources. If there is a particular way that works for you then that is fine. These categories and examples are listed on the answer sheet from the 2017 exam so we know they have been listed like this in the past. In order to pass this question you only need 3 categories with one example of each, so you can relax a little bit about needing to mention every single thing.

   Describe the stages of haemorrhagic shock

   There are three main stages
   - *Non progressive* - where reflex compensatory mechanisms are able to maintain vital organ perfusion
   - *Progressive-* which is characterised by tissue hypo-perfusion and the onset of some early metabolic disturbances
   - *Irreversible -* characterised by non reversible cellular injury, manifesting as multi-organ failure

   What happens at the cellular and tissue level during the irreversible phase?

   - At a cellular level there is lysosomal rupture, cell membrane damage and mitochondrial dysfunction
   - At a tissue level, it is useful to think about the major organs critically affected in the shock process:

- Decreased myocardial contractility
- Acute tubular necrosis leading to acute renal failure
- Ischaemic gut leading to bacteraemic shock

Describe the initial clinical presentation of shock

- Tachycardia
- Tachypnoea
- Reduced urine output
- Cool peripheries, clammy skin and Increased capillary refill time
- *Narrowed pulse pressure*
- As shock progresses - hypotension, altered mental state and cyanosis

2. **Septic Shock**
   What are the mechanisms of gram negative sepsis?

Combination of direct microbial injury and overwhelming activation of host inflammatory responses by endotoxins.

These mechanisms include:

- Activation of the innate cells of the immune system - neutrophils, macrophages and monocytes
- Humoral interaction to activate complement and coagulation pathways
- Direct endothelial injury and activation

This leads to

- Inflammatory mediator release - TNF, IL (1,6,8,10), PGS, NO, PAF, ROS.
- Metabolic abnormalities (insulin resistance, hyperglycaemia, glucocorticoid disturbances)
- Immune suppression via activation of counter regulatory mechanisms with anti-inflammatory mediators, lymphocyte apoptosis and hyperglycaemic inhibition of neutrophils.

Tip for this one: we have just listed almost every component of the immune system - if all else fails, just list your best guess and you might be pretty close

What is an endotoxin?

Endotoxin refers to bacterial cell wall lipopolysaccharides, usually associated with gram negative bacilli. These are only produced when the bacteria lyses - or ‘ends’ hence endotoxin).
In contrast exotoxins are proteins which are produced and actively excreted by bacteria (excreted exotoxins, life ending endotoxins)

Consists of a generic fatty acid core and a complex polysaccharide coat unique for each species.

What is the effect of endothelial cell activation and injury during septic shock?

Thrombosis, increased vascular permeability and vasodilation.

What chemical mediators are involved in septic shock?

- Vasoactive amines - histamine and serotonin
- Plasma proteases - complement, kinins
- Platelet activating factor
- Cytokines - IL-1 and TNF
- Lysosomal constituents - proteases, lysozymes
- Oxygen free radicals, neuropeptides and nitric oxide

What are the effects of the inflammatory mediators on the coagulation pathway?

Microvascular thrombosis, decreased fibrinolysis and DIC

What factors determine the severity and outcome of septic shock in an individual?

- Disease factors: Extent and virulence of the infection
- Host factors: Immune status, Presence of other comorbidity, Pattern and level of mediator production

What are the potential outcomes of septic shock?
Because this is a pathology question we are wanting the pathological outcomes for organ systems

Good to try and break it down by organ here:

- At the heart we might see depression of myocardial activity, or cardiomyopathy
- Our large blood vessels dilate causing distributive hypotension
- In our lungs, leaky blood vessels permit fluid accumulation in small airways causing ARDS
- Inappropriate activation of the clotting cascade results in DIC
- Finally theres a cascade of progressive multi organ dysfunction / failure leading to confusion, coma and death
- *Liver failure*
- *Renal failure*

3. **Haemostasis**
   Describe the sequence of events at the site of a vascular injury

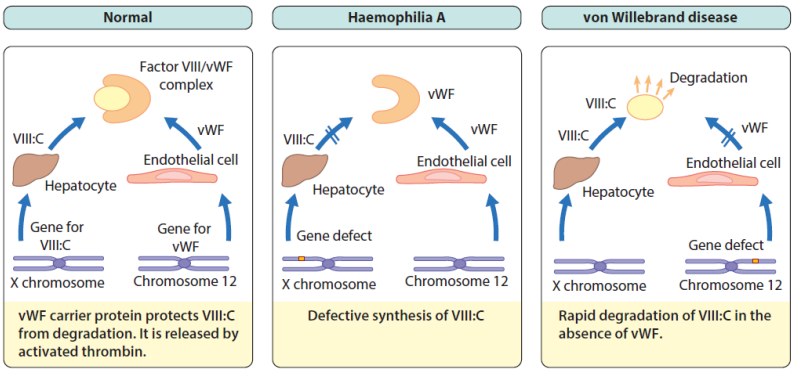
- *Immediate local blood vessel response: reflexive vasoconstriction* mediated by endothelin
- *Primary haemostasis, activated by exposed ECM permits platelet plug formation*
- *Secondary haemostasis* activated by intrinsic / extrinsic pathways permits stabilisation of the platelet plug with fibrin meshwork
    - Tissue factors exposed, Factor III, thromboplastin, Fac tor VII, consolidation of the platelet plug with the generation of thrombin and fibrin
- All the while, counter regulatory mechanisms (including tPA) prevent inappropriate clot extension and local vessel occlusion

Describe the process of primary haemostasis
Primary haemostasis refers to formation of the platelet plug.
These steps include: (1) adherence (2) activation (3) aggregation

- Endothelial damage exposes extracellular matrix (collagen, vWF)
- Platelet adhesion via GP1b to the von Willebrand Factor (vWF) on exposed ECM
- Platelets activate, causing shape change from flat to round and secrete granules - ADP, TXA2 and phospholipids
- Platelet aggregation via platelet GpIIb-IIIa receptor binding to fibrinogen

What are the haematological and clinical effects of von Willebrand disease?

- Von Willebrand Disease (VWD) refers to either a deficiency in von Willebrand Factor. This can either be a functional or true deficiency.
- The main function of vWF is facilitation of the adhesion of platelets to subendothelial collagen in haemostasis.
- It also leads to factor VIII dysfunction because in normal physiology vWF forms a complex with Factor VIII preventing it from being degraded.



Factor VIII synthesis: normal, haemophilia A and von Willebrand disease.
Source : Illustrated Textbook of Paediatrics Fourth Edition

Haem effects: Increased bleeding time with normal platelets, (Types 1 & 3)
Clinical effects: Spontaneous bleeding from mucous membranes, increased bleeding from wounds, menorrhagia, bleeding into joints is rare outside of type 3

What are the types?
Three main types:

- Type 1 most common (70%), autosomal dominant, decreased circulating vWF, usually mild.
- Type 2 less common(15-20%), autosomal dominant, defective vWF, mild.
- Type 3 rare, autosomal recessive, decreased circulating vWF, severe.

Arranged in order of increasing severity and rarity.

4. **Coagulation Cascade**
Give an overview of the coagulation cascade.

Coagulation cascade is what we're talking about when we're looking at secondary hemostasis.

- It is the component of haemostasis resulting in *thrombosis.*
- It involves a series of conversions of inactive *pro-enzymes to activated enzymes,* culminating in the formation of thrombin and insoluble fibrin meshwork.
- It comprises extrinsic and intrinsic pathways.
- The *extrinsic pathway* is activated by tissue factor exposed at sites of tissue injury
- The *intrinsic pathway* is activated by Factor XII
- These pathways converge at the activation of Factor X into the common pathway
- The common pathway involves factor X, prothrombin, thrombin, Factor V, Calcium and ultimately leads to the conversion of the soluble plasma protein fibrinogen to fibrin, which is an insoluble protein.
- Fibrin then ultimately becomes cross linked.

Summarise again with underlined key words

What does prothrombin time measure?
Extrinsic and common coagulation pathways (factors VII, V, X, prothrombin, and fibrinogen).

What does the partial thromboplastin time measure?
Intrinsic and common pathways
The way I remember this is that the PT, which is a shorter acronym, tests the shorter pathway (extrinsic)

In the normal coagulation cascade, what happens after factor X is activated?

Activation of factor 10 marks the start of the of the common coagulation cascade

- Conversion of prothrombin (II) to thrombin (IIa) requires calcium and activated Factor V (Va) as cofactors. It occurs on the surface of damaged endothelium

- Activated factor 2 (also known as thrombin) catalyses fibrinogen (I) to fibrin (Ia) in the presence of calcium
- Thrombin also catalyses factor XIII to XIIIa, which is known as stabilising factor, permitting increased cross linking of fibrin and the formation of a stable fibrin clot

Note: You are almost guaranteed to be asked questions about these pathways in the written - its useful to be able to write down the full coagulation cascade from memory so when you sit down you can jot it down (next to the brachial plexus) and refer to it for the remainder of the exam

5. **Regulation of Clot Formation**
   What mechanisms restrict the activity of the coagulation cascade to the site of a vascular injury?
   - Firstly Factor activation is restricted to the site of exposed phospholipids
   - Secondly, there are Natural anticoagulants, of which there are three types
     - *Antithrombins* (e.g AT3) inhibit the activity of thrombin and other serine proteases (IXa, Xa, XIa, XIIa). AT3 is activated by binding to heparin like molecules on the endothelium - which is the mechanism we take advantage of when we use heparin for anticoagulation
     - *Protein C & S* - these are vitamin K dependent proteins which directly inactivate factors Va and VIIIa.
     - *Tissue Factor Pathway Inhibitor (TFPI)* impedes the early stages of the coagulation cascade through affinity for factors VIIa and Xa
   - Fibrinolytic Cascade Activation:
     - *Plasmin -* Plasminogen is converted to plasmin by factor XII or by the two other plasminogen activators (u-PA or t-PA). It breaks down fibrin and interferes with polymerisation. The resulting fibrin degradation products also act as weak anticoagulants.
   - Endothelial cells modulate the coagulation/anticoagulation balance by releasing Plasminogen activator inhibitor (PAI) which blocks fibrinolysis by inhibiting the binding of t-PA to fibrin

   Describe the process of normal fibrinolysis
   - Plasmin is produced from circulating plasminogen either by factor XIIa dependent pathway or by plasminogen activators
   - Plasmin breaks down fibrin to fibrin degradation products (detected by D-dimer test) and disrupts polymerisation
   - t-PA from endothelial cells is the most important PA and is most active when attached to fibrin. Urokinase is similar to t-PA (u-PA) and is a circulating protein that has the same effect
   - Free plasmin is inactivated by alpha 2 plasmin inhibitor

6. **Haemophilia**

What is Haemophilia A?

A reduction in the amount or activity of factor VIII (also called anti-haemophilic factor)
Factor VIII is a cofactor for factor IX in the activation of Factor X

How is it inherited?

X-linked recessive trait, so affects males and homozygous females
30% have no family history so it can occur as a result of random mutation

Why do patients with Haemophilia A bleed?

Lack of Factor VIII affects the intrinsic pathway, leading to inadequate coagulation. Normally the extrinsic pathway produces the initial burst of thrombin activation that then activates the intrinsic pathway. In haemophilia this is not possible.

What is the association between clinical severity and Factor VIII levels

<1% severe
2-5% moderate
>6% mild

(Bonus Q) What are the other types of haemophilia?

Haemphilia B - Christmas disease, affects Factor IX
Haemophilia C - Affects factor XI
These are less severe and happen higher up in the coagulation cascade.

7. **Disseminated Intravascular Coagulation (DIC)**

What is DIC?

Dysregulation between the processes of coagulation and fibrinolysis causing widespread clotting and bleeding

Mediated by tissue factor release from endothelial cells and macrophages → overwhelming coagulation cascade activation and formation of microthrombi in the circulation.

Because this is such an overwhelming / widespread process, Consumption of platelets, fibrin and clotting factors Leads to coagulopathy. Simultaneous activation of fibrinolytic mechanisms aggravates the potential for haemorrhage.
Clinical picture is of infarction/tissue hypoxia as well as haemorrhage and microangiopathic haemolytic anaemia

What are some common triggers for DIC?

- *Sepsis* - particularly from gram negative endotoxins as well as meningococcal, malaria, histoplasmosis disease
- *Major trauma*/burns/surgery

- *Certain cancers* - AML, adenoCa of lung, colon, stomach
- *Obstetric complications* - placental abruption, amniotic fluid embolism, dead foetal tissue, toxaemia
- *Others* - heat stroke, snakebite, liver disease

When DIC develops, what is the process?
This is a question about pathogenesis.
DIC is triggered via 2 major mechanisms:

- Widespread endothelial damage, causing exposure of subendothelial matrix which activates platelets and coagulation cascade. TNF is an important mediator in this case. Seen with heat stroke, burns, trauma, meningococcal infections.
- Release of tissue factor or thromboplastic substances into the circulation. Seen with endotoxins, amniotic fluid embolism, adenocarcinoma mucus)

This leads to a procoagulant state, further perpetuated by the following:

- TNF causes more Tissue Factor to be expressed from endothelial cells
- Altered levels of Thrombomodulin (which is an anticoagulant)
- Decreased fibrinolysis by increased presence of the inhibitors of plasminogen activator
- Decreased production of protein C
- Stasis of blood, which decreases the washout of activated coagulation factors

All of these combine to promote the activation of thrombin and fibrin rich thrombi

What are the pathological consequences of DIC?
In DIC both sides of the clotting cascade are activated
This leads to 2 major consequences

- Deposition of fibrin within microcirculation leading to microthrombosis within vulnerable organs, haemolytic anaemia and ischaemia
- A consumptive coagulopathy where platelets and clotting factors are used up leading to a bleeding diathesis

In DIC, what would you expect to find on a FBC and coag profile?
↓ Hb due to haemolysis (MAHA)
↓ platelets
↓Fibrinogen and ↑ fibrinogen degradation products

↑ WCC
↑ INR/PT
↑ aPTT

8. **Thrombosis**

What pathological mechanisms might contribute to venous thrombus formation in a vessel?

Virchow's triad!
Endothelial injury + alteration to blood flow (either stasis or turbulence) + hypercoagulability of blood

What are some of the different risk factors for venous thrombosis?

Primary / genetic factors

- Mutations - factor V leiden, prothrombin gene
- Increased leveld of factors VIII, IX, XI
- Deficiencies - AT3, Protein C/S
- Fibrinolysis defects
- Non -O blood group

Secondary (acquired)

- Stasis from travel, bed rest, immobilisation
- Tissue injury - burns/fracture
- AF
- Cancer
- Prosthetic valves/intravascular devices
- External vessel compression (pregnancy included)
- Platelet abnormalities
- Hyperoestrogenic states i.e. OCP, post partum, pregnancy
- Sickle cell anaemia
- Smoking
- Antiphospholipid syndrome

What are the possible outcomes of a venous thrombus in an area?

- Propagation (resulting in occlusion)
- Embolisation - pulmonary or systemic
- Dissolution - due to fibrinolytic activity
- Organisation - fibrosis
- Recanalisation

What is an embolus?

A detached intravascular solid liquid or gaseous mass that is carried by the blood to a site distant to its point of origin

What are the different types of emboli/.

- Thromboembolus - venous to pulmonary, arterial to systemic
- Fat embolus
- Gas embolus
- Amniotic fluid embolus
- Air embolus

What is a systemic thromboembolism?
Refers to emboli in the arterial circulation

What are the possible sources of systemic thromboembolism?
Most (80%) are associated with intracardiac mural thrombi, ⅔ of which are associated with LV infarction and another ¼ associated with left atrial dilation and fibrillation
The remainder originate from aortic aneurysms, thrombi on ulcerated atherosclerotic plaques or fragmentation of a valvular vegetation with a small fraction due to paradoxical emboli

Where are they most likely to lodge?
Systemic thromboemboli are most likely to lodge in the lower limbs (75%), the brain (10%) or in the intestines/kidney/spleen or upper limbs

9. **Infarction**

What is an infarct?
An area of ischemic necrosis caused by arterial or venous occlusion

What mechanisms can lead to an infarction?
Arterial thrombus, embolism, vasospasm, haemorrhage into a plaque, extrinsic vascular compression (by mass or oedema), torsion of a vessel, traumatic rupture, entrapment in hernial sac, venous thrombosis

What factors determine the development of an infarct?
Nature of the vascular supply (end artery vs presence of collateral supply)
Rate of occlusion (may give time for collaterals to develop)
Vulnerability to hypoxia of the tissue type
Oxygen content of blood
Calibre of occluded vessel

10. **Oedema**

What factors govern the movement of fluid between the vascular and interstitial spaces?
Starling forces
Hydrostatic pressure, colloid osmotic pressure and normal capillary walls that retain most protein in the intravascular space, allow fluid to leak out.

What is oedema?
Increased interstitial fluid

Outline the pathogenesis of oedema
Can either be inflammatory (occuring as a result of increased capillary membrane permeability / leakiness) or non-inflammatory (occuring due to an imbalance of aforementioned starling forces)

Hydrostatic pressure and osmotic pressure normally balance to ensure that net fluid into and out of capillaries remains equal, with a small amount also removed by lymphatics. Increased hydrostatic pressure or diminished osmotic pressure OR overload of the lymphatics will cause fluid to build up in the tissues.

What are the major mechanisms of oedema formation and give examples of each.
Inflammatory
- Infection, issue necrosis, foreign body, immune, traumatic

Non Inflammatory
- Increased hydrostatic pressure
    - Local venous - venous obstruction, compression, thrombosis
    - Local arterial - dilation, heat, neurohumeral dysregulation
    - Systemic - CCF, constrictive pericarditis, impaired venous return
- Reduced plasma oncotic pressure - mainly vis protein loss i.e. nephrotic syndrome of poor production i.e. cirrhosis, malnutrition
- Lymphatic obstruction - inflammatory, neoplastic, post surgical, post irradiation
- Sodium retention with water - renal insufficiency, activation of renin-angiotensin system , renal hypoperfusion

What is the difference in composition of fluid between inflammatory and non-inflammatory oedema?
Inflammatory is ***exudate*** - high protein concentration (same composition as plasma)
Non inflammatory is ***transudate*** - low protein, filtered by an intact cellular membrane

What are the clinical features of heart failure?
- Lung - dyspnoea, orthopnoea, PND, pulmonary oedema, pleural effusions
- Cardiac - 3rd heart sound, displaced apex beat, AF, murmurs, JVP elevation
- Renal - fluid retention pedal oedema AKI
- Brain - confusion secondary to hypoxia
- Hepatic - congestion, ascites, cirrhosis (late)

What is the pathogenesis of cardiogenic oedema?
Decreased cardiac output, decreased renal perfusion, secondary hyperaldosteronism, increased blood volume leads to increased venous pressure

11. Anaemia

What are the causes of iron deficiency anaemia?

- Chronic blood loss - GI tract, menorrhagia
- Increased requirements - pregnancy, children
- Dietary lack - developing nations, infants with prolonged breastfeeding, elderly, restricted diet
- Impaired absorption - coeliac, gastrectomy

What are the symptoms of iron deficiency anaemia?

- General anaemia symptoms - fatigue, pallor, weakness, dyspnoea on exertion, angina
- Features of cause - menorrhagia, melaena
- Specific to iron deficiency - Koilonychia, alopecia glossitis, pica, pharyngeal web

What are the lab findings of iron deficiency anaemia? (Note - they may also hand you the results and ask you to interpret them)

- Microcytic, hypochromic anaemia
- Low Hb
- Low serum ferritin
- Low serum iron
- High transferrin iron binding capacity
- Low transferrin saturation

What is the pathogenesis of pernicious anaemia?

Immune mediated (likely autoimmune) destruction of gastric mucosa leading to chronic atrophic gastritis. This causes a Loss of parietal cells and reduced intrinsic factor production which in turn leads to reduced Vit B12 absorption from the gut, resulting in macrocytic anaemia

What are the clinical manifestations of the disease?

- Insidious onset due to large B12 stores
- Progressive unless treated
- Moderate to severe megalopbastic anaemia
- Weakness, tiredness, pallor
- Mild jaundice due to ineffective erythropoesis and enhanced peripheral haemolysis
- Leukopaenia and thrombocytopaeia
- Atrophic glossitis (shiny, glazed tongue)
- Neurologic manifestations including spasticity, sensory ataxia and lower limb paraesthesias

12. Sickle cell disease

What is sickle cell disease?

Hereditary haemoglobinopathy
Generally heterozygous (40%) which is asymptomatic unless hypoxic.
In homozygous disease, HbS instead of normal Hb. leads to alteration of the Hb when deoxygenated causing sickling + red cell membrane changes.

What are the major pathological manifestations of sickle cell disease?

- Haemolysis and haemolytc anaemia
- Microvascular occlusions - pain crises from tissue ischaemia in the bone, lungs, liver and spleen
- Splenic enlargement, infarcts and dysfunction (increased susceptibility to infection with encapsulated organisms e.g. strep pneumoniae, heumophilus influenzae.

What are the major precipitants for a sickle cell crisis in a prone individual?

Hypoxia, dehydration and/or a drop in pH

In general, how are haemolytic anaemias classified?

- Inherited genetic defects - spherocytosis, enzyme defects (G6PD), haemoglobinopathies - thalassemia, sickle cell
- Antibody mediated destruction - transfusion reactions, autoimmune
- Mechanical trauma, HUS, TTP, cardiac valves
- Infection in red cells - malaria
- Toxic - envenomation

13. Thrombocytopaenia

What are the causes of thrombocytopaenia?

Decreased production of platelets

- Generalised bone marrow depression (aplastic anaemia), marrow infiltration (leukaemia/cancer)
- Impaired platelet production via drugs (alcohol, medications) infections (HIV, measles)
- Ineffective megakaryopoiesis megaloblastic anaemia, myelodysplastic syndromes

Decreased platelet survival

- Immune destruction (autoimmune), iso-immune (transfusion, neonatal), drugs (quinine, heparin) infections (HIV, CMV)
- Non immune destruction (DIC, haemorrhage, TTP)
- Hypersplenism

Dilutional

What is the pathogenesis of immune thrombocytopaenic purpura?

- Formation of antibodies against platelet membrane glycoproteins (IIb-IIIa or Ib-IX)
- Antibodies evident in 80%
- Opsonised platelets are susceptible to phagocytosis
- Spleen is the major site of removal - 80% of patients improve with splenectomy
- Triggers: primary/idiopathic can be acute or chronic,
- Secondary via drugs or infection
- Can occur after viral infection and is self limiting - resolves in 6 months