Anticoagulation Cases

Dr J Mainwaring
Case 1

- 35 year old lady receiving a COCP falls at work and injures her left ankle

- Referred to A and E after the ankle becomes acutely swollen and painful.
Obvious very swollen left ankle with painful reduced ROM in all directions

Xray confirms a fracture-dislocation
Ankle reset and POP cast applied

She has a previous history of a pregnancy related left leg DVT from 8 years ago

Commenced on aspirin 150 mg daily – is this effective thromboprophylaxis?
Post-op Thromboprophylaxis

- Aspirin has an antiplatelet effect and is effective at reducing arterial rather than venous thromboembolic events.

- Recommend clexane 40 mg s/c daily +/- compression stockings until the patient is mobile and independent.
3 weeks later she is re-referred to the orthopaedic team because of increasing left calf pain.

POP cast removed and examination reveals a very swollen left calf.

Investigations?
- D-Dimers raised at 800 (NR < 300)
- Venous doppler scan confirms a left popliteal DVT
- Treatment?
Plasminogen

- tPA release

Plasmin

- Fibrinogen
  - Soluble fibrin
    - Fragment X, Y
    - Fragment D, E

- Factor XIIIa
  - activates thrombin

Crosslinked fibrin

- X-oligomers
  - D-dimer
Clexane 1.5 mg / kg / daily started plus warfarin as per a standard regimen

What are the usual starting doses of warfarin?
Clexane continued for at least 5 days and until the INR is > 2 – why is this required?

Could you have just treated him with warfarin?
Treatment of a DVT

- Clexane activates the naturally occurring anticoagulant antithrombin in order to destabilise the clot and encourage lysis.

- Warfarin reduces vitamin K dependant factors II, VII, IX, X hence reduces the risk of recurrence but does not aid clot lysis.
Treatment of a DVT

- Warfarin also reduces vitamin K dependant anticoagulants Protein C and S before it suppresses factors II, VII, IX and X, hence until the INR is > 2 the patient remains prothrombotic.

- Warfarin is therefore not an effective treatment for an acute DVT
Duration of warfarin

- Below knee DVT – At least 12 weeks and aiming for an INR of 2 to 3
- Above knee DVT or PE – At least 24 weeks
- Only stop warfarin if the symptoms / signs have resolved
Duration of warfarin

- If persisting swelling affecting the leg – arrange a repeat venous doppler scan.

- If the scan still shows a significant DVT with poor venous flow continue the warfarin

- Risk of recurrence is increased at least 3-fold if the scan remains abnormal or if the patient has a persistently elevated D-Dimer.
Case 2

- 89 year old man with AF has an elective total hip replacement performed

- Usually receiving 1 mg of warfarin per day with target INR 2 – 3.

- Warfarin stopped 5 days pre-op and INR is 1.2 on the morning of the operation? Safe to proceed
Safe INRs and procedures

- < 4  dental filling
- < 3  dental extraction
- < 1.5 major surgery
12 hours post-op started on Clexane 40 mg daily.

Day 3 post-op warfarin restarted, his INR is 1.0.

Initially started on 10 mg daily for 2 days followed by a check INR
Any thoughts regarding the warfarin dosing?
INR is checked on the 3rd day after warfarin has been restarted and the result is 3.9

Management at this stage?
Recommend stopping the clexane and warfarin then repeating an INR the following day.

Suggest daily INRs and restarting warfarin 1 mg daily when the INR is < 3.
Post-THR the incidence of a lower limb DVT is 40 – 80% hence recommend anticoagulation for at least 4 weeks post-op

Post-TKR the incidence of a DVT is 20 – 30% hence anticoagulation recommended for at least 2 weeks post-op
Case 3

A 29 year old woman with a post-partum PE diagnosed 9 days ago. She is well with no abnormal symptoms of note. Her INRs and warfarin doses for the past 4 days have been:-

- 1/4/07  INR 1.6  5mg
- 2/4/07  INR 1.3  7mg
- 3/4/07  INR 1.5  7mg
- 4/4/07  INR 1.4  ? warfarin dose
- With her falling INR despite 7 mg daily I would increase her INR to 8 or 9 mg that evening and retest 2 days later.

- Adjustment in the warfarin dose usually takes 2 days to cause the INR to change because Factor II has a half life of 2 – 3 days.
Clexane at treatment dose is required until the INR is > 2 and the patient is clinically improving.
Case 4

A 42 year old woman, recently diagnosed left leg DVT. During past 5 days the INR results and warfarin doses have been:-

- 1/4/07: INR 1.0 10 mg
- 2/4/07: INR 1.2 10 mg
- 3/4/07: INR 1.7 6 mg
- 4/4/07: INR 2.4 5 mg
- 5/5/07: INR 3.2 ? warfarin dose
- Rapidly rising INR hence suggest 3 to 4 mg of warfarin and repeat INR the following day

- If INR was > 4 suggest stopping warfarin and if > 8 consider low dose oral or IV vitamin K 0.5 to 2 mg
52 year old man with a femoral DVT diagnosed 3 months earlier, receiving 4 mg of warfarin per day, is admitted with haematemesis plus malaena.

BP 60/40 despite colloid infusions. Hb 52 g/l and INR 3.5. OGD reveals a bleeding gastric ulcer.
What treatment would you recommend?
- Ongoing resuscitation
- Local Rx for the bleeding ulcer
- Stop warfarin, PPI
- IV Vitamin K 2 mg and consider a Prothrombin complex concentrate such as BERIPLEX at a dose of at least 25 iu/kg
Beriplex

- Plasma derived
- Factor II, VII, IX, X concentrate
- Main indication – emergency reversal of warfarin in the context of a major bleed or emergency surgery
Aim for normal INR of < 1.3

Would you restart the warfarin once the patient has stabilised?
Safer to keep off warfarin and consider compression stockings plus mobilisation initially.

No need for temporary IVC filter 3 months post initial DVT

After 3 to 4 days could consider prophylactic Clexane 40 mg daily if his mobility is poor but only if there is no suggestion of ongoing GI bleeding.
Arrange a further venous doppler scan

If this shows a resolved DVT no need to restart warfarin
Transfusion cases
Case 1

- 36 year old man admitted to ITU with septicaemia
- Requires a central line to be inserted
- Hb 90 WBC 25 Neuts 17.9 Plts 70
- INR 1.45 APTT ratio 1.2 Fibrinogen 1.75
Does he need a platelet transfusion pre-central line insertion?

Does he need a FFP infusion pre-central line insertion?
Platelet transfusion thresholds

- < 50  central line, LP, liver biopsy, most ops
- < 80  epidural
- < 100 CNS, retinal, major vascular surgery and major trauma with CNS injury
Platelet transfusions

- 1 ATD (unit) contains $240 \times 10^9/l$ plts
- 1 ATD suffices for most indications
- Check plt count pre and 1 hour post-transfusion
- Good response associated with plt count rising by $20 - 40 \times 10^9/l$
Case 2

- 67 year old male 2 weeks post-sigmoid colectomy following a ruptured diverticular abscess
- Not eating, receiving IV antibiotics plus TPN
- Hb 90 WBC 3.8 Neuts 1.8 Plts 90
- INR 2.1 APTT ratio 1.6 Fibrinogen 5.5
• Likeliest causes of the pancytopenia?

• Is a red cell transfusion required?

• Likeliest cause of the abnormal coag screen and treatment required?
Likely acute dietary folate deficiency
- No need for red cell transfusion

Likely dietary vitamin K deficiency
- Rx with oral or IV vit K, no need for FFP
General red cell transfusion thresholds

- < 70 symptomatic, no haematinic deficiency, otherwise fit and well
- < 80 symptomatic, no haematinic deficiency, plus elderly or cardiorespiratory disease
Generally 1 unit of red cells will raise the Hb by 7 to 10 g/l

Poor response with active bleeding, sepsis, haemolysis and hypersplenism
Case 3

- 36 year old man involved in a major RTA presenting with multiple fractures and a significant head injury
- Severe generalised bleeding
- Hb 72 WBC 22 Plts 30
- INR 2.5 APTT ratio 2.9 Fibrinogen 0.4

**Cause of the abnormal coag screen?**

**Management?**
Disseminated intravascular coagulation related to major trauma and generalised tissue damage

Resuscitation, transfusions of red cells, FFP and platelets
Aims of treatment

- Hb > 80
- Plts > 75
- INR / APTT ratio < 1.5
- Fibrinogen > 1
Indications for FFP

- INR / APTT > 1.5 and acute bleed or surgery required related to:-
  - Liver disease
  - Disseminated intravascular coagulation
  - Factor II, V, X deficiencies
FFP

- Contains all 13 clotting factors
- Thawing takes 20 minutes
- Infuse at 15 mls / kg, each unit over 15 – 20 minutes
Cryoprecipitate

- Contains fibrinogen and factors VIII, XIII plus VWF
- Main indication is hypofibrinogenemia
- Dose = 2 units for adults
Severe acute transfusion reactions within 15 minutes

- Acute haemolytic transfusion reaction
- Bacterial contamination of the donor unit
- Acute anaphylaxis
Requesting a group and crossmatch

- Identify the patient and take a 6 ml EDTA sample
- Label the blood tube at the bedside
- Both the blood tube and blood request form require 4 points of ID
4 points of patient ID

- Christian name
- Surname
- Hospital number
- Dob
Other info on the request form

- Indication for transfusion
- Number of units required
- Special requirements e.g. irradiated
- When needed
**Blood Transfusion Request Form**

- **Cons/GP code:** 
- **Ward/Surg code:** 
- **Copy to:** Cons/GP code: __________ Ward/Surg code: __________
- **Patient category:** NHS □ PP(in) □ PP(out) □ Cat 2 □
- **Date taken:** 
- **Time taken:** 
- **Taken by:** (print)
- **Clinical Details / Reason for request:**
  - **High risk procedure?** Yes/No.
  - **6ml EDTA sample required (adult)**
  - **ID on sample must be hand written**
  - **Check following are completed:**
    - □ Full Name (no abbreviation)
    - □ Hospital No./First line of address
    - □ Date of Birth
    - □ Date and time sample taken
    - □ Signature

**Investigations required:**

- **No. RBC units**
- **Date required**
- **Time required**
- **CMV Neg** □
- **Irradiated** □
- **Paed.pack** □

**Other products:** FFP, Platelets, Cryoprecipitate, other special requirements, order by telephone request ONLY Ext.4620 bleep 2116 (1700-0900)

**Previous transfusion / atypical antibodies:**
- Yes / No
- Reactions? Yes / No

**Obstetric History:**
- Gravida ________ Parity ________ EDD ________
- Prophylactic anti-D date given ________

**See reverse for blood ordering schedule.**

**Blood transfusion Ext.4620 (Bleep 2116 (1700-0900))**

**Requesting MO's Sign.**

**PRINT**

**Bleep No**
<table>
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## Compatible ABO Groups for Red Cell Transfusions

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<tr>
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<th>DONOR GROUP →</th>
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<tr>
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More transfusion cases
Case 1

- A busy doctor takes blood for cross-matching from 2 patients on the same ward (JONES and SMITH) using a syringe and needle rather than vacutainers.

- Already pre-labelled the blood tubes and transfers the blood in the 2 syringes in to the separate tubes away from the bedside
Case 1

- Neither patient had their blood group checked before so no historical results available

- JONES is grouped as A Rh D negative and SMITH as O Rh D negative
Case 1

- 1st unit of red cells started on JONES at 10 am

- All checks indicate this is the correct red cell unit for the patient

- Within 10 minutes of starting a red cell transfusion becomes unwell with shortness of breath, chest and abdominal pain, rigors.
Findings

- Heart rate 140 SR
- BP 70 / 50
- Pyrexial 39°C but normal respiratory examination
- Normal obs pre-transfusion
Case 1 – Potential Diagnoses

- Acute Haemolytic Transfusion Reaction
- Bacterial contamination of donor unit
Acute HTR

- Classically Group O recipient given Group A, B or AB donor red cells
- Usually follows a clerical error
- Symptoms appear rapidly within 10 minutes of starting the transfusion
Bacterial contamination

- Strep / Staph
- Gram negatives – Ecoli, Pseudomonas
- Anaerobes
Symptoms / signs of acute HTR and bacterial contamination

- Feeling of apprehension
- Chest, back and abdominal pain
- Pain at venflon site
- Fevers and rigors
- Hypotension
- Bleeding from venepuncture sites
Management

- Stop transfusion
- Start fluids – aim BP ≥ 90 systolic and urine output ≥ 0.5 ml / kg / hour
- Urinary catheter
- Post-cultures start IV Tazocin / Gentamicin
- Contact seniors / haematologist
- May need transfer to ITU
Management

- Check details between recipient and donor unit
- Repeat ABO / D type on recipient
- Repeat crossmatch (pre and post-transfusion reaction samples)
- Blood cultures – patient and donor unit
- Return donor unit to blood bank
What went wrong

- Blood from SMITH was added to the tube marked with JONES’s details.

- Inadvertently it then looked like JONES was group A Rh D negative even though his true group was O Rh D negative.
What went wrong

Once group A blood was transfused to JONES his naturally occurring anti-A interacted with the A antigen on the donor red cells triggering an acute HTR!
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Indications for red cell transfusion

- **Hb < 70 g/l** – symptomatically anaemic, no treatable haematinic deficiency.

- **Hb < 80 g/l** – as above + elderly or significant cardiorespiratory disease.
How to avoid this

- Check patient details before taking samples
- Add blood to the tube and label this at the patient’s bedside
Case 2

- 56 year old woman. Multiparous, previous red cell transfusions relating to post-partum bleeds.

- Post-hysterectomy Hb falls to 95 g/l. Starts to receive 1\textsuperscript{st} unit of red cells.

- Within 10 minutes becomes acutely short of breath.
Case 2

- HR 140 SR
- BP 80 / 60
- Pyrexial 37.7°C
- Widespread inspiratory and expiratory wheezes
- Swollen lips and eyelids
- Hypoxic – pO2 7.5 kPas on air
Diagnosis?
Anaphylaxis

- Can be seen in IgA deficient recipients who have been previously transfused and now have Anti-IgA antibodies.

- The recipient’s Anti-IgA antibodies react against IgA in donor unit and trigger complement activation.
Anaphylaxis

- Severe urticaria, angioedema, hypotension, bronchospasm.
- Stop the transfusion
- IV Piriton 10 m, high flow O2, nebulised ventolin, steroids and even adrenaline for severe reactions.
Should she have been transfused in the first place

- Hb 95 hence would have recommended oral or IV iron instead of red cells
If transfusions are required in the future

- Use IgA deficient donors
- Washed red cells
Case 3

- Post-op patient, receiving TPN and IV antibiotics
- Hb 105 Platelets 120
- Mildly prolonged PT and APTT
Clotting cascade

Coagulation Cascade

Intrinsic Pathway
(Factor XII) → Factor XI → Factor IX → Factor VIII → Factor X → Factor V → Factor II (Prothrombin-Thrombin) → Factor I (Fibrinogen)
Case 3

- Patient has no bleeding and does not require an invasive procedure but treated with 4 units of FFP

- Within 8 hours of the FFP infusion becomes unwell with increasing dyspnoea
Case 3

- Examination reveals a sinus tachycardia, bilateral crepitations but no wheezes

- Hypoxic on air
Diagnosis?

- LVF
- TRALI
TRALI

- Neutrophil antibodies within the donor plasma react with recipient neutrophil antigens

- Neutrophil aggregation, degranulation and enzyme release occurs within the lungs
TRALI

- Usually within 6 to 24 hours of a transfusion
- Presents like LVF
- May initially need respiratory support
- Most recover within 5 – 7 days
What went wrong

- Likely acute vitamin K deficiency hence should have been treated with oral or IV Vit K rather than FFP
Once thawed

- Use FFP within 4 hours if kept at room temperature
- Use FFP within 24 hours if kept at 4C
Basic Haemostasis

- Fibrinogen
- Platelet
- von Willebrand's factor
- Endothelial cell
- Subendothelium
- GPIIb/IIIa receptor
- GP1b/IX

- Red blood cell
- Platelet
- Activated platelet
- Clot
- Fibrin
- Broken blood vessel wall
Normal Coagulation

- Vessel wall repaired.
- Natural anticoagulants (Protein C, Protein S, Antithrombin) and Plasmin prevent further clot formation and break down FIBRIN.
Bleeding Can Occur If

- Low platelet count
- Abnormal platelet function
- Reduced clotting factor(s)
Abnormal Bleeding history

- Spontaneous Bruising
- Recurrent nose bleeds
- Chronic Menorrhagia
- Protracted bleeding after dental extractions / operations / childbirth
- Positive Family history
Assessment of coagulation – blood tests
Prothrombin Time

- Assesses the so-called extrinsic clotting pathway.
- Addition of tissue factor (thromboplastin) and calcium to patients plasma
- Time to fibrin / clot formation = PT
- Normal PT 10 to 15 seconds
- PT assesses clotting factors VII, X, V, II and Fibrinogen
INR

- Used to monitor warfarin

\[ \text{INR} = \frac{\text{Ratio of Patients PT}}{\text{Normal control PT}} \]

- Target INR 2 to 3: - DVT, PE, AF
- Target INR 2.5 to 4: - mechanical heart valve
**APTT**

- Assesses the so-called intrinsic clotting pathway.
- Addition of synthetic collagen, platelet phospholipid and calcium to patients plasma
- Time to fibrin / clot formation = APTT
- Normal APTT 25 to 35 seconds
- APTT assesses clotting factors XII, XI, IX, VIII, X, V, II and fibrinogen
APTT

- Used to monitor effectiveness of IVI Heparin

- \[ \text{APTT ratio} = \frac{\text{Patients APTT}}{\text{Normal control APTT}} \]

- Target range 1.5 to 3.0
Commoner congenital Bleeding disorders

- Von Willebrand’s disease – low VWF
- Haemophilia A – low factor VIII
- Haemophilia B – low factor IX
Management of inherited bleeding disorders

- Avoid aspirin / minimise use of NSAIDS
- s/c rather than IM vaccinations
- DDAVP – mild VWD and mild Haemophilia A
- Various factor concentrates available to manage bleeds
Haemophilia A / B

- X-linked recessive disorders
- Affected males, carrier females
Severe Haemophilia A

- FVIII or IX < 1 iu/dl (normal level 50-150)
- Spontaneous muscle and joint bleeds
- Many need regular prophylactic FVIII or FIX concentrate Rx given 2 to 4 x per week to prevent bleeds.
Acute right knee bleed
Low platelets

- Pseudo-thrombocytopenia (artefact)
- Congenital
- Drugs – quinine, heparin, chemotherapy etc
- Autoimmune Thrombocytopenia (ITP)
- Liver disease
- Disseminated intravascular coagulation
Purpura
Artefactual platelet clumping in EDTA
Vitamin K deficiency

- Diet deficient in green vegetables
- Fat malabsorption – biliary / pancreatic obstruction
- Warfarin therapy
Liver disease

- Reduced synthesis of multiple clotting factors
- Bilary disease – fat and vit K malabsorption
- Low platelets - Hypersplenism
- Abnormal platelet function
Disseminated intravascular coagulation

- Endothelial damage, activation of coagulation and consumption of platelets plus clotting factors, hyperfibrinolysis

- Septicaemia, major trauma are typical causes

- Results similar to those obtained with liver disease

- Very high D-Dimers