Blood transfusion quiz

Michaela Lewin
Martin Besser
Andrew Klein
Papworth Hospital
1 The first IV transfusion

- A) Recorded by Galen in the 3rd century AD in a gladiator
- B) From Calf to Man by Denys in the 1660s
- C) First Battlefield transfusion recorded in the battle of Gettysburg in the American Civil War by the Confederates
- D) First Battlefield transfusion in the Boulogne Casualty Station 1870 by the French
- E) The world’s first blood bank was in Ipswich, UK
2 FFP was conceived by

- A) Albert Einstein in his time at the patent office in Bern, Switzerland 1903
- B) In the plasma for Britain campaign by Max Strumia 1940
- C) Spanish Nationalists in the Spanish civil war 1937
- D) Ferdinand Porsche as “Volksplasma” in the German war effort during WW2
- E) Yamamoto of the Japanese navy in preparation for the attack on Pearl Harbor
3 Cryo precipitate

- A) Should be irradiated
- B) Is rich in Factor IX
- C) Is rich in Fibrinogen and Factor VIII
- D) Is a pasteurised product and not made from UK plasma
- E) Is the preferred treatment for coagulation factor deficiencies for which there is no concentrated / recombinant factor available
4 Universal Leukodepletion

• A) Was introduced in 1999 to reduce the risk of vCJD transmission
• B) Was introduced to reduce the risk of Transfusion associated Graft versus Host Disease
• C) Reduces the risk of bacterial transmission
• D) Is performed in blood bank prior to issue from blood fridge
• E) Abolishes the risk of transfusion associated lung injury
5 Plasma fractionation (one FALSE)

A) Removes blood borne pathogens
B) Is no longer performed on UK plasma
C) Exposes the patient to more than 20,000 donations
D) Reduces the risk of Transfusion Associated Lung Injury
E) Allows the production of a number of products including Human Albumin, Fibrinogen concentrate, Prothrombin complex and Antithrombin
6 Irradiated blood

- A) Is only required by neonates and intrauterine transfusions
- B) Should be given to all pregnant women
- C) Is required life long in Hodgkin’s disease, regardless of remission status and after Fludarabine or Campath
- D) Removes the risk of CMV transmission
- E) Reduces the shelf life of the product
7) The most likely transfusion transmitted infection

- A) Staph Epidermidis
- B) MRSA
- C) Yersinia Enterocolitica
- D) Hepatitis B
- E) Hepatitis C
8) Donations from relatives

- A) Are encouraged to prevent the spread of blood borne pathogens
- B) Should not be irradiated
- C) Can be arranged at short notice with your local blood bank
- D) Are usually only considered in extremely rare blood groups or for white cell donations
- E) Do not carry a risk of Transfusion Associated Graft versus Host Disease
9) Autologous predeposit

- A) Can be arranged with your local blood bank
- B) Is not subject to good manufacturing practice
- C) Is acceptable to patients even who refuse blood transfusion for faith reasons
- D) Can cause AB0 incompatibility
- E) Is increasing in the UK
10) Intraoperatively venesected blood

- A) Should be stored in the blood fridge to prevent bacterial contamination
- B) Should be send to blood bank for safe keeping
- C) Should not leave the patient’s bed side
- D) Is regulated by the MHRA
- E) Can be mixed with drugs prior to reinfusion
11 Transfusion associated Graft versus Host Disease

- A) Can affect patients who have depressed T-cell immunity
- B) Is responsive to steroids
- C) Manifests within 48 hours of transfusion
- D) Is reported 1-2 dozen of times in a typical year in the UK SHOT report
- E) The NBS maintains a national registry with patients with this requirement
12 White cell transfusions

• A) Are not possible
• B) Are not irradiated
• C) Should be administered through a white cell filter
• D) Can be obtained by the NBS in exceptional circumstances
• E) Are superior to GSCF in the critically ill patient
13 Transfusion Reactions

A) All should be reported to MHRA
B) Could herald delayed postoperative haemolysis
C) AB0 incompatibility does not cause febrile reactions
D) Bacterial contamination has been virtually eliminated in the UK platelet supply
E) Are typically due to IgA deficiency
14 TRALI

- A) Affects only female patients
- B) Is caused by donor antineutrophil antibodies recognising antigen in the host and depositing in the lung
- C) Can be increased when pooled products are given
- D) Is prevented with leukodepletion
- E) Is caused by Rh incompatible platelet/blood transfusions
15. Platelets

- A) RhD prophylaxis should be considered if Rh+ platelets are given to Rh- recipients
- B) Are kept at 4 C
- C) Are now up to 30 days old
- D) Have the lowest risk of bacterial contamination of all blood products
- E) Contain no more than 50 x10^9 platelets in an adult dose
16. vCJD

- A) Has never been transmitted by transfusion
- B) All patients who received more than 70 donor exposures should receive a card by your blood bank
- C) All patients who received a UK plasma concentrate between 1980 and 2000 should have been notified by the DOH
- D) All surgical instruments need to be quaranteened if used in a patient at risk of vCJD from a public health perspective
- E) Can only be excluded by lymphocyte cross matching
17. HLA antibodies

• A) Are unheard of in patients that have never been transfused
• B) Are acquired by platelet transfusions only
• C) Recognize class II antigen on platelets
• D) May be responsible for poor platelet increment even in previously never platelet transfused patients
• E) Are treated with steroids
18. Blood Donation

A) As long as a patient has only received UK blood they are not excluded from donation

B) As long as a patient has only received blood from directed donations they are not excluded from blood donation

C) All patients who have received blood should be encouraged to donate blood to ‘pay back’ to society

D) A family history of vCJD should not preclude blood donation

E) Where possible only female plasma is used to produce FFP
19. Consent and Record keeping

A) Blood transfusion does not require consent
B) Records pertaining to blood transfusion are kept for 30 years
C) There is no need to document the indication for transfusion in the patient’s notes
D) A statement of life time transfusion received and special requirement will be sent to the patient’s GP by the National Blood Service
E) Fractionated products are not regulated by the MHRA blood bank regulations
ANSWERS
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Extracorporeal Membrane Oxygenation and the Haematologist the Devil is in the detail

Martin Besser
Consultant Haematologist
Papworth Hospital
Why disturb your haematologist?
Objectives

• Some practical advice

• What is ECMO and what has it got to do with blood
• Making sense of the advice from the haematologist
  – Blood and Plasma
  – Anticoagulation
  – Monitoring
• The bleeding patient
• What is von Willebrand factor
• Thrombocytopenia
Extracorporeal Membrane Oxygenation (ECMO) or Extracorporeal Life Support (ECLS)

- Life support by partial or total lung or heart and lung replacement by means of an extracorporeal oxygenator and pump(s)
What is it?

VA ECMO (central)

VA ECMO (peripheral)

VV ECMO (single cannula)

Courtesy of Dr. Guillermo Martinez, Papworth Hospital
The History of ECMO/ECLS

1952: Gibbon performs first successful CPB

1971: First Adult Survivor of CPB (NEJM 286:629)


1989: O’Rourke (Pediatrics 84:957-63) Success

1996: UK collaborative ECMO Trial Group (Paed) (Lancet 348:75-82) Success

2009 CESAR Trial Peek (Lancet 374:1351) Success

2011: Specialist Commissioning in the UK for 5 Adult ECMO centres

H1N1 – Swine Flu Pandemic
Why talk about the blood?

- Heparinized blood is aspirated through a cannula at a rate of approx 3l/min into a heparin bonded circuit
- propelled by a centrifugal pump with several thousand revs per minute
- trickled through a hollow fibre oxygenator with a high dwell time
- reinjected into either large vein or large artery and potentially then subject to normal pulsatile flow
ECMO

• Bleeding is common cause of death
• 50% of ECMO patients suffer neurological events (bleeding, stroke, other)
• Often subclinical vascular pathology at post mortem
• In our hands an ECMO patient day consumes in £1000 in blood & blood products in 2010/11
What we practice

• FBC; U&Es; LFTs; CRP Clotting (APTT, PT, APR, INR and antithrombin).

• Baseline low range ACT

• Inform haematology about ECMO plan and request
  – RBCs: 6 units in fridge initially then a minimum of 2 or 4 (if bleeding)
  – Platelets: ensure platelets available on site
Anticoagulants

• Unfractionated Heparin

• UFH 15U/kg/hr never above 20 U/kg (i.e approx 25,000/24h)
• APR 1.7-2.0, LRACT every 6hrs

• Hb >10 and keep Plt >150,000 if bleeding (i.e >2 ml/kg/hr or > 1g drop in 6hr)
• 2 Units of blood available at all times

• Aspirin for VA ECMO if bleeding <2 ml/kg/hr after d2
• TEG
Taming the Serin Proteases

- Heparin is a heterogeneous bioextract
- Plasma level and heparin effect highly variable between individuals
Heparin Effect
Not enough Heparin
Not enough Antithrombin
Too much Thrombin
Glossary: Blood vs Plasma

• Whole blood
  – Unstable, not suitable for light transmission based assays

• Plasma = Blood minus cellular particles
  – Subject to Volume variations during IV therapy

• Serum: Not of much interest to the haematologist: Plasma after clotting
How do we measure Heparin?

Heparin Level vs Heparin Effect

- Desired range is based on animal experiments with Protamine titration for VTE
- Or based on clinical experience with CPB
- Or extrapolation
ACT

• Heparin effect in whole blood
• Standard ACT unreliable at Heparin levels <1.0 U/ml
• Low Range ACT sensitive at levels 0.0 and up
• Not used for Heparin dosing outside CPB
• Poor agreement with AntiXa level
aPTT and APR

- Plasma assay
- Unusable for Heparin levels > 1U/ml
- Kaolin and Phospholipid
  - Organic source / natural source
  - Ranges vary
  - Designed to be sensitive to Lupus and deficiencies of VIII, IX, XI <40% of normal
  - Not all reagent / analyzer combinations fit for purpose
  - APR is only a crude tool
Plasma options

- AntiXa
- aPTT
- Protamin titration

MacDonald, S et al. unpublished
Bleeding
Paper cut or Melaena?

- Treatment locale specific
  - Drain site
  - Internal
  - ENT

- The “supraclavicular” and infradiaphragmatic bleeding history, i.e. Tonsils, teeth, epistaxis and groin (post angio)

- Harass your haematologist for more than platelets
Other Factors

- Assess degree of anticoagulation
- Exclude frank coagulopathy (i.e. check PT and Fibrinogen even when the aPTT/APR is in range)
- ?Bleeding History
- ?Paradoxical VTE/ischaemia
- ?CPB in last 24 hours
- ?cell saver in place
- ?recent fibrinolytics
- ?renal failure – your haematologist can’t spot the haemofilter from the lab
Papworth practice

- Keep Plt > 100, consider 150
- Keep PT < 20 sec (FFP, maybe Prothrombin complex)
- Keep aPTT < 48 sec (if not on Heparin)
- Keep Fibrinogen > 1.5g/l (Cryo, maybe Fg concentrate)
- Topical Haemostasis e.g. extra stitches, fibrin glues
- Check platelet increment
- Consider additional therapy
  - Tranexamic acid 1 g TDS +++
  - Topical Tranexamic Acid +
  - DDAVP 0.3ug/kg
- Is it acquired vWD?
Von Willebrand Factor

- Tethers platelets to collagen at sites of vascular injury, carries Factor VIII
- Multimer, contained in endothelium, liver, platelets
Antigen – Number of spanners
No information on function

Function assays:
Ricof screen

Collagen binding

Ristocetin induced Platelet aggregation (RIPA)

Ricof ≠ Ricof
Collagen binding ≠ Collagen binding
ECMO
- High vWF:Ag
- normal activity
- but disproportionate
What’s in the bag

• a population of platelets $240 \times 10^9$ in a dose
  – 750 – 2000 $\times 10^9$ already present in healthy recipient
    • i.e a platelet count of 100 -> 500$\times 10^9$ total circulating mass
    • $500 \times 10^9 + 240 \times 10^9 = 740 \times 10^9$
  – Or expressed in counts a net increase of 10 -15 $\times 10^9$ /l is expected

• express HLA class I
• up to 7 days old now
• stored at room temperature

• What are the options
  – Pool
  – Single donor apheresis
  – HLA Matched
The Increment

• Satisfactory if >10x10⁹/l 1 hour after infusion

• Lower increments can be caused by
  – Drugs
  – Other intervention (eg. Balloon pump)
  – Sepsis
  – HLA antibodies
Can I catch platelet refractoriness?

- Incidence of allo-immunisation is 10-25% (post introduction of leukodepletion)
- Induced by contaminant lymphocytes in PRBC that express Class I and II
- Platelets (components) alone are responsible for <3%

### Immune
- Platelet alloantibodies
- HLA
- HPA
- Other antibodies
  - Platelet autoantibodies
  - Drug-dependent platelet antibodies
  - ABO
- Immune complexes

### Non-immune
- Infection and its treatment, especially amphotericin B
- Splenomegaly
- Disseminated intravascular coagulation (DIC)
- Bleeding
Patients likely to receive multiple platelet transfusions

Assess transfusion response

Poor responses to random donor platelets on two or more occasions\(^1\) (Immediate or 24 hour increment of \(<10 \times 10^9/L\))

Test for HLA antibodies

If tests are awaited consider trial of HLA-matched platelets. If no matched donors give \(<3 \text{ d old ABO matched platelets}

HLA antibodies

Positive - use HLA matched platelets

Good response to HLA-matched platelets

Continue with HLA selected platelets

Retest serum every month during transfusion

Poor response

Factors associated with non-immune platelet destruction

Absent

Present

1. Treat cause
2. Make decision about further platelet transfusions based on the clinical status of the patient e.g. increase dose of platelets or discontinue prophylactic platelet transfusions

HPA antibodies

Positive

Provide HLA and HPA selected platelets (if available)

Consider:
1. HLA incompatibility
2. Non-immune consumption
3. ABO antibodies

Negative

Discuss further serological investigation with NBS consultant

Dr. C. Brown, NBS, 2008
What we practice

• Taxi the sample & Phone NBS Colindale !!!
  – Class I type maybe already available from transplant work-up

• NBS keeps a donor panel of known HLA type. If ordered in advance – the NBS will specifically call up donors to ensure sufficient stocks of certain HLA type

• All such platelets are irradiated due to the high-risk of TAGvHD in such a donation

• Reserved for patients who have proven antibodies
A case

• 31 y.o mother, delivered a baby boy 6 month ago, smoker
• Attended A&E with chest infection, sent home
• Returned 6 days later with pleural effusion and respiratory failure
• Admitted to ITU, chest drain insertion leads to haematotherax and eventually over the next 12 days progressive respiratory failure requiring Nova Lung followed by transfer to Papworth for VV ECMO
• Protracted bleeding
Local A&E  Papworth

- PT 16.9  PT 21.7
- aPTT 32.9 aPTT 57.4
- Plt 165  Plt 48
Discharged home, out of sight out of mind

• Was it all iatrogenic?
• 18 months later
• Haemophilia nurse mentions in passing that the mother of a little boy of 2.5 yrs with newly diagnosed platelet storage pool disorder had been in Papworth on ECMO
• Patient’s father currently in a local DGH with postop bleeding complications
• Questions ?
Blood Products or Factor Concentrates – what should I use?

Andrea Kelleher
Royal Brompton Hospital
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Blood

• Transfusion is one of the most important life saving medical treatments available to man
• First human blood transfusion 1665 by Richard Lower
• Karl Landsteiner discovered human blood groups in 1901 and instantly made transfusion safer
• Cardiac surgery consumes 10-15% of all the blood donated in the UK
• Blood product usage remains 70-80% in complex cases
Blood Components

- Whole blood is now rarely transfused
- Blood components are produced by separating a whole blood donation usually from a single donor and include:
  - Red cells
  - Platelets
  - Granulocytes (filtered)
  - Fresh-frozen plasma
  - Cryoprecipitate
  - Cryoprecipitate-depleted plasma
Fresh Frozen Plasma

- The acellular liquid component of whole blood i.e. what is left after removing the red cells, platelets and leucocytes by centrifugation.
- The use of FFP has increased tenfold between the years 2000-2010 and cardiac surgery patients are the largest recipient group.
- Contains the major plasma proteins, including the labile coagulation factors (V and VIII).
- It can be stored below -30°C for up to 2 years.
What is in FFP?

- FFP contains one international unit/ml (IU/ml) of all coagulation factors.
- 400 mg of fibrinogen per unit.
- Also contains anticoagulant proteins and ADAMTS13.
- Though not used for therapeutic benefit, FFP has a relatively full complement of all other plasma proteins, including immunoglobulins, cytokines (TNF-α, IL-8, IL-10) and albumin.
- These proteins may cause problems with allergic reactions (ranging from mild urticaria to anaphylaxis).

Coagulation factors in FFP
The Risks of FFP

- Possibly the highest risk of all the blood components
- Transfusion transmitted infection (and prion disease)
- Allergic reactions (1-3%)
- Alloimmunization
- Fluid overload

- Transfusion Related Acute Lung Injury (TRALI)
- 4% increased risk of infection per unit (including surgical wound infections).
- If not blood type matched agglutination reactions are possible, though rare.
Pathogen Inactivated Plasma

• **Includes:**
  – Solvent-detergent (pooled plasma 300-5000 donations)
  – Methylene blue + visible light (single units)
  – Amotosalen treatment (psoralens) + UVA light

• Virally inactivated FFP is used in the UK for children under the age of 16 years of age, and is sourced from the USA to reduce the risk of vCJD transmission

Maximum infusion rate
1ml/kg/min
The Role of FFP

• The prophylactic use of FFP for transfusion is not supported by evidence from good-quality randomized trials.
  Stanworth SJ Hematology 2007; 179-186

• FFP is often transfused in the basis of an INR / PT >1.5 times normal however Segal and Dzik in a systematic review showed that PT/INR had very poor predictive value for bleeding
  Segal JB, Dzik WH Systematic Review Transfusion 2005;45: 1413-1425

• In addition to vitamin K, UK guidelines recommend FFP or prothrombin complex concentrates (PCC) for reversal of over anticoagulation; but only in patients with major bleeding
The Role of FFP in Cardiac Surgery

- Systematic review of six trials (363 patients)
- Poor quality studies due to small patient numbers and inadequate blinding
- No evidence that the prophylactic use of fresh frozen plasma affected perioperative blood loss in cardiac surgery

Casbard AC et al. Anaesthesia 2004; 59: 550-558
The Role of FFP in Cardiac Surgery

Figure 5 Forest plot for prothrombin time results. Values are prothrombin time expressed as a percentage of normal.

Figure 6 Forest plot for activate partial thromboplastin time results. Values are activate partial thromboplastin time in seconds.
The Role of FFP in Intensive Care

- Dara et al reported a single centre retrospective cohort study of FP use in medical ICU patients.
- They identified patients with an INR ≥ 1.5 during their ICU stay and evaluated FP use in the subgroup who were not actively bleeding.
- In addition to variability in FFP transfusion practice, the authors observed that patients who received FFP had a similar rate of haemorrhage to matched cases but had a higher incidence of “acute lung injury” during the 48 hours after transfusion (18% vs 4%; $P = .02$)

“Physicians continue to use an often ineffective intervention in many clinical situations (e.g. mild-moderate derangements of coagulation) when there is at best frank uncertainty of benefit but also for which there is evidence of harm”.

FFP

• FFP seems to be intuitively such an appropriate product to replace or supplement plasma constituents in patients with abnormal coagulation tests

• This intervention has over time become so accepted that paradoxically it has not been subjected to the clinical research scrutiny required to demonstrate effectiveness now demanded in the world of evidence-based transfusion practice.
There is a need to undertake new trials evaluating the efficacy and adverse effects of plasma, both in bleeding and non-bleeding patients, to understand whether the *presumed* benefits outweigh the *real* risks.
Plasma Utilization following Cardiac Surgery (PUCS) Study

• Primary outcome measures:
  – FFP use: in all patients, those with an INR of >1.2, >1.5, no coagulation tests

• Secondary outcome measures:
  – Transfusion triggers: haemoglobin, chest drain loss, potential loss, INR/PT/aPTT results / haemodynamic instability / haemodilution

• Currently recruiting
The Zero PLASma Trial (ZEPLAST)

- Prospective randomised double blind trial in high risk cardiac surgery
- Two groups of 60 patients each, control vs fibrinogen and PCC
- Primary end point avoidance of allogeneic transfusion
- Not yet open for recruitment
Cryoprecipitate

- The thawed FFP is then centrifuged to retain the majority of these proteins in a small volume at the bottom of the bag, and the rest of the plasma (cryoprecipitate-depleted plasma, CDP) is removed.
- Cryoprecipitate is only licensed in the UK as a source of fibrinogen for patients with low levels.
- Historically it was used to treat patients with haemophilia A (who lack factor VIII) or von Willebrand Disease (who lack von Willebrand factor), but these patients now receive purified or recombinant products.
- Cryoprecipitate and CDP can be stored below -30°C for up to 2 years.

Thawing FFP at 4oC causes the HMW proteins to precipitate out.
What is in Cryoprecipitate?

- Thawing FFP at 4°C causes the HMW proteins to precipitate out including:
  - fibrinogen
  - factor VIII
  - von Willebrand factor
  - Fibronectin
  - FXIII

- It is currently licensed for documented isolated hypofibrinogenemia only
Cryoprecipitate

- Few studies available, small and generally observational:
- Tomita Y et al looked at 2 groups of 15 undergoing thoracic aortic surgery
- Group 1 received cryo + FFP, group 2 received FFP alone
- Significant differences in post operative blood loss Group 1: 544+/- 233mls Group 2: 888 +/- 339mls

Tomita Y et al Masui 2011; 60(7): 830-4
Factor Concentrates

- factor VIII (used to treat haemophilia A)
- factor IX (use to treat haemophilia B)
- von Willebrand Factor (used to treat von Willebrand Disease).
- Prothrombin Complex Concentrate
- Recombinant factor VIIa
- Fibrinogen
- Factor XIII
Prothrombin complex concentrate (PCC)

- Octaplex, Beriplex
- provide a source of the four vitamin K dependent coagulation factors (II, VII, IX and X)
- Protein C and S
- recommended for emergency anticoagulant reversal and treatment of haemophilia with inhibitors
Prothrombin complex concentrate (PCC)

- Virally inactivated, produced by fractionation of pooled plasma and contain coagulation factors II, VII, IX and X at a significantly higher concentration than FFP.
- The levels of factors vary between different PCCs.
- PCCs achieve more rapid and complete reversal of abnormalities of coagulation tests than FFP.
- Uncertain yet whether this translates into clinical benefit, without an increased risk of thromboembolic complications.

What is in Prothrombin complex concentrate (PCC)?

<table>
<thead>
<tr>
<th></th>
<th>Beriplex 20mls</th>
<th>Octaplex 20mls</th>
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</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>400-960 IU</td>
<td>220-760 IU</td>
</tr>
<tr>
<td>Factor VII</td>
<td>200-500 IU</td>
<td>180-480 IU</td>
</tr>
<tr>
<td>Factor IX</td>
<td>400-620 IU</td>
<td>400-620 IU</td>
</tr>
<tr>
<td>Factor X</td>
<td>440-1200 IU</td>
<td>360-600 IU</td>
</tr>
<tr>
<td>Protein C</td>
<td>300-900 IU</td>
<td>140-620 IU</td>
</tr>
<tr>
<td>Protein S</td>
<td>260-520 IU</td>
<td>140-640 IU</td>
</tr>
<tr>
<td>Heparin</td>
<td>8-40 IU</td>
<td>80-310 IU</td>
</tr>
<tr>
<td>Total Protein</td>
<td>6-14 mg/ml</td>
<td>13-41 mg/ml</td>
</tr>
</tbody>
</table>
Prothrombin complex concentrate (PCC) in Cardiac Surgery

- Dosage 500 – 1000iu (1-2 vials equivalent to 1-2L FFP)
- Individualized dosing based on initial INR and weight
- Close laboratory / POCT monitoring is essential
- Monitor and maintain fibrinogen concentration above 1g/L
Prothrombin complex concentrate (PCC) in Cardiac Surgery

- Units of blood products administered before and after PCC administration.
- Data shown are total numbers of units transfused for all patients ($n = 23$)
- Most patients received less than 1500iu PCC (range 500 – 4,000iu)

Probe Study

- Observational study of PCC in cardiac surgery
- 400 patients, data collected
- publication awaited
Recombinant Factor VIIa

- Vessel injury leads to exposed tissue factor (TF)
- TF binds to and activates factor VII → supranormal thrombin burst at the site of vascular injury
- Neutrophils and monocytes can also secrete TF
- Serum albumin correlates well with factor VII levels
Recombinant Factor VIIa

- Initial cumulative doses >400µg/kg reduced to 10-20µg/kg to reduce thromboembolic complications (5.3%)
- rFVIIa used in the management of life-threatening bleeding after cardiac surgery unresponsive to conventional therapy
- Prophylactic use

Highly efficacious but an associated risk of thrombotic complications particularly arterial thromboses and high mortality
Recombinant Factor VIIa

- Caution in patients who have hypercoagulable state and confirmation that anticoagulation is therapeutic in patients with ongoing activation states (e.g. ECMO, VADs etc.)
- The optimum dose remains unclear
Recombinant Factor VIIa
Fibrinogen

- Fibrinogen (factor 1) is a soluble plasma glycoprotein
- Human fibrinogen concentrate (HFCP) 100ml vial fibrinogen reconstituted with 50mls water
- Licensed for use in fibrinogen deficiency:
  - Hypofibrinogenemia (<1.5g/L)
  - Afibrinogenemia 0.5 – 1.0/million autosomal recessive
  - Dysfibrinogenemia
What is in Fibrinogen Concentrate?

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>900-1300mg</td>
</tr>
<tr>
<td>Albumin</td>
<td>400-700mg</td>
</tr>
<tr>
<td>L-Arginine</td>
<td>375-660mg</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>50-100mg</td>
</tr>
<tr>
<td>Sodium chlorine</td>
<td>200-350mg</td>
</tr>
</tbody>
</table>
Fibrinogen

- Low preoperative fibrinogen levels are a good predictor of bleeding following cardiac surgery
  
  Ucar HI et al Heart Surg Forum 2007; 10(5): E392-6

- Fibrinogen concentrate corrects fibrinogen levels and reduces bleeding in those bleeding post CPB
  
  Solomon C et al BJA 2010: 104(5); 555-62

- The administration of fibrinogen concentrate when the level fell below 1.5g/L in massive haemorrhage results in 30% reduction in blood loss and 30-60% reduction in transfusion
  
  Yamamoto K Rinshi Byori 2011; 59(7): 678-83
Preoperative Fibrinogen levels as a Predictor of Postoperative Bleeding

Figure 2. Relation between fibrinogen levels and postoperative bleeding.

Ucar HI et al Heart Surg Forum 2007; 10(5): E392-6
Fibrinogen

• Whilst FFP contains fibrinogen, the levels are not sufficient for the treatment of severe deficiency

• Uncertainty persists about the dose:
  – Congenital fibrinogen deficiency 70mg/kg
  – Cardiac surgery 2-6.5g
  – Target fibrinogen 2.25g/L

• Risks of high fibrinogen

• Laboratory / POCT Monitoring
REPLACE Study

• RCT of fibrinogen use in in aortic surgery
• Following the reversal of heparin if the swabs collected over a 5 minute period weigh between 60-250g patients are randomised to fibrinogen or placebo
• 152 patients recruited so far
• Publication awaited
RiaSTAP Study

- 4g fibrinogen vs platelets (1 unit) after reversal of heparin if evidence of microvascular bleeding
- If still bleeding after 15 minutes → conventional therapy
- Primary outcome measures: total blood product transfusion
- Recruiting, aim of 60 patients
Factor XIII

- Fibrin is stabilized by factor XIIIa through an amide or isopeptide bond that binds adjacent fibrin monomers
- Leads to improved clot firmness in haemodilution
- Dose 15-30U/kg
- Recently completed multinational study of the effect and safety of RfXIII on transfusion needs in cardiac surgery n=480
<table>
<thead>
<tr>
<th>Product</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma</td>
<td>£27.66</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>£189.21</td>
</tr>
<tr>
<td>Platelets</td>
<td>£227.45</td>
</tr>
<tr>
<td>Red Cells</td>
<td>£124.85</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrate</td>
<td>£165</td>
</tr>
<tr>
<td>Recombinant VIIa (1-5mg)</td>
<td>£683.76 – £3418.78</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>£260</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>£106.50</td>
</tr>
</tbody>
</table>
What are we hoping to achieve?

- 15mls/kg FFP will result in a rise in factor levels by 30%
- 10 units of cryoprecipitate will increase fibrinogen by 1gL⁻¹
- Human fibrinogen concentrate 70mg/kg increases fibrinogen by 1.8 1gL⁻¹
- 1 pool of platelets will result in a 30-60,000µL⁻¹ in platelet count
Prophylaxis

• The prophylactic use of FFP to prevent bleeding or correct an abnormal PT or aPTT is inappropriate and ineffective.

• The prophylactic use of factor concentrates may reduce blood loss but
  – is expensive
  – patients may receive it when they would not bleed anyway
  – and risks side effects such as thromboembolism or anaphylaxis
Moderate Haemorrhage

• May be effectively managed by conventional blood components:
  – Warm TEG / Rotem
  – If MA / MCF is narrow → platelets and consider cryoprecipitate (consider preoperative fibrinogen)
  – If fibrinogen is <1.5g/L give cryoprecipitate
  – If the R time is prolonged consider FFP bearing in mind the disadvantages (volume overload, TRALI, infection), cryoprecipitate may be a better option
Severe Haemorrhage

• First line conventional therapy as above
• Second line:
  – Consider replacing fibrinogen to a target value of 2.25g/L
  – PCC as an alternative to FFP to avoid volume issues
  – Consider rFVIIa 10-20mcg/kg in life threatening bleeding especially if the preoperative serum albumin was low
Severe Haemorrhage

- A combination of POCT and laboratory tests vital in monitoring the ongoing derangement of coagulation
- Consider temperature, serum calcium, antifibrinolytics, glues, sealants etc
- Limit crystalloid, colloid and vasodilatation
- Have a high suspicion for thrombotic complications:
  - Factor VIIa associated with arterial thrombosis
  - Fibrinogen may be associated with venous thrombosis
Conclusions

• overall haemostasis depends on a complex inter-relationship among endothelium, platelets, fibrinolysis, and inhibitors as well as procoagulant factors

• The prophylactic use of FFP to prevent bleeding or correct an abnormal PT or aPTT is inappropriate

• The large volume of FFP required to correct a significant coagulopathy limits its usefulness

• Fibrinogen may play a pivotal role making cryoprecipitate / fibrinogen concentrate more useful

• However treatment with factors is expensive, dosing remains uncertain, thromboembolism may be a significant risk and many of the trials so far are small and observational
Finally

- Maintain an ongoing dialogue with the haematologist
- Keep an awareness of new developments in clinical trials
- Get involved in developing local treatment protocols to rationally guide the use of factors in your own institution
Blood conservation in major vascular surgery: point-of-care testing

Dr Alastair Nimmo, Dept of Anaesthesia
Royal Infirmary of Edinburgh
Disclosure

• I’m going to mention thromboelastography analysers from two companies: TEG® (Haemonetics) and ROTEM® (Tem International) and a fibrinogen concentrate made by CSL Behring.

• These companies have paid expenses for me to attend meetings about coagulation.

• TEM International has made donations to my Department research fund and CSL Behring has provided research funding.

• I haven’t accepted personal payments from any company involved in coagulation monitoring or treatment.
Causes of coagulopathy in TAAA surgery

- Acidosis; anaemia; hypothermia
- Low platelets - consumption, dilution
- Low fibrinogen - consumption, dilution
- Low coagulation factors - consumption, dilution, warfarin, congenital
- Hyper-fibrinolysis
- Dysfunctional platelets - drugs, partial bypass
- Heparin (not full heparinisation)
Measured blood loss (l) in 20 consecutive TAAA s in 2009/10
The problem

• Massive haemorrhage during surgery from a combination of surgical bleeding and coagulopathy

• Potential demand for very large quantities of red cells, FFP and platelets from the Blood Bank within a few hours
The aim

• Prevent / correct severe anaemia and coagulopathy while avoiding inappropriate or excessive use of blood components
• Limit demand for blood components from the Blood Bank
• Return the patient to ITU or HDU with satisfactory haemostasis and little need for postoperative transfusion
The methods

1. Red cell salvage and retransfusion
2. Point of care testing of haemostasis with rapid targeted correction of abnormalities
3. Use of fibrinogen concentrate as an alternative to FFP / cryoprecipitate
The methods

1. Red cell salvage and retransfusion

2. Point of care testing of haemostasis with rapid targeted correction of abnormalities

3. Use of fibrinogen concentrate as an alternative to FFP / cryoprecipitate
### 63 TAAA cases Jan 2006 - July 2010

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured blood loss</td>
<td>13.4 l</td>
</tr>
<tr>
<td>Salvaged RCC reinfused</td>
<td>5.4 l</td>
</tr>
<tr>
<td>Salvaged RCC (units equivalent)</td>
<td>20 units</td>
</tr>
<tr>
<td>Allogeneic RCC in theatre</td>
<td>8.9 units</td>
</tr>
<tr>
<td>Allogeneic RCC total to day 5</td>
<td>10 units</td>
</tr>
<tr>
<td>Hb pre-op</td>
<td>131 g/l</td>
</tr>
<tr>
<td>Hb post-op</td>
<td>93 g/l</td>
</tr>
</tbody>
</table>

Max blood loss 53 litres – received 13 units allogeneic RCC in theatre
### 10 consecutive Extent 4 TAAA repairs*

<table>
<thead>
<tr>
<th>Case</th>
<th>Blood loss (ml)</th>
<th>Red cells (units)</th>
<th>Platelets (pools)</th>
<th>FFP (units)</th>
<th>Hb</th>
<th>Platelet count</th>
<th>Fibrinogen (g/l)</th>
<th>PT ratio</th>
<th>APTT ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 300</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>105</td>
<td>89</td>
<td>1.4</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>5 500</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>98</td>
<td>100</td>
<td>1.6</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>3 200</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>90</td>
<td>76</td>
<td>1.4</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>13 600</td>
<td>6</td>
<td>2</td>
<td>16</td>
<td>87</td>
<td>58</td>
<td>1.4</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>11 800</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>78</td>
<td>71</td>
<td>1.4</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>7 200</td>
<td>6</td>
<td>3</td>
<td>12</td>
<td>93</td>
<td>70</td>
<td>1.7</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>16 000</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>108</td>
<td>104</td>
<td>1.8</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>4 300</td>
<td>6</td>
<td>0</td>
<td>8</td>
<td>90</td>
<td>53</td>
<td>1.6</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>9</td>
<td>8 000</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>86</td>
<td>83</td>
<td>1.4</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>6 000</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>83</td>
<td>93</td>
<td>1.6</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*the most recent 10 cases treated with FFP before starting a randomised trial
The methods

1. Red cell salvage and retransfusion

2. Point of care testing of haemostasis with rapid targeted correction of abnormalities

3. Use of fibrinogen concentrate as an alternative to FFP / cryoprecipitate
Point-of-care testing of coagulation in major haemorrhage

- Coagulation is a dynamic phenomenon - great changes in the nature and severity of coagulopathy may occur within a few minutes in bleeding patients.
- Lab results typically come back too slowly to be relevant.
- Treatment given blindly or on the basis of “old” lab results is often ineffective, and may result in potentially harmful blood products being given unnecessarily.
Point-of-care haemostasis analysers

1. Coagulation time analysers
   - PT, APTT, ACT, LMWH

2. “Viscoelastic” whole-blood analysers
   thromboelastography / thromboelastometry

3. Platelet function analysers (aspirin, clopidogrel)
1. Coagulation time analysers

- Tube-based - ACT
- Cuvette-based - ACT
  - APTT
  - PT
  - LMWH
2. thromboelastography / thromboelastometry

- “viscoelastic” test of whole blood coagulation
- usually a point-of-care test → rapid results
- provides information on onset of coagulation, development of clot strength, maximum clot strength and clot lysis
Causes of coagulopathy in surgery/trauma

• Acidosis; anaemia; hypothermia
• Low platelets - consumption, dilution
• Low fibrinogen - consumption, dilution
• Low coag factors - consumption, dilution, warfarin, congenital
• Hyper-fibrinolysis
• Dysfunctional platelets - drugs, CPB
• Heparin
Treatment of coagulopathy in surgery/trauma

- General measures - resuscitation, rewarming
- Correction of acidosis
- Correction of anaemia
- Platelets
- Fibrinogen - FFP, cryoprecipitate, fibrinogen
- Coagulation factors – FFP, PCC
- Tranexamic acid; Epsilon-aminocaproic acid
- Protamine
- Desmopressin
- (Recombinant Factor VIIa)
thromboelastography / thromboelastometry

• provides information on onset of coagulation, development of clot strength, maximum clot strength and clot lysis

• permits rapid identification of:
  - thrombocytopenia / platelet dysfunction*
  - low fibrinogen / impaired fibrin polymerisation
  - low coagulation factor levels
  - heparin effect
  - hyperfibrinolysis

*but standard tests don’t show aspirin / clopidogrel effects
Thromboelastography / thromboelastometry

• Two analysers based on the same principle from two different companies

TEG® Haemonetics, Niles, Illinois, USA

ROTEM® Pentapharm, Munich, Germany
Thromboelastography (TEG®)
H. Hartet 1948
Rotational thromboelastometry
(rotational thromboelastography)
ROTEM® (ROTEG ®)    A.Calatzis 1996
ROTEM® - samples & tests

- venous or arterial blood
- fresh - analysed shortly after sampling or citrated - standard coagulation tube
- non-activated or activated
- ± inhibitor of heparin
- ± inhibitor of platelet aggregation
- ± inhibitor of fibrinolysis
4 different tests on one blood sample

- InTEM
  - St.: 19h49
  - Run: 61.7′
  - CT: 135s
  - CFT: 147s
  - MCF: 54mm
  - alp: 67°

- HepTEM
  - St.: 19h49
  - Run: 61.1′
  - CT: 167s
  - CFT: 140s
  - MCF: 52mm
  - alp: 67°

- FibTEM
  - St.: 19h47
  - Run: 63.2′
  - CT: 37s
  - CFT: >3754s
  - MCF: 12mm

- ExTEM
  - St.: 19h47
  - Run: 62.8′
  - CT: 40s
  - CFT: 172s
  - MCF: 52mm
  - alp: 58°

Normal
Activators/Inhibitors

InTEM: Activation of Intrinsic pathway using ellagic acid (same pathway as the APTT)

HepTEM: Heparin inactivation (using Heparinase)

ExTEM: Activation of Extrinsic pathway with tissue factor (same pathway as the PT)

FibTEM: Specific Assessment of Fibrinogen (blocking of platelet function by cytochalasin D)

ApTEM: In vitro inhibition of fibrinolysis (using Aprotinin)
Interpretation – look at 3 parts of the trace

1. Middle of the trace – clot strength
2. First part of the trace – clot initiation
3. Latter part of the trace – clot stability
ROTEM® - interpretation

3 questions

1. Is the firmness / strength of the clot reduced (middle of trace)
2. Does it take too long for detectable clot to form (first part of trace)
3. Does the clot break down after it has formed (latter part of trace)
ROTEM® - interpretation

3 questions

1. Is the firmness / strength of the clot reduced (middle of trace)

2. Does it take too long for detectable clot to form (first part of trace)

3. Does the clot break down after it has formed (latter part of trace)
Q1. Middle of the trace – clot strength

Measures the structural components of the clot

Maximum Amplitude (MA) or Maximum Clot Firmness (MCF) mm
Q1. Middle of the trace – clot strength

Measures the structural components of the clot
FIBTEM

EXTEM activator plus Cytochalasin D
(inhibitor of platelet aggregation)

TEG® equivalent: functional fibrinogen assay
4 different tests on one blood sample

InTEM
- St.: 19h49
- Run: 61.7'
- CT: 135s
- CFT: 147s
- MCF: 54mm
- alp: 67°

HepTEM
- St.: 19h49
- Run: 61.1'
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FibTEM
- St.: 19h47
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- CT: 37s
- CFT: >3754s
- MCF: 12mm

ExTEM
- St.: 19h47
- Run: 62.8'
- CT: 40s
- CFT: 172s
- MCF: 52mm
- alp: 58°

Normal
Q1 – Clot Strength

• Is the clot strength (MCF or A10) reduced
• If so is this the result of a deficiency of
  - fibrinogen
  - platelets
  - both fibrinogen and platelets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Severely abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCF (except FibTEM)</td>
<td>50 – 70mm</td>
<td>&lt; 40mm</td>
</tr>
<tr>
<td>MCF (FibTEM)</td>
<td>10 – 20mm</td>
<td>&lt; 5mm</td>
</tr>
</tbody>
</table>
Major obstetric haemorrhage

- 36 yr old woman
- Previous LSCS
- Placenta praevia & placenta accreta
- LSCS → hysterectomy
- 15 litre blood loss; packs left in abdomen
- Transferred to Royal Infirmary
- Theatre for embolisation → tying off internal iliac arteries
Major obstetric haemorrhage
Major obstetric haemorrhage

Low platelets
After platelets
Major obstetric haemorrhage

- Bleeding controlled
- Removal of packs and extubated the following day
- Transferred back to referring hospital the day after to be with her baby
Major obstetric haemorrhage

During surgery
Hb 76
Plts 35
PT 13

Post-op
Hb 73
Plts 87
PT 12
Bleeding after colectomy
Bleeding after colectomy

low fibrinogen
Bleeding after colectomy

- FFP requested and given
- Lab sample (sent before FFP was given)
  Plts 120
  PT 16
  APTT 53
  Fibrinogen 0.6
Very abnormal MCF / A10

Usually indicates very low fibrinogen and platelets
Very abnormal MCF / A10

Lab results:  
Hb 10.8  
Plts 23  
PT 50/12  
APTT 210/32  
Fib 0.3
<table>
<thead>
<tr>
<th>CLOT FIRMNESS</th>
<th>A10 in EXTEM / INTEM / HEPTEM / APTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 22 mm</td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>Low fibrinogen</td>
</tr>
<tr>
<td></td>
<td>Low platelets</td>
</tr>
<tr>
<td>5-7 mm</td>
<td>Low platelets</td>
</tr>
<tr>
<td></td>
<td>Low fibrinogen</td>
</tr>
<tr>
<td>≥ 8 mm</td>
<td>Low platelets</td>
</tr>
</tbody>
</table>

*Typically fibrinogen < 1.5 g/l & platelets 50-100. Also consider giving platelets if ongoing bleeding*
Intermediate part of the trace

Time after clotting starts until amplitude reaches 20 mm
K-time or Clot Formation Time (CFT)
Intermediate part of the trace

Alpha angle (α) = the angle between a tangent to the curve and the horizontal
K-time / CFT and alpha angle may be affected by

- Thrombin generation
- Fibrinogen concentration and fibrin polymerisation
- Platelet count
Veklich Y, Weisel JW. NATURE 2001; 413:6855
Major obstetric haemorrhage

Low platelets
Bleeding after colectomy

low fibrinogen
Platelets or fibrinogen?

Thrombocytopenia and low fibrinogen both reduce
CFT (k-time)
$\alpha$ angle
MCF (MA)
Effect on fibrinogen levels on clot strength in EXTEM

Figure 2. Effect of platelet count on clot strength in EXTEM. Clot strength is given in maximum clot elasticity (MCE). Each curve represents one healthy volunteer. Fibrinogen concentration was determined by the Clauss method.
In a laboratory study, blood samples with dilutional coagulopathy (low fibrinogen) and with thrombocytopenia (mean platelet count 20 x 10^9/l) gave similar values for R-time, K-time, α-angle and MA.

Anesthesiology. 2011 Aug;115:294-302
Thromboelastography-Guided Transfusion Algorithm Reduces Transfusions in Complex Cardiac Surgery

Microvascular Bleeding

1. TEG R>2X hTEG R
   - Protamine

2. Platelet Count<100K AND MA<45mm
   - Platelets

3. hTEG R>20mm
   - FFP

4. TEG LY30>7.5%
   - EACA

5. Fibrinogen<100mg/dl
   - Cryoprecipitate

Shore-Lesserson L. Anesth Analg 1999; 88:312-319
<table>
<thead>
<tr>
<th>CLOT FIRMNESS</th>
<th>A10 in EXTEM / INTEM / HEPTEM / APTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 22 mm</td>
</tr>
<tr>
<td>A10 in FIBTEM</td>
<td>&lt; 5 mm</td>
</tr>
<tr>
<td></td>
<td>5-7 mm</td>
</tr>
<tr>
<td></td>
<td>≥ 8 mm</td>
</tr>
</tbody>
</table>

* Typically fibrinogen < 1.5 g/l & platelets 50-100. Also consider giving platelets if ongoing bleeding
ROTEM® - interpretation

3 questions

1. Is the firmness / strength of the clot reduced (middle of trace)
2. Does it take too long for detectable clot to form (first part of trace)
3. Does the clot break down after it has formed (latter part of trace)
Measures clot initiation – initial thrombin generation. Prolonged by coagulation factor deficiency or heparin.
Q2 – Clot Initiation

• Does it take too long for detectable clot to form i.e. is the CT prolonged?
• If so is this reversed by heparinase i.e. normal CT in HEPTEM test?
  YES - heparin effect
  NO  - low coagulation factors or very low fibrinogen – see Q1
Elective aortic aneurysm
Elective aortic aneurysm

Heparin effect
ROTEM® - interpretation

3 questions

1. Is the firmness / strength of the clot reduced (middle of trace)

2. Does it take too long for detectable clot to form (first part of trace)

3. Does the clot break down after it has formed (latter part of trace)
Latter part of the trace – clot stability

Measures fibrinolysis
Q3 – Clot Stability

• Does the Clot Firmness decrease markedly after the clot has formed suggesting excessive fibrinolysis?
• Maximum Lysis (ML) is the max % decrease that occurs after MCF is attained. Normal value < 15 %
• Absence of the decrease in Clot Firmness in Aptem confirms hyper-fibrinolysis
Ruptured AAA - case 1
Q3 – Clot Stability

- CT, A10/ MCF which are better in the Aptem test than in the Extem test may give an early indication that excessive fibrinolysis is occurring.
Ruptured AAA - case 2

- 74 yr old man transferred from another hospital with shock and abdo pain
- On arrival, taken rapidly to theatre
- Platelets 1 pool & FFP 3 units given after aortic clamping
Pre-op sample
5 minutes after aortic clamping
After aprotinin

0' 1 after aprotinin InTEM
St.: 22h36
CT: 240s
CFT: 202s
MCF: 38mm
alp: 55°

0' 2 after aprotinin ApTEM
St.: 22h37
CT: 51s
CFT: 266s
MCF: 40mm
alp: 47°

0' 3 after aprotinin FibTEM
St.: 22h36
CT: 98s
CFT:>1245s
MCF: 7mm
ML: 19%

0' 4 after aprotinin ExTEM
St.: 22h37
CT: 58s
CFT: 248s
MCF: 38mm
alp: 49°
Post-partum haemorrhage  02:44

ExTEM

CT = 161  
A10 = 0  
ML = 100

InTEM

CT = 275  
A10 = 0  
ML = 100

FibTEM

CT = *2506  
A10 = --  
ML = --

ApTEM

CT = 181  
A10 = 28  
ML = *0
After tranexamic acid 03:37

**ExTEM**
- CT = 244
- A10 = 18
- ML = *0
- CFT = 720
- MCF = *28

**InTEM**
- CT = 309
- A10 = 21
- ML = *0
- CFT = 524
- MCF = *29

**FibTEM**
- CT = 494
- A10 = 3
- ML = *15
- CFT = --
- MCF = 3

**ApTEM**
- CT = 238
- A10 = 18
- ML = *0
- CFT = 725
- MCF = *27
04:40

**ExTEM**
- CT = 141
- A10 = 24
- MCF = *33
- ML = *0

**InTEM**
- CT = 296
- A10 = 24
- MCF = *32
- ML = *0

**FibTEM**
- CT = 1137
- A10 = 2
- MCF = 3
- ML = *28

**ApTEM**
- CT = 149
- A10 = 23
- MCF = *32
- ML = *0
05:23

ExTEM

CT = 41
A10 = 33
ML = *0

CFT = 284
MCF = 47

InTEM

CT = 212
A10 = 33
ML = *1

CFT = 230
MCF = 45

FibTEM

CT = 50
A10 = 10
ML = *3

CFT = --
MCF = 11

ApTEM

CT = 47
A10 = 32
ML = *1

CFT = 293
MCF = 47
**DIAGNOSIS**

1. **Clot firmness**
   - In the presence of heparin use the HEPTEM result
   - If there is hyperfibrinolysis (ML > 15%) use the APTEM result

<table>
<thead>
<tr>
<th>CLOT FIRMNESS</th>
<th>A10 in EXTEM / INTEM / HEPTEM / APTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 22 mm</td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>Low fibrinogen</td>
</tr>
<tr>
<td>5-7 mm</td>
<td>Low platelets</td>
</tr>
<tr>
<td>≥ 8 mm</td>
<td>Low fibrinogen</td>
</tr>
</tbody>
</table>

*Typically fibrinogen < 1.5 g/l & platelets 50-100. Also consider giving platelets if ongoing bleeding.

2. **Clotting time**
   - In the presence of heparin run a HEPTEM test

**Causes of a prolonged CT**

- Fibtem A10 < 5 mm = Low fibrinogen
- CT prolonged in INTEM but normal in Heptem = Heparin effect
- Fibtem A10 > 5 mm and no heparin effect = Low coagulation factors

**When to treat CT**

- CT in INTEM / Heptem > 300 or CT in Extem / Aptem > 100s
- CT in INTEM / Heptem 240 - 300 s or CT in Extem / Aptem 80 - 100s
- CT in INTEM / Heptem < 240 s or CT in Extem / Aptem < 80 s

3. **Hyperfibrinolysis**

- Lysis of clot within 20 mins = Fulminant lysis
- Lysis of clot within 20 - 40 mins = Early lysis
- Lysis of clot after more than 40 mins = Late lysis - ?treat

Repeat Rotem tests including Aptem after treatment (or if no treatment is given)

---

**TREATMENT**

- Treat
- Treat if bleeding / high risk of bleeding
- See below*

- Low fibrinogen – FFP or fibrinogen concentrate or cryoprecipitate
- Low platelets – platelets
- Low coagulation factors – FFP or PCC
- Heparin – protamine (if reversal appropriate)
- Hyperfibrinolysis – tranexamic acid (1 g – 2 g bolus)

*IMPORTANT

- Rotem® does not detect the effect of aspirin, clopidogrel or Reopro® on platelets
- Rotem® is not a sensitive test for some anticoagulants e.g. warfarin, LMWH
- Rotem® does not detect von Willebrand factor deficiency
### 10 consecutive Extent 4 TAAA repairs*

<table>
<thead>
<tr>
<th>Case</th>
<th>Blood loss (ml)</th>
<th>Given during surgery</th>
<th>Post-op blood results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood loss (ml)</td>
<td>Red cells (units)</td>
<td>Platelets (pools)</td>
</tr>
<tr>
<td>1</td>
<td>11 300</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>5 500</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3 200</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>13 600</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>11 800</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>7 200</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>16 000</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>4 300</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>8 000</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>6 000</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*the most recent 10 cases treated with FFP before starting a randomised trial
Extent  4 TAAA Repair – 19 consecutive cases

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood loss ml</th>
<th>Cell salvage ml</th>
<th>INTRA-OP</th>
<th>1st 24 hrs POST-OP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCC</td>
<td>FFP</td>
<td>Plt</td>
<td>Cryo</td>
</tr>
<tr>
<td>1</td>
<td>4500</td>
<td>1650</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>5195</td>
<td>1786</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>4380</td>
<td>2000</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>4000</td>
<td>1400</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>4000</td>
<td>1450</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>6000</td>
<td>2000</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>11300</td>
<td>4545</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>5508</td>
<td>2156</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>3200</td>
<td>1040</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>13600</td>
<td>4000</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>11</td>
<td>11800</td>
<td>4250</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>7200</td>
<td>2900</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>16000</td>
<td>6000</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>4300</td>
<td>1700</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>8000</td>
<td>3300</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>6000</td>
<td>2418</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>17</td>
<td>10070</td>
<td>2581</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>11000</td>
<td>3400</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>7311</td>
<td>3793</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>
3. Platelet function analysers

Use anticoagulated whole blood samples. A number of different methods are used to measure platelet aggregation in response to agonists:

- Light transmittance aggregometry - VerifyNow®
- Impedance aggregometry - Multiplate®, TEMplate®
- Platelet count before & after agonist - Plateletworks®
- Thromboelastography – TEG® PlateletMapping®
- Time taken for platelets to block an aperture in a membrane - PFA-100®
Multiplate® analyser

- Impedance aggregometry
- 5 independent channels
- **Normal aggregation**

- **100 mg aspirin qd**
  - TRAPtest: 113 U
  - ASPItest: 102 U
  - ADPtest: 89 U
  - ADPtest HS: 81 U

- **75 mg clopidogrel qd**
  - TRAPtest: 139 U
  - ASPItest: 17 U
  - ADPtest: 134 U
  - ADPtest HS: 112 U

- **100 mg aspirin+ 75 mg clopidogrel qd**
  - TRAPtest: 98 U
  - ASPItest: 89 U
  - ADPtest: 31 U
  - ADPtest HS: 18 U

- **Tirofiban i.v.**
  - TRAPtest: 88 U
  - ASPItest: 8 U
  - ADPtest: 17 U
  - ADPtest HS: 3 U

- **Tirofiban i.v.**
  - TRAPtest: 7 U
  - ASPItest: 3 U
  - ADPtest: 3 U
  - ADPtest HS: 2 U
Preoperative Multiplate results in 100 patients having vascular surgery
Multiplate results in 100 patients having elective vascular surgery
Pre-procedure Multiplate® results and bleeding in patients undergoing PCI

Pre-op Multiplate® results and bleeding in patients undergoing cardiac surgery

Units for aggregation have been converted from those in the original paper by multiplying by 10.

Suggested scheme for interpreting pre-op Multiplate® results in patients on clopidogrel

<table>
<thead>
<tr>
<th>ADP test result</th>
<th>Platelet inhibition by clopidogrel</th>
<th>Risk of excessive bleeding because of clopidogrel effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>Marked</td>
<td>High</td>
</tr>
<tr>
<td>300 - 600</td>
<td>Some</td>
<td></td>
</tr>
<tr>
<td>&gt;600</td>
<td>Little or none</td>
<td>Low</td>
</tr>
</tbody>
</table>

Assumptions:
• normal platelet count
• hirudin anticoagulant used for the Multiplate® blood sample
Point-of-care haemostasis analysers

1. Coagulation time analysers
   - patients on warfarin, heparin

2. “Viscoelastic” whole-blood analysers
   - thromboelastography / thromboelastometry

3. Platelet function analysers (aspirin, clopidogrel)
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   - to diagnose the cause of impaired
   haemostasis during and after surgery

3. Platelet function analysers (aspirin, clopidogrel)
   - preoperative testing of patients on
   clopidogrel
The methods

1. Red cell salvage and retransfusion

2. Point of care testing of haemostasis with rapid targeted correction of abnormalities

3. Use of fibrinogen concentrate as an alternative to FFP / cryoprecipitate
Role of fibrinogen concentration

When major surgical blood loss is replaced with red cell concentrates (RCCs) and colloids, the fibrinogen concentration falls to a level associated with impaired haemostasis before the platelet count or concentrations of other coagulation factors do.

Target fibrinogen concentration

“Levels below 1 g l\(^{-1}\), in the context of massive haemorrhage, are usually insufficient, and emerging evidence suggests that a level above 1.5 g l\(^{-1}\) is required. Higher levels are likely to improve haemostasis further.”
Concerns regarding cryoprecipitate / FFP

- Delay/thawing
- Immune effects
- Viral infection
- vCJD

- Cryo is no longer used in EU countries apart from the UK and the Baltic states because of safety concerns. Fibrinogen concentrate and/or FFP is used instead to give fibrinogen
Fibrinogen concentrate
(Haemocomplettan® / Riastap®)

- Pooled plasma product
- Non-UK donors
- Pasteurised
- Purified
- Freeze-dried
- No ABO issues
- No thawing
- Potentially no delay

Marketing authorisation in the UK is currently only for congenital fibrinogen deficiency.
Fibrinogen concentrate in Extent 4 TAAA repair

- In three patients we infused fibrinogen concentrate during surgery rather than FFP when the ROTEM® indicated a low fibrinogen concentration.
- Platelets were given if the ROTEM® indicated severe thrombocytopenia
- FFP could be given if the ROTEM® indicated low coagulation factors
Intraoperative blood loss and blood component administration - fibrinogen

<table>
<thead>
<tr>
<th>Blood loss (ml)</th>
<th>Salvaged red cells returned (ml)</th>
<th>Blood components administered intraoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fibrinogen (g)</td>
</tr>
<tr>
<td>10 070</td>
<td>2 581</td>
<td>16</td>
</tr>
<tr>
<td>11 000</td>
<td>3 400</td>
<td>12</td>
</tr>
<tr>
<td>7 300</td>
<td>3 793</td>
<td>12</td>
</tr>
</tbody>
</table>
Fibrinogen concentrate in Extent 4 TAAA repair

- No postoperative bleeding or thrombotic complications
- No red cells were required in the first 24 hours after surgery
- No FFP was required during or after surgery despite an intraoperative blood loss of up to 11 litres
- We have now begun a randomised trial comparing administration of fibrinogen concentrate with FFP during extent 4 TAAA repair
Randomised study - methods

- Randomised, non-blinded study in 20 patients having Extent 4 TAAA repair
- Fibrinogen concentrate or FFP infused to maintain Fibtem in the normal range during surgery (A10 ≥ 8 mm)
- ROTEM® tests and POC Hb, H+, Ca²⁺ every 30-60 mins during surgery; 2 & 24 h after surgery
- Predefined triggers for giving red cells, platelets, coagulation factors (as FFP) and tranexamic acid
- Surgeon’s assessment of microvascular bleeding and samples for future laboratory analysis at the same time points as the POC tests
## Blood loss & blood component administration – intraop & up to 24 hours after surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood loss (ml)</th>
<th>Blood components administered</th>
<th>Fibrinogen (g)</th>
<th>FFP (units)</th>
<th>Platelets (pools)</th>
<th>RCC (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1* FIB</td>
<td>8 800</td>
<td></td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2 FFP</td>
<td>8 500</td>
<td></td>
<td>12</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3 FFP</td>
<td>16 500</td>
<td></td>
<td>25</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>4 FIB</td>
<td>4 100</td>
<td></td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 FIB</td>
<td>5 000</td>
<td></td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>6 FFP</td>
<td>4 900</td>
<td></td>
<td>12</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>7 FIB</td>
<td>12 200</td>
<td></td>
<td>18</td>
<td>4</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

*also 2 g tranexamic acid*
Massive haemorrhage ≠ massive transfusion

In TAAA surgery with a blood loss of around 10 litres:

• Cell salvage markedly reduces the requirement for allogeneic red cells – often to 6 units or less.

• Use of fibrinogen concentrate usually avoids the need to give either cryo or FFP

• Platelet transfusion may be reduced or avoided by maintaining fibrinogen concentration
Preoperative anaemia: investigation and treatment

Blood Conservation in Cardiac Surgery
February 2012

Robert Kong FRCA
Consultant Cardiac Anaesthetist
Royal Sussex County Hospital
Brighton
Financial disclosures

• Travel expenses for lectures and research support by Pharmacosmos
Background
Length of stay after cardiac surgery according to gender and preoperative haemoglobin

Data from Sussex Cardiac Centre 2004
Isn’t preoperative anaemia just an indicator of severity of illness?
Risks associated with preoperative anaemia in non-cardiac surgery

1. Maryland, USA 1995-2000 (n=6301)\(^1\). Preoperative anaemia defined as Hct<36%
   – 34% of patients
   – Increased blood transfusion requirements, postoperative pneumonia, length of stay and mortality

2. USA NSQIP 1997-2004 (n>300,000)\(^2\). Hct<39%
   – 43% of patients
   – Increased 30-d mortality and cardiac events

2. Wu et al. JAMA 2007
Risks associated with preoperative anaemia in non-cardiac surgery

3. Toronto 2003-6 (n=7759)³.
   – Anaemia = WHO definition
   – 39.5% men; 39.9% women
   – Increased mortality independent of blood transfusion.

4. Worldwide NSQIP 2008 (n>227,000)⁴. Preoperative anaemia defined as Hct <39% M; <36% F
   - Increased 30-d mortality and morbidity in both sexes, all ages, and all types of surgery. Increased the risk associated with other co-morbidities

Risks associated with preoperative anaemia in cardiac surgery

5. Data from perioperative ischaemia (McSPI) EPII: CABG in 17 countries, 72 centres (n=4304)\(^5\).
   – Anaemia = WHO definition
   – Low preoperative Hb independent predictor of non-cardiac adverse outcomes

Risks associated with preoperative anaemia in cardiac surgery

6. Canadian hospitals (7), cardiac surgery – CABG 67%; valve 9%; other 24% (n=3500)\(^6\).
   - Anaemia = Hb<12.5 g/dl
   - Retrospective data
   - Risk adjusted: multivariable logistic regression and propensity-matching
   - Preoperative anaemia independently associated with composite adverse outcome
     • +/- intraoperative blood transfusion
     • Elective or non-elective surgery

Investigations
Step 1

What is anaemia?
It is recommended that, in future studies, anaemia should be considered to exist in those whose haemoglobin levels are lower than the figures below (the values given are in g/100ml of venous blood of persons residing at sea level):

- children aged 6 months to 6 years: 11
- children aged 6-14 years: 12
- adult males: 13
- adult females, non pregnant: 12
- adult females, pregnant: 11

Other definitions of anaemia

• Textbook references
  – cutoff values from a selection of 5 references
  – M: from 13.2 – 14.2 g/dl
  – F: from 11.6 – 12.4 g/dl

• Laboratory-specific normal ranges
  – M: 13.5 - 18.0 / F: 11.5 – 16.5 g/dl

• Qualitative or arbitrary limits
  – “mild”, “moderate”, etc...
  – < 10; <11 g/dl etc...
<table>
<thead>
<tr>
<th>Group</th>
<th>Hemoglobin g/dl*</th>
</tr>
</thead>
<tbody>
<tr>
<td>White men, y</td>
<td></td>
</tr>
<tr>
<td>20-59</td>
<td>13.7</td>
</tr>
<tr>
<td>60+</td>
<td>13.2</td>
</tr>
<tr>
<td>White women, y</td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>12.2</td>
</tr>
<tr>
<td>50+</td>
<td>12.2</td>
</tr>
<tr>
<td>Black men, y</td>
<td></td>
</tr>
<tr>
<td>20-59</td>
<td>12.9</td>
</tr>
<tr>
<td>60+</td>
<td>12.7</td>
</tr>
<tr>
<td>Black women, y</td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>11.5</td>
</tr>
<tr>
<td>50+</td>
<td>11.5</td>
</tr>
</tbody>
</table>

* Proposed lower limit of normal (5%) based on exclusion of anaemic persons from Scripps-Kaiser and NHANESIII databases

From Beutler E and Waalen J. Blood 2006;1747-50
When does a low preoperative Hb matter?

• Physiological reserve
  – Oxygen delivery
  – Organ function

• Therapy
  – Blood transfusion

• Postoperative complications

• Mortality
RBC transfusion rates as a function of preoperative Hb in 2003 and 2007

Data from Sussex Cardiac Centre
Step 2

Look at the Hb and act on it
Normal distribution of preoperative Hb

Data from Sussex Cardiac Centre 2011
Prevalence of preoperative low Hb in cardiac surgery patients in Brighton

- All patients (last consecutive 1250)
  - 22% M Hb<13.0
  - 24% F Hb<12.0

- Elective surgery (74%)
  - 17% M Hb <13 (18.5% M Hb ≤13)
  - 18% F Hb <12 (52% F Hb ≤13)

- 27 % all elective patients Hb≤13
Anaemia in the population age > 65y

Guralnik, Hematology 2005 (using NHANES III data)
Routine investigation of anaemia

• Full blood count
• U&Es, Creatinine and eGFR
• C reactive protein
• Serum ferritin
• Transferrin saturation
• Thyroid function test
• (Vitamin B12)†
• (Serum folate)†

† den Elzen et al. Arch Intern Med 2008
† Metz. Food Nutr Bull 2008
Aetiology of anaemia – before cardiac surgery

1. Iron-deficient erythropoiesis
   – Absolute iron deficiency
   – Iron-sequestration
2. Relative erythropoietin deficiency
   – Renal failure, inflammatory diseases, diabetes
3. Other chronic diseases
   – Hypothyroidism, myelodysplasia
4. Dietary (iron, B12, folate)
5. Drug-related
   – Antiplatelet agents, warfarin, H2 blockers, PPI, ACEI
6. Unknown

7. Goodnough L, Nemeth E & Ganz T Blood 2010
Iron flux and the central roles of hepcidin and ferroportin

from Ganz. Blood 2011
Hepcidin decreases iron availability

- 25 amino acid peptide
- Secreted by liver
- Induced by inflammation (IL6)
- Regulates iron metabolism (2001)
- Binds ferroportin – internalise and degrade.
- Decreases efflux of iron from enterocytes and macrophages
- Decreases iron availability

From Ganz T and Nemeth E. Semin Hematol 2009
Serum ferritin

- Circulating form of intracellular iron storage protein
- <15 to 40 µg/L = absent iron stores
  - higher cut-off value improves sensitivity
- 1µg/L ~ 10 mg stored iron
- Iron stores in adults – 500 to 1000 mg
- Ferritin level increases in inflammation
  - i.e. normal or elevated ferritin may not be indicative of adequate iron stores

Goodnough et al. Blood 2000
Transferrin saturation

• Transferrin serves as the intercellular iron transporter ("taxi")
  – 0.1% of total body iron in circulation – bound to transferrin
  – Each transferrin mol binds 2 Fe\(^{3+}\) ions
• Normally 20-45% of transferrin binding sites are bound by iron
• TSAT <16% when iron stores depleted
• Transferrin binds to its receptors at erythroid precursor cells

Goodnough et al. Blood 2000
Aetiology of anaemia – before cardiac surgery

1. Iron-deficient erythropoiesis\(^7\)
   – Absolute iron deficiency
   – Iron-sequestration
2. Relative erythropoietin deficiency
   – Renal failure, inflammatory diseases, diabetes
3. Other chronic diseases
   – Hypothyroidism, myelodysplasia
4. Dietary (iron, B12, folate)
5. Drug-related
   – Antiplatelet agents, warfarin, H2 blockers, PPI, ACEI
6. Unknown

7. Goodnough L, Nemeth E & Ganz T Blood 2010
Absolute iron deficiency

• Chronic (usually) blood loss
  – Antiplatelet drugs or warfarin
    • Upper GI blood loss may be asymptomatic
    • Anaemia develops months after starting antiplatelet therapy
  – Lower GI blood loss usually symptomatic
  – GI disease leading to impaired iron absorption i.e. celiac disease, helicobacter pylori, atrophic gastritis

• Failure to respond to oral iron does not rule out iron deficiency

• We do not routinely refer patients upper/lower GI endoscopy
Iron sequestration

• Anaemia of inflammation (chronic disease)
  – Presumed secondary to coexistent inflammatory condition/s
    • Infection, heart failure, arthritis, malignancy, renal failure, recent surgery
  – May develop quickly
  – Often coexists with iron-deficiency
  – Anaemia is probably an infrequent finding in chronic inflammatory diseases
Prevalence of low Hb and renal function

http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p6_comp_g8.htm
Renal failure

• Erythropoietin secreted by interstitial cells
  – GFR may not be a reliable indicator of adequate erythropoietin release
• Inappropriately low erythropoietin level for the degree of anaemia (compared to no kidney disease)
• Anaemic preoperative patients with GFR<60 are frequently iron-deficient (our experience)
• Chronic kidney disease often associated with elevated ferritin
Treatment
Principles

1. Identify anaemia at the earliest stage of the “patient journey” because treatment takes time
2. Investigate as soon as possible
3. Treat if treatable
   - Iron deficiency
   - Thyroid disease
   - B12/folate
4. Do not postpone surgery unless other interventions indicated or treatment benefits likely to outweigh risks of delayed surgery
TREATMENT
Admit to Cardiac ward for 1-5th
iv iron + heparin

Ideally 2-8 weeks

Home
Outpatient clinic

Lase with CP

Hb, U&E, creatinine

CRP, ferritin, transferrin saturation (TSAT),
B12, folate, TFT

Hb, U&E, creatinine
Biochemical criteria

• Hb <13 g/dl and
  – Ferritin <100µg/L
  – or Transferrin saturation <20%
• Elevated CRP may help to differentiate anaemia of inflammation from iron deficiency
• Hypo or hyperthyroidism – usual cutoffs
• Low serum B12 or folate
Oral iron: why NOT?

• Side effects
  – Nausea, epigastric pain, diarrhoea, constipation, black stools
  – Parker et al 2010: 17% SE (10% discontinued)

• Compliance

• Efficacy
  – Diminished absorption – foods, drugs, inflammation
  – Dose α side effects
  – Dose limit
Intravenous iron

- Iron dextran
  - High MW dextran (historical, frequent SEs)
  - Low MW dextran: Cosmofer® (InFed® – USA)
  - Total dose infusion (TDI): 20 mg/kg over 4-6h
  - Test dose required in first 15 mins
- Iron sucrose (Venofer®)
  - Slow i.v. 200mg/dose max.
- Iron carboxymaltose (Ferinject®)
  - TDI 15mg/kg up to 1000mg over 30-60 mins
- Iron isomaltoside (Monofer®)
  - TDI: 20 mg/kg over 1 hour
Adverse reactions

• Legion – documented – but uncommon in practice
• More likely with higher doses†
• Cosmofer® – potential for serious anaphylaxis, but rare.
  – Test dose; slow infusion (4-6 hours)
  – Other SE: hyper/hypotension, myalgia
• Ferinject®
  – Infusion over 15 minutes
  – Generally well-tolerated

†Auerbach et al. Am J Hematol 2008
I.V. or Oral iron?

• i.v. iron resulted in higher Hb, iron stores or both compared to oral iron in:
  – Chronic renal failure without dialysis
  – Chronic renal failure with dialysis
  – Pregnancy
  – Postpartum
  – Inflammatory bowel disease
  – Chemotherapy
  – Preoperatively + rHuEPO

• Hepcidin would decrease iron absorption
If only...
Erythropoiesis-stimulating agents

• Low or inappropriately low levels of erythropoietin
• Epoetin alfa (r-HuEPO) licensed for treatment of moderate preoperative anaemia in patients undergoing major orthopaedic surgery.
  – Short half-life
  – Weekly x 4 weeks before surgery
  – Accepted standard of care for Jehovah Witness before major surgery
• Darbepoetin – not licensed for preoperative anaemia
  – Glycosylated = longer half life
  – Biologically equivalent to r-HuEPO
  – 200IU epoetin alfa = 1 µg darbepoetin
## Drug costs

<table>
<thead>
<tr>
<th>Drug, dose</th>
<th>Hospital price (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmofer, 1g</td>
<td>96.00</td>
</tr>
<tr>
<td>Ferinject, 1g</td>
<td>229.00</td>
</tr>
<tr>
<td>Monofer, 1g</td>
<td>200.00</td>
</tr>
<tr>
<td>(Venofer, 1g)</td>
<td>113.00</td>
</tr>
<tr>
<td>Darbepoetin, 200µg</td>
<td>96.00</td>
</tr>
</tbody>
</table>
Elective patients 2009-2010 (n=71)
Hb increase after treatment with iv iron and darbepoetin

<table>
<thead>
<tr>
<th></th>
<th>Pre- treatment</th>
<th>Post treatment (preoperative)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, mean (range) g/dl</td>
<td>11.5 (9.1 - 13.3)</td>
<td>12.9 (10.3 -15.1)</td>
<td>1.4 (-0.4 – 4.1)</td>
</tr>
</tbody>
</table>
Elective patients 2009-2010 (n=71)

Hb increase after treatment with iv iron + darbepoetin

Hb increase (g/dl)

<table>
<thead>
<tr>
<th>Hb increase (g/dl)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5</td>
<td>21</td>
</tr>
<tr>
<td>0.5 – 0.9</td>
<td>9</td>
</tr>
<tr>
<td>1.0 – 1.4</td>
<td>18</td>
</tr>
<tr>
<td>1.5 – 1.9</td>
<td>24</td>
</tr>
<tr>
<td>2.0 – 2.4</td>
<td>10</td>
</tr>
<tr>
<td>2.5 – 2.9</td>
<td>8</td>
</tr>
<tr>
<td>≥3.0</td>
<td>2</td>
</tr>
</tbody>
</table>
Impact of anaemia treatment on perioperative transfusion

• Compare transfusion rates (Day 0-7) between treated cohort (2009-10) and untreated elective patients Hb <13
• Transfusion trigger ≤7 g/dl unless bleeding, LCOS, coagulopathy

<table>
<thead>
<tr>
<th></th>
<th>Not treated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>123</td>
<td>71</td>
</tr>
<tr>
<td>Hb at initial presentation (mean) g/dl</td>
<td>11.7</td>
<td>11.5 (preop= 12.9)</td>
</tr>
<tr>
<td>Transfused</td>
<td>100</td>
<td>48</td>
</tr>
<tr>
<td>Not transfused</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>% transfusion</td>
<td>81.3</td>
<td>67.6</td>
</tr>
</tbody>
</table>

• Fisher’s exact test: p=0.0362 (2 sided)
Unanswered questions

• Transfusion rate
  – Influenced by changing practice – fluids, CPB (filtration), coagulation management

• Other adverse outcomes
  – Treatment related (iv iron)
  – Other postoperative outcomes

• Length of stay

• Post discharge recovery

• Cost effectiveness
Anaemia and Surgery

“Anaemia is believed to increase the risk of surgery...Common practice for non-urgent surgery to be postponed if the patient is anaemic.”

– 2441 anaesthetic records reviewed
– 50% had preoperative Hb documented
– Significant association between Hb and mortality
– Postoperative length of stay increased in men with low Hb

“...hypothesis which best explains the association...is that preoperative haemoglobin level reflects the severity of the underlying condition which has necessitated surgery. A randomised clinical trial would test the alternative hypothesis that anaemia constitutes an additional risk in surgical procedures.”

Thank You

AAGBI
ACTA
Andrew Klein