FFP - where are we now & where are we going?

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THE PERFECT FFP-----

- 100% correction of coagulation defects
- No virus or vCJD transmission
- No side effects
- No additives
- No need to ABO or RhD match
- Easy to store, instantly available, long shelf life
- Cheap
- -------doesn’t exist.
Risks of FFP

• Transfusion-related acute lung injury
• Viruses
• vCJD???
• Wrong ABO group- leading to haemolysis
• Acute reactions
• Fluid overload
6 years of SHOT reports
1996-2002 (n=1711)

- IBCT (1093) 63.9%
- ATR (209) 12.2%
- DTR (196) 11.5%
- PTP (43) 2.5%
- TRALI (113) 6.6%
- TA-GVHD(13) 0.8%
- TTI (37) 2.2%
- Unclassified (7) 0.4%
Transfusion Related Acute Lung Injury

- SHOT - “Acute dyspnoea with hypoxia and bilateral pulmonary infiltrates occurring during or in the 24 hours after transfusion, with no other apparent cause”

- Frequency - ? 1 in 1,000-1 in 2,500 patients transfused.

- Would expect to see 300-750 cases/year
6 years of TRALI in UK

103 evaluable cases, 25 fatal (25%)  
26 new cases in last 12 month reporting period

**Red cells**  23/12 million = 1: 520,000  
**FFP /cryo**  31/1.8million = 1: 58,000  
**Platelets**  16/1.2million = 1: 75,000

Major cause of transfusion-related morbidity and mortality
How does TRALI occur?

A male donor with a history of blood transfusion

A female donor with history of pregnancy - antibodies in 10-15%

HLA/HNA antibodies.
How does TRALI occur?

1. HLA/HNA abs
   - HLA
   - HNA

2. C’ activation
   - C
   - C5
   - Chemotactic factor

- Adherence of neutrophils to pulmonary endothelium or epithelium
- Cell membrane permeabilisation
- Lung oedema
- Secretion of IL-1β, TNFα, IL-8 may amplify the reaction
HLA antibodies in female donors
(McLennan, Lucas Navarrete et al)

- 1188 female donors tested
- 1014 (86%) negative for HLA class I and II
- 174 (14%) antibody positives
  - 77 (6%) HLA class I only
  - 49 (4%) HLA class II only
  - 48 (4%) HLA class I and II

- Specificities found in 85 samples e.g.
  - HLA-A2, A28
  - HLA-B7 B27
  - HLA-DR1, DR103
Products implicated in TRALI including likelihood of each case being TRALI

- **Unlikely**
- **Possible**
- **Probable**
- **Highly likely**

**Products:**
- FFP
- Platelets
- Red cells
- Not stated
Diagnostic groups who developed TRALI 2002-02

- 9 cardiac surgery
- 8 haematological disease
- 5 liver disease
- 3 obstetric/gynaecology haemorrhage
- 3 warfarin reversal
- 1 TTP
<table>
<thead>
<tr>
<th>COMMONEST USES OF FFP</th>
<th>No</th>
<th>FFP</th>
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<tbody>
<tr>
<td>Coronary artery/valve surgery</td>
<td>80</td>
<td>337</td>
</tr>
<tr>
<td>Malignant neoplasms of lymphoid, haematopoietic and related tissues</td>
<td>53</td>
<td>110</td>
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<tr>
<td>Aortic surgery</td>
<td>27</td>
<td>200</td>
</tr>
<tr>
<td>Diseases of liver</td>
<td>27</td>
<td>177</td>
</tr>
<tr>
<td>Renal failure</td>
<td>9</td>
<td>64</td>
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TRALI prevention strategies under consideration

- FFP - male donors only - NBS Newcastle piloting
  - OR pooled Solvent Detergent FFP
- Platelet pools - resuspend in male plasma OR replace 70% plasma with additive solution
- Apheresis platelets- screen female donors OR platelet additive solution
- Red cells- discourage use of whole blood
Residual viral risks of FFP in UK

- FFP IS NOT MANUFACTURED FROM NEW OR LAPSED DONORS
- HIV: 1 in 10 million
- HCV: 1 in 50 million since genome testing
- HBV: 1 in 1.2 million
- New viruses- West Nile Virus in USA
- Hepatitis A/parvovirus B19: both rare
- CMV and HTLV not transmitted by plasma (nor bacteria)
‘Virus- safer’ FFP

(1) Pathogen inactivation
   - Solvent detergent
   - Methylene blue

(2) Quarantining- rejected for UK as so much plasma discarded already

• Standard FFP no longer permitted in Norway, Portugal, France, Netherlands
Solvent detergent FFP

- Needs POOLING of 500-1000 donations
- SD dissolves lipid coated viruses (4-6 log kill HIV, HBV, HCV) - SD is removed
- No effect on parvovirus B19 or hepatitis A - so genome testing required for those
- Available commercially from Octapharma- ‘Octaplas’ - 200ml units
- No definite TRALI reported (1 possible to SHOT this year)
Solvent-detergent FFP -coagulation data

- 20-30% loss factor VIII
- 15-20% loss factor XI
- 10-15% loss factor XIII
- All others < 5%
- Randomised trial in liver disease/transplant showed equivalent correction of coagulation

Increased risk of thrombosis with SDFFP - an American problem??

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<tr>
<th>U/100ml</th>
<th>Vitex</th>
<th>Octaplas</th>
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<tr>
<td>Protein C</td>
<td>96</td>
<td>85</td>
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<tr>
<td>Protein S</td>
<td>24</td>
<td>64</td>
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<tr>
<td>PI</td>
<td>14</td>
<td>23</td>
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BUT ? Risk in TTP
Methylene blue FFP
Currently provided for children born on or after 1st Jan 1996

- Photodynamic process-oxygen radicals
- Single units - Blood Centres can do
- MB + white light - then MB removal
- No predicted toxicity at residual levels
- 30% loss factor VIII
- 20-30% fibrinogen loss
- >1 million units used but few trials
- Licensed as a device
Does use of MBFFP increase demand?

- 56% increase in FFP:red cell ratio after changing to MB
- increased cryoprecipitate demand x2-3
- BUT FFP:red cell ratio was >1 (0.11 in UK)
- different prescribing patterns in Spain (all CABG patients get FFP)

Atance et al Transfusion 2001; 41:1548-52.
Prion protein - change in structure

Normal Conformer

Rogue Conformer (speculative)

Adapted from http://www.cmpharm.usf.edu/cohen/research/gallery/aw_prion.gif
Importation of FFP from USA

- DoH instruction August 2002
- Import FFP for neonates and children born on or after 1st Jan 1996 (foodban)
- VOLUNTEERS from USA; males only
- Virus inactivated by NBS using MB
- Will be available in 50 and 300 ml packs
- Start date end 2003/early 2004
West Nile Virus

- Epidemic in USA 2002
- Spread by mosquitoes to humans & birds
- Asymptomatic through to encephalitis
- Transfusion- transmitted in 2002

2003- USA genome testing- 160/1.1million
  - sensitive to methylene blue (and SD?)
  - travellers to USA deferred for 28 days
Where are we headed?

- Virus treated FFP does not meet cost-effectiveness criteria
- More recent evaluations take TRALI into account
- No vCJD cases yet due to transfusion
- NBTC recommend VIP for all recipients
- DoH considering whether to offer to more patients
Figure 4a Age distribution of recipients of all FFP units (n=2125)

<table>
<thead>
<tr>
<th>Age Decade</th>
<th>% of Total FFP Units Tx</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>17 : 83</td>
</tr>
<tr>
<td>1-10</td>
<td>44 : 56</td>
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<tr>
<td>11-20</td>
<td>28 : 72</td>
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<td>21-30</td>
<td>64 : 36</td>
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<td>31-40</td>
<td>40 : 60</td>
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<td>41-50</td>
<td>49 : 51</td>
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<td>51-60</td>
<td>46 : 54</td>
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<td>61-70</td>
<td>75 : 25</td>
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<tr>
<td>71-80</td>
<td>65 : 35</td>
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<tr>
<td>81-90</td>
<td>58 : 42</td>
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<tr>
<td>&gt;90</td>
<td>40 : 60</td>
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| Gender | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 | 90+
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<tbody>
<tr>
<td>F</td>
<td>0.2</td>
<td>1.6</td>
<td>1.8</td>
<td>0.9</td>
<td>5.0</td>
<td>5.0</td>
<td>9.3</td>
<td>7.4</td>
<td>7.3</td>
<td>2.4</td>
</tr>
<tr>
<td>M</td>
<td>0.0</td>
<td>1.3</td>
<td>0.7</td>
<td>1.6</td>
<td>3.3</td>
<td>4.7</td>
<td>7.9</td>
<td>21.8</td>
<td>13.9</td>
<td>3.2</td>
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Audits of FFP usage - recurrent themes

- Poor documentation of reason - ? Many patients transfused inappropriately
- Poor use of coagulation tests before and after
- Underdosing
- Wastage high
- New BCSH Guidelines forthcoming
What would we like in future?

- Better technology for assessment of causes of bleeding
- Research into ‘transfusion trigger’ for FFP on which to base guidelines
- Balance between virus safety and other hazards eg TRALI
- Balance between safety and cost