Plasma Transfusion

Evidence-based clinical practice guidelines

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Plasma transfusion

- US: approximately 4 million units of plasma transfused per year
- 150% increase over last 25 years
- Other nations with advanced health care systems transfuse similar (or slightly lower) amounts of plasma
- Many recognized adverse effects of plasma: viral transmission, TRALI, etc...
Why develop plasma transfusion practice guidelines?

- Guidelines identify best clinical practices
- Guidelines provide useful and needed information to those in your specialty as well as related specialties
- If stakeholders are deeply involved, guidelines can promote more acceptance of these practices
- Guidelines can also stimulate research initiatives into areas where evidence addressing efficacy is lacking.....
Practice guidelines as a “ratchet”

Evidence from clinical studies

**Evidence-based guidelines** are developed/revised

Guidelines inform study designs

Studies improve quality of evidence
Typical “guidelines” for plasma transfusion

- Massive transfusion
- Active bleeding
- Multiple coag factor deficiency with (risk of) bleeding
  - Warfarin reversal
  - Liver disease
- Single coag factor deficiency without concentrate available
- Plasma exchange
Recognized contra-indications to plasma transfusion

- Volume replacement/expander
- Nutritional supplement
- When warfarin can be reversed with Vit K
- When recombinant/virus-inactivated products are available
- When INR is < 1.7

Unfortunately, guideline compliance is often limited...
Fig. 1. Changes in recipients' INRs after transfusions of FFP that were within guidelines (INR, 1.6; ○; n = 10 units) compared to transfusions of FFP outside guidelines (●; n = 68 units). Only 20 filled circles appear in the figure because 48 additional results were overlapping.
Fresh frozen plasma is ineffective for correcting minimally elevated international normalized ratios

Results

- Minimally prolonged INRs decreased with treatment of the underlying disease alone (FFP had no impact).
- With an observed analytic variation of 3.2%, a **significant change in the INR following FFP transfusion is expected only at an INR of > 1.7**.

Conclusion

- Transfusions not meeting current FFP guidelines do not reliably reduce the INR.
- However, **20-30%** of transfusions were **outside guidelines**
Approaches to developing guidelines

- Literature reviews
- Consensus conferences
- Systematic reviews
  - A key component of evidence-based medicine
- Explicit, transparent systematized approaches for deriving practice guidelines from study evidence
- **GRADE**: Grading of Recommendations, Assessment, Development, and Evaluation
GRADE:

a widely-accepted transparent methodology for developing evidence-based practice guidelines
Organizations that have endorsed GRADE

World Health Organization
Endocrine Society
American College of Chest Physicians
Up To Date
Agenzia Sanitaria Regionale, Bologna-Italy
Ministry of Health and Long-Term Care, Ontario-Canada
Surviving Sepsis – International
Arztliches Zentrum fur Qualitat in der Medizin-Germany
American Thoracic Society- USA
American College of Physicians-USA
The Cochrane Collaboration-International
European Society of Thoracic Surgeons-International
British Medical Journal
Journal of Infection in Developing Countries-international
Agency for Healthcare Research and Quality-USA
Society of Critical Care Medicine-USA
National Institute for Clinical Excellence-UK
Norwegian Knowledge Centre for the Health Services
The UPenn Center for Evidence-Based Practice

German Center for Evidence-Based Nursing
Evidence-Based Nursing Sudtirol-Italy
Society for Vascular Surgery-USA
BMJ Clinical Evidence
EBM Guidelines-Finland/International
Polish Institute for EBM
European Respiratory Society (ERS)-Europe
Japanese Society for Temporomandibular Joint-Japan
National Board of Health and Welfare-Sweden
COMPUS at the Canadian Agency for Drugs and Technologies in Health-Canada
Infectious Diseases Society of America-USA
Major steps for developing guidelines using GRADE

1. Assemble the guidelines review group
2. Formulate the clinical question(s)
3. Perform a thorough search of the relevant literature followed by a systematic review and statistical analysis
4. Prepare evidence-based guidelines following the explicit step-by-step methodology of the GRADE system
# The Guidelines Group

**AABB CTMC**
- Jeff Carson, UMDNJ
- Rob Davenport, U Michigan
- Mary Jo Drew, ARC
- Mark Fung, U Vermont
- Marilyn Hamilton, CMHC
- John Hess, U Maryland
- Anne Eder, ARC
- John Roback, Emory
- Bruce Sachais, U Penn
- Toby Silverman, CBER FDA
- John Waters, U Pittsburgh

**Outside stakeholders**
- Stephen Caldwell, UVA (AASLD)
- Naomi Luban, CNMC (AAP)
- Jeremy Perkins, Walter Reed (military)
- Aryeh Shander, MSSM (ASA)
- Ed Snyder, Yale (ASH)
- Christopher Tormey, Yale (ASH)

**Consultants**
- Ben Djulbegovic, Moffitt
- Victor Montori, Mayo
- Hassan Murad, Mayo

**AABB staff**
- Theresa Wiegmann
- Aaron Lyss
Questions with FFP transfusion

1. Should plasma transfusion be used (vs. no plasma) in patients requiring massive transfusion?
2. Should a plasma:RBC transfusion ratio $\geq 1:3$ (vs. $<1:3$) be used in patients requiring massive transfusion?
3. Should plasma transfusion (vs. no plasma) be used in patients undergoing surgery without massive transfusion?
4. Should plasma transfusion (vs. no plasma) be used for patients with anticoagulation-related intracranial haemorrhage?
5. Should plasma transfusion (vs. no plasma) be used to reverse anticoagulation in patients without intracranial haemorrhage?
6. Should plasma transfusion (vs. no plasma) be used in medical patients who are not bleeding, not undergoing surgery, or massive transfusion?
Figure 1: Study Flow

1005 Potentially relevant references identified by search

- 163 References selected for full text retrieval
  - 842 Excluded after screening of title/abstract
  - 126 Excluded after full text screening
    - 13 Not original research
    - 40 Irrelevant Interventions
    - 68 Not controlled
    - 5 Outcomes of interest not reported

- 37 studies included in systematic review
### Table 2: Study description

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of patients</th>
<th>Mean Age (years)</th>
<th>Female (%)</th>
<th>Comorbidities</th>
<th>Liver Disease</th>
<th>Operative Status</th>
<th>Anti-coagulation</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazzard, 1975</td>
<td>20</td>
<td>26</td>
<td>NR</td>
<td>Acetaminophen overdose and coagulopathy</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>7 d</td>
<td>plasma 300 ml/6hr until PT ratio normalize</td>
<td>No treatment</td>
</tr>
<tr>
<td>Mannucci, 1976</td>
<td>21</td>
<td>NR</td>
<td>NR</td>
<td>Cirrhosis/ hepatitis</td>
<td>Yes</td>
<td>Needle biopsy</td>
<td>No</td>
<td>365 d</td>
<td>plasma 12ml/kg</td>
<td>Prothrombin complex 25 Units/ml</td>
</tr>
<tr>
<td>Belcher, 1984</td>
<td>73</td>
<td>53</td>
<td>7</td>
<td>Elderly, Cardiac surgery</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>180 d</td>
<td>Plasma Protein fraction</td>
<td>Hydroxy ethyl Starch</td>
</tr>
<tr>
<td>Boughton, 1984</td>
<td>10</td>
<td>42</td>
<td>NR</td>
<td>20 to 70% burns</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>21 d</td>
<td>plasma</td>
<td>Human Plasma Protein Fraction</td>
</tr>
<tr>
<td>Leese, 1987</td>
<td>198</td>
<td>59</td>
<td>52</td>
<td>Severe acute pancreatitis, no coagulopathy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>105 d</td>
<td>plasma 2 U Daily for 3 days.</td>
<td>albumin solution</td>
</tr>
<tr>
<td>Hedstrand, 1987</td>
<td>275</td>
<td>69</td>
<td>55</td>
<td>Elderly, elective surgery (abdominal, hip, knee and others), in need of blood transfusion</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>14 d</td>
<td>plasma</td>
<td>6% Macrodex &amp; Ringer dex</td>
</tr>
<tr>
<td>Martinowitz, 1990</td>
<td>40</td>
<td>60</td>
<td>28</td>
<td>Cardiopulmonary bypass patients who received prophylactic plasma postoperatively</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>1 d</td>
<td>plasma</td>
<td>Fresh packed cells</td>
</tr>
</tbody>
</table>
**Figure 2: Mortality, massive transfusion**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Events / Total Plasma</th>
<th>Events / Total Control</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borgman, 2007</td>
<td>0.29</td>
<td>0.16</td>
<td>0.51</td>
<td>31 / 162</td>
<td>38 / 84</td>
<td></td>
</tr>
<tr>
<td>Cotton, 2009</td>
<td>0.46</td>
<td>0.28</td>
<td>0.75</td>
<td>54 / 125</td>
<td>88 / 141</td>
<td></td>
</tr>
<tr>
<td>Holcomb, 2008</td>
<td>0.58</td>
<td>0.40</td>
<td>0.84</td>
<td>87 / 252</td>
<td>102 / 214</td>
<td></td>
</tr>
<tr>
<td>Kashuk, 2008</td>
<td>0.44</td>
<td>0.22</td>
<td>0.88</td>
<td>23 / 59</td>
<td>44 / 74</td>
<td></td>
</tr>
<tr>
<td>Maegle, 2008</td>
<td>0.59</td>
<td>0.42</td>
<td>0.81</td>
<td>76 / 229</td>
<td>222 / 484</td>
<td></td>
</tr>
<tr>
<td>Teixeira, 2009</td>
<td>0.18</td>
<td>0.12</td>
<td>0.28</td>
<td>58 / 226</td>
<td>103 / 157</td>
<td></td>
</tr>
<tr>
<td>Scalea, 2008 MT</td>
<td>1.49</td>
<td>0.63</td>
<td>3.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snyder, 2009</td>
<td>0.84</td>
<td>0.47</td>
<td>1.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duchesne, 2008 MT</td>
<td>0.05</td>
<td>0.02</td>
<td>0.13</td>
<td>19 / 71</td>
<td>56 / 64</td>
<td></td>
</tr>
<tr>
<td>Dente, 2009</td>
<td>0.12</td>
<td>0.02</td>
<td>0.67</td>
<td>7 / 50</td>
<td>4 / 7</td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>0.38</td>
<td>0.24</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Meta Analysis**
Figure 5: Acute lung injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Events / Total</th>
<th>Odds Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanderwerff, 1997</td>
<td>4.30</td>
<td>1.29</td>
<td>14.31</td>
<td>12 / 83</td>
<td>Plasma: 1.74, Control: 0.42</td>
</tr>
<tr>
<td>Martin, 2003</td>
<td>4.10</td>
<td>1.55</td>
<td>10.85</td>
<td>7 / 177</td>
<td>Plasma: 2.20, Control: 0.81</td>
</tr>
<tr>
<td>Gajic, 2004</td>
<td>2.28</td>
<td>1.15</td>
<td>4.54</td>
<td>8 / 44</td>
<td>Plasma: 1.72, Control: 0.55</td>
</tr>
<tr>
<td>Dara, 2005</td>
<td>5.04</td>
<td>1.26</td>
<td>20.16</td>
<td>3 / 71</td>
<td>Plasma: 2.44, Control: 0.72</td>
</tr>
<tr>
<td>Khan, 2007</td>
<td>2.48</td>
<td>1.29</td>
<td>4.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.92</td>
<td>1.99</td>
<td>4.29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors plasma | Favors control

Meta Analysis
**Recommendation:** We suggest that plasma be transfused to trauma patients requiring massive transfusion

**Quality of evidence = Moderate**
Quality of Evidence

- The extent of confidence that an estimate of effect is correct, i.e. represents the “truth”
  - **High**: Considerable confidence in the estimate of effect. Future research is unlikely to change the estimate of the health intervention’s effect.
  - **Moderate**: Further research is likely to have an important impact on confidence in the estimate, and may change the estimate of the health intervention’s effect.
  - **Low**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
  - **Very low**: Any estimate of effect is very uncertain.
Strength of Recommendation

Confidence that adherence to recommendations will do more good than harm).

- **Strong**: indicating the judgment that most well informed people will make the same choice. The terminology “We recommend...” is used for these situations.

- **Weak**: indicating the judgment that a majority of well informed people will make the same choice, but a substantial minority will not. “We suggest...” is used in these situations.

- **Uncertain**: indicating that the panel made no specific recommendations for or against interventions, or made recommendations only in the context of research. “We cannot recommend for or against...”
**Recommendation:** We *suggest* that plasma be transfused to trauma patients requiring massive transfusion

Quality of evidence = *Moderate*
**Recommendation:** We cannot recommend for or against transfusion of plasma at a plasma:RBC ratio of \( \geq 1:3 \) in trauma patients during massive transfusion

**Quality of evidence = Low**
**Figure 3: Mortality, surgical patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Events / Total</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedstrand, 1987</td>
<td>3.83</td>
<td>0.42</td>
<td>34.68</td>
<td>4 / 142</td>
<td></td>
</tr>
<tr>
<td>Swisher, 1996</td>
<td>1.14</td>
<td>0.93</td>
<td>1.40</td>
<td>1 / 133</td>
<td></td>
</tr>
<tr>
<td>Gajic, 2004</td>
<td>2.15</td>
<td>0.97</td>
<td>4.76</td>
<td>13 / 35</td>
<td></td>
</tr>
<tr>
<td>Massicotte, 2005</td>
<td>3.54</td>
<td>1.31</td>
<td>9.61</td>
<td>30 / 135</td>
<td></td>
</tr>
<tr>
<td>Scalea, 2008 noMT</td>
<td>0.57</td>
<td>0.19</td>
<td>1.68</td>
<td>14 / 118</td>
<td></td>
</tr>
<tr>
<td>Duchesne, 2008 noMT</td>
<td>0.50</td>
<td>0.25</td>
<td>1.00</td>
<td>28 / 132</td>
<td></td>
</tr>
<tr>
<td>Kaibori, 2008</td>
<td>1.02</td>
<td>0.17</td>
<td>6.26</td>
<td>2 / 11</td>
<td></td>
</tr>
<tr>
<td><strong>Overall surgical patients</strong></td>
<td><strong>1.22</strong></td>
<td><strong>0.73</strong></td>
<td><strong>2.03</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors plasma  Favor control

**Meta Analysis**
**Recommendation:** We **cannot recommend** for or against transfusion of plasma for patients undergoing surgery in the absence of massive transfusion.

**Quality of evidence:** **Very Low**
Figure 4: Mortality, medical patients

<table>
<thead>
<tr>
<th>FFP Indication</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Events / Total</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leese, 1987</td>
<td>0.88</td>
<td>0.32</td>
<td>2.38</td>
<td>8 / 99</td>
<td></td>
</tr>
<tr>
<td>Leese, 1991</td>
<td>1.17</td>
<td>0.35</td>
<td>3.91</td>
<td>7 / 35</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.99</strong></td>
<td><strong>0.41</strong></td>
<td><strong>2.38</strong></td>
<td><strong>8 / 99</strong></td>
<td><strong>9 / 99</strong></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gazzard, 1975</td>
<td>0.44</td>
<td>0.03</td>
<td>5.88</td>
<td>1 / 10</td>
<td></td>
</tr>
<tr>
<td>Etemadrezaie, 2007</td>
<td>3.28</td>
<td>1.38</td>
<td>7.78</td>
<td>26 / 44</td>
<td>16 / 46</td>
</tr>
<tr>
<td>Khan, 2007</td>
<td>1.58</td>
<td>1.05</td>
<td>2.38</td>
<td>49 / 298</td>
<td>60 / 543</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>2.00</strong></td>
<td><strong>1.11</strong></td>
<td><strong>3.59</strong></td>
<td><strong>11 / 10</strong></td>
<td><strong>31 / 46</strong></td>
</tr>
<tr>
<td>No coagulopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guven, 2004</td>
<td>0.28</td>
<td>0.01</td>
<td>5.96</td>
<td>0 / 9</td>
<td>3 / 21</td>
</tr>
<tr>
<td>Organophosphate toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjöblom, 2001</td>
<td>0.29</td>
<td>0.09</td>
<td>0.98</td>
<td>10 / 18</td>
<td>34 / 42</td>
</tr>
<tr>
<td>Dara, 2005</td>
<td>0.85</td>
<td>0.36</td>
<td>2.00</td>
<td>11 / 44</td>
<td>20 / 71</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.57</strong></td>
<td><strong>0.25</strong></td>
<td><strong>1.30</strong></td>
<td><strong>11 / 18</strong></td>
<td><strong>34 / 42</strong></td>
</tr>
<tr>
<td>Warfarin anticoagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall medical patients</td>
<td>0.93</td>
<td>0.41</td>
<td>2.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meta Analysis
**Recommendation:** We suggest that plasma be transfused in patients with warfarin anticoagulation-related intracranial hemorrhage.

**Quality of evidence:** Low
**Recommendation:** We cannot recommend for or against transfusion of plasma to reverse warfarin in patients without intracranial hemorrhage.

**Quality of evidence:** Very Low
**Recommendation:** We suggest against plasma transfusion in the absence of massive transfusion, surgery, bleeding or overanticoagulation.

**Quality of evidence:** Very Low
Conclusions

- Current indications for transfusion are based on limited evidence
- Clinical studies, and resulting guidelines, are improving but still have far to go
- In every scenario, the need for additional studies was identified
- In particular, there was an absence of studies that quantified plasma efficacy in patients with varying INRs
- Appropriately designed studies are expected to lead to stronger guideline recommendations