Supporting practice with evidence:
The management of massive transfusion

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Sections of Hematology
& Critical Care
Disclosures

None
Objectives

• Discuss the role of massive transfusion protocols

• Explore the impact of frozen plasma to red blood cell ratio (FP:RBC)
…What is a ‘Massive Transfusion?’

- Replacement of one blood mass, or 10 units of RBCs in a 24 hour period

Dynamic Definitions
- Transfusion of ≥4 PRBC units with 1 hour when ongoing need is foreseeable
- Replacement of 50% of the total blood volume within 3-4 hours
Logistics of a massive transfusion

- Complex medical scenarios
- High mortality

Common Pitfalls
- Poor planning
- Poor communication
- Infrequent laboratory monitoring
- Significant delay in ordering/administering plasma
- Under-appreciation for hypothermia & low use of fluid warmers
- Early reliance on cryoprecipitate and rescue medications
Massive Transfusion Protocols (MTPs)

- Comprehensive institutional plan
- Facilitate/protocolize communication
- Ensure frequent laboratory monitoring
- Reduce delay in ordering and administering blood products
- Deliver a reasonable ratio of plasma to red blood cells (FP:RBC)
Are MTPs evidence-informed?

Riskin et al, 2009

- Mortality rate - 45% before MTP implemented - 19% post-implementation

<table>
<thead>
<tr>
<th>Product and ratio</th>
<th>Pre-MTP, mean (95% CI)</th>
<th>Post-MTP, mean (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBCs</td>
<td>23.9 (18.7–29.1)</td>
<td>20.5 (15.5–25.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>FFP</td>
<td>12.3 (9.6–15.0)</td>
<td>10.7 (7.8–13.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Plt</td>
<td>2.3 (1.7–2.9)</td>
<td>2.8 (1.8–3.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>FFP:PRBCs</td>
<td>1:1.8 (1:1.5–1:2.2)</td>
<td>1:1.8 (1:1.5–1:2.1)</td>
<td>0.97</td>
</tr>
<tr>
<td>Plt:PRBCs</td>
<td>1:1.7 (1:1.4–1:2.1)</td>
<td>1:1.3 (1:1.1–1:1.5)</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

- Improved communication
- Better systems flow and optimize blood product availability
Predefined Massive Transfusion Protocols are Associated With a Reduction in Organ Failure and Postinjury Complications

Bryan A. Cotton, MD, Brigham K. Au, BS, Timothy C. Nunez, MD, Oliver L. Gunter, MD, Amy M. Robertson, MD, and Pampee P. Young, MD, PhD


<table>
<thead>
<tr>
<th></th>
<th>Pre-TEP (n = 141)</th>
<th>TEP (n = 125)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h survival (%)</td>
<td>61</td>
<td>69</td>
<td>0.185</td>
</tr>
<tr>
<td>30-d survival (%)</td>
<td>37.6</td>
<td>56.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital length of stay, d (±SD)</td>
<td>16.4 (±20.1)</td>
<td>12.0 (±12.1)</td>
<td>0.049</td>
</tr>
<tr>
<td>ICU length of stay, d (±SD)</td>
<td>6.6 (±9.4)</td>
<td>5.0 (±8.3)</td>
<td>0.239</td>
</tr>
<tr>
<td>Ventilator days, d (±SD)</td>
<td>8.2 (±9.7)</td>
<td>5.7 (±7.2)</td>
<td>0.017</td>
</tr>
<tr>
<td>IO blood products, units (±SD)</td>
<td>11.0 U (±SD)</td>
<td>14.7 U (±SD)</td>
<td>0.001</td>
</tr>
<tr>
<td>IO crystalloid, L (±SD)</td>
<td>7.0 L (±SD)</td>
<td>4.8 L (±SD)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h blood products (±SD)</td>
<td>38.7 U (±SD)</td>
<td>31.2 U (±SD)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

SD, standard deviation; IO, intraoperative.
...so what should you do??

- 85% of U.S. level I trauma centres have an MTP
  - Most were adopted in the past 5 years

- Considerable variation exists among specific protocols

- Lack of high quality data to inform optimal design and implementation
Therapeutic targets in massive transfusion

Eminence-based (but practical) guidelines:

• Red cells - Hemoglobin of 80 – 100 g/L

• Frozen Plasma - Target INR ≤ 1.4

• Platelets - >50 x10⁹/L (~100 in intracranial or ocular bleeding)

• Cryoprecipitate - Over-used and rarely indicated
### MEDICATION ORDERS TO BE INITIATED OR DISCONTINUED

**Massive Blood Transfusion Order Set**  
(Adults >16 yrs of age only)  
Please check all that apply and specify as required

Criteria for activating the Massive Transfusion Protocol (MTP):  
Transfusion of ≥4 RBC units within 1 hour when ongoing need is expected

1. [ ] Activate Massive Transfusion Protocol (MTP) order set
2. [ ] Physician or physician’s designate will Inform Transfusion Medicine Doctor on call that the Massive Transfusion Protocol is activated for this patient
3. [ ] Reverse anticoagulation if the patient is systematically anticoagulated  
   (See Appendix II for specific drugs and doses)

### GENERAL ORDERS

**Massive Blood Transfusion Order Set**  
(Adults >16 yrs of age only)  
Please check all that apply and specify as required

- Use a Fluid/Blood warmer to prevent hypothermia
- Use forced air heater, or an alternate method of warming if temperature is <37 degrees Celsius
- Collect Baseline Blood work - STAT
  - Type and Screen
  - CBC
  - Lytes (Na⁺, Cl⁻, K⁺, Ca²⁺, HCO₃⁻)
  - INR
  - Fibrinogen
  - aPTT if the patient is heparinized
IF RBCs or plasma are required IMMEDIATELY and the type and screen is UNKNOWN:
4. □ Transfuse 4 units of Emergency group O red blood cell units
Use O negative blood for female patients less than 45 years of age. Otherwise use O positive units
5. □ Transfuse 1000 mL of AB plasma

6. □ Transfuse the first Massive Transfusion Pack (it will be sent automatically from hospital blood bank). The pack will contain:
   • 6 units red blood cells
   • 1000 mL frozen plasma

IF ADDITION PRODUCTS ARE NECESSARY IN THE FIRST MTP, PLEASE ORDER THESE BELOW:
□ ______ dose(s) of adult pooled platelets
Consider platelet transfusion if the patient is known to be thrombocytopenic (<50 x10^9/L) or if platelet dysfunction is suspected (e.g. patient on clopidogrel, IIb/IIIa inhibitors or post-op cardiopulmonary bypass) (Usual practice is 1 adult dose)
□ ______ mL of frozen plasma
(Consider additional plasma if initial INR is >2.0 or coagulopathy is highly suspected) (Usual dose is 15 mL/kg or 1000-1500 mL)

Perform Initial Resuscitation
• Establish large bore IV access (e.g. a Cordis, Vascath, or 14-16 gauge peripheral IVs.) A triple lumen central venous catheter is NOT recommended
• Resuscitate with readily available IV fluids to provide adequate blood volume replacement (e.g. target systolic BP >90 mmHg)

Haemostatic Monitoring during Massive blood Transfusion:
□ CBC + platelet count - every 1 hour
□ INR – every 1 hour
□ Claus fibrinogen - every 1 hour
□ Arterial blood gases PRN
□ Temperature every hour
### MEDICATION ORDERS TO BE INITIATED OR DISCONTINUED

| 8. | Transfuse subsequent Massive Transfusion Packs as they arrive. Packs will arrive hourly and will contain:  
|    | • 6 units of red blood cells  
|    | • 1000 mL frozen plasma  
|    | • 1 adult unit of platelets – in EVERY pack |

### GENERAL ORDERS

| 9. | If the corrected serum calcium is <2.1 mmol/L, or if the ABG ionic calcium is <1.15 mmol/L – |

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**Goals of Therapy**

- **a.** Adequate blood volume replacement (CVP>6 and BP >90 mmHg)
- **b.** Maintain tissue oxygenation (provide supplemental oxygen or intubate)
- **c.** Prevent acidosis and hypothermia
- **d.** Prevent coagulopathy
- **e.** Achieve haemostasis – EARLY surgical intervention or mechanical means to stop bleeding are STRONGLY recommended. Blood components are only supportive.
Give 1 gram of calcium chloride (1 ampule) via a central line, over 3-5 minutes
OR
Give 2 grams of calcium gluconate (2 amps) via a peripheral line, over 3-5 minutes each

Close Out Orders
As soon as one of the following criteria has been satisfied:
• Patient has stopped bleeding or bleeding is under control
• The patient has died or resuscitation efforts have been withdrawn

10. Physician or physician’s designate will call the transfusion medicine physician on call and communicate that the MTP has ended
11. Physician or physician’s designate will inform the hospital blood bank that the MTP has ended (73508)
12. Promptly return unused blood products to the hospital blood bank

ORDERING BLOOD COMPONENTS
Red Blood Cells
• Advised to maintain haemoglobin >80 g/L in the face of serious bleeding
• Consider haemoglobin >90 g/L if there is evidence of myocardial ischaemia

Platelet transfusion
• Maintain platelets >50 x10^9/L (>100 in the setting of intracranial or intraocular bleeding)
• Consider empiric platelet transfusion if platelet dysfunction is suspected

Frozen Plasma
• Maintain INR <1.5
• Transfuse 10-15 ml/kg (1 to 1.5 Litres)
• Anticipate further needs based on on-going losses as it can take up to 60 minutes to order, thaw and administer frozen plasma

Cryoprecipitate
• Frozen plasma is the fluid of choice to correct coagulopathy in severe bleeding
• Cryoprecipitate is RARELY necessary due to the presence of multiple factor deficits that requires plasma to reverse
• If fibrinogen is <1.0 g/L but the INR is >1.5 then plasma is typically indicated
FP:RBC ratios in massive transfusion

2005 United States Army’s Institute of Surgical Research recommended the immediate delivery of transfusion in the form of a 1:1:1

2007 Borgman et al. Retrospective chart review - Increased survival at 24 hours with higher FP:RBC ratio

2008 50% increase in AB plasma use in Canada
Objective:
To determine the clinical benefit of a high vs. low FP:RBC ratio in severely bleeding patients
Included studies

• 11 studies enrolling 3,107 patients between 2007 and 2009
  • 7 retrospective registries
  • 3 prospective cohorts
  • 1 case-control study

• No randomized controlled trials
Studies comparing a 1:1 FP:RBC ratio to higher or lower ratios

- 5 studies reported mortality with a 1:1 FP:RBC ratio vs. higher or lower ratios
- 3 studies reported a survival benefit favoring 1:1 or higher
- 2 two studies reported no advantage of a 1:1 ratio

<table>
<thead>
<tr>
<th>Reference</th>
<th>FP:RBC ratio</th>
<th>Late Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchesne et al.</td>
<td>1:4 1:1</td>
<td>88% 26%</td>
</tr>
<tr>
<td>Maegele et al.</td>
<td>&lt; 1:1 1:1 &gt; 1:1</td>
<td>46% 36% 24.%</td>
</tr>
<tr>
<td>Zink et al.</td>
<td>&lt; 1:4 1:4 to 1:1 &gt; 1:1</td>
<td>55% 41% 26%</td>
</tr>
</tbody>
</table>
6 remaining studies

• Higher FP:RBC ratios were associated with improved survival
Limitations

• Retrospective analyses

• Weak analytic techniques repeated in the literature
  • Mortality at a fixed time
  • Inadequate adjustment of confounders
  • No attention paid to the process, procedure, or to physician competence
  • Influence of secular trends over time not recognized

• Uncertain generalizability outside of trauma
MCDONALD'S

MULTIPLE
WEAK STUDIES
DO NOT = DATA
Survival bias

• Bias that is introduced when subjects die before they have the opportunity to be exposed to the treatment

• FP takes time to order and administer
• Deaths occur relatively early in massive transfusion

• Patients who ‘survive’ to get plasma are more likely to be ‘survivors’ and thus more likely to have a higher FP:RBC
Survival bias and the existing literature

Synder et al.  J Trauma, 2009

• 134 trauma patients receiving $\geq 10$ units of RBCs in 24 hours

• Analyzed FP:RBC ratio as a fixed value at 24 hours AND as a time-varying covariate
Processes of Care in Massive Transfusion


- Retrospective review of all massive transfusion events in the Winnipeg Regional Health Authority from 2004 to 2010

Data Source
- The Canadian Blood Services data warehouse

Primary outcome:
- Association between FP:RBC ratio and hospital mortality
Processes of Care in Massive Transfusion


- What make this study different?
  - Multicentre
  - Comprehensive time-varying analysis
  - Adjustment for factors known or believed to be associated with survival
    - Age, sex, reason for transfusion, size of transfusion
## Demographics

<table>
<thead>
<tr>
<th>Demographic Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>218</td>
</tr>
<tr>
<td><strong>Age (mean, SD)</strong></td>
<td>60.4 (±16.8)</td>
</tr>
<tr>
<td><strong>Male sex (n %)</strong></td>
<td>150 (69%)</td>
</tr>
<tr>
<td><strong>Reasons for Transfusion (n %)</strong></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>33 (14.7%)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>44 (20.2%)</td>
</tr>
<tr>
<td>CVT surgery</td>
<td>75 (34.4%)</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>26 (11.9%)</td>
</tr>
<tr>
<td>Obstetrical hemorrhage</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Other surgery</td>
<td>48 (22.0%)</td>
</tr>
</tbody>
</table>
## Blood components administered

<table>
<thead>
<tr>
<th></th>
<th>N=218</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red blood cells</strong></td>
<td></td>
</tr>
<tr>
<td>Patients receiving emergency RBCs</td>
<td>61 (28.0%)</td>
</tr>
<tr>
<td>Mean # of total RBC units transfused</td>
<td>16.2 units (∆6.1)</td>
</tr>
<tr>
<td><strong>Frozen plasma</strong> (mean, SD)</td>
<td>12.7 units (∆8.0) (∼3.0 L)</td>
</tr>
<tr>
<td><strong>Platelets</strong> (mean, SD)</td>
<td>15.3 units (∆8.9)</td>
</tr>
<tr>
<td><strong>Use of cyroprecipitate</strong></td>
<td>100 (46%)</td>
</tr>
<tr>
<td><strong>Use of factor VIIa (n %)</strong></td>
<td>47 (21.6%)</td>
</tr>
</tbody>
</table>
### Processes of care

<table>
<thead>
<tr>
<th></th>
<th>N=218</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of a blood warmer?</strong></td>
<td>58%</td>
</tr>
<tr>
<td><strong>How long does it take to receive product?</strong></td>
<td></td>
</tr>
<tr>
<td>From emergency RBCs to cross-matched RBCs (n=61)</td>
<td>121 minutes [73, 310]</td>
</tr>
<tr>
<td>From first RBC to plasma</td>
<td>175 minutes [90, 395]</td>
</tr>
<tr>
<td>From first RBC to platelets</td>
<td>330 minutes [185, 615]</td>
</tr>
</tbody>
</table>
Frozen plasma : RBC ratio over time

**OVERALL** study population

![Bar graph showing the FP:RBC ratio over time](image-url)
Frozen plasma : RBC ratio over time

TRAUMA subgroup

FP:RBC ratio over time

< 1:10

1:2
**Survival**

<table>
<thead>
<tr>
<th></th>
<th>N=218</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL hospital survival</td>
<td>106 (48.6%)</td>
</tr>
<tr>
<td>Death due to hemorrhage</td>
<td>42.0%</td>
</tr>
</tbody>
</table>
**Fixed time vs. time varying survival**

**High (≥1:2) vs Low (<1:2) FP: RBC ratio**

<table>
<thead>
<tr>
<th></th>
<th>Death Censored at 24 hr Hazard Ratio (95% CI)</th>
<th>In Hospital Deaths Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FP:RBC at 24 hours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariable model</td>
<td>0.69 (95%CI 0.37, 1.29)</td>
<td>1.23 (95%CI 0.80, 1.89)</td>
</tr>
<tr>
<td>Multivariable model*</td>
<td>0.57 (95%CI 0.28, 1.14)</td>
<td>0.95 (95%CI 0.59, 1.52)</td>
</tr>
<tr>
<td><strong>FP:RBC as a time varying covariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariable model</td>
<td>0.89 (95%CI 0.46, 1.70)</td>
<td>1.34 (95%CI 0.86, 2.10)</td>
</tr>
<tr>
<td>Multivariable model*</td>
<td>0.76 (95%CI 0.37, 1.56)</td>
<td>1.06 (95%CI 0.65, 1.72)</td>
</tr>
</tbody>
</table>

*Adjusted for: Age, sex, reason for transfusion, and the number of RBC units transfused
**TRAUMA - Fixed time vs. time varying**

**High (≥1:2) vs Low (<1:2) FP: RBC ratio**

<table>
<thead>
<tr>
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<th>Death Censored at 24 hr Hazard Ratio (95% CI)</th>
<th>In Hospital Deaths Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[FP:RBC at 24 hours]</td>
<td></td>
</tr>
<tr>
<td>Univariable model</td>
<td>0.65 (95% CI 0.13, 3.36)</td>
<td>0.71 (95% CI 0.21, 2.39)</td>
</tr>
<tr>
<td>Multivariable model*</td>
<td>[FP:RBC as a time varying covariate]</td>
<td>0.98 (95% CI 0.24, 3.97)</td>
</tr>
<tr>
<td>Univariable model</td>
<td>0.86 (95% CI 0.16, 4.56)</td>
<td>0.83 (95% CI 0.24, 2.83)</td>
</tr>
<tr>
<td>Multivariable model*</td>
<td>1.05 (95% CI 0.26, 4.30)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for: Age, sex, reason for transfusion, and the number of RBC units transfused
Conclusions of this study:

- Trauma accounts for a small minority of patients requiring massive transfusion in the Winnipeg region.
- 24 hour survival may be increased in patients who receive higher FP:RBC ratios...BUT,
- Hospital survival does not appear to be influenced by the FP:RBC ratio.
…In conclusion

• Massive transfusions are highly complex medical procedures associated with high mortality

• MTPs appear to improve communication and decrease blood product delay
  • May decrease the overall amount of blood used
  • May improve mortality
  • Can facilitate delivery of a reasonable FP:RBC ratio

• Impact on non trauma patients and patients not needing a massive transfusion warrants caution and further study
...In conclusion

• FP:RBC ratios are likely important, but the current literature is not sufficient to dictate practice
  • Poor quality studies
  • Based on trauma
  • Economic and ‘systems’ costs have not been considered

• Prospective studies are needed
Acknowledgements

• **Source Data**
  • Canadian Blood Services
  • Debra Lane

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  • Bryce Makar

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  • Aaron Webb
  • Harold Peters
  • Ryan Iwasiw
  • Kym Wiebe
  • Nicole Marten

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• **Statistical Lead**
  • Steve Doucette