Current Evidence based management of Massive Haemorrhage

Kerry Gunn
Department of Anaesthesia and Perioperative Medicine
Auckland City Hospital
- A small proportion (4%) need an aggressive approach to transfusion
- Systems that include plasma and platelets improve outcome
- The key component in plasma is fibrinogen
- The challenge is to develop systems that deliver fibrinogen rapidly enough to the ones that need it and leave the others without it

- TEG improves decision-making and reduces waste
MT Bleeding Context
>5600 MT cases, 25 hospitals

Cardiac surgery
Other surgery
Trauma
GI haemorrhage
Vascular surgery
Obstetric haemorrhage
Liver transplant
Medical other
Mortality after trauma was high

- Trauma presentations to Auckland Hospital resus room in 1983
- 602 patients of whom 223 subsequently shown to have major trauma.
- Mortality 60/223 (26.9%)
Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock


A Survival

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>0</th>
<th>48</th>
<th>96</th>
<th>144</th>
<th>192</th>
<th>240</th>
<th>288</th>
<th>336</th>
<th>384</th>
<th>432</th>
<th>480</th>
<th>528</th>
<th>576</th>
<th>624</th>
<th>672</th>
<th>720</th>
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</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>230</td>
<td>183</td>
<td>172</td>
<td>170</td>
<td>169</td>
<td>168</td>
<td>168</td>
<td>168</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard care</td>
<td>271</td>
<td>194</td>
<td>181</td>
<td>179</td>
<td>173</td>
<td>172</td>
<td>172</td>
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</tr>
</tbody>
</table>

Percentage of Patients

Hours since Randomization

0 48 96 144 192 240 288 336 384 432 480 528 576 624 672 720
The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study

Comparative Effectiveness of a Time-Varying Treatment With Competing Risks

John B. Holcomb, MD; Deborah J. del Junco, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Mitchell J. Cohen, MD; Martin A. Schreiber, MD; Louis H. Alarcon, MD; Yu Bai, MD, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Bryan A. Cotton, MD, MPH; Nena Mattijevic, PhD; Peter Muskat, MD; John G. Myers, MD; Herb A. Phelan, MD, MScS; Christopher E. White, MD; Jiajie Zhang, PhD; Mohammad H. Rahbar, PhD; for the PROMMTT Study Group

- 10 US Trauma centres
- 906 patients > 3 units pRBC (of 35,000 admissions)
- Within first 24 hrs mortality from bleeding reduced 3-4 times with 1:1 ratio
- NO difference in outcome after 24hrs
Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma
The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Mitchell Jay Cohen, MD; Brian A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kemi Inaba, MD, PhD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O’Keefe, MRCMB, MSPH; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group
Table 2  Multivariable logistic regression analysis for patients alive and free from massive transfusion within 24 h

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00 (0.98, 1.01)</td>
<td>0.768</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>0.98 (0.95, 1.00)</td>
<td>0.071</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.055</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.00 (0.99, 1.01)</td>
<td>0.929</td>
</tr>
<tr>
<td>Haemoglobin level</td>
<td>1.11 (0.95, 1.30)</td>
<td>0.186</td>
</tr>
<tr>
<td>AIS score (head) ≥ 3</td>
<td>0.53 (0.27, 1.04)</td>
<td>0.065</td>
</tr>
<tr>
<td>Total amount of blood products used</td>
<td>0.81 (0.77, 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High ratio of plasma to RBCs</td>
<td>2.07 (1.03, 4.13)</td>
<td>0.040</td>
</tr>
<tr>
<td>High ratio of platelets to RBCs</td>
<td>2.67 (1.24, 5.77)</td>
<td>0.012</td>
</tr>
<tr>
<td>Use of tranexamic acid</td>
<td>2.71 (1.29, 5.71)</td>
<td>0.009</td>
</tr>
<tr>
<td>Use of fibrinogen products</td>
<td>1.45 (0.60, 3.48)</td>
<td>0.409</td>
</tr>
</tbody>
</table>

Values in parentheses are 95 per cent confidence intervals. Patients were clustered within each hospital. AIS, Abbreviated Injury Scale; RBC, red blood cell.

Table 3  Multivariable logistic regression analysis for correction of coagulopathy within 24 h

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.01, 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fluids per 100 ml in 24 h</td>
<td>0.98 (0.97, 0.99)</td>
<td>0.001</td>
</tr>
<tr>
<td>High ratio of plasma to RBCs</td>
<td>0.89 (0.45, 1.78)</td>
<td>0.747</td>
</tr>
<tr>
<td>High ratio of platelets to RBCs</td>
<td>0.63 (0.32, 1.26)</td>
<td>0.194</td>
</tr>
<tr>
<td>Use of tranexamic acid</td>
<td>1.64 (0.82, 3.29)</td>
<td>0.165</td>
</tr>
<tr>
<td>Use of fibrinogen products</td>
<td>1.61 (0.74, 3.54)</td>
<td>0.233</td>
</tr>
</tbody>
</table>

Values in parentheses are 95 per cent confidence intervals. Patients were clustered within each hospital. RBC, red blood cell.
The ‘revised’ MTP

Blood Bank Responsibilities:
- Ensure X-match sample processed ASAP after O-neg release
- Notify NZBS Medical Officer after issuing MTP Box One
- Thaw next box in advance and await request
- Ensure supply of platelets

Contacts:
- Blood Bank - Ext 24015
- Coagulation Lab - Ext 7572
- Level 8 Anaesthetist - 021 496 374

TXA is suggested

REQUEST, DELIVER AND TRANSFUSE AS BELOW:

MTP BOX ONE
2 Whole Blood or 2U RBC and 2U FFP

MTP BOX TWO
4 RBC
4 FFP
3U Cryoprecipitate

MTP BOX THREE
4 RBC
4 FFP
1U Platelets

MTP BOX FOUR
4 RBC
4 FFP

Check Coags / Platelets /FBC ABGs / Ca**
Repeat every 30 min

Cytro comes before platelets
Does mortality drop with Fibrinogen concentrate?

Fibrinogen levels

≥1.8g/L
>1.0–<1.8g/L
≤1.0g/L

Mortality

24-hour  In hospital
4.3%  18.5%
5.3%  25.4%
31.5%  51.9%

ADHB Adult
Code Crimson
MTP

Team Leader Responsibilities
- Team leader should be a trauma team member
- Notify Coag Lab and send Coag requests on the Labplus Urgent form (orange border)
- Activate protocol by ringing Blood Bank (ext 24015) and say “I am activating the “Code Crimson MTP”
- Call for each box as required
- Make a decision to cease MTP and contact Blood Bank

Blood Bank Responsibilities
- Ensure X-match sample processed ASAP after O-neg release
- Notify NZBS Medical Officer after issuing MTP Box Four
- Thaw next box in advance and await request
- Ensure supply of platelets

Additional treatment thresholds:
- If PR >1.5 or APTT >40 consider additional 4 units FFP
- If fibrinogen <1g/L consider additional 3U Cryoprecipitate
- If platelets <75 x10^9/L consider additional one pack platelets
- If ionized Ca++ <1mmol/L give 10mls Calcium
## Sources of Fibrinogen

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen Content</th>
<th>Thaw Time Delay</th>
<th>Factors Present</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>1.6G/L</td>
<td>30 min. + Transport</td>
<td>Fibrinogen (I), II, VII, IX, X, XII [V &amp; VIII 65% (N)]</td>
<td>Weak TACO, TRALI immunomodulation</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>1.3G/150ml</td>
<td>30 min. + Transport</td>
<td>Fibrinogen (I), vWF, VIII XIII fibronectin</td>
<td>Availability, no viral inactivation</td>
</tr>
<tr>
<td>Fibrinogen Concentrate</td>
<td>1.0G/50ml</td>
<td>NIL</td>
<td>Fibrinogen (I)</td>
<td>Cost 20% greater than cryoprecipitate</td>
</tr>
</tbody>
</table>
Fibrinogen and Hemostasis: A Primary Hemostatic Target for the Management of Acquired Bleeding

Jerrold H. Levy, MD, FAHA, Fania Szlam, MMSc, Kenichi A. Tanaka, MD, and Roman M. Sniecienski, MD
Cyro use (ADHB)

Auckland DHB Monthly Net Sales - Cryoprecipitate

Auckland DHB Cryoprecipitate Net Sales
Electron microscopic scan of a ×2000 magnified blood clot.

- fibTEM > 10mm
- Fibrinogen > 1.5-2.0 g/L

Post fibrinogen administration

65% haemodiluted

undiluted
Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial

N. Curry1,*, C. Rourke2, R. Davenport2, S. Beer1, L. Pankhurst3, A. Deary3,

Fig 2 Comparison of Mean Fibrinogen Concentrations (Standard Deviation) between Study Arms for the Duration of the Trial. Changes of Clauss fibrinogen concentrations were compared using a two way ANOVA with repeated measures for patients in each arm of the trial. No evidence of a difference between changes in mean Clauss fibrinogen concentrations at 24 h and 72 h and the arm of the trial.
Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial

Nicola Curry1,2*, Claire Foley3, Henna Wong1,4, Ana Mora1, Elinor Curnow3, Agne Zarankaite3, Renate Hodge3, Valerie Hopkins3, Alison Deary3, James Ray3, Phil Moss6, Matthew J. Reed7, Suzanne Kellett8, Ross Davenport9 and Simon Stanworth1,2,4,10

Table 2  Fibrinogen levels over time, by treatment arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fibrinogen concentrate arm (n = 24)</th>
<th>Placebo arm (n = 24)</th>
<th>Overall (n = 48)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>1.6 (0.7)</td>
<td>2.1 (0.9)</td>
<td>1.9 (0.8)</td>
<td>n/a</td>
</tr>
<tr>
<td>At 2 h from admission</td>
<td>2.8 (1.3)</td>
<td>1.8 (0.6)</td>
<td>2.3 (1.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>during first active haemorrhagea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 days from admission</td>
<td>6.7 (1.8)</td>
<td>7.5 (1.9)</td>
<td>7.1 (1.9)</td>
<td>0.2843</td>
</tr>
</tbody>
</table>

*P value adjusted for value at admission
Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy
A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays

Eduardo Gonzalez, MD,¹ Ernest E. Moore, MD,¹ Hunter B. Moore, MD,¹ Michael P. Chapman, MD,¹ Theresa L. Chin, MD,¹ Arsen Ghasabyan, MPH,¹ Max V. Wohlaer, MD,¹ Carlton C. Barnett, MD,¹ Denis D. Bensard, MD,¹ Walter L. Biffl, MD,¹ Clay C. Burlew, MD,¹ Jeffrey L. Johnson, MD,¹ Fredric M. Pieracci, MD, MPH,¹ Gregory J. Jurkovich, MD,¹ Anirban Banerjee, PhD,¹
Christopher C. Silliman, MD, PhD,°‡ and Angela Sauaia, MD, PhD*•

FIGURE 1. Kaplan-Meier estimates of survival by randomization group for patients analyzed as intention-to-treat. Survival in the TEG group was significantly higher than the CCA group (log-rank P = 0.0324, Wilcoxon P = 0.0275).
<table>
<thead>
<tr>
<th></th>
<th>TEG ACT</th>
<th>R</th>
<th>K</th>
<th>ANGLE</th>
<th>MA</th>
<th>LY30</th>
<th>FLEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>10.7</td>
<td>3.4</td>
<td>55.0</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>144.0</td>
<td>1.0</td>
<td>1.6</td>
<td>68.6</td>
<td>52.6</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>CKH</td>
<td>10.4</td>
<td>1.7</td>
<td>69.5</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CFF</td>
<td></td>
<td></td>
<td></td>
<td>22.9</td>
<td>417.9</td>
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<td></td>
</tr>
</tbody>
</table>

Patient ID: HUX8660

8/1/2017 1:51 PM  CM Citrated K,KH,RT,FF  TEG 6s

Add Note
TEG ALGORITHM FOR MANAGEMENT OF BLEEDING PATIENTS

**Kaolin TEG**

- **R time 10-14**
  - **FACTOR DEFICIENCY**
    - Give 2 units FFP
  - **Heparin effect possible?**
    - Check Heparinase TEG
  - Difference in R time > 2 min
    - Give Protamine 25-50mg

- **R time >14**
  - **FACTOR DEFICIENCY**
    - Give 4 units FFP

- **MA <49 or α <52**
  - Measure
  - Functional Fibrinogen

- **Ly30 >8**
  - **FIBRINOLYSIS**
    - Tx A 10-20mg/kg

- **MA <49 FFma <7**
  - **LOW FIBRINOGEN**
    - Give 4u Cryo (or 4g Fibrinogen)

- **MA <49 FFma 7-14**
  - **LOW FIBRINOGEN**
    - Give 2u Cryo (or 2g Fibrinogen)

- **MA 45-49 FFma >14**
  - **LOW PLATELETS**
    - Give 2 units platelets

- **MA <45 FFma >14**
  - **LOW PLATELETS**
    - Give 1 unit platelets
Trauma flowsheet in the Gold Coast

**CRITICAL BLEEDING ROTEM TRANSFUSION ALGORITHM**

**GOLD COAST UNIVERSITY HOSPITAL**

**Physiological Targets:**
- Temp >36°C
- pH >7.2
- ICa >1 mmol/L
- Hb >70g/L

**STEP 1: HYPERFIBRINOLYSIS**
- FIBTEM CT > 600 sec AND EXTEM A5 < 35 mm
  - TXA 1g + FIB CONC 4g
- OR
  - ML% > 5%
  - TXA 1g

**STEP 2: FIBRINOGEN**
- FIBTEM A5 ≤ 8 mm
  - FIB CONC 1g/25Kg BW
- OR
  - FIBTEM A5 ≤ 10 mm
  - CRYO 1 Unit/50Kg BW

**STEP 3: PLATELETS**
- FIBTEM A5 > 10 mm AND EXTEM A5 ≤ 35 mm
  - PLATELETS 1 dose

**STEP 4: FACTORS**
- FIBTEM A5 > 10 mm AND EXTEM CT ≥ 90 sec
  - PCC 10 IU/Kg
  - OR
  - FFP 2-4 Units

**STEP 5: TARGETS**
- FIBTEM A10 > 15 mm AND EXTEM A10 > 45 mm AND EXTEM CT < 80 sec

*ALWAYS repeat ROTEM tests 10 mins after treatment*

*Version 4.0 February 2016*
Rotational thromboelastometry significantly optimizes transfusion practices for damage control resuscitation in combat casualties

Nicolas J. Prat, MD, PhD, Andrew D. Meyer, MD, Nichole K. Ingalls, MD, Julie Trichereau, MS, Joseph J. DuBose, MD, and Andrew P. Cap, MD, PhD, San Antonio, Texas

Figure 1. Percentage of transfused patients receiving 1+ unit of each product pre- and post-ROTEM. Data represented in percentage of total patients who received a transfusion over the pre- and post-3 month study period, n = 134 and n = 85, respectively.

Figure 2. Total blood products (units) transfused in the pre- and post-ROTEM periods. Data represented as mean ± SD.
Table 3 Administration of allogeneic blood products, coagulation factors and resuscitation fluids in the two cohorts (2005–2007 and 2012–2014). Values are number (proportion) and mean (SD).

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>RBC; units</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ED</td>
<td>3.3 (6.3)</td>
<td>1.1 (3.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>First 24 h</td>
<td>4.8 (7.8)</td>
<td>1.9 (6.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>FFP; units</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ED</td>
<td>2.4 (5.0)</td>
<td>0.3 (1.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>First 24 h</td>
<td>3.4 (6.9)</td>
<td>1.0 (3.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Platelets; units</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ED</td>
<td>0.2 (0.7)</td>
<td>0.1 (0.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>First 24 h</td>
<td>0.3 (1.2)</td>
<td>0.3 (0.2)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>FFP:RBC ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ED</td>
<td>0.6 (0.6)</td>
<td>0.1 (0.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>First 24 h</td>
<td>0.6 (1.0)</td>
<td>0.4 (0.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Fibrinogen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administered</td>
<td>126 (39%)</td>
<td>135 (33%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Dose; g</td>
<td>2.0 (3.3)</td>
<td>1.8 (4.0)</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>Prothrombin complex concentrate (four-factor)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administered</td>
<td>14 (4.3%)</td>
<td>37 (9%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Dose; IU</td>
<td>46 (230)</td>
<td>116 (510)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Tranexamic acid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administered</td>
<td>3 (0.9%)</td>
<td>203 (50%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Factor XIII concentrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administered</td>
<td>–</td>
<td>52 (13%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dose; IU</td>
<td>–</td>
<td>228 (714)</td>
<td></td>
</tr>
<tr>
<td><strong>Desmopressin</strong></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Administered</td>
<td>1 (0.3%)</td>
<td>4 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Factor VII a</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Crystallloid; ml</td>
<td>2836 (2473)</td>
<td>2672 (3094)</td>
<td>0.001</td>
</tr>
<tr>
<td>Colloid (starch); ml</td>
<td>1062 (1037)</td>
<td>36 (207)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Colloid (gelatin); ml</td>
<td>77 (402)</td>
<td>527 (1228)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

A p value of < 0.01 was considered significant.

RBC, red blood cells; FFP, fresh frozen plasma; ED, emergency department.
Administer RiaSTAP® at room temperature by slow intravenous injection at a rate not exceeding 5 mL per minute.
- ISS >16
- Lactate >2 x normal
- PT >1.5
- Pulse >120
- Systolic <90
- Ongoing non surgical bleeding.
- Abnormal TEG