Bleeding in private places

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Obstetric bleeding

- Obstetric haemorrhage
  - Antepartum 20%
  - Postpartum 80%
    - 500 mL post NVD
    - 1000 mL post C/S

- Incidence PPH
  - 3-6% no transfusion
  - 1% with transfusion
  - 0.5% with massive transfusion

- 1 of 2 most common reasons for peripartum ICU admission
Scope of the problem

- Obstetric haemorrhage:
  - 8.4% of direct maternal deaths in the UK
  - 14.3% of direct maternal deaths in New Zealand
  - 78,000 maternal deaths worldwide in 2012
    - WHO fact sheets

- 99% of maternal deaths due to PPH occur in resource-poor countries
- Haemorrhage is also an important cause of maternal mortality in resource-rich countries.
Scope of the problem

- 876,641 deliveries 2004 (NIS data)
  - PPH 2.93 per 100 deliveries
    - Uterine atony 79%
    - Many no identifiable antepartum risk factors
    - Incidence higher in hospitals with lower delivery volumes

- Rate of PPH increased 27.5% 1995 – 2004
  - Increased rate of uterine atony
  - Other causes of PPH stable
  - Not accounted for by:
    - Change in maternal demographics
    - Delivery mode
    - Maternal comorbidity

Contributors: Uterine blood flow

- 1% of cardiac output in non-pregnant

- 15% of cardiac output at term (5-7 L/min)
  - Blood flow to uterine spiral arteries 400-550 mL/min

- Sometimes slow to declare
  - Covert bleeding
  - Physiological tolerance age related
Contributors: Coagulopathy

- Dilutional
  - Massive transfusion and volume replacement

- DIC
  - Massive tissue factor exposure
  - Common: Amniotic fluid embolism, infection, abruption, pre-eclampsia
  - Uncommon: atony and trauma

- Fibrinolysis
  - Increased tissue plasminogen activator
  - Common: Amniotic fluid embolism, abruption, pre-eclampsia, FDIU
  - Uncommon: atony and trauma

- Plt count <100 x 10^9/L or Fibrinogen <2.9 g/L + 20x increase PPH.
  - Br J Anaesth 1997;78(6):678-683
- Fibrinogen <2 g/L  100% PPV for worsening haemorrhage
## Risk factors for PPH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine atony (Tone)</td>
<td>Coagulopathy (Thrombin)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>Congenital bleeding disorders</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>Acquired coagulopathies</td>
</tr>
<tr>
<td>Previous PPH</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Patient age &gt;40</td>
<td>Placental abruption</td>
</tr>
<tr>
<td>Patient BMI &gt;35</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>Asian ethnicity</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Amniotic fluid embolism</td>
</tr>
<tr>
<td>Trauma/Surgery (Trauma)</td>
<td>Placenta (Tissue)</td>
</tr>
<tr>
<td>Perineal of vaginal trauma</td>
<td>Retained placenta</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>Morbidly adherent placenta (accrete/percreta)</td>
</tr>
<tr>
<td>Instrumental vaginal delivery</td>
<td>Placental abruption</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>Placenta praevia</td>
</tr>
</tbody>
</table>

Majority do not have recognizable risk factors. All women “at risk”
Prenatal prediction

- Congenital bleeding disorder
  - Von Willebrand disease
  - Platelet dysfunction
  - Haemophilia carriers / FXI deficiency

- Acquired bleeding disorders
  - Anticoagulants
  - Rarely FVIII inhibitors

- Previous gestational history
  - Surgical intervention
  - Previous PPH

- BMI
  - >30 - 50% more likely to have a severe PPH >1000 mL (OR 1.4)
Antenatal prediction

- Placental aberrations
- Uterine distension
  - Polyhydramnios
  - Multiple pregnancy
- Hypertensive disorders of pregnancy
  - Associated DIC and thrombocytopenia
## Three Pillars of Patient Blood Management

### Pillar One: Optimize RBC Mass
- Detect/treat anaemia & iron deficiency
- Treat underlying causes
- Optimize haemoglobin
- Cease medications

### Pillar Two: Minimize Blood Loss
- Identify, manage & treat bleeding/bleeding risk
- Minimize phlebotomy
- Plan/rehearse procedure

### Pillar Three: Manage Anaemia
- Patient's bleeding history & develop management plan
- Estimate the patient's tolerance for blood loss
- Optimize cardiopulmonary function

#### Preoperative
- Time surgery with optimisation of erythropoiesis & red blood cell mass

#### Intraoperative
- Meticulous haemostasis/surgical/anaesthetic techniques
  - Cell salvage techniques
  - Avoid coagulopathy
  - Patient positioning/warming
  - Pharmacological agents

#### Postoperative
- Manage anaemia & iron deficiency
- Manage medications & potential interactions
- Monitor & manage post-op bleeding
- Keep patient warm
- Minimize phlebotomy
- Awareness of drug interactions & adverse events
- Treat infections promptly

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Labour and delivery

- Prolonged labour
- Uterine atony
  - Increased uterotonic exposure
- Surgical intervention
- Abruption
- Retained products
- HELLP / PET / ET
Increasing rate of PPH – Australia, Canada, US

Increasing C/S, induction, multiple births, advanced maternal age, BMI

Associations and outcomes with PPH from Nationwide Inpatient Sample data for 2004

Trends in incidence PPH from 1995-2004
Independent risk factors for PPH with atony leading to transfusion:

- Age <20
- Age >39
- C/S with/without labour
- Hypertension
- Polyhydramnios
- Chorioamnionitis
- Multiple gestation
- Retained placenta
- APH

Greater oxytocin exposure

Only 38.8% of cases had recognizable independent risk factors
PPH markedly increased the odds of in-hospital mortality (OR 7.8)

19.1% of in-patient mortality for this cohort
Risk factors

- Risk factors need to be continually assessed and re-assessed through pregnancy
- Most effective prenatal and antenatal causes
  - Most unexpected and labour & delivery related.
- Multidisciplinary delivery plan
  - Communication about patients at risk to lab
- When will labour occur?
Facility related risks

- Expertise related
  - Low delivery numbers
    - Facility unfamiliar with care of obstetric bleeding
    - Lack of protocols and practice runs

- Procedure related:
  - Failure to use/have available medical, radiological or surgical interventions e.g. uterotonics, hysterectomy, etc

- Pathology related:
  - Inadequate access to blood and blood products
  - Inadequate access to pathology assessment
    - 25% of MOH associated with coagulopathy
Management of bleeding
| EOP3 | All maternity services must have procedures in place to manage the critically bleeding maternity patient. This includes agreed communication and transport arrangements, access to transfusion medicine expertise and defined escalation strategies. | 4.2 |
| EOP4 | All maternity services should liaise with their local pathology provider to ensure that information on local blood access arrangements is available to all clinicians (e.g. time to process ‘group and hold’ and cross-match blood, and availability of products). | 4.2 |
| EOP5 | Maternity services in rural and remote areas should develop management plans to minimise any delay in accessing specialist health-care services and resources, including blood products. | 3.6 | 4.2 |
| EOP6 | Women with identifiable risk factors for obstetric haemorrhage should, wherever possible, give birth in a maternity service capable of providing the appropriate level of care. | 4.2 |
Massive transfusion protocol (MTP) template

The information below, developed by consensus, broadly covers areas that should be included in a local MTP. This template can be used to develop an MTP to meet the needs of the local institution’s patient population and resources.

Senior clinician determines that patient meets criteria for MTP activation

Baseline:
- Full blood count, coagulation screen (PT, INR, APTT, fibrinogen), biochemistry, arterial blood gases

Notify transfusion laboratory (insert contact no.) to:
- “Activate MTP”

Laboratory staff
- Notify haematologist/transfusion specialist
- Prepare and issue blood components as requested
- Anticipate repeat testing and blood component requirements
- Minimise test turnaround times
- Consider staff resources

Haematologist/transfusion specialist
- Liaise regularly with laboratory and clinical team
- Assist in interpretation of results, and advise on blood component support

Senior clinician
- Request:
  - 4 units RBC
  - 2 units FFP
- Consider:
  - 1 adult therapeutic dose platelets
  - tranexamic acid in trauma patients
- Include:
  - cryoprecipitate if fibrinogen < 1 g/L
  - or locally agreed combination

AIM FOR:
- temperature > 35°C
- pH > 7.2
- base excess < –6
- lactate < 4 mmol/L
- Ca²⁺ > 1.1 mmol/L
- platelets > 50 x 10⁹/L
- PT/APTT < 1.5 x normal
- INR ≤ 1.5
- fibrinogen > 1.0 g/L

OPTIMISE:
- oxygenation
- cardiac output
- tissue perfusion
- metabolic state

MONITOR
(every 30–60 mins):
- full blood count
- coagulation screen
- ionised calcium
- arterial blood gases

Blooding controlled?
- YES
- NO

Notify transfusion laboratory to:
- “Cease MTP”

Transfusion trigger Fib >1.0 did not include MOH
<table>
<thead>
<tr>
<th>PP17</th>
<th>Values indicative of critical physiologic derangement include:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• temperature &lt; 35°C</td>
</tr>
<tr>
<td></td>
<td>• pH &lt; 7.2, base excess worse than -6, lactate &gt; 4 mmol/L</td>
</tr>
<tr>
<td></td>
<td>• ionised calcium &lt; 1.1 mmol/L</td>
</tr>
<tr>
<td></td>
<td>• platelet count &lt; 50 x 10⁹/L</td>
</tr>
<tr>
<td></td>
<td>• PT &gt; 1.5 x normal</td>
</tr>
<tr>
<td></td>
<td>• INR &gt; 1.5</td>
</tr>
<tr>
<td></td>
<td>• APTT &gt; 1.5 x normal</td>
</tr>
<tr>
<td></td>
<td>• fibrinogen level &lt; 2.0 g/L</td>
</tr>
</tbody>
</table>
Fibrinogen levels

- Fibrinogen 4-6 g/L (cf non-pregnancy range of 2-4 g/L)

- Critical levels of FII, FV, FVII and platelets are reached after a loss of > 200% calculated blood volume, critical levels of fibrinogen are reached after a loss of only 140% of the calculated blood volume

- Low levels predict for more severe haemorrhage
  - No severe PPH Fib >4 g/L
  - 4/5 Fib <2 g/L massive transfusion
<table>
<thead>
<tr>
<th>Component</th>
<th>Content and characteristics</th>
<th>Volume per bag*</th>
<th>Typical adult dose (~70 kg)</th>
<th>Number of bags to provide typical dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>• Plasma recovered from a whole blood donation or apheresis collection&lt;br&gt;• Contains all coagulation factors</td>
<td>250-334 mL</td>
<td>10-15 mL/kg</td>
<td>3-4</td>
</tr>
<tr>
<td>Platelets: pooled</td>
<td>• A pool of platelets derived from the buffy coat of four whole blood donations&lt;br&gt;• Leucodepleted</td>
<td>&gt;160 mL</td>
<td>1 bag</td>
<td>1</td>
</tr>
<tr>
<td>Platelets: apheresis</td>
<td>• A suspension of platelets prepared from a single apheresis donor&lt;br&gt;• Leucodepleted</td>
<td>100-400 mL</td>
<td>1 bag</td>
<td>1</td>
</tr>
<tr>
<td>Cryo-precipitate</td>
<td>• Prepared from a single donated whole blood unit&lt;br&gt;• Contains an average of &gt; 0.35 g/bag&lt;br&gt;• Contains high levels of fibrinogen, factor VIII, von Willebrand factor, factor XII, fibronectin</td>
<td>30-40 mL</td>
<td>3-4 g fibrinogen</td>
<td>8-10</td>
</tr>
<tr>
<td>Cryo-precipitate apheresis</td>
<td>• Prepared from FFP obtained from a plasmapheresis donor&lt;br&gt;• Contains an average of &gt; 0.8 g/bag</td>
<td>50 mL (+ 10%)</td>
<td>3-4 g fibrinogen</td>
<td>4-5</td>
</tr>
</tbody>
</table>

FFP: fresh frozen plasma
*Actual volume indicated on label
Blood product ratios

Four Level III studies examined the effect of FFP or platelet transfusion on mortality or morbidity. An RBC:FFP ratio of ≤2:1 was reported to be associated with reduced mortality. However, this outcome is potentially confounded by survivor bias. No studies investigated the use of fibrinogen or cryoprecipitate as an intervention.

**Evidence statement**

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Consistency</th>
<th>Clinical Impact</th>
<th>Generalisability</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

In trauma patients with critical bleeding requiring massive transfusion, an RBC:FFP ratio of ≤2:1 is associated with reduced mortality.

(See evidence matrix 10 in Appendix E.)

FFP: fresh frozen plasma; RBC, red blood cell

Reduced mortality >0.2 g fibrinogen/rcc (24% vs 52%)

J Trauma 2008;64:S79-85

**Scenario of trauma may not translate to MOH**
## EVIDENCE STATEMENTS – combination of fixed ratio therapy (bleeding patients)

<table>
<thead>
<tr>
<th>Evidence Statements</th>
<th>Evidence</th>
<th>Consistency</th>
<th>Clinical impact</th>
<th>Generalisability</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with postpartum haemorrhage, the effect of combination or fixed ratio</td>
<td>X</td>
<td>NA</td>
<td>NA</td>
<td>✓✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>therapy (FFP, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion),</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>on transfusion requirements is uncertain.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(See evidence matrix 03.D in Volume 2 of the technical report)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients with postpartum haemorrhage, the effect of combination or fixed ratio</td>
<td>X</td>
<td>NA</td>
<td>X</td>
<td>✓✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>therapy (FFP, plasma, cryoprecipitate, fibrinogen concentrate and/or platelet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>transfusion), on the need for additional interventions to control bleeding is</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uncertain.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(See evidence matrix 03.E in Volume 2 of the technical report)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ES, evidence statement; FFP, fresh frozen plasma

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable
Reasons to minimise exposure

- Transfusion reactions:
  - Haemolytic, allergic, septic, immunological, overload

- Error:
  - Procedural errors account for at least 50% of transfusion events

- Alloimmunisation
  - Greater chance of exposure to Ag of significance (Kell, rhesus)
  - Antibody development 3-4%
<table>
<thead>
<tr>
<th>Transfusion risk</th>
<th>Estimated rate a (highest to lowest risk)</th>
<th>Calman rating b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion-associated circulatory overload (iatrogenic)</td>
<td>Up to 1 in 100 transfusions</td>
<td>High</td>
</tr>
<tr>
<td>Haemolytic reactions</td>
<td>Delayed: 1 in 4,000–9,000</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Acute: 1 in 12,000–77,000</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis (IgA deficiency)</td>
<td>1 in 20,000–50,000</td>
<td>Very low</td>
</tr>
<tr>
<td>Bacterial sepsis: platelets</td>
<td>1 in 75,000</td>
<td>Very low</td>
</tr>
<tr>
<td>Bacterial sepsis: RBCs</td>
<td>1 in 50,000</td>
<td>Minimal</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury</td>
<td>1 in 5,000–10,000</td>
<td>Low to minimal</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 in 739,000</td>
<td>Minimal</td>
</tr>
<tr>
<td>HIV</td>
<td>1 in 5.4 million</td>
<td>Negligible</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 in 2.7 million</td>
<td>Negligible</td>
</tr>
<tr>
<td>Malaria</td>
<td>1 in 4.9 million – 10.2 million</td>
<td>Negligible</td>
</tr>
<tr>
<td>Variant CJD (not tested)</td>
<td>Never reported in Australia</td>
<td>Negligible</td>
</tr>
<tr>
<td>Transfusion-associated graft-versus-host disease</td>
<td>Rare</td>
<td>Negligible</td>
</tr>
<tr>
<td>Transfusion-related immunomodulation</td>
<td>Not quantified</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

CJD, Creutzfeldt-Jakob disease; IgA, immunoglobulin A; RBC, red blood cell
a Risk per unit transfused unless otherwise specified
b See Calman 1996

Source: Australian Red Cross Blood Service website (www.transfusion.com.au), accessed 9 December, 2009

Note: The above estimates may change over time. Refer to the Australian Red Cross Blood Service website (www.transfusion.com.au) for the most recent risk estimates.
Fresh Frozen Plasma

- Requires 30+ mins thaw time 😏
- Prethaw – extended life plasma 😊

- Blood group compatibility required 😏
- AB plasma in short supply 😊

- Donor exposure 😏
  - No additional protection from infectious complications

- Multiple factor components potentially of value 😊

- Not accurate dosing fibrinogen 😏

- High volume transfusion to achieve levels 😏

- Increased multi-organ failure (MOF) and acute-respiratory distress syndrome with higher volumes of FFP in massive transfusion protocols
  - Not seen with cryoprecipitate
    - J Trauma, 2009. 67(2): p. 221-7
Cryoprecipitate

- Requires 30+ mins thaw time 😞
- Blood group compatibility preferred 😞
- Multiple donor exposures 😞
  - No additional protection from infectious complications
- Multiple components potentially of value 😊
  - VWF, FVIII, fibronectin, FXIII
- Not accurate dosing fibrinogen 😞
- Not pooled – handling issues 😞
- Smaller volume than FFP 😊
  - An estimated 1000mL FFP or 233 mL of cryoprecipitate is required to raise plasma fibrinogen concentration by 1g/L in a 70kg adult
- Extended storage being considered 😊
  - No loss of factors over 24-48 hours 😊
  - Maintenance of sterility limiting factor 😊
Cryoprecipitate demand

<table>
<thead>
<tr>
<th>Year</th>
<th>Actual Demand</th>
<th>Forecasted Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY11</td>
<td>70,108</td>
<td></td>
</tr>
<tr>
<td>FY12</td>
<td>78,095</td>
<td></td>
</tr>
<tr>
<td>FY13</td>
<td>85,710</td>
<td></td>
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<tr>
<td>FY14</td>
<td>90,283</td>
<td></td>
</tr>
<tr>
<td>FY15</td>
<td>98,594</td>
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<tr>
<td>FY16</td>
<td>110,599</td>
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<tr>
<td>FY17</td>
<td>118,462</td>
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<td>FY18</td>
<td>123,278</td>
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<tr>
<td>FY19</td>
<td>127,391</td>
<td></td>
</tr>
<tr>
<td>FY20</td>
<td>131,040</td>
<td></td>
</tr>
</tbody>
</table>

National

Actual and Forecasted Demand
<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>2015/18</th>
<th>2016/17</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>Whole Blood - Leucodepleted</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2b</td>
<td>WB Red Cell - Leucodepleted</td>
<td>$374.72</td>
<td>$401.94</td>
</tr>
<tr>
<td>2d</td>
<td>WB Paediatric Red Cell - Leucodepleted  (Set of 4)</td>
<td>$96.92</td>
<td>$105.17</td>
</tr>
<tr>
<td>2f</td>
<td>WB Washed Red Cell - Leucodepleted</td>
<td>$422.69</td>
<td>$406.90</td>
</tr>
<tr>
<td>2g</td>
<td>Apheresis Red Cell - Leucodepleted</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3b</td>
<td>WB Platelet Pool - Leucodepleted</td>
<td>$387.01</td>
<td>$277.88</td>
</tr>
<tr>
<td>3d</td>
<td>Apheresis Platelet - Leucodepleted</td>
<td>$541.70</td>
<td>$619.31</td>
</tr>
<tr>
<td>3e</td>
<td>Paediatric Apheresis Platelet - Leucodepleted  (Set of 4)</td>
<td>$133.85</td>
<td>$199.39</td>
</tr>
<tr>
<td>4b</td>
<td>WB Clinical FFP - Buffy Coat Poor</td>
<td>$304.22</td>
<td>$176.12</td>
</tr>
<tr>
<td>4c</td>
<td>Paediatric WB Clinical FFP  (Set of 4)</td>
<td>$86.49</td>
<td>$52.14</td>
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<td>4d</td>
<td>Apheresis Clinical FFP</td>
<td>$340.75</td>
<td>$262.48</td>
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<tr>
<td>5a</td>
<td>WB Cryoprecipitate</td>
<td>$177.15</td>
<td>$155.09</td>
</tr>
<tr>
<td>5b</td>
<td>Apheresis Cryoprecipitate</td>
<td>$314.25</td>
<td>$325.58</td>
</tr>
<tr>
<td>5a</td>
<td>WB Cryo-depleted Plasma</td>
<td>$93.82</td>
<td>$139.88</td>
</tr>
<tr>
<td>6b</td>
<td>Apheresis Cryo-depleted Plasma</td>
<td>$159.03</td>
<td>$320.25</td>
</tr>
</tbody>
</table>
Fibrinogen concentration and use of fibrinogen supplementation with cryoprecipitate in patients with critical bleeding receiving massive transfusion: a bi-national cohort study

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Summary
We aimed to compare fibrinolysis prevalence in major bleeding patients across all clinical contexts, fibrinogen supplementation practice, and explore the relationship between fibrinogen concentrations and mortality. This cohort study included all adult patients from 20 hospitals across Australia and New Zealand who received massive transfusion between April 2011 and October 2015. Of 2566 patients, 2829 (79%) had fibrinogen concentration recorded, with a median first and lowest concentration of 2.6 g/L (interquartile range [IQR] 1.5–2.7) and 1.8 g/L (IQR 1.3–2.4), respectively. Liver transplant (1.7 g/L, IQR 1.2–2.1), trauma (1.8 g/L, IQR 1.3–2.5) and vascular surgery (1.9 g/L, IQR 1.4–2.5) had lower concentrations. Total median fibrinogen dose administered from all products was 7.3 g (IQR 3.9–12.6). Overall, 1732 (67%) received cryoprecipitate and 9 (0.4%) fibrinogen concentrate. Time to cryoprecipitate issue in those with initial fibrinogen concentration <1 g/L was 2.3 h (IQR 1.2–4.5 h). After adjustment, initial fibrinogen concentration had a U-shaped association with in-hospital mortality (adjusted odds ratio: fibrinogen <1 g/L, 2.51; 95% confidence interval [CI] 1.48–3.86; 1–1.9 g/L, 1.29; 95% CI 0.49–3.67 and >4 g/L, 2.63; 95% CI 1.35–5.01). The findings indicate areas for practice improvement including timely administration of cryoprecipitate, which is the most common source of concentrated fibrinogen in Australia and New Zealand.

Keywords: fibrinogen, haemorrhage, red blood cell transfusion, trauma, pregnancy complications.

- Data from ANZ massive transfusion registry
  - 2829 MTP
- Replacement in 76% pt with fib 1-1.5 g/L
- Median time to release of cryoprecipitate 2.5 hrs regardless of fibrinogen level
  - Obstetrics issued earlier
  - Median dose MOH 5.4 g
  - Fibrinogen:RCC 0.7
- Mortality higher when initial fib not in RR
  - <1 g/L adjusted OR 2.31
  - >4 g/L adjusted OR 2.03
- <1% received fibrinogen concentrate
Fibrinogen concentrate

- Virally inactivated
- Long shelf life
- No refrigeration
- Standard dose
- No thaw, no delay
- No blood group required
- Rapid reconstitution and administration
  - Preparation and infusion 5-6 mins

- 1 gm/ vial
  - $740/g
  - Only funded for congenital deficiency

- Positive studies for reduction in total red cell exposure in
  - CTS and radical cystectomy

Melbourne Pathology
Quality is in our DNA
<table>
<thead>
<tr>
<th>Attribute</th>
<th>Fibrinogen concentrate</th>
<th>Cryoprecipitate</th>
<th>Human plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constituents</td>
<td>Pure preparation of fibrinogen (Few other constituents)</td>
<td>Contains clotting factors VIII and XIII as well as fibrinogen Also contains von Willebrand factor</td>
<td>Contains all clotting factors and numerous other proteins</td>
</tr>
<tr>
<td>Safety and transmission of pathogens</td>
<td>Viral inactivation, therefore minimal risk of pathogen transmission</td>
<td>No viral inactivation, therefore potential risk of pathogen transmission</td>
<td>No viral inactivation (except commercially produced plasma products), therefore potential risk of pathogen transmission</td>
</tr>
<tr>
<td></td>
<td>No unwanted clotting factors</td>
<td>Transfusion of large quantities can raise levels of several coagulation factors</td>
<td>Risk of transfusion-related reactions (e.g. TRALI) and hypervolemia</td>
</tr>
<tr>
<td></td>
<td>Low thrombogenic potential</td>
<td>Thrombotic risk established</td>
<td></td>
</tr>
<tr>
<td>Dosing: control and consistency</td>
<td>Well-defined quantity of fibrinogen</td>
<td>Variable fibrinogen levels, which are donor dependant</td>
<td>Variable fibrinogen levels, which are donor dependant</td>
</tr>
<tr>
<td></td>
<td>Accurate and consistent dosing</td>
<td>Accurate dosing not possible</td>
<td>Accurate dosing not possible</td>
</tr>
<tr>
<td></td>
<td>Low infusion volume</td>
<td>Low infusion volume, albeit larger than fibrinogen concentrate</td>
<td>Only modest increase in fibrinogen is possible</td>
</tr>
<tr>
<td>Administration</td>
<td>Rapidly reconstituted – administered with minimal delay (5 min)</td>
<td>Must first be thawed, delaying administration (45 min)</td>
<td>Must first be thawed, delaying administration (45 min)</td>
</tr>
<tr>
<td></td>
<td>No cross-matching required</td>
<td>Cross-matching is required</td>
<td>Donor-recipient AB compatibility is required</td>
</tr>
</tbody>
</table>

TRALI, transfusion-related lung injury.
Double blind randomised pilot study trial of efficacy of upfront fibrinogen in management of postpartum haemorrhage.

- **Aims**
  - To assess the impact of early administration of fibrinogen in addition to standard management of women with persistent severe PPH (ongoing blood loss >1000ml in the postpartum period that is unresponsive to first line uterontonic therapy and manual uterine compression).
  - To observe correlation of fibrinogen levels with whole blood clotting point of care testing during persistent, severe PPH

- **Hypothesis:**
  - Fibrinogen replacement (4g dose) early in the course of severe, persistent PPH will reduce the total blood volume lost by 25%.
  - This study will be powered to assess reductions in important clinical morbidity - total estimated blood loss, rather than mortality (as mortality rare)

- The reduction in total blood volume loss is a surrogate measure of improved clinical outcomes including a reduction the need for transfusion of red blood cells and other blood products (FFP, cryoprecipitate and platelets), a reduction other measures of maternal morbidity and the requirement for haemostatic interventions such as balloon tamponade, uterine artery embolisation and peripartum hysterectomy.

- Just under 100 randomised to each group
- ROTEM/TEG 0 min and hourly
Novoseven (rVIIa)

- Haemophilia inhibitor therapy
  - Activation of the tissue factor pathway

- Increasing off label use for other haemorrhage

- Haemostasis registry data Australia and NZ (2002-2008)
  - 105 PPH
  - 78% single dose
  - 64% decreased bleeding
  - Hysterectomy 56 women
  - VTE 2 women (non fatal)
    - Anaesth Analg 2009; 109: 1908-15

- Nth European registry
  - 92 PPH
  - 82% single dose
  - 83% decreased bleeding
    - Obstet Gynecol 2007;110:1270-8

- Timing of the dose is controversial

$1300+ per mg
Novoseven

RECOMMENDATION

R2
GRADE B
GRADE C

The routine use of rFVIIa in trauma patients with critical bleeding requiring massive transfusion is not recommended because of its lack of effect on mortality (Grade B) and variable effect on morbidity (Grade C).

(See table 2.3 for definitions of NHMRC grades for recommendations)

Practice points

PP8
An MTP should include advice on the administration of rFVIIa when conventional measures – including surgical haemostasis and component therapy – have failed to control critical bleeding.

NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances where survival is considered a credible outcome (see Template MTP example).

PP9
When rFVIIa is administered to patients with critical bleeding requiring massive transfusion, an initial dose of 90 μg/kg is reasonable.

MTP, massive transfusion protocol; PP, practice point; R, recommendation; rFVIIa, recombinant activated factor VII

36 Patient Blood Management Guidelines: Module 1 | Critical Bleeding/Massive Transfusion
<table>
<thead>
<tr>
<th>Identifier and grade</th>
<th>Guidance – recommendations, practice points and expert opinion points</th>
<th>Relevant section of document</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOMBINANT ACTIVATED FACTOR VII</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PP29**
The administration of rFVIIa may be considered in maternity patients with life-threatening haemorrhage, but only after conventional measures (including surgical haemostasis and appropriate blood component therapy) have failed.\(^a\)

\(^a\) Refer to PP8, PP9 in *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion*\(^1\) and PP20 in *Patient Blood Management Guidelines: Module 2 – Perioperative*\(^a\)

NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances.

| PP30 | Ideally, rFVIIa should only be administered to maternity patients as part of a locally adapted MTP. The MTP should include strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance. | 3.5.4 |
| PP31 | When rFVIIa is administered to maternity patients with life-threatening haemorrhage, an initial dose of 90 µg/kg is suggested. | 3.5.4 |
Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial

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rVIIa in PPH

- 84 severe PPH
  - >1500 mL loss within 24 hours unresponsive to uterotonics
  - Single dose randomisation 60 ug/kg

- Reduction in second line therapy
  - Interventional haemostatic procedures, blood loss, transfusion
    - 52% (treatment) vs 93% (standard care)
      - Interventional embolization reduced
      - Hysterectomy NOT reduced
      - Blood loss measures failed protocol
      - No difference in blood product use
    - Used fibrinogen replacement value of <1 g/L
    - TXA optional

- Safety
  - Deaths and thrombosis over 5 days post dose
    - 0 deaths
    - 2 VTE (ovarian vein thrombosis and DVT/PE)
<table>
<thead>
<tr>
<th>PILLAR ONE</th>
<th>PILLAR TWO</th>
<th>PILLAR THREE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimise RBC Mass</strong></td>
<td><strong>Minimise Blood Loss</strong></td>
<td><strong>Manage Anaemia</strong></td>
</tr>
<tr>
<td>&gt; detect/treat anaemia &amp; iron deficiency</td>
<td>&gt; identify, manage &amp; treat bleeding/bleeding risk</td>
<td>&gt; patient’s bleeding history &amp; develop management plan</td>
</tr>
<tr>
<td>&gt; treat underlying causes</td>
<td>&gt; minimise phlebotomy</td>
<td>&gt; estimate the patient’s tolerance for blood loss</td>
</tr>
<tr>
<td>&gt; optimise haemoglobin</td>
<td>&gt; plan/rehearse procedure</td>
<td>&gt; optimise cardiopulmonary function</td>
</tr>
<tr>
<td>&gt; cease medications</td>
<td>&gt; meticulous haemostasis/surgical/anaesthetic techniques</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; cell salvage techniques</td>
<td>&gt; optimise cardiopulmonary function</td>
</tr>
<tr>
<td></td>
<td>&gt; avoid coagulopathy</td>
<td>&gt; optimise ventilation &amp; oxygenation</td>
</tr>
<tr>
<td></td>
<td>&gt; patient positioning/warming</td>
<td>&gt; restrictive transfusion strategies</td>
</tr>
<tr>
<td></td>
<td>&gt; pharmacological agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; maximise oxygen delivery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; minimise oxygen use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; treat infections promptly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; tolerance of anaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; restrictive transfusion strategies</td>
</tr>
</tbody>
</table>

Cell salvage

Infection, haemolysis, DIC and amniotic fluid embolism **not** considered clinically significant

Risk of alloimmunization from foetal red cells (Kleihauer and anti-D)
## CELL SALVAGE

<table>
<thead>
<tr>
<th>PP23</th>
<th>In maternity patients, cell salvage should be considered if anticipated blood volume loss is likely to result in transfusion.(^a)</th>
<th>3.5.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(^a) In accordance with <em>Guidance for the provision of intraoperative cell salvage</em>.(^b)</td>
<td></td>
</tr>
<tr>
<td>PP24</td>
<td>In maternity patients who are at increased risk of bleeding and in whom transfusion is not an option, cell salvage should be considered.</td>
<td>3.5.2</td>
</tr>
<tr>
<td>PP25</td>
<td>Cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure that they are familiar with and proficient in the technique.</td>
<td>3.5.2</td>
</tr>
</tbody>
</table>
Full Blood Analysis

Random access in manual mode with result in mins
Minimal volume

ADD COURIER AND SRA TIME

Alternatives: Blood gas analysers or Haemacue
Coagulation Profile Analysis

Specimen spin – 11 mins
Analysis time – 4 mins
Reflex repeat if abnormal – 4 mins

ADD COURIER AND SRA TIME

High F8, F7 and fibrinogen in pregnancy shorten aPTT and PT
POCT

- Whole blood analysis
- Rapid TAT

- Time to first clot formation
- Velocity of clot formation
- Strength of clot
- Fibrinolysis

- Limited information about reference ranges in pregnancy

- Fibtem (ROTEM) at 1-1.5L loss independent predictor for >2.5L loss
KEMH ROTEM Algorithm for Critical Bleeding

**Key Points:** This algorithm should be used in conjunction with the KEMH Blood Product Guidelines for Major Obstetric Haemorrhage. Only treat abnormal values if active bleeding or at high risk of bleeding. Repeat ROTEM analysis 10 mins after intervention to assess response.

<table>
<thead>
<tr>
<th>ABNORMAL ROTEM</th>
<th>CRITERIA</th>
<th>DIAGNOSIS</th>
<th>INTERVENTION</th>
<th>CORRECTED ROTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIBRINOGEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FiBTEM A5 ≤10mm</td>
<td>Low fibrinogen</td>
<td>Cryoprecipitate OR Fibrinogen concentrate (see dosing guide) AND Tranexamic acid 1 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PLATELETS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTEM A5 ≤35mm and FiBTEM A5 ≤10mm</td>
<td>Low platelets</td>
<td>Platelets: 1 adult dose (correlate with platelet count)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTEM A5 ≤25mm and FiBTEM A5 ≤10mm</td>
<td>Low fibrinogen</td>
<td>Platelets and fibrinogen (correlate with platelet count)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COAGULATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTEM CT 90-140s and FiBTEM A5 ≤10mm</td>
<td>Low fibrinogen</td>
<td>Correct fibrinogen and reassess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTEM CT &gt;140s and FiBTEM A5 ≤10mm</td>
<td>Low fibrinogen and Low coagulation factors</td>
<td>FFP 1-2U + Fibrinogen as indicated (Consider Prothrombinase see below)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FIBRINOLYSIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Diagnosis EXTEM A5 ≤35mm or FiBTEM CT ≤500s</td>
<td>High likelihood of excess fibrinolysis</td>
<td>Tranexamic acid 1g</td>
<td>Consider repeat dose if has lost over 1 blood volume since initial dose</td>
<td></td>
</tr>
<tr>
<td>Late Diagnosis EXTEM or FiBTEM ML ≤5%</td>
<td>Excess fibrinolysis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fibrinogen Dosing Guide**

- FiBTEM A5 Target: ≤12mm
  - FiBTEM A5 ≤10mm: 1-2 doses
  - FiBTEM A5 ≤7mm: 2 doses
  - FiBTEM A5 ≤3mm: 4-8 doses
  - FiBTEM A5 <2mm: 8-16 doses

**Fibrinogen Concentrate**

- **Guidelines For Use**
  1. Consult haematologist or haematologist approved
  2. Patients must be receiving the appropriate treatment
  3. Fibrinogen concentrate may be infused instead of or in addition to fibrinogen in the FiBTEM A5 ≤10mm. Administer clinically as indicated for the following conditions:
     - **Hemorrhage**
     - **Hemostatic failure**

**Cryoprecipitate**

- 1 dose is equivalent to 15 whole blood units or 5pheres units
- May be supplied as 1 whole blood unit of cryoprecipitate (or a combination 1-2 whole blood units)
- Availability generally available for 12 hours of request being made

**Prothrombinase**

- Hemorrhagic states
- Consider as alternative to FFP for patients with coagulation factor deficiency in g

*Note this algorithm assumes patients have already received TXA – thus fibrinolysis is now 4th*
Applying the KEMH algorithm:
- 1 – Fibtem A5 is 15mm, the target is 14mm, no treatment needed.
- 2 – Fibrinolysis – no evidence fibrinolysis (she has already had Tranexamic acid 1g)
- 3 – Platelets – Her Extem A5 is 39 mm no treatment with platelets needed
- 4 – Extem CT 67s – this is normal. No FFP or Prothrombinex needed.

- Most women in the third trimester have high fibrinogen and cope very well without developing a coagulopathy.
- A normal ROTEM is actually the most common finding in healthy woman with a postpartum haemorrhage of less than 2.5 – 3 litres. (Beware abruption / amniotic fluid embolism / HELLP syndrome).
Applying the KEMH algorithm:

- Fibrinogen: ROTEM A5 – probably about 2mm – critical fibrinogen deficiency. Note traditional clauss fibrinogen conc 1.4g/L misleading. Aim for fibrin A5 = 14mm, treat with Fib conc 5g or cryo 25units (patient only 60kg).
- Tranexamic Acid – no evidence of fibrinolysis – unknown whether she has had TXA – probably at risk of developing fibrinolysis – consider giving 1g.
- Platelets – Extem A5 > 25mm (probably about 30-32mm) – no need for platelets (confirmed by plt count of 135).
- Clotting factors (thrombin generation) – EXTEM CT is prolonged at 118s but this will probably correct with fibrinogen treatment alone. No need for FFP or prothrombinex – if any is given 1 unit FFP would suffice (60kg pt).
Massive transfusion protocol (MTP) template

The information below, developed by consensus, broadly covers areas that should be included in a local MTP. This template can be used to develop an MTP to meet the needs of the local institution's patient population and resources.

Senior clinician determines that patient meets criteria for MTP activation

Baseline:
- Full blood count, coagulation screen (PT, INR, APTT, fibrinogen), biochemistry, arterial blood gases

Notify transfusion laboratory (insert contact no.) to: "Activate MTP"

Laboratory staff
- Notify haematologist/transfusion specialist
- Prepare and issue blood components as requested
- Anticipate repeat testing and blood component requirements
- Minimise test turnaround times
- Consider staff resources

Haematologist/transfusion specialist
- Liaise regularly with laboratory and clinical team
- Assist in interpretation of results, and advise on blood component support

Senior clinician
- Request:
  - 4 units RBC
  - 2 units FFP
- Consider:
  - 1 adult therapeutic dose platelets
  - tranexamic acid in trauma patients
- Include:
  - cryoprecipitate if fibrinogen < 1 g/L
  - locally agreed complication

Optimise:
- oxygenation
- cardiac output
- tissue perfusion
- metabolic state

Monitor (every 30–60 mins):
- full blood count
- coagulation screen
- ionised calcium
- arterial blood gases

Aim for:
- temperature > 35°C
- pH > 7.2
- base excess < –6
- lactate < 4 mmol/L
- Ca²⁺ > 1.1 mmol/L
- platelets > 50 × 10⁹/L
- PT/INR < 1.5 x normal
- INR ≤ 1.5
- fibrinogen > 1.0 g/L

Notify transfusion laboratory to: "Cease MTP"

Blood controlled?
- YES
- NO

MELBOURNE PATHOLOGY
Quality is in our DNA
Communication

- Co-ordination b/w anaesthetist and haematologist
  - Scientists and O&G/Surgeons free to do their job

- Notification of risk
  - Current or expected including pre-labour planning, e.g. abnormal placentation
    - Request forms
    - Bat phone
  - Change of status – e.g. successful delivery no bleeding
    - Don’t forget to “Stand down”

- Consistent and agreed wording

- Direct phone access theatre/ward, name of staff
  - Mobile better
  - Patients move

- Product plan
  - In light of results
  - In light of continued bleeding

- Documentation +++
  - Running sheets – results, orders, calls
Hospital staff preparation

- Defined roles during event:
  - Communicator
  - Scribe
  - Blood product checker
  - Runner

- Understanding of product availability
  - Time to receipt
  - Who provides rVIIa?

- Use of prompts
  - pre-printed MTP request forms help avoid missed tests

- Commitment to early test collection (not just Hb)
Laboratory staff preparation

- Access Haematologist support
  - Record and provide contact details

- Inventory management
  - Sufficient rcc, plasma, platelets of appropriate group
  - Acute replacement of used stock
  - Planned group compatibility vs group identical

- Product preparation
  - Elective
    - Extended life plasma (routine)
    - MTP pack
  - Urgent
    - Immediate cryoprecipitate thaw

- Technical
  - Rapid blood grouping procedure

- Priming
  - Couriers, specimen reception, data entry, front bench
Preparation

‣ Mock scenarios and dry runs
  ‣ Practice makes perfect

‣ Debrief each event
  ‣ All parties
  ‣ Riskman capture
  ‣ Learn and finesse
Summary

› Prediction – assessment & notification of risk

› Pals – team support

› Preference – right products, right time

› Point of care – consider implementation

› Preparation – practice makes perfect