St. Michael's

Inspired Care.
Inspiring Science.

MHP: TM Protocol Large Hospital

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Objectives

1. *Identify components of trauma packs for large hospitals*
2. *Identify selection criteria (Rh neg/irradiated etc) for blood components*
3. *Discuss options for fibrinogen supplementation*

Three Approaches to Transfusion Management During MHP

- Lab-based
- Ratio-based
- Point-of-care testing driven
  - TEG (thromboelastography), ROTEM (thromboelastometry)
  - Emphasis on clotting factor concentrates

Laboratory-based Hemotherapy

- Old and comfortable
- Goal-directed and individualized

- Based on poor evidence
  - consensus, anecdotal, elective surgery literature
- Relies on standard coagulation testing
  - Turnaround times are too long for results to be meaningful
  - Tests do not adequately assess *in vivo* hemostatic capacity
- Based on the faulty assumption that coagulopathy develops late

Ratio-based Hemotherapy

- Addresses early coagulopathy
- No need for tests
- Automatic, no cognitive effort required
- Improved patient mortality(?)

- Based on poor evidence:
  - Retrospective studies, no adequate controls, heterogeneous population, survivorship bias
  - Impact of protocolized care
- Higher risk of transfusion related complications
- Potential for overcall/undercall
- One size does not fit all (women, children, TBI)
- May not be adequately hemostatic

PROPPR

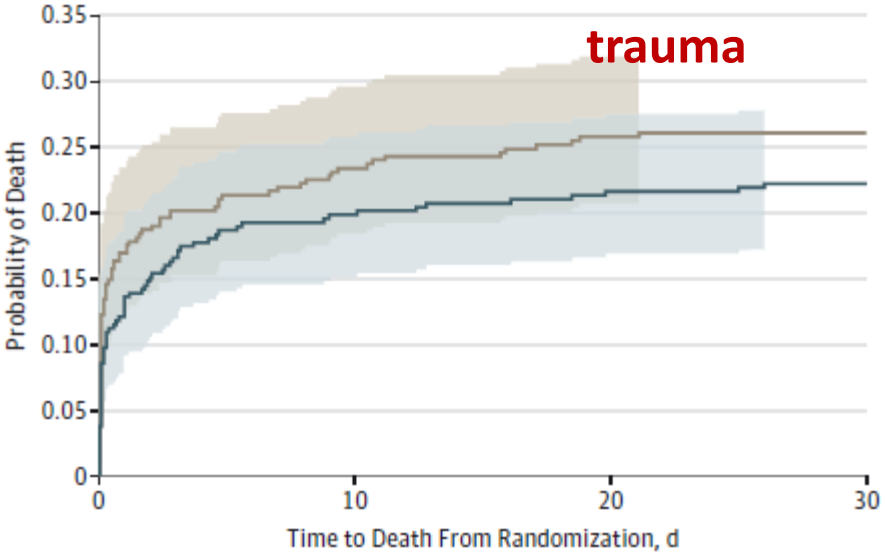
- Multi-centre RCT
- Severely injured patients (median ISS 26) predicted to require massive transfusion by ABC score randomized to 1:1:1 (n=338) vs. 1:1:2 ratios (n=342)

- **No significant differences** in primary outcomes:
  - mortality at 24 hrs (12.7% in 1:1:1 group vs 17.0% in 1:1:2 group; difference, −4.2% [95% CI, −9.6% to 1.1%]; *P* = .12)
  - mortality at 30 days (22.4% vs 26.1%, respectively; difference, −3.7% [95% CI, −10.2% to 2.7%]; *P* = .26)

Holcomb et al 2015

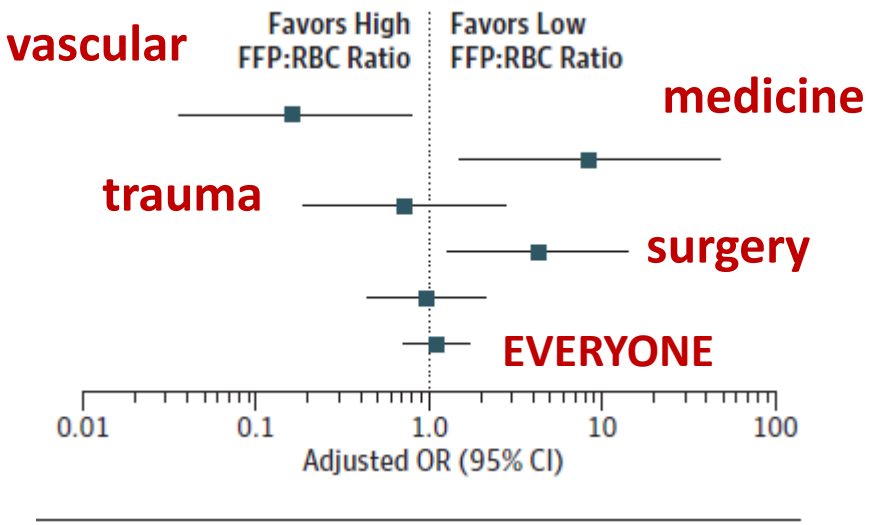
Right Ratio?

PROPRR



Holcomb, JAMA 2015; 313: 471-482

JAMA SURG HARVARD



Mesar, JAMA Surg 2017; March 8.

POCT-based Hemotherapy

- Goal-directed and individualized
- Fast
- Likely able to identify early coagulopathy and predict need for MTP

- Evidence is scarce (but rapidly growing)
  - Lack of randomized studies
- Poor availability of instruments and trained operators
- Lack of evidence-based transfusion guidelines utilizing POCT data

Hagemo et al 2015; Hunt et al 2015

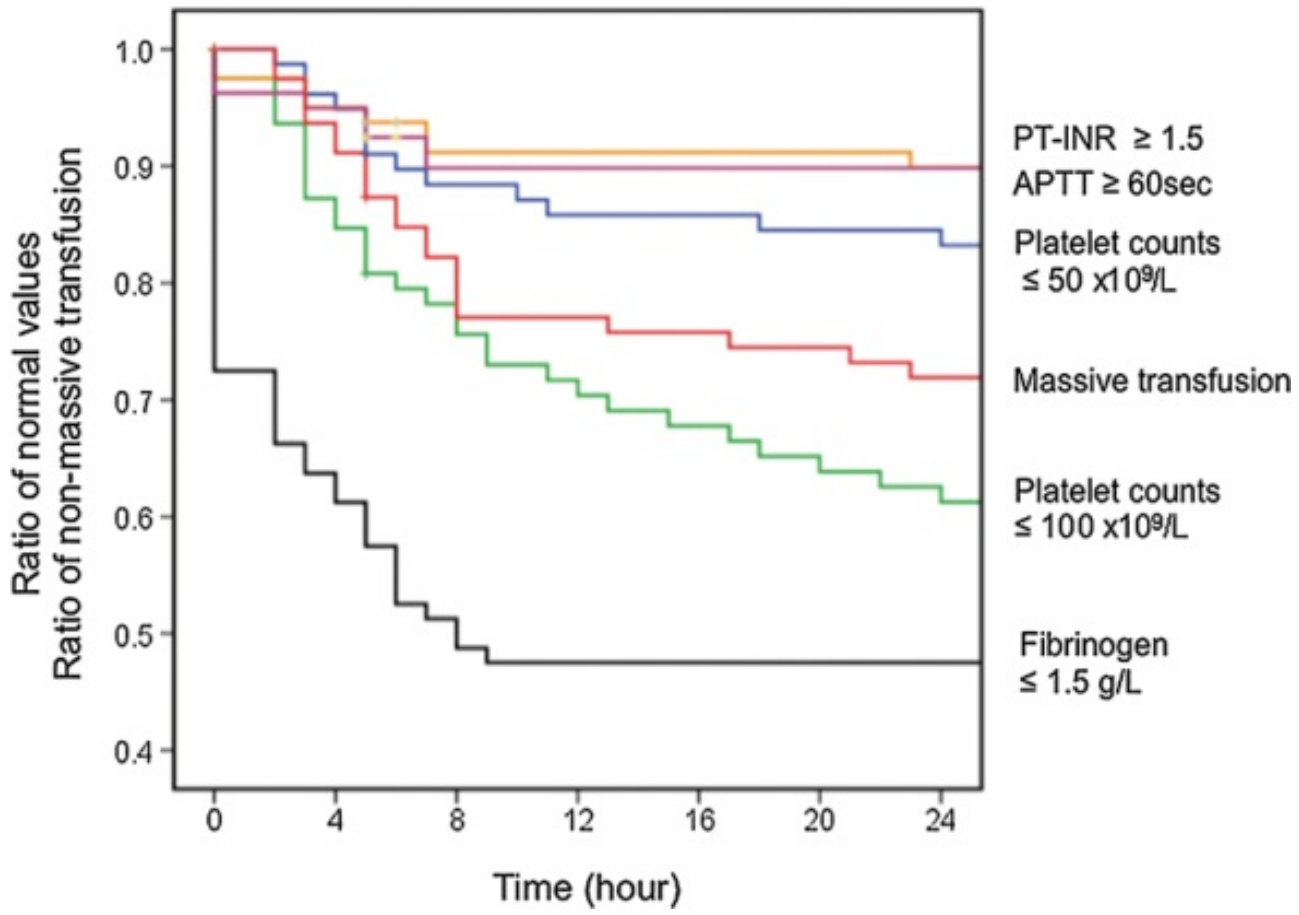
Large Hospital/Trauma Centre

- Inventory usually includes
  - Trauma stock (O Rh negative and O Rh positive RBC)
  - RBC of all blood groups
  - Plasma of all blood groups
    - May have thawed plasma - stock vs. left-over
  - Platelets
  - Cryoprecipitate, fibrinogen concentrate
  - PCC
  - Other…

State of the Art MHP

- Transfuse RBC to maintain hemoglobin >80g/L
- Aim for plasma to RBC ratio of 1:2
  - adjust component therapy as per INR/fibrinogen or ROTEM results
- Transfuse cryoprecipitate (or alternative) to maintain fibrinogen >1.5-2.0g/L
- Transfuse platelets to maintain platelet count >$50x10^9$/L during any active hemorrhage or >$100x10^9$/L in case of CNS bleeding or traumatic brain injury

Time From Arrival in ED to Critical Levels



Gando & Hayakawa 2016

Sample MHP Summary

TM Shipments (q30min):

- **1a**: 6 RBC
- **1b**: 4 FP
- **2**: 4 RBC, 2 FP, 1 PLT dose, 10 units of cryoprecipitate
- **3 and subsequent**: 4 RBC, 4 FP

- Additional PLT or CRYO must be requested and as per labs

Initial Labs:

•Group & Screen

•MTP panel: CBC, INR, aPTT, fibrinogen, ionized calcium, venous lactate

•MTP trauma panel: MTP panel + ROTEM

•ABG /VBG

•Electrolytes, Cr

•Maintenance Labs:

•MTP panel q1h

•ABG/VBG q0.5-1.0h

•Others prn

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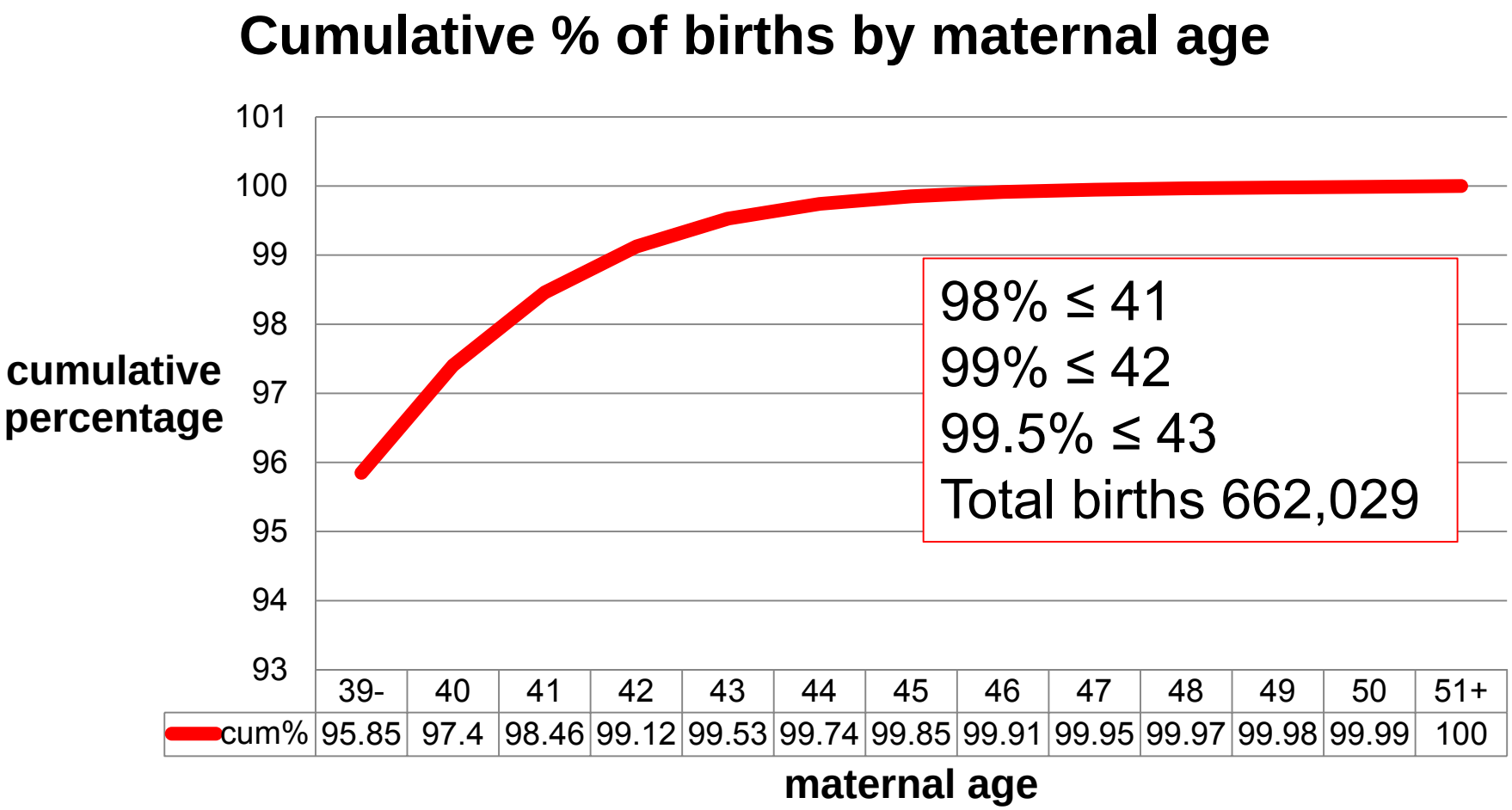
If Blood Group is Not Known...

- **RBC**
  - **Issue O Rh negative RBC to female patients less than 45 years old** and O Rh positive RBC to all other patients
  - Switch to group specific RBC as soon as the group has been determined (<10mL of plasma per unit)
  - Switch to crossmatched RBC as soon as the compatibility testing has been completed

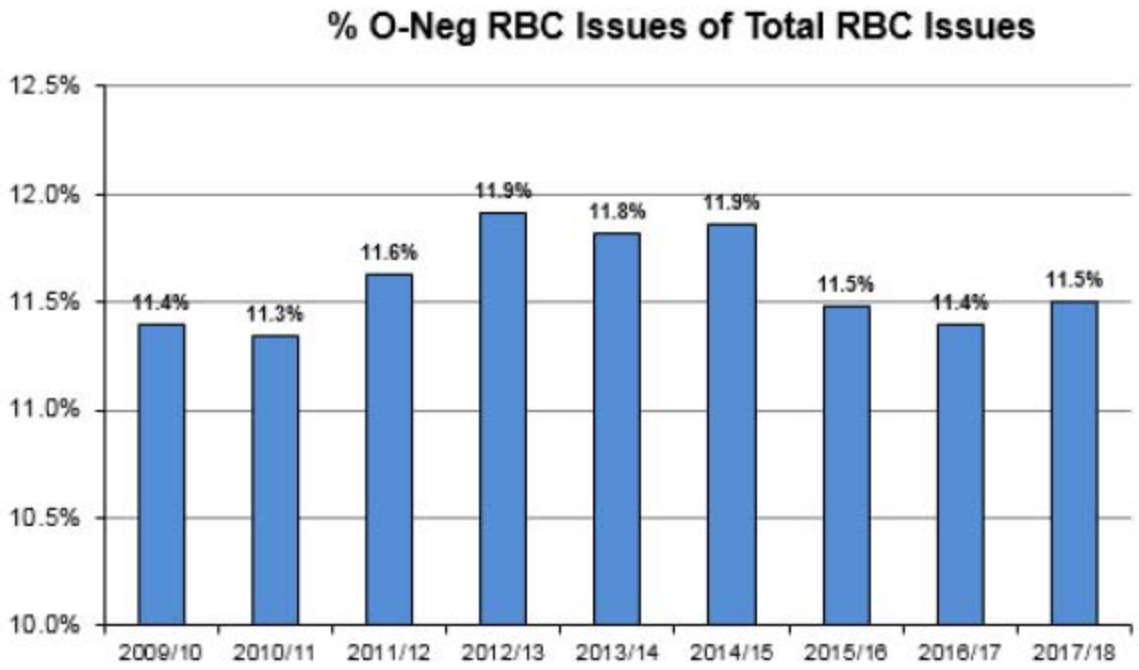
Births by Maternal Age: Ontario



	39-	40	41	42	43	44	45	46	47	48	49	50	51+
cum%	95.85	97.4	98.46	99.12	99.53	99.74	99.85	99.91	99.95	99.97	99.98	99.99	100

c/o A. Collins, data source: CIHI

O Rh Negative RBC Issues (CBS data)



Canadian Blood Services
it's in you to give

Only 6 to 7% of the general population in most areas in Canada are O Rh-negative

NAC Position Paper on Utilization of Group O Rh negative RBC

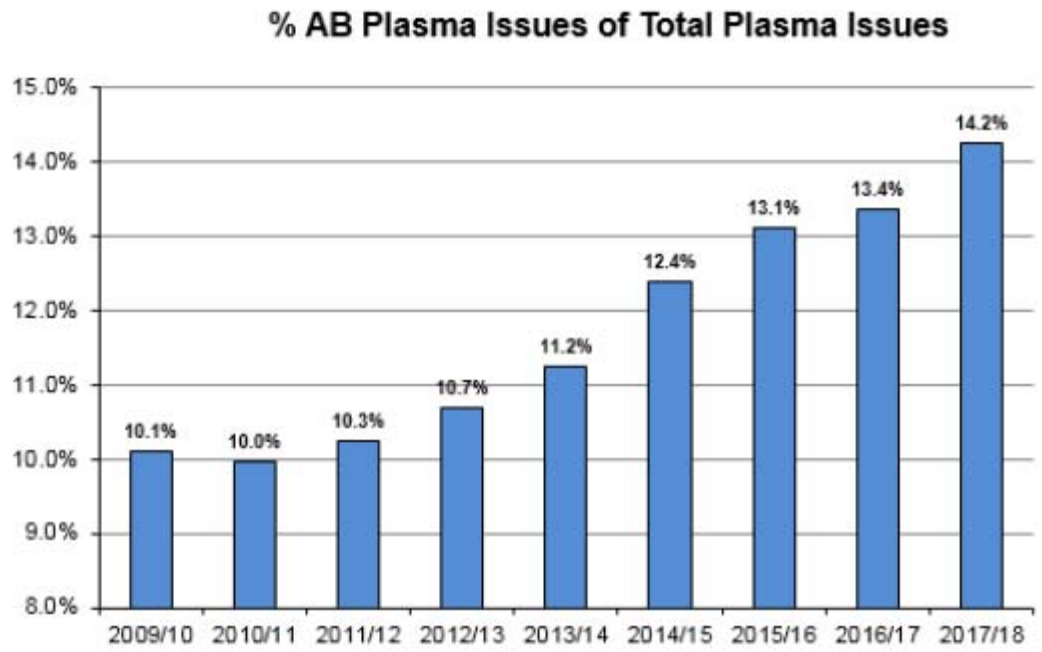
Mandatory indications: O Rh-negative red cells should always be used for these indications
• O Rh-negative females of child-bearing potential (≤45 years of age) • O Rh-negative males and females with anti-D • Emergency use for females of child-bearing potential (≤45 years of age) when blood group is unknown • Intrauterine transfusions (intravascular and/or intraperitoneal transfusions)
Highly recommended indications. When possible, O Rh-negative red cells should likely be used for these indications
• O Rh-negative individuals (any age) who are expected to receive chronic transfusions (for example, individuals with hemoglobinopathies or with chronic transfusion requirement)
Generally acceptable indications. The use of O Rh-negative red cells may be considered acceptable for these indications
• O Rh-negative males requiring non-massive transfusion* • O Rh-negative females (older than child-bearing potential, >45 years of age) requiring non-massive transfusion* • Non-O-Rh-negative infants less than 1 year of age where group specific units are not available • Non-O-Rh-negative patients requiring phenotypically matched or antigen negative units when group specific units are unavailable
Likely unacceptable indications. The use of O Rh-negative red cells is likely unacceptable for these indications. (Likely indications for O Rh-positive red cells)
• Any O Rh-negative male without anti-D requiring a large volume transfusion (> 4-6 units)* • Any O Rh-negative female (older than child bearing potential, >45 years) without anti-D requiring a large volume transfusion (> 4-6 units)* • Non-O-Rh-negative patient because unit is approaching expiry

**For O Rh-negative patients who are males or females older than 45 years and do not have anti-D AND are undergoing large volume transfusion (greater than 4-6 units), hospitals are strongly encouraged to have a policy on switching to O Rh-positive red cells after 4-6 units have been transfused*

If Blood Group is Not Known...

- **Plasma**
  - Issue AB plasma
  - To reduce utilization of AB plasma:
    - Switch to group specific or compatible plasma as soon as group is known and plasma thawed
    - Do not store thawed AB plasma but consider MHP pre-activation
    - Consider using group A plasma as universal plasma

AB Plasma Issues (CBS data)



Canadian Blood Services
it's in you to give

If Blood Group is Not Known...

- **Platelets**
  - Issue any group
  - RhIg should be offered to all Rh-negative female patients less than 45 years old and who have received Rh-positive platelets
    - except if they have also received Rh positive RBC or have evidence of alloimmunization with anti-D

Nahirniak et al 2015

If Blood Group is Not Known...

- **Cryoprecipitate**
  - Issue any group (switch to group specific or compatible if available and as soon as group is known)
  - Consider fibrinogen concentrate if cryoprecipitate not available, cryoprecipitate shortage or refractory hypofibrinogenemia

What if the Patient Has Special Requirements?

- Irradiated
  - Not practical to provide irradiated RBC during MHP, even if have an on site irradiator
    - risk of exsanguination due to delayed transfusion outweighs very low risk of TAGVHD
  - Options to consider:
    - Issue pre-storage leukoreduced RBC that have been stored for more than 14 days
    - Issue what you have
- Washed, phenotypically matched
  - Issue what you have and monitor for complications

Fibrinogen: MVP

- Key coagulation factor needed to ensure hemostasis (direct precursor to fibrin)
- Earliest coagulation factor to reach a critically low level in bleeding patients (Hippala 1995; Hayakawa et al 2015)
  - **F**ibrinogen **f**alls **f**irst, **f**alls **f**ast
- Increased bleeding may be observed at levels of fibrinogen <1.5-2.0g/L (Fries 2010)
- Low fibrinogen (<1.5-2.0g/L) on arrival predicts massive transfusion and death in trauma (Sawamura et al 2009)
- Early coagulopathy predicts initial or delayed fibrinogen deficit in patients with severe trauma (Deras et al 2014)
  - 29% of patients with INR between 1.20 and 1.49 will have fibrinogen <1.5g/L

Fibrinogen: Outstanding Questions

- What product (FP vs. CRYO vs. fibrinogen concentrate)?
- What dose (CRYO 10 units vs. 20 units for a 70 kg male)?
- When? (upfront vs. later in resuscitation)
- What threshold?
  - Fibrinogen <1.5-2.0g/L (Spahn et al 2007)
  - Fibrinogen measurement by TEG/ROTEM

Fibrinogen vs. Cryoprecipitate

Fibrinogen

- Blood product (made from human plasma)
- Contains fibrinogen
- Licensed only for congenital hypofibrinogenemia
- Consistent dose per vial
- Needs to be reconstituted
- Once reconstituted, good for 8 hrs
- Pathogen inactivated
- Infuse no faster than 5cc/min (6g/300cc over 60 min)
- AE: thrombosis

Cryoprecipitate

- Blood component
- Contains fibrinogen, VWF, FVIII, FXIII, fibronectin, etc.
- Primarily used for secondary hypofibrinogenemia
- Unit to unit variability
- Need blood group, thawing, diluting and pooling
- Once pooled, good for 4 hrs
- Not pathogen inactivated
- Infuse 10 units in 20 minutes
- AE: transfusion reaction, thrombosis?

Cryoprecipitate vs. FC

Pool of 10 units

FC 2-4 grams

NAC Fibrinogen Statement

Fibrinogen

December 15, 2014

Recommendations for Use of Fibrinogen Concentrate in Acquired Hypofibrinogenemia

While there is evidence that fibrinogen replacement plays an important role in management of bleeding post cardiac surgery or trauma as well as in obstetrical hemorrhage, there is still uncertainty as to the optimal fibrinogen replacement product or dose. Fibrinogen concentrate (FC), frozen plasma (FP), and cryoprecipitate are currently used to treat acquired hypofibrinogenemia.

Fibrinogen content of the above mentioned products is as follows:

1 vial FC =	0.9 – 1.3 g fibrinogen
1000 ml FP =	2.94 +/- 0.63 g fibrinogen (1 SD)
1 unit cryoprecipitate =	0.432 +/- 0.264 g fibrinogen (2 SD)

Optimal dosing of the above mentioned products is unclear as it is affected by:

- The inter-donor variability of fibrinogen content in blood components/products
- Patient's unique clinical situation, including patient's baseline fibrinogen level and a situation-appropriate fibrinogen target.

At this time, there is insufficient evidence of superiority of FC over FP or cryoprecipitate. Until the results of on-going trials are known, NAC cannot recommend FC over other means of fibrinogen replacement as the preferred method of replacing fibrinogen in acquired hypofibrinogenemia in a bleeding patient.

Fibrinogen Replacement: Published Evidence

- No good quality evidence: mainly retrospective studies
  - Fibrinogen substitution can improve survival in combat-related trauma (Stinger 2008)
  - Possible synergy with TXA (MATTERs II)
  - SR
    - 4 case reports, 7 retrospective studies and 1 prospective observational study (3 studies were not limited to trauma)
    - FC associated with reduced blood product requirement
    - ++ methodological flaws

Morrison et al 2013; Aubron et al 2014

Fibrinogen Replacement: Active Trials

- **Active**

- FC vs. CRYO pediatric cardiac surgery (UK)
- FC vs. CRYO adult cardiac surgery (Can)
- FC vs. placebo adult cardiac surgery (Can)

- **Completed/awaiting results**

- FC vs. CRYO in severe trauma (FEISTY) (UK)
- FC vs. CRYO pediatric cardiac surgery (USA)
- FC vs. placebo in trauma (Can)

clinicaltrials.gov

Conclusions

- For a large hospital, use a blended approach
- Aim for RBC to plasma ratio 2:1
- Replace fibrinogen when fibrinogen level is below 1.5g/L by giving plasma, CRYO or FC
- Transfuse platelets to maintain platelet count $>50x10^9$/L during any active hemorrhage or $>100x10^9$/L in case of CNS bleeding or traumatic brain injury
- For transfusion of patients with unknown blood group, restrict transfusion of O Rh negative RBC to women under age 45