Role of Plasma in Massive Hemorrhage

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Objectives

- Role of ratio-based plasma to red cell transfusion
- Group A plasma
- Plasma alternatives

Disclosures

- None

Case

- *28 year old man suffered motorcycle collision*
- *Presented to your hospital as a transfer from another hospital due to hemodynamic instability and need for trauma care*
- *Patient required CPR, intubation, 7 units of Group O+ Red Blood Cells (RBCS) and 1 unit of Group AB Frozen Plasma (FP)*
- *On arrival, he is requiring ongoing vasopressor support and has bilateral pneumothorax, significant intra-abdominal collections and a long bone fracture of his femur.*
- *Labs are drawn and pending*
- *Massive transfusion protocol is started*

Question 1

What is the optimal initial FP:RBC ratio for him in the massive transfusion protocol?

A. 1 to 1

B. 1 to 2

C. 2 to 1

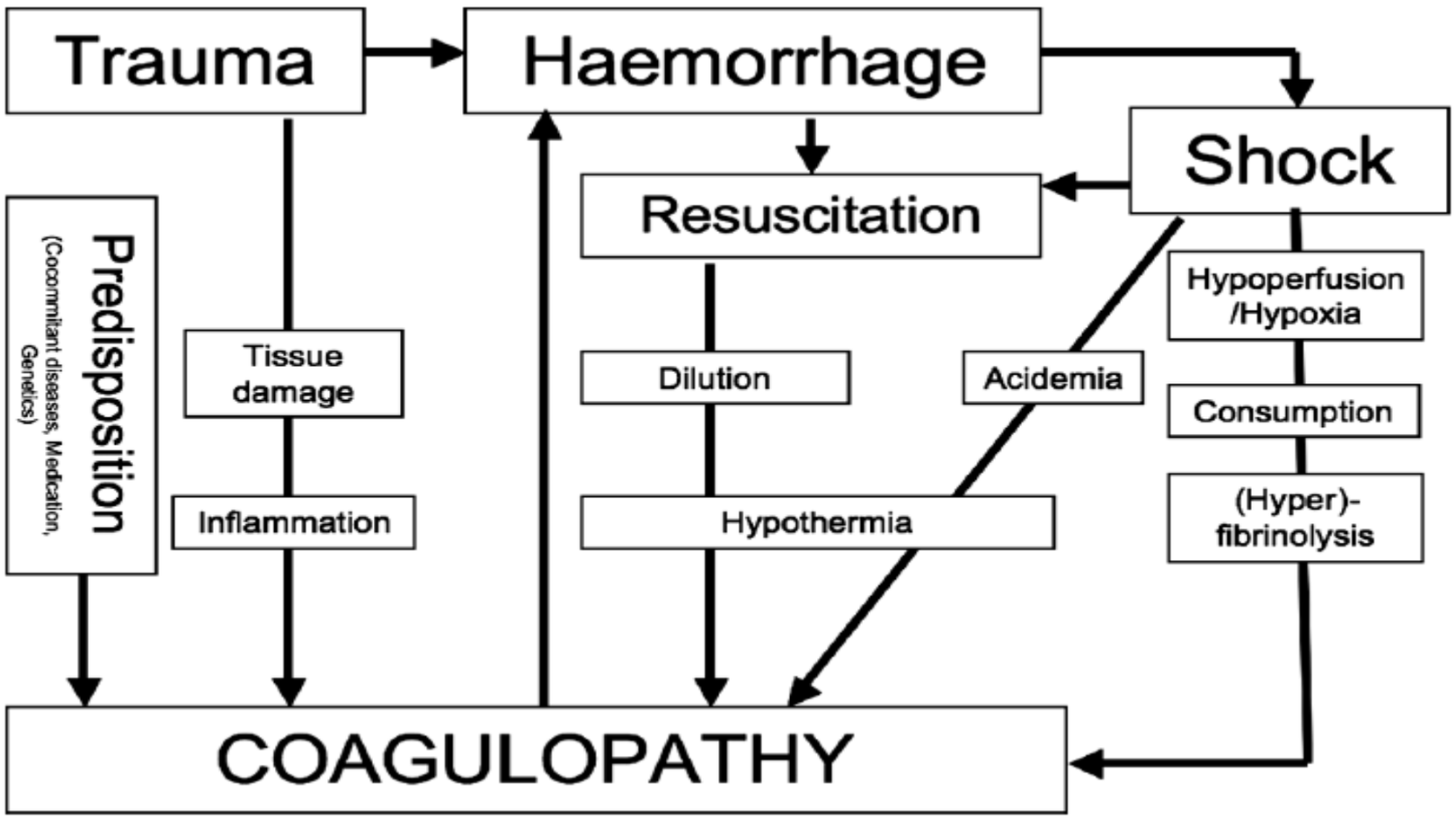
D. 1 to 3

Definition of Massive Hemorrhage

- No widely accepted universal definition
  - Loss of 1 blood volume in 24 hours
  - 50% loss of 1 blood volume in 3 hours
  - Blood loss of > 150ml/min
  - >10 units of RBCs in 24 hours, 6 units of RBCs in 4 hours etc.
  - Anticipated blood loss ≥10 units of RBCs within 6 hours
  - Clinical parameters – hypotension, tachycardia
- Complex and stressful medical situations
- High mortality

Johansson et al. Blood 2014 Nov 13;124(20):3052-8
Hunt et al. BJH 2015 Sep;170(6):788-803.

Acute Coagulopathy of Trauma



Maegele M et al., Shock. 2012 Nov;38(5):450-8.

Coagulopathy of Trauma

- Coagulopathy is common in trauma and associated with increased mortality
- Observational cohort study of 1088 trauma patients
  - Coagulopathy: PT > 18s, aPTT > 60s, or TT > 15s
  - **24%** of patients were coagulopathic on arrival
  - Incidence of coagulopathy increased with the severity of injury
  - Patients with coagulopathy had higher mortality (46% vs 10.9%, p< 0.001)

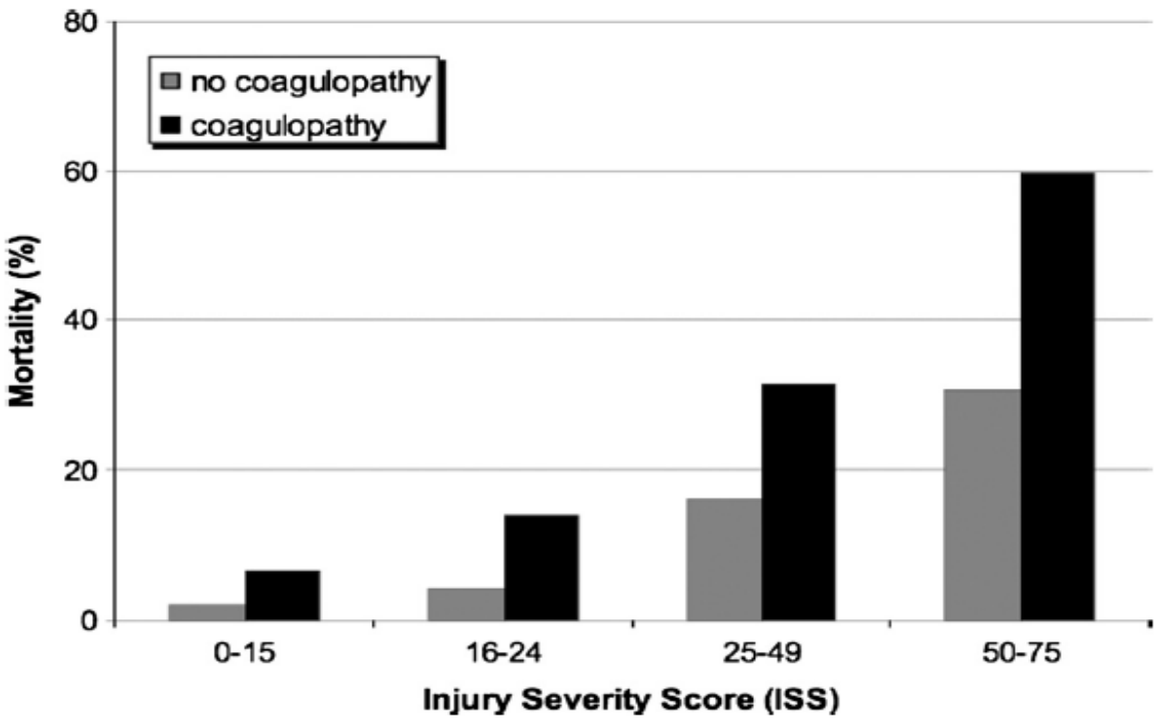


FIG. 4. **Mortality in patients with and without coagulopathy upon ER admission with respect to the magnitude of injury sustained (adopted and modified from Maegele et al. [13]).**

Brohi K et al., J Trauma 2003 Jun;54(6):1127-30.
Magele M et al., Injury 2007 Mar;38(3):298-304.

Research

Original Investigation

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
Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD,
Bryan A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Pete
Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS;
Jeannie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jear
Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

		Container 1	Container 2
Group 1[a]	Platelets	1	1
1:1:1	Plasma	6	6
	RBCs	6	6
Group 2[b]	Platelets	0	1
1:1:2	Plasma	3	3
	RBCs	6	6

[a]Group 1: Platelets first, then alternate RBCs and Plasma, as clinically required
[b]Group 2: Platelets first (if available), then alternate 2 RBCs and 1 Plasma, as clinically required

- 680 patients with major bleeding from severe trauma randomized to FP:PLT:RBC of 1:1:1 versus 1:1:2
- Mortality at 24h and d30 not different (Primary outcome)
- 1:1:1 more likely to have adequate hemostasis (86% versus 78%) and had fewer deaths from exanguination at 24 hours (9.2% versus 14.6%)
- No differences in 23 other ancillary clinical outcomes

Holcomb et al. JAMA. 2015 Feb 3;313(5):471-82.

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage:
https://www.journals.elsevier.com/transfusion-medicine-reviews/

Optimal Dose, Timing and Ratio of Blood Products in Massive Transfusion: Results from a Systematic Review

Zoe K. McQuilten [a,b,*], Gemma Crighton [a], Susan Brunskill [c], Jessica K. Morison [a], Tania H. Richter [a], Neil Waters [a], Michael F. Murphy [c], Erica M. Wood [a]

- 6 RCTs (5 adult trauma, 1 pediatric burn), 10 RCTs ongoing
- 3/6 (2 adult trauma, 1 pediatric burn) investigated effect of FP:RBC ratio on patient outcomes
- Data from the 2 trauma trials were pooled for meta-analysis of 28d mortality
- Higher FP:RBC ratios associated with more FP use, without significant difference in morbidity/mortality (pooled effect measure for 28d mortality 1.26, 95% CI 0.49-3.22, p=0.64, I^2=75%)
- **Insufficient evidence to recommend 1:1 (FP:RBC) over 1:2 (FP:RBC)**

McQuilten Z et al. Transfus Med Rev. 2018 Jan;32(1):6-15

Non Trauma Massive Hemorrhage

Obstetrics

- 25% of cases of OB hemorrhage is associated with coagulopathy
- Fibrinogen is key
  - Low levels are a predictor of PPH severity (normal 4-6 g/L in pregnancy)
  - Fibrinogen replacement and TXA (WOMAN trial) are key

GI bleeding

- Less coagulopathy
- ~5% of cases require FP transfusion (TRIGGER trial)

Cardiac surgery

- Coagulopathy different – secondary to bypass mediated platelet activation and factor consumption

Liver surgery

- Coagulopathy different – balance of lack of clotting factors and lack of natural anticoagulants
- Have intact thrombin generating capacity and have hypo-fibrinolytic state

Charbit B et al., JTH 2006
Pavord S et al. Blood 2015
Hunt B et al. BJH 2015.
WOMAN Trial Collaborators. Lancet 2017.
Jairath V et al. Lancet 2015
Myles P et al. NEJM 2017
Lisman T et al. J Thromb Haemost 2012.

Non Trauma Massive Hemorrhage

Obstetrics

- 25% of cases of OB hemorrhage is associated with coagulopathy
- Fibrinogen is key
  - Low levels are a predictor of PPH severity (normal 4-6 g/L in pregnancy)
  - PPV of fibrinogen < 2g/L for PPH was 100%
  - Fibrinogen replacement and TXA (WOMAN trial) are key

GI bleeding

- Less coagulopathy
- ~ 95% of cases require RBC transfusions only (TRIGGER trial)

Cardiac surgery

- Coagulopathy different – secondary to bypass mediated platelet activation and factor consumption

Liver surgery

- Coagulopathy different – balance of lack of clotting factors and lack of natural anticoagulants
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FP:RBC Ratios in Non-Traumatic MH

- Etchell et al. Critical Care Med 2017
  - Retrospective single-center study of 601 massively bleeding non-trauma patients
  - Primary outcome: 30 day mortality
- Cardiac Sx, GI, hepato-biliary bleeds were most common
- Higher FP:RBC ratios (> 1:2) was NOT associated with increased 30-day mortality

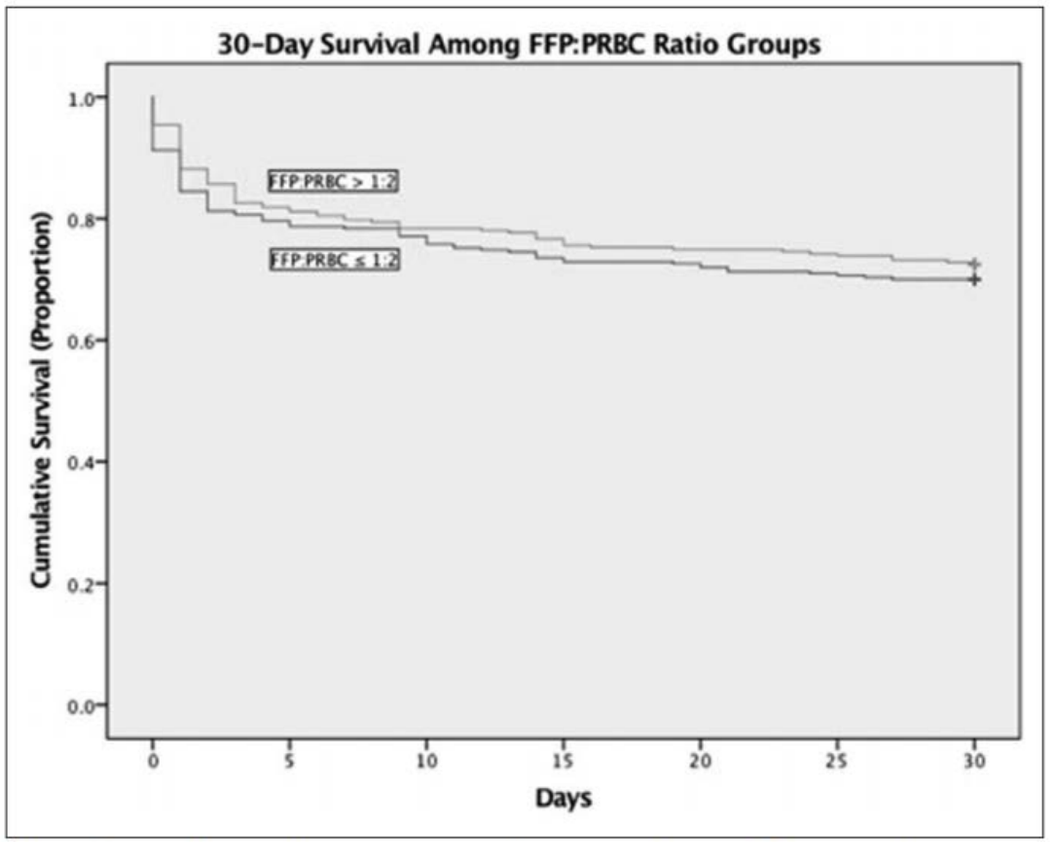


Figure 2. Kaplan-Meier cumulative incidence of mortality over days after massive transfusion by fresh frozen plasma-to-packed RBC (FFP:PRBC) ratio groups. Curves were derived from Kaplan-Meier survival estimates. *$p = 0.438$.

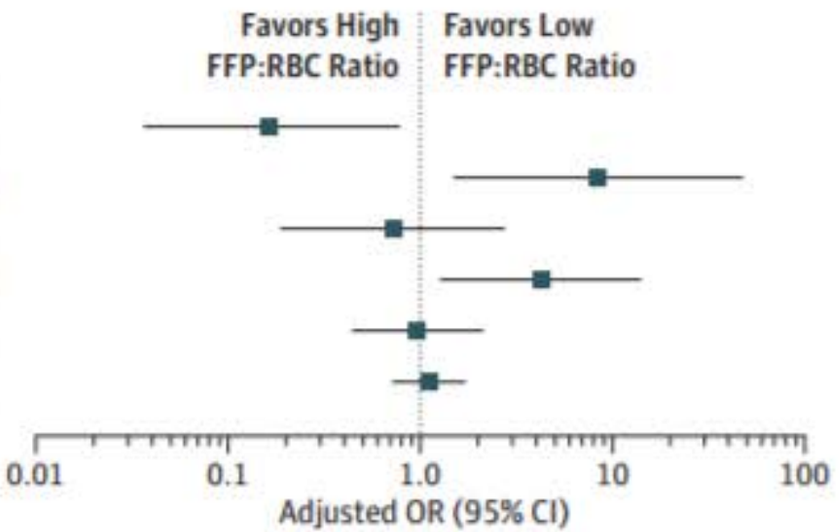
Etchell E et al. Critic Care Med 2017; Aug;45(8)

FP:RBC Ratios in Non-Traumatic MH

- Retrospective study of 865 massive transfusion events in a single academic center

Figure. Adjusted Odds Ratio (OR) for Death

Surgical Service	No. of Patients	Adjusted OR (95% CI)
Vascular surgery	78	0.16 (0.03-0.79)
Medicine	76	8.48 (1.50-47.75)
Trauma surgery	99	0.63 (0.17-2.35)
General surgery	86	4.27 (1.28-14.22)
Cardiac surgery	272	0.98 (0.45-2.14)
All patients without trauma	767	1.10 (0.72-1.70)



Overall, no benefit was observed for high or low fresh frozen plasma (FFP) to red blood cells (RBC) ratio. In vascular surgery, a high FFP:RBC ratio was associated with a survival benefit. In medicine and general surgery, a high FFP:RBC ratio was associated with increased mortality.

Mesar T et al. JAMA Surg 2017 Jun 1;152(6):574-580

Ratio vs Lab-Driven Plasma Transfusion

- Fixed-ratio based = continuing with pre-set transfusion ratio until bleeding stops/protocol deactivated/death
- Lab-based = transfusing based on lab results instead of empiric ratios
- Ratio-based increases in plasma wastage
- Starting with fixed-ratio → lab directed
  - Routine coagulation tests (INR, aPTT, fibrinogen)
    - INR<1.8
    - Fibrinogen>1.5 g/L
  - Point of care whole blood clotting assays (TEG®, ROTEM®)

Hunt B et al. BJH 2015
Nascimento B et al. CMAJ 2013
Tapia N et al. J Trauma Acute Care Surg 2013
Winearls J et al. Anesth Analg 2016

Case

- *28M traumatic massive hemorrhage → what is the best FP:RBC ratio for him?*

- *No established benefit to a 1:1 transfusion ratio of FP:RBC, and associated with more plasma use*
- *Therefore, a target of ~1:2 (FP:RBC) is likely sufficient until labs or point of care tests are available to guide further therapy*

Case

- *Patient taken to OR*
- *40 units of O+ RBCs*
- *7 doses of platelets*
- *24 units of Group AB plasma*
- *12g of fibrinogen concentrate*
- *G/S just drawn, pending*

It's Friday heading into a long weekend and we will have NO more AB plasma if this keeps up! What should we DO?

https://www.123rf.com/clipart-vector/surprised_doctor.html

Question 2

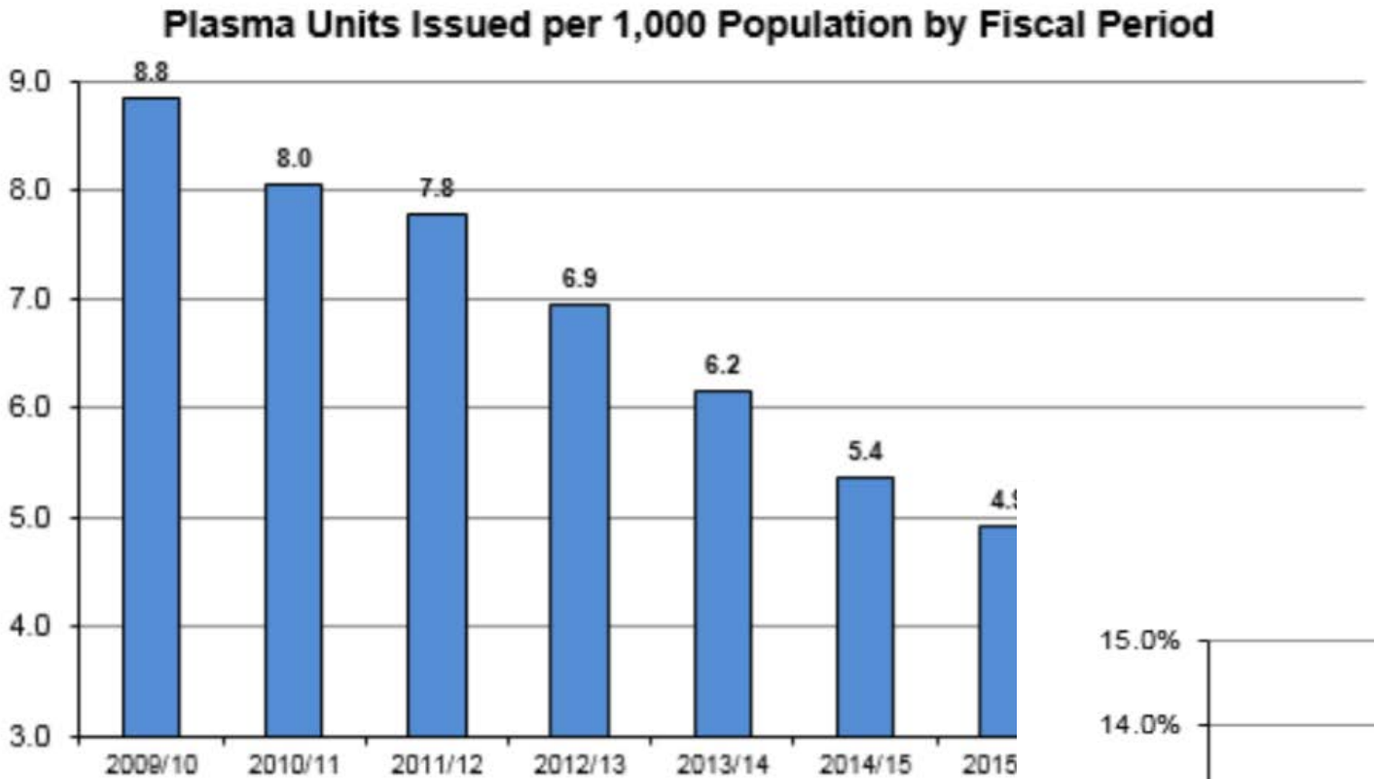
Running out of AB plasma stock

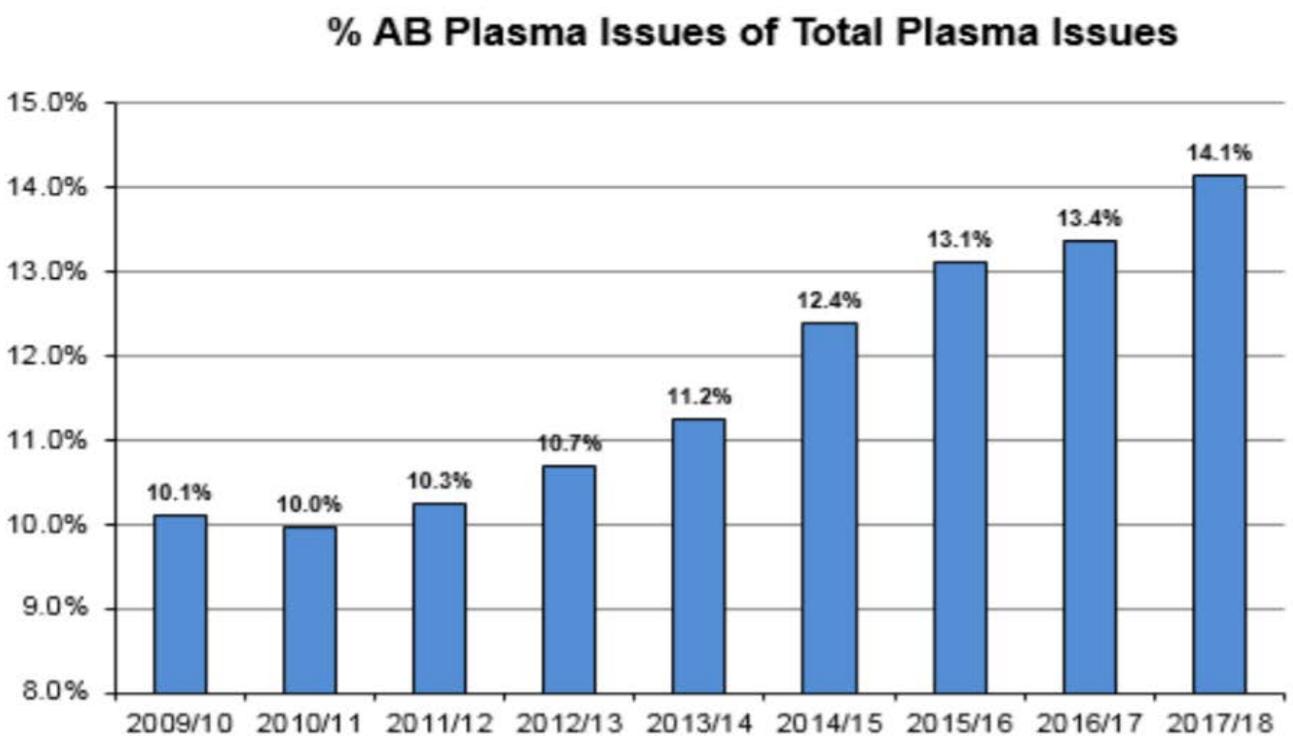
A. Continue with AB plasma, until G/S back
B. Switch to A plasma, until G/S back
C. Switch to O plasma, until G/S back
D. Stop plasma transfusions for awaiting G/S

AB Plasma

- AB plasma is an universal product
- A limited resource (3-4% of the population is group AB)
- Multinational survey BEST: 73% of AB plasma is transfused to non-AB patients
  - Highest % occurred in ER
  - Most common indication was emergency issue to patients without valid G/S (69%)
  - Group AB plasma close to expiry (16.4%)
- Survey of 10 US blood centers: 27% increase in demand for AB plasma in 2011 when compared to 2006
  - Widespread adoption of massive transfusion protocols

Yazer et al. Transfusion. 2013;53(8):1627–1633
Zeller et al. Transfusion, 2018; 58(1):151-157.





Emergency issue
Massive transfusion protocols

Data courtesy of Dr. Michelle Zeller

Can we use Group A plasma instead?

- Group A plasma contains anti-B antibodies
- If given to group B or group AB patient
  - Acute hemolytic transfusion reaction
  - Other adverse events: activate complement cascade, DIC, acute renal failure etc.

Percentages of Blood Groups in Canada (%)			
O	A	B	AB
46	42	9	3

- >80% of the population is Group A or O
- Transfused anti-B will be diluted in much larger plasma volume
- Patients are receiving O RBCs
- Most B and AB patients are secretors – with free floating B antigens in their plasma to neutralize the anti-B

https://blood.ca/en/blood/facts-about-whole-blood
Isaack et al. Immunohematology 2011;27:61-65

Can we use Group A plasma instead?

- We transfuse platelets containing non-identical plasma but hemolytic reactions are rare
- Cold stored, low-titer, Group O whole blood to trauma patients of unknown ABO type not associated with hemolysis or renal failure among non-group O patients

Mair B et al. Transfusion 1998;38:51-5
McManigal S, Sims KL. Am J Clin Pathol. 1999;111:202Y206.
Berseus et al. Transfusion. 2013 Jan;53 Suppl 1:114S-123S
Seheult et al. Transfus Med 2017;27:30-5
Yazer et al. Transfusion. 2018 Feb;58(2):532-538

Are there any alternatives for transfusion of AB plasma as universal donor in an emergency release setting?

Kirsten Balvers,[1,2] Sarah Saleh,[1,2] Sacha S. Zeerleder,[3,4] J. Henriette Klinkspoor,[5] J. Carel Goslings,[1] and Nicole P. Juffermans[2]

- **Systematic review** identified **6 studies** (5 retrospective cohort, 1 sub-study of RCT)
- 4/6 compared ABO compatible with incompatible plasma in emergency issue
  - **No differences** in complications or mortality between transfusion of ABO compatible and ABO incompatible plasma
- 2/6 compared ABO identical with ABO compatible plasma
  - Associated increased incidence of lung injury and mortality (odds ratio, 1.10; 95% confidence interval, 1.04-1.15, p = 0.0003)

Balvers et al. Transfusion 2016;56;1469–1474

Safety of the use of group A plasma in trauma: the STAT study

Nancy M. Dunbar[1] and Mark H. Yazer,[2] on behalf of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative and the STAT Study Investigators[†]

- Multicenter retrospective observational study of 17 trauma centers using group A plasma for patients of unknown ABO group
- Group A VS Group B or AB patients who received ≥ 1 unit of A plasma
- Primary outcome: in-hospital mortality

Dunbar N et al. Transfusion. 2017 Aug;57(8):1879-1884.

- 354 group B or AB trauma patients vs 809 group A trauma patients
- For group B/AB patients, mean 4 units of group A FP (range 1-58)
- 76% of participating centers did not measure anti-B titers
- No reported acute hemolytic transfusion reactions

TABLE 3. Outcome data between groups*

	Identical (n = 809)	Incompatible (n = 354)	p value
In-hospital mortality			
Survival to discharge	572 (71)	253 (71)	0.83
In-hospital death	237 (29)	101 (29)	
Early mortality (<24 hr)			
Yes	114 (14)	59 (17)	0.28
No	695 (86)	295 (83)	
Hospital LOS (days)	14 (0-111, 17)	14 (0-128, 18)	0.89

* Categorical data are reported as number (%), and continuous data are reported as mean (range, SD).

Case

- *28M traumatic massive hemorrhage → ++ AB plasma*

- *GET THAT GROUP AND SCREEN!!!*
- *Reasonable to consider switching to group A plasma*

Plasma Alternatives

- **Prothrombin Complex Concentrate (PCC)**
  - Human plasma derived product with Factor II, VII, IX, X (and protein C, S, heparin)
  - Reversal of VKA

	INR < 3	INR 3-5	INR > 5
Dose	**1000IU**	**2000IU**	**3000IU**

  - Reversal of direct oral anticoagulants (Apixaban, Rivaroxaban, Edoxaban)
    - 50IU/kg
    - 2000IU

Innerhofer P et al. Lancet Hematology 2017.
Spahn D et al. Critical Care 2019; 23:98.
https://www.nacblood.ca/resources/guidelines/downloads/PCC-Recommendations-Final-2014-05-16.pdf

Plasma Alternatives

- PCCs can be used as an alternative for plasma in massively bleeding patients when plasma is not available
- **RETIC trial** Lancet Hematology 2017
  - Single center, parallel-group, open label RCT
  - Adult patients with bleeding and coagulopathy (defined by ROTEM) randomized to:
  - FP VS clotting factor concentrate (primarily fibrinogen concentrate or 4 factor PCC)
  - Study was terminated early for futility and safety after 100 patients enrolled
- Increased thrombin generation over days

Innofer P et al. Lancet Haematol. 2017 Jun;4(6):e258-e271.

Plasma Alternatives

- **Freeze-dried/lyophilized plasma**
  - France, Germany, South Africa
  - FDA grants emergency use freeze dried plasma (France) to US Department of Defense in July 2018
  - French and German products in trials of trauma and pre-hospital settings
  - US products in phase 1 clinical trials

https://www.fda.gov/news-events/press-announcements/fda-takes-action-support-american-military-personnel-granting-authorization-freeze-dried-plasma

Conclusions

- Plasma is an important component of transfusion therapy in massively bleeding patients
- Empiric ratio > 1:2 (FP:RBC) may not be necessary in trauma and non-trauma patients with massive bleeding
- Group A plasma is likely a reasonable alternative to AB plasma
- More data needed for PCCs and lyophilized plasma