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
    - BJOG, 2011. **118**(11): p. 1402-3
  - 14.3% of direct maternal deaths in New Zealand
    - *Sixth Annual Report of the Perinatal and Maternal Mortality Review Committee. Reporting mortality*, H.Q.a.S. Commission, Editor 2012: Wellington.
  - 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

      - Anesth Analg 2010:110:1368-73

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
  - J Thromb Haemost 2007;5(2):266-273

Risk factors for PPH

Uterine atony (Tone)	Coagulopathy (Thrombin)
Multiparity	Congenital bleeding disorders
Multiple pregnancy	Acquired coagulopathies
Previous PPH	Anticoagulants
Patient age >40	Placental abruption
Patient BMI >35	Pre-eclampsia
Asian ethnicity	Sepsis
	Amniotic fluid embolism
Trauma/Surgery (Trauma)	**Placenta (Tissue)**
Perineal of vaginal trauma	Retained placenta
Caesarean delivery	Morbidly adherent placenta (accrete/percreta)
Instrumental vaginal delivery	Placental abruption
Uterine rupture	Placenta praevia

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

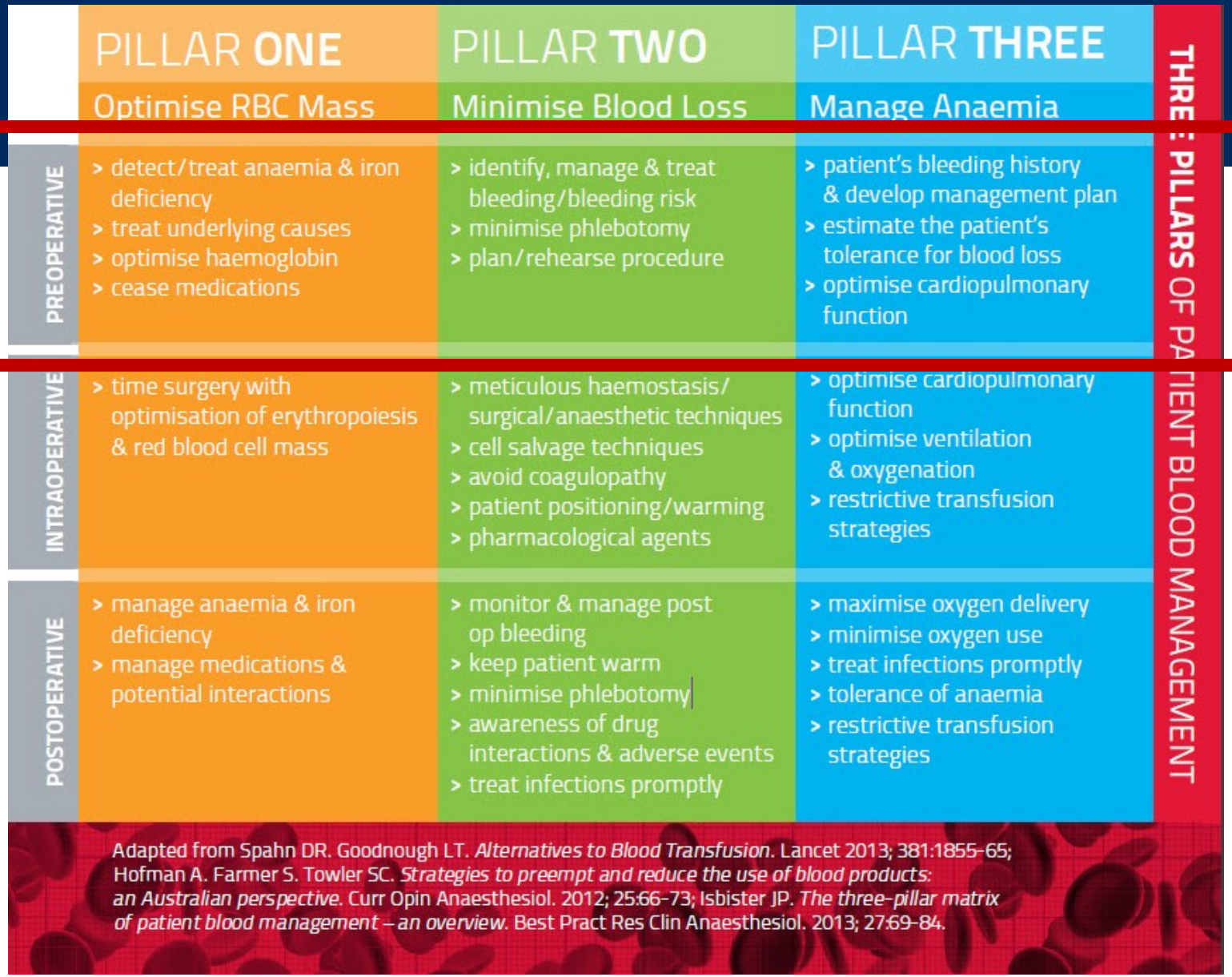
Blood 2015;125(18):2759 - 2770

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



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Labour and delivery

- Prolonged labour
- Uterine atony
  - Increased uterotonic exposure
- Surgical intervention
- Abruption
- Retained products
- HELLP / PET / ET

Society for Obstetric Anesthesia and Perinatology

Section Editor: **Cynthia A. Wong**

The Epidemiology of Postpartum Hemorrhage in a Large, Nationwide Sample of Deliveries

Brian T. Bateman, MD,* Mitchell F. Berman, MD, MPH,† Laura E. Riley, MD,‡ and Lisa R. Leffert, MD*

BACKGROUND: In this study, we sought to (1) define trends in the incidence of postpartum hemorrhage (PPH), and (2) elucidate the contemporary epidemiology of PPH focusing on risk factors and maternal outcomes related to this delivery complication.
METHODS: Hospital admissions for delivery were extracted from the Nationwide Inpatient Sample, the largest discharge dataset in the United States. Using *International Classification of Diseases, Clinical Modification* (ninth revision) codes, deliveries complicated by PPH were identified, as were comorbid conditions that may be risk factors for PPH. Temporal trends in the incidence of PPH from 1995 to 2004 were assessed. Logistic regression was used to identify risk factors for the most common etiology of PPH—uterine atony.
RESULTS: In 2004, PPH complicated 2.9% of all deliveries; uterine atony accounted for 79% of the cases of PPH. PPH was associated with 19.1% of all in-hospital deaths after delivery. The overall rate of PPH increased 27.5% from 1995 to 2004, primarily because of an increase in the incidence of uterine atony; the rates of PPH from other causes including retained placenta and coagulopathy remained relatively stable during the study period. Logistic regression modeling identified age <20 or ≥40 years, cesarean delivery, hypertensive diseases of pregnancy, polyhydramnios, chorioamnionitis, multiple gestation, retained placenta, and antepartum hemorrhage as independent risk factors for PPH from uterine atony that resulted in transfusion. Excluding maternal age and cesarean delivery, one or more of these risk factors were present in only 38.8% of these patients.
CONCLUSION: PPH is a relatively common complication of delivery and is associated with substantial maternal morbidity and mortality. It is increasing in frequency in the United States. PPH caused by uterine atony resulting in transfusion often occurs in the absence of recognized risk factors. (Anesth Analg 2010;110:1368–73)

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

Table 2. Univariate Analysis of Predictors of Postpartum Hemorrhage Because of Uterine Atony With Blood Transfusion, 2004

	Patients with atony resulting in transfusion *n* (%)	All others *n* (%)	*P*
Totals	1634	875,007	
Age (y)			
<20	238 (14.6)	89,829 (10.3)	<0.001
20–34	1093 (66.9)	654,465 (74.8)	
35–39	219 (13.4)	105,931 (12.1)	
≥40	84 (5.1)	24,782 (2.8)	
Delivery type			
Vaginal	893 (54.7)	610,852 (69.8)	<0.001
Cesarean without labor	354 (21.7)	142,941 (16.3)	
Cesarean with labor	387 (23.7)	121,214 (13.9)	
Hypertensive diseases of pregnancy	328 (20.1)	73,003 (8.3)	<0.001
Diabetes mellitus	99 (6.1)	47,895 (5.5)	0.30
Uterine fibroid	30 (1.8)	8799 (1.0)	0.001
Previous cesarean delivery	249 (15.2)	123,123 (14.1)	0.18
Polyhydramnios	18 (1.1)	5613 (0.6)	0.02
Chorioamnionitis	90 (5.5)	15,995 (1.8)	<0.001
Precipitate labor	17 (1.0)	19,420 (2.2)	0.001
Long labor	29 (1.8)	7924 (0.9)	<0.001
Medical induction of labor	278 (17.0)	135,290 (15.5)	0.08
Multiple gestation	117 (7.2)	15,917 (1.8)	<0.001
Stillbirth	23 (1.4)	5928 (0.7)	<0.001
Antepartum hemorrhage	124 (7.6)	14,559 (1.7)	<0.001
Retained placenta	73 (4.5)	8992 (1.0)	<0.001

PPH markedly increased the odds of in-hospital mortality (OR 7.8)

19.1% of in-patient mortality for this cohort

Table 4. Complication Rates in Patients with Postpartum Hemorrhage and the Association of Postpartum Hemorrhage with the Unadjusted Odds of Developing These Complications in 2004 Deliveries

	n (%)	Odds ratio (95% CI)	*P*
Acute renal failure	82 (0.3)	13.8 (10.6–17.8)	<0.001
Acute respiratory failure	105 (0.4)	10.9 (8.7–13.6)	<0.001
Prolonged mechanical ventilation (≥96 h)	13 (0.1)	6.5 (3.6–11.8)	<0.001
Coagulopathy	445 (1.8)	4.7 (4.2–5.2)	<0.001
Sepsis	25 (0.1)	3.7 (2.5–5.6)	<0.001
Hysterectomy	529 (2.1)	89.1 (75.7–104.9)	<0.001
In-hospital mortality	13 (0.1)	7.8 (4.3,14.4)	<0.001
Discharge other than home	91 (0.4)	3.0 (2.4–3.7)	<0.001
Length of stay more than 7 d	656 (2.6)	2.1 (1.9–2.3)	<0.001

[a] Excludes patients whose only postpartum hemorrhage code is 666.3 (*n* = 1099).

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.

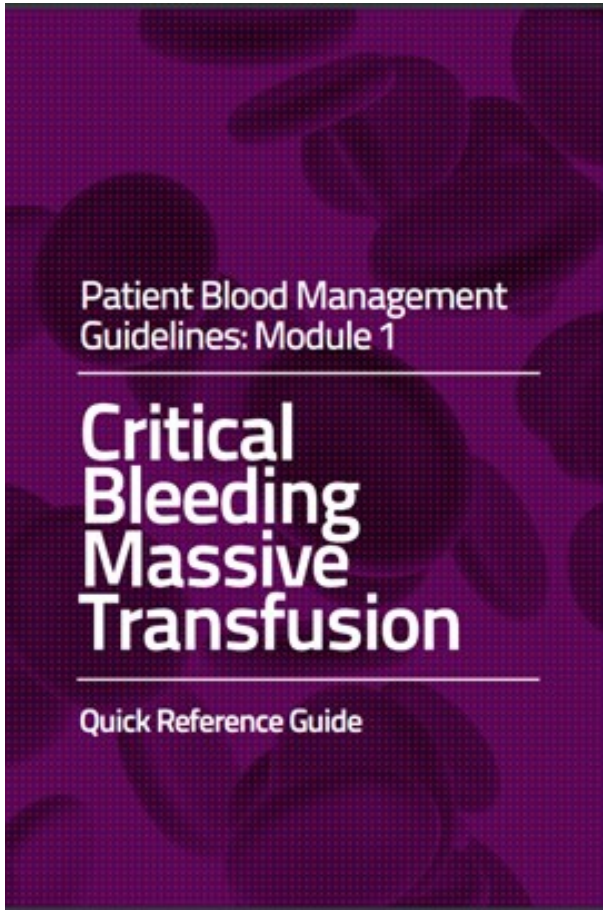
- Multidisciplinary delivery plan
- Communication about patients at risk to lab

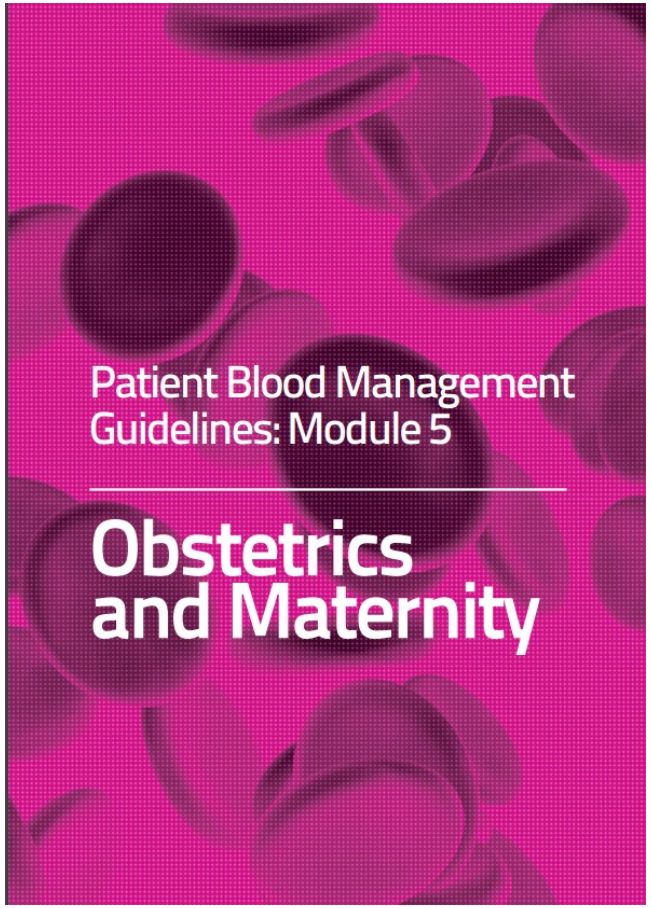
- When will labour occur?

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





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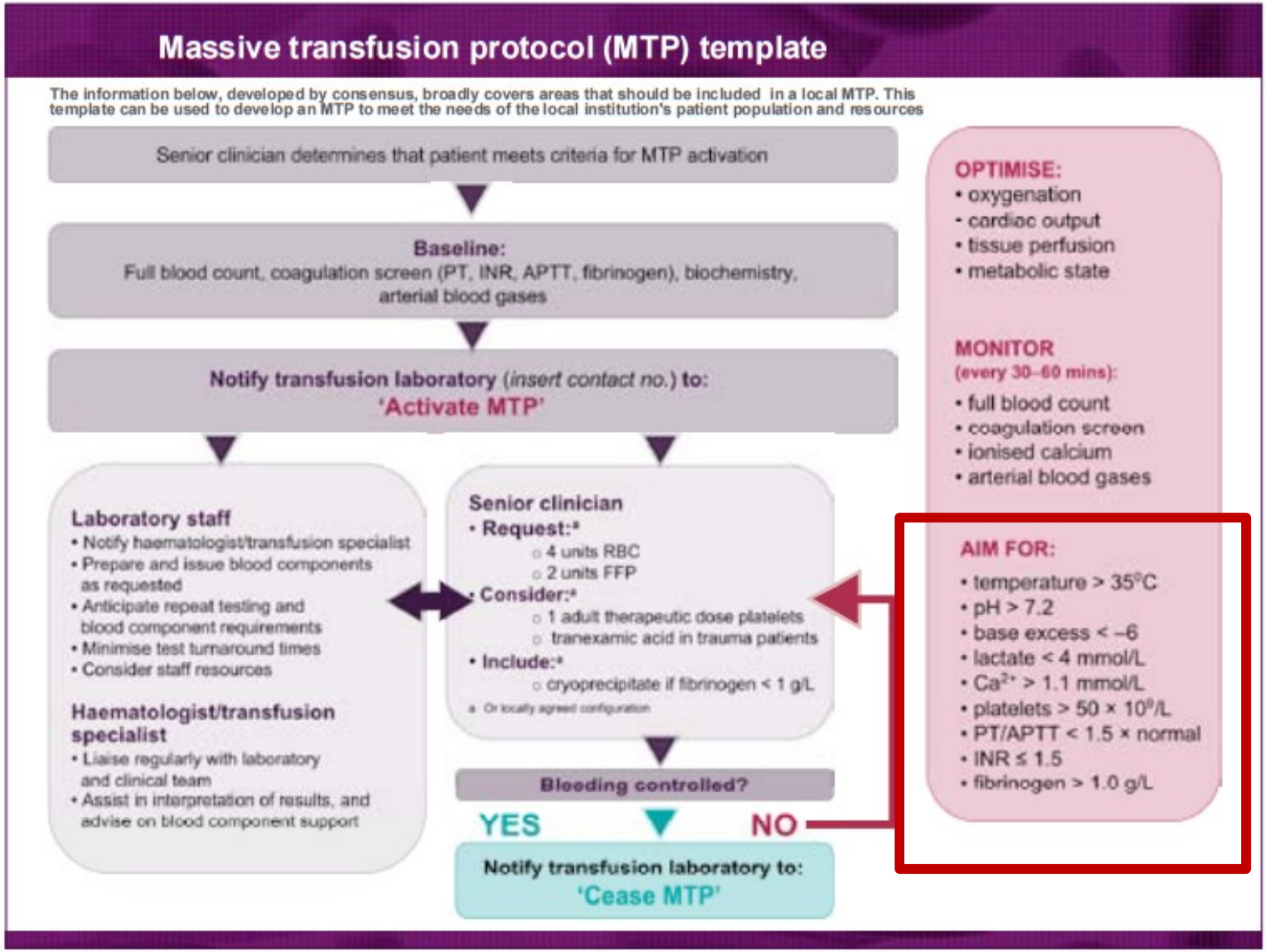
OBSTETRIC HAEMORRHAGE/CRITICAL BLEEDING – TRANSFUSION SUPPORT FOR MATERNITY SERVICES		
EOP3	All maternity services must have procedures in place to manage the critically bleeding maternity patient. This includes agreed communication and transport arrangements, access to transfusion medicine expertise 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



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Transfusion trigger Fib >1.0 did not include MOH

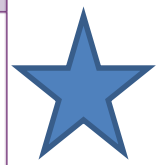
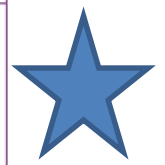
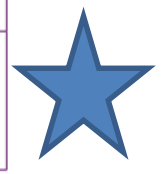
PP17	Values indicative of critical physiologic derangement include: ▪ temperature <35°C ▪ pH <7.2, base excess worse than –6, lactate >4 mmol/L ▪ ionised calcium <1.1 mmol/L ▪ platelet count <50 × 10^9/L ▪ PT >1.5 × normal ▪ INR >1.5 ▪ APTT >1.5 × normal ▪ fibrinogen level <2.0 g/L.	3.4

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
  - Anesth Analg, 1995. **81**(2): p. 360-5.
- Low levels predict for more severe haemorrhage
  - No severe PPH Fib >4 g/L
  - 4/5 Fib <2 g/L massive transfusion
    - J Thromb Haemost, 2007. **5**(2): p. 266-73.
    - Br J Anaesth, 2012. 108(6): p. 984-9

Table F.1 Blood component product information and dosage – Australia

Component	Content and characteristics	Volume per bag[a]	Typical adult dose (~ 70 kg)	Number of bags to provide typical dose
FFP	▪ Plasma recovered from a whole blood donation or apheresis collection ▪ Contains all coagulation factors	250–334 mL	10–15 mL/kg	3–4
Platelets: pooled	▪ A pool of platelets derived from the buffy coat of four whole blood donations ▪ Leucodepleted	>160 mL	1 bag	1
Platelets: apheresis	▪ A suspension of platelets prepared from a single apheresis donor ▪ Leucodepleted	100–400 mL	1 bag	1
Cryo-precipitate	▪ Prepared from a single donated whole blood unit ▪ Contains an average of > 0.35 g/bag ▪ Contains high levels of fibrinogen, factor VIII, von Willebrand factor, factor XIII, fibronectin	30–40 mL	3–4 g fibrinogen	8–10
Cryo-precipitate: apheresis	▪ Prepared from FFP obtained from a plasmapheresis donor ▪ Contains an average of > 0.8 g/bag	60 mL (± 10%)	3–4 g fibrinogen	4–5

FFP, fresh frozen plasma
[a] Actual volume indicated on label

Blood product ratios

Four Level III studies examined the effect of FFP or platelet transfusion on mortality or morbidity.[5,61,75,95] An RBC:FFP ratio of ≤ 2:1 was reported to be associated with reduced mortality.[61,75] However, this outcome is potentially confounded by survivor bias. No studies investigated the use of fibrinogen or cryoprecipitate as an intervention.

Evidence statement	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
In trauma patients with critical bleeding requiring massive transfusion, an RBC:FFP ratio of ≤ 2:1 is associated with reduced mortality.[61,75] (See evidence matrix 10 in Appendix E.)	X	✓✓	✓	✓	✓

FFP, fresh frozen plasma; RBC, red blood cell
✓✓✓ = A ✓✓ = B ✓ = C X = D (See table 2.2)

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

J Trauma 2008;64:S79-85

Scenario of trauma may not translate to MOH

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EVIDENCE STATEMENTS – combination or fixed ratio therapy (bleeding patients)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.17	In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (FFP, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on transfusion requirements is uncertain. (See evidence matrix D3.D in Volume 2 of the technical report)	**X**	**NA**	**NA**	✓✓	✓✓
ES3.18	In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (FFP, plasma, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D3.E in Volume 2 of the technical report)	**X**	**NA**	**X**	✓✓	✓✓

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 B.2 Transfusion risks in perspective

Transfusion risk	Estimated rate [a] (highest to lowest risk)	Calman rating [b]
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Haemolytic reactions	Delayed: 1 in 4,000–9,000 Acute: 1 in 12,000–77,000	Low Very low
Anaphylaxis (IgA deficiency)	1 in 20,000–50,000	Very low
Bacterial sepsis: platelets	1 in 75,000	Very low
Bacterial sepsis: RBCs	1 in 500,000	Minimal
Transfusion-related acute lung injury	1 in 5,000–190,000	Low to minimal
Hepatitis B	1 in 739,000	Minimal
HIV	1 in 5.4 million	Negligible
Hepatitis C	1 in 2.7 million	Negligible
Malaria	1 in 4.9 million – 10.2 million	Negligible
Variant CJD (not tested)	Never reported in Australia	Negligible
Transfusion-associated graft-versus-host disease	Rare	Negligible
Transfusion-related immunomodulation	Not quantified	Unknown

CJD, Creutzfeldt-Jakob disease; IgA, immunoglobulin A; RBC, red blood cell
[a] Risk per unit transfused unless otherwise specified
[b] See Calman 1996 [99]

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

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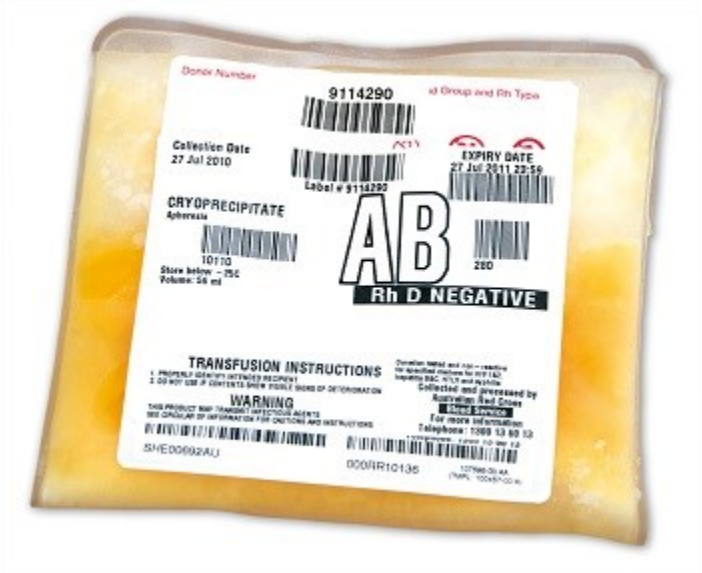
Cryoprecipitate

- 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 ☹



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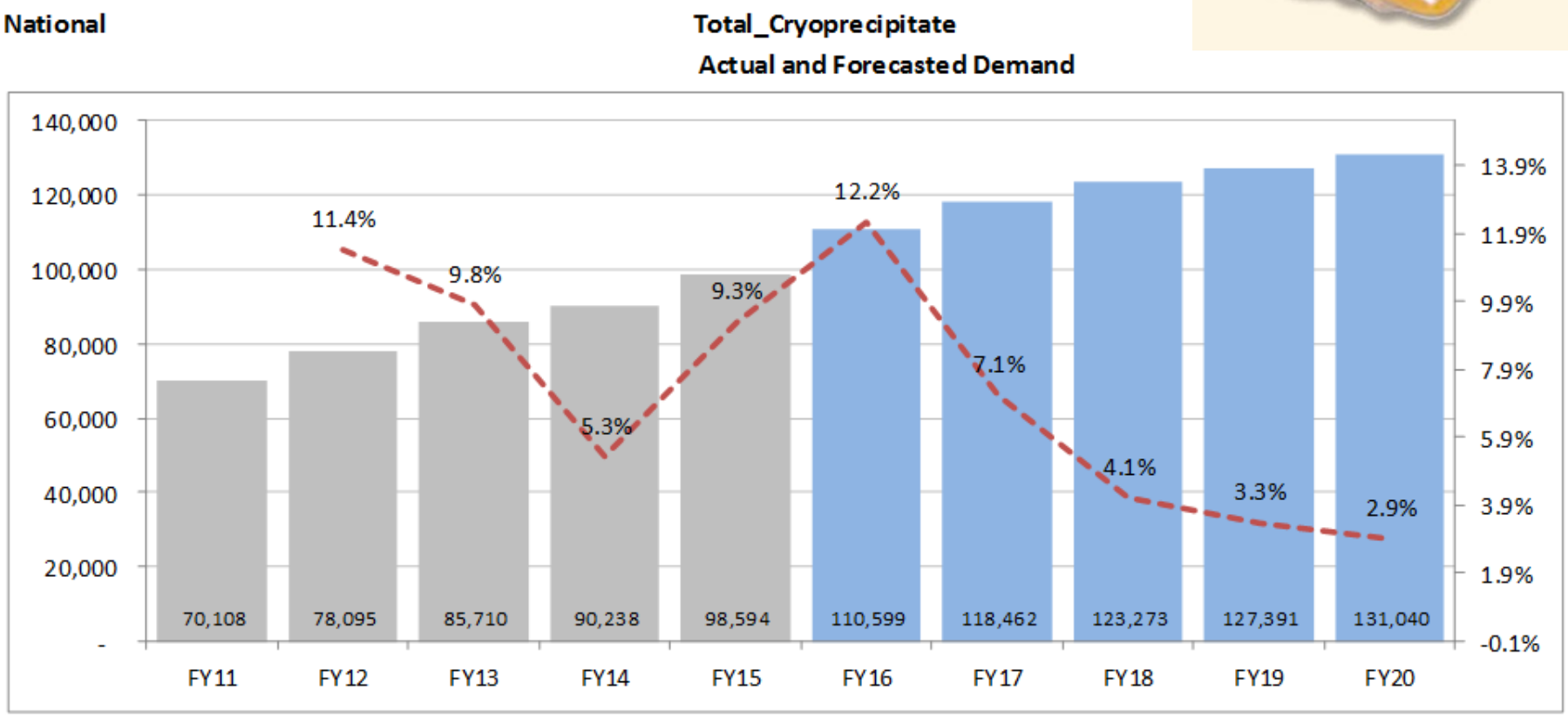
Cryoprecipitate demand



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Product	Description	$ MC on Label (2015/16)	*NEW* $ MC on Label (2016/17)
1b	Whole Blood - Leucodepleted	N/A	**N/A**
2b	WB Red Cell - Leucodepleted	$374.72	**$401.94**
2d	WB Paediatric Red Cell - Leucodepleted (Set of 4)	$96.92	**$105.17**
2f	WB Washed Red Cell - Leucodepleted	$422.69	**$405.90**
2g	Apheresis Red Cell - Leucodepleted	N/A	**N/A**
3b	WB Platelet Pool - Leucodepleted	$387.01	**$277.88**
3d	Apheresis Platelet - Leucodepleted	$541.70	**$619.31**
3e	Paediatric Apheresis Platelet - Leucodepleted (Set of 4)	$133.85	**$199.39**
4b	WB Clinical FFP - Buffy Coat Poor	$304.22	**$176.12**
4c	Paediatric WB Clinical FFP (Set of 4)	$88.49	**$52.14**
4d	Apheresis Clinical FFP	$340.76	**$262.48**
5a	WB Cryoprecipitate	$177.15	**$155.09**
5b	Apheresis Cryoprecipitate	$314.25	**$325.58**
6a	WB Cryo-depleted Plasma	$55.62	**$139.86**
6b	Apheresis Cryo-depleted Plasma	$159.03	**$320.25**

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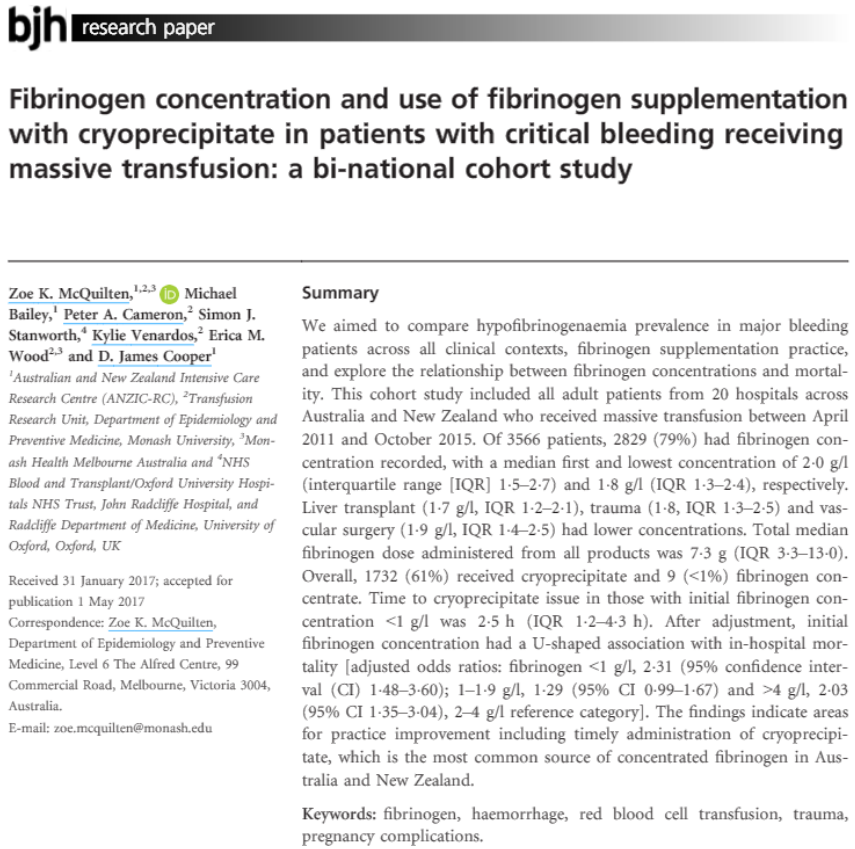

bjh research paper

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 hypofibrinogenaemia 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 3566 patients, 2829 (79%) had fibrinogen concentration recorded, with a median first and lowest concentration of 2·0 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, 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 3·3–13·0). Overall, 1732 (61%) received cryoprecipitate and 9 (<1%) fibrinogen concentrate. Time to cryoprecipitate issue in those with initial fibrinogen concentration <1 g/l was 2·5 h (IQR 1·2–4·3 h). After adjustment, initial fibrinogen concentration had a U-shaped association with in-hospital mortality [adjusted odds ratios: fibrinogen <1 g/l, 2·31 (95% confidence interval (CI) 1·48–3·60); 1–1·9 g/l, 1·29 (95% CI 0·99–1·67) and >4 g/l, 2·03 (95% CI 1·35–3·04), 2–4 g/l reference category]. 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

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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

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Table 1 Comparison of attributes of FFP, cryoprecipitate and fibrinogen concentrate

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

TRALI, transfusion-related lung injury.

J Thromb Haemost 2011; 9: 1–5.

FibUpFront trial

- **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 additional 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

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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

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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)[6] and variable effect on morbidity (Grade C).6

(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

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
RECOMBINANT ACTIVATED FACTOR VII		
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*[2] NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances.	3.5.4
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

Journal of Thrombosis and Haemostasis, **13**: 520–529 DOI: 10.1111/jth.12844

ORIGINAL ARTICLE

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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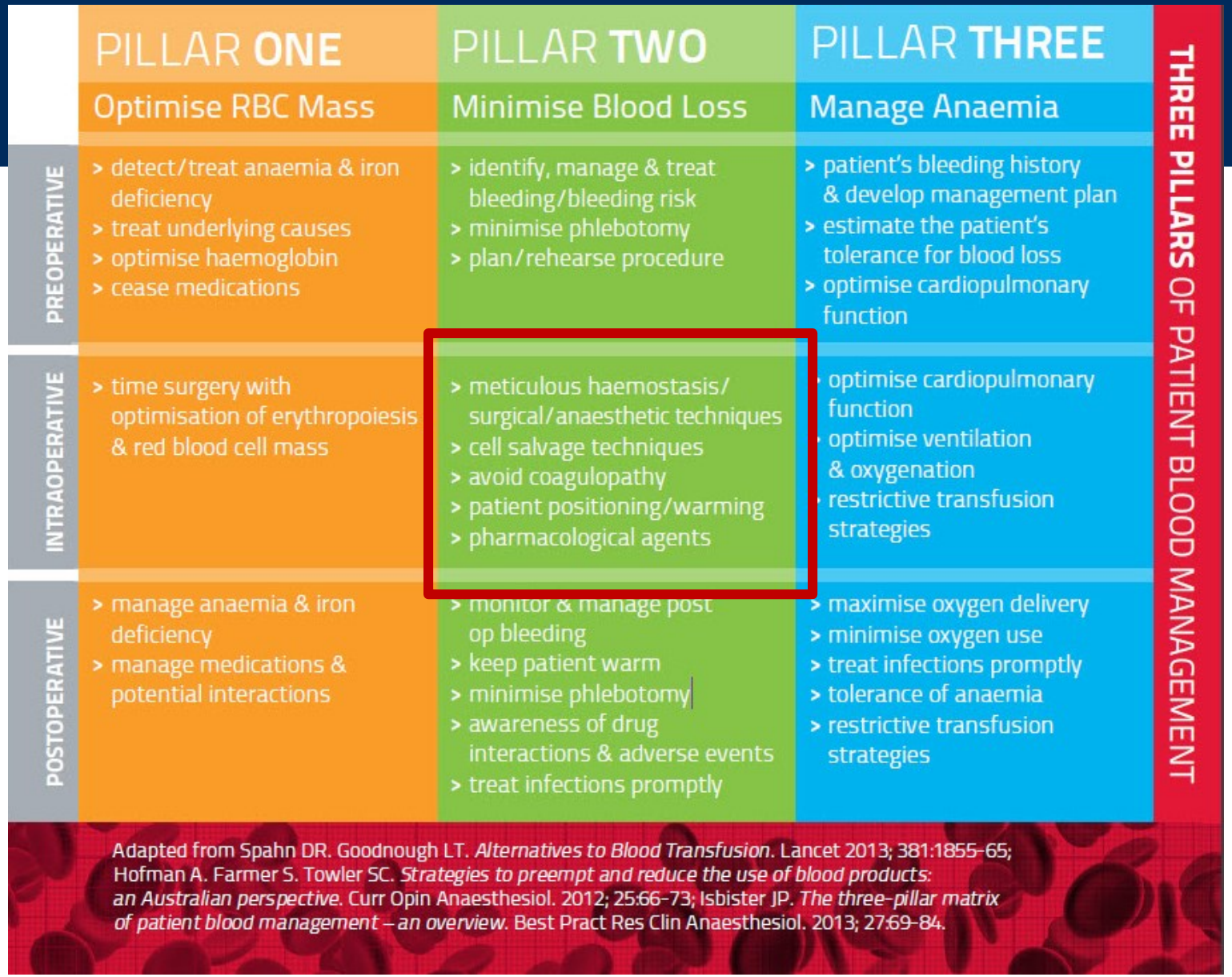
rVIIa in PPH

- 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)



Adapted from Spahn DR. Goodnough LT. *Alternatives to Blood Transfusion*. Lancet 2013; 381:1855-65; Hofman A. Farmer S. Towler SC. *Strategies to preempt and reduce the use of blood products: an Australian perspective*. Curr Opin Anaesthesiol. 2012; 25:66-73; Isbister JP. *The three-pillar matrix of patient blood management – an overview*. Best Pract Res Clin Anaesthesiol. 2013; 27:69-84.

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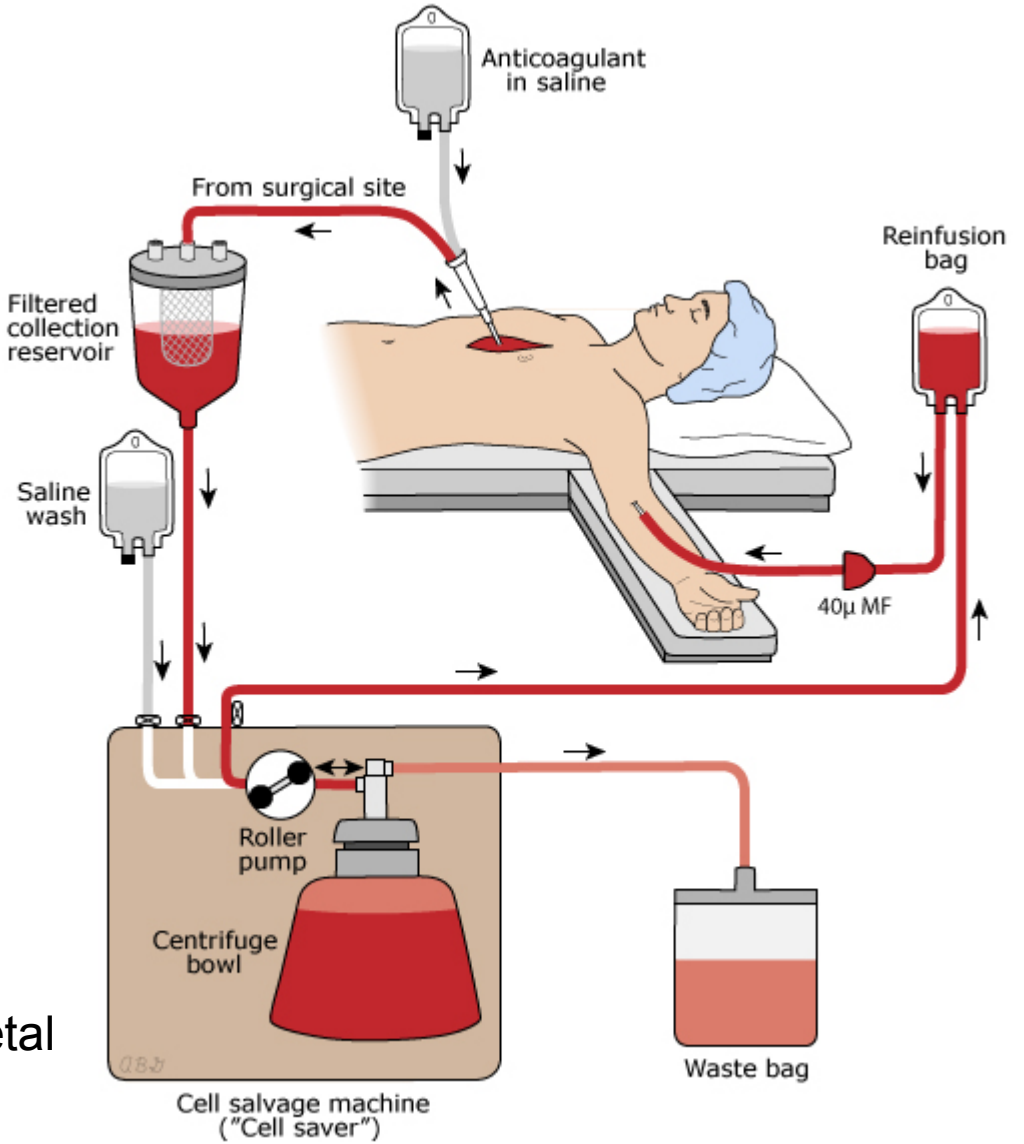
Cell salvage



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

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

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CELL SALVAGE		
PP23	In maternity patients, cell salvage should be considered if anticipated blood volume loss is likely to result in transfusion.[a] [a] In accordance with *Guidance for the provision of intraoperative cell salvage.*[10]	3.5.2
PP24	In maternity patients who are at increased risk of bleeding and in whom transfusion is not an option, cell salvage should be considered.	3.5.2
PP25	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.	3.5.2

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

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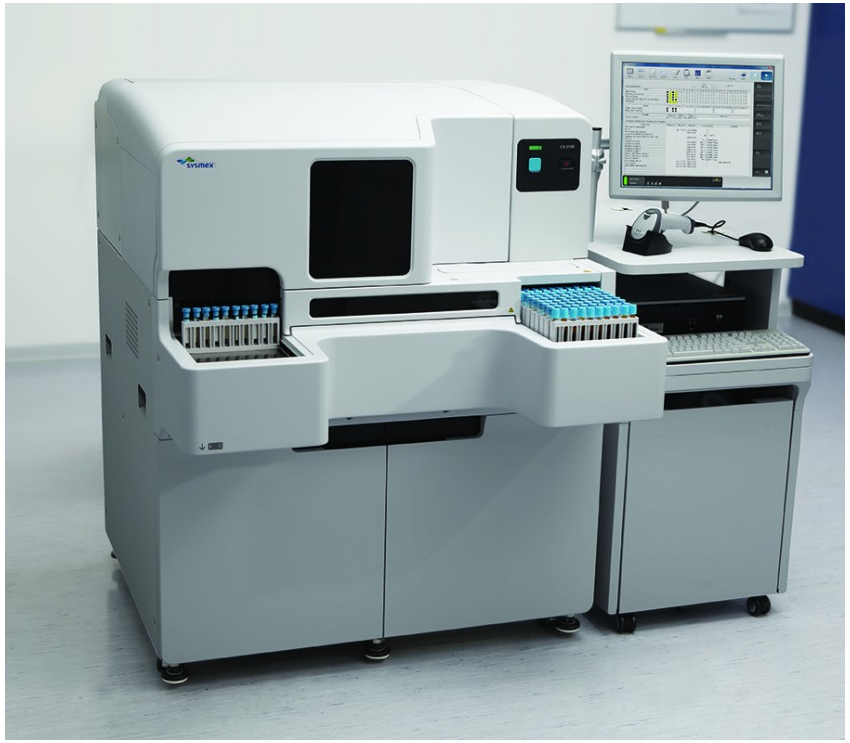
Coagulation Profile Analysis



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

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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

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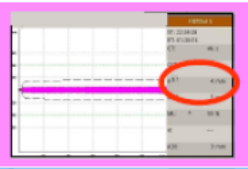
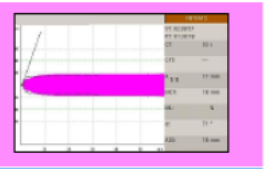
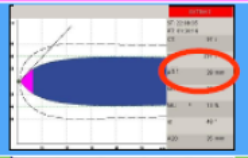
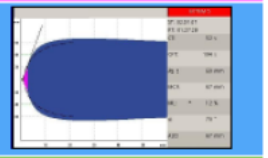
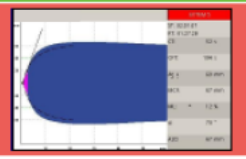
* Note this algorithm assumes patients have already received TXA – thus fibrinolysis is now 4th

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.

	ABNORMAL ROTEM	CRITERIA	DIAGNOSIS	INTERVENTION	CORRECTED ROTEM
FIBRINOGEN		**FIBTEM A5≤10mm**	**Low fibrinogen**	**Cryoprecipitate OR Fibrinogen concentrate** (see dosing guide) **AND Tranexamic acid 1 g**	
PLATELETS		**EXTEM A5 ≤35mm** and FIBTEM A5 ≥10mm	**Low platelets**	**Platelets: 1 adult dose** (correlate with platelet count)	
		EXTEM A5 ≤25mm and FIBTEM A5 ≤10mm	**Low platelets** and **Low fibrinogen**	**Platelets and fibrinogen** (correlate with platelet count)	
FACTORS		**EXTEM CT 80-140s** and FIBTEM A5 ≤10mm	**Low fibrinogen**	Correct **fibrinogen** and reassess	
		EXTEM CT >140s and FIBTEM A5 ≤10mm	**Low fibrinogen and Low coagulation factors**	**FFP 1-2U + Fibrinogen as indicated** (Consider Prothrombinex-see below)	
FIBRINOLYSIS		Early Diagnosis **EXTEM A5≤35mm or FIBTEM CT >600s**	**High likelihood of excess fibrinolysis**	**Tranexamic acid 1g** Consider repeat dose if has lost over 1 blood volume since initial dose	
		Late Diagnosis **EXTEM or FIBTEM ML ≥5%**	**Excess fibrinolysis**		

Fibrinogen Dosing Guide

FIBTEM A5 Target: ≥12mm

FIBTEM A5	Increase required	Cryoprecipitate	Fibrinogen Concentrate
9-10mm	2-3 mm	1-2 doses	2g*
7-8mm	4-5 mm	1-2 doses	3g*
4-6mm	6-8 mm	2 doses	4g
<4mm	≥9mm	2 doses	5g

*Outside of currently approved guidelines, must be discussed with haematologist

Fibrinogen Concentrate

Guidelines For Use

- Consultant anaesthetist or haematologist approval required.
- Patients must be experiencing life threatening haemorrhage.
- Fibrinogen concentrate may be indicated instead of, or in addition to, cryoprecipitate if the FIBTEM A5 is 6mm or below, OR there is a high suspicion of coagulopathy in a life threatening haemorrhage.
- Use at higher FIBTEM values may be appropriate in patients refusing cryoprecipitate.

Administration

- Reconstitute 1g in 50ml warm sterile water (use prepared kit in fluid warmer).
- Swirl gently and do not shake (to avoid foaming).
- Administer each 1g via syringe driver over 2-4 mins if life-threatening haemorrhage or over 10 mins if not.

Cryoprecipitate

1. 1 dose is equivalent to 10 whole blood units or 5 apheresis units.
2. May be supplied as whole blood units or as apheresis units (or a combination) 1 apheresis unit = 2 whole blood units.
3. Availability time: generally available within 10 minutes of request being made

Prothrombinex

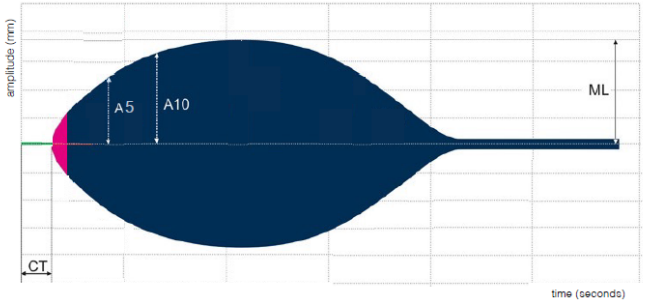
1. Haematologist approval required
2. Consider as an alternative to FFP for patients with coagulation factor deficiency (e.g. prolonged EXTEM CT see above) in the following circumstances:
   - Circulatory overload
   - Rapid correction in extreme coagulopathy

Endorsed by the Department of Anaesthesia and Pain Medicine and the Hospital Transfusion Committee on 31/05/2017

ROTEM

ROTEM INTERPRETATION

Key **ROTEM** derived variables (note this trace shows hyperfibrinolysis)



Normal **obstetric** values

Normal values (where available)	FIBTEM	EXTEM
CT Clotting Time		31-63 seconds
A5 Amplitude at 5 minutes	11-27mm	41-64mm
A10 Amplitude at 10 minutes	12-38mm	48-74mm
ML Maximum Lysis (within 60 mins)	<10%	<5%

FIBRINOGEN DOSING GUIDE

Replace fibrinogen as below to **target a FIBTEM A5 of ≥14mm** (obstetric target)

Targeted increase in FIBTEM A5	Fibrinogen amount required	Fibrinogen concentrate dose	Cryoprecipitate dose
2mm	12.5mg/kg	1g per 80kg	5U per 80kg
4mm	25mg/kg	2g per 80kg	10U per 80kg
6mm	37.5mg/kg	3g per 80kg	15U per 80kg
8mm	50mg/kg	4g per 80kg	20U per 80kg
10mm	62.5mg/kg	5g per 80kg	25U per 80kg

FIBRINOGEN CONCENTRATE GUIDELINES

1. Consultant anaesthetist approval required and patients must be experiencing critical bleeding.
2. Fibrinogen concentrate is indicated if the FIBTEM A5 ≤ 6mm or there is a high clinical suspicion of coagulopathy in a life-threatening haemorrhage.
3. Patients refusing cryoprecipitate may require supplementation at higher FIBTEM values.

version 1.11 updated 17/9/15

Endorsed by the Department of Anaesthesia and Pain Medicine and the Hospital Transfusion Committee on September 8th 2015

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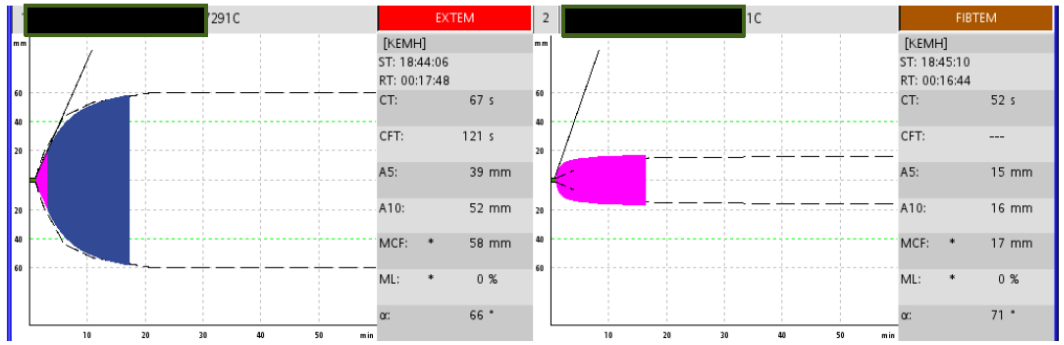
ROTEM

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).

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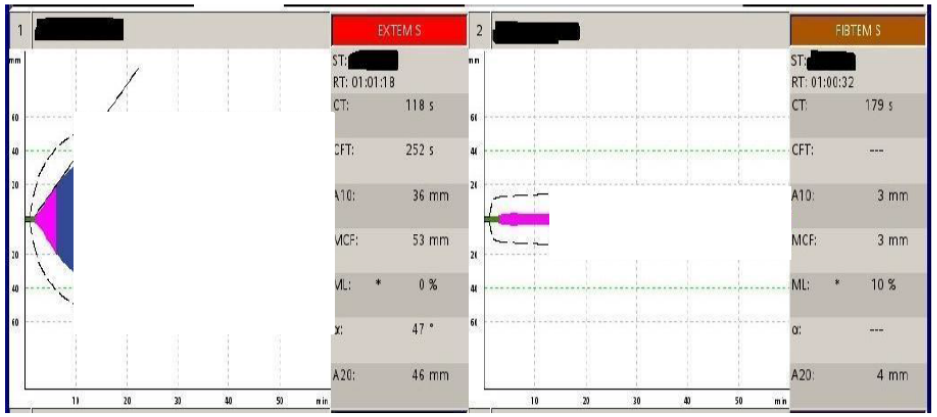
ROTEM

Applying the KEMH algorithm:

- Fibrinogen: Fibtem A5 – probably about 2mm – critical fibrinogen deficiency. Note traditional clauss fibrinogen conc 1.4g/L misleading. Aim for fibtem 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).



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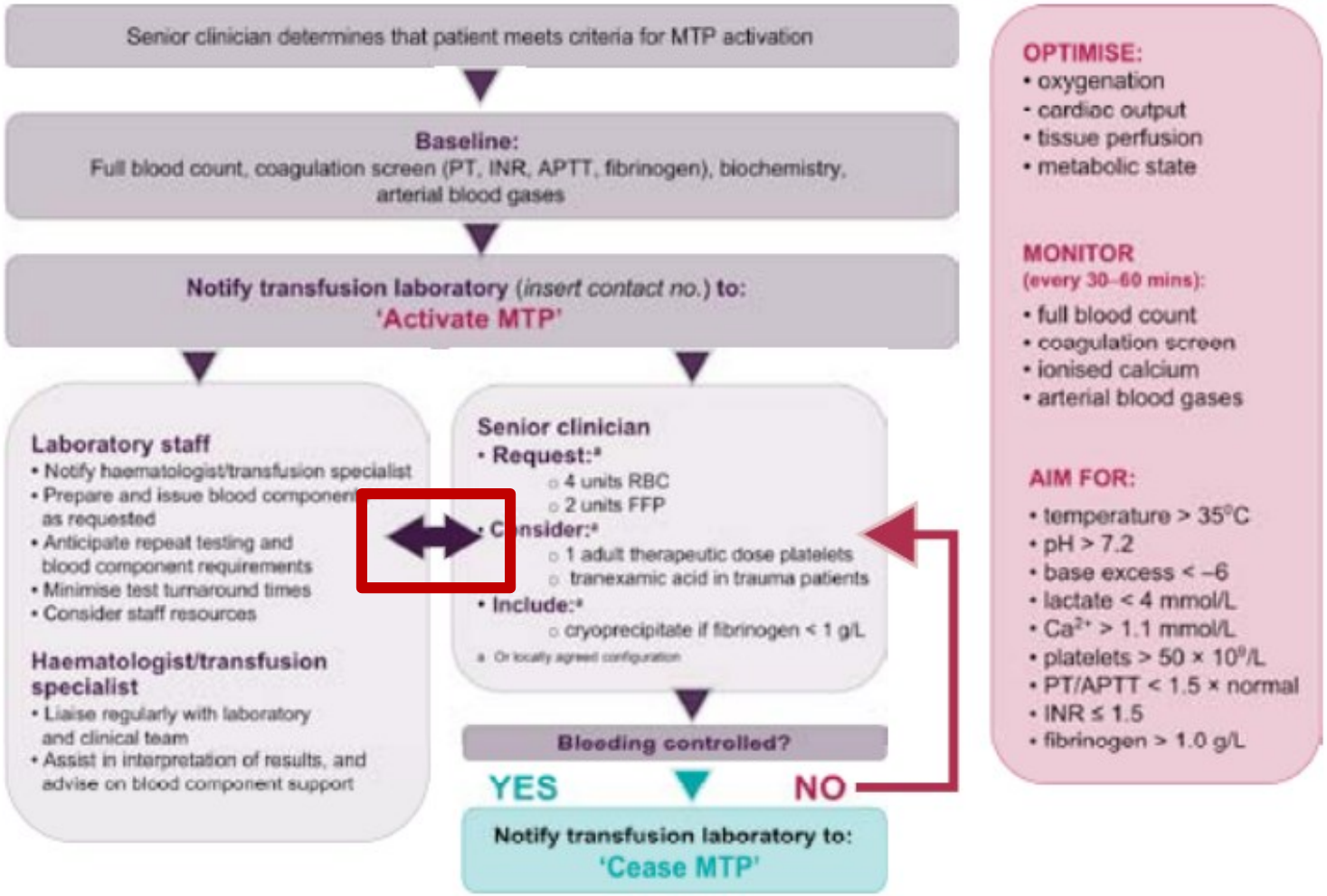
Massive transfusion protocol (MTP) template

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



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

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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)

Epworth Pathology

Blood Support Protocol
Epworth Freemasons Medical Centre, Victoria Parade

LIFE THREATENING

Blood required immediately
(no blood crossmatched)

Give onsite O NEG uncrossmatched blood

Notify Melbourne Pathology
9287 7715

Request replacement O NEG immediately

State LIFE THREATENING
Send EDTA sample to lab
Use LIFE THREATENING label

LIFE THREATENING

Additional O NEG uncrossmatched approx. 5-10 minutes
(plus courier time)

To request Haematologist assistance contact 9287 7715

URGENT

Blood required within 2 hours

Notify Melbourne Pathology
9287 7715

State URGENT
Send EDTA sample to lab
Use URGENT label

URGENT

ROUTINE

Blood required within next 12 hours

Send EDTA sample to lab

ACCESSING BLOOD PRODUCTS

PLATELETS
Notify Melbourne Pathology
9287 7715
Request anticipated time of arrival

FFP/ CRYOPRECIPITATE
Notify Melbourne Pathology
9287 7715
30-40 minutes thawing/ processing time

COLLOIDS

Gelofusine available in DPC theatre and delivery suite

AVAILABILITY OF GROUP COMPATIBLE CROSSMATCHED

No antibodies
10 minutes with existing group and hold
50 minutes with new specimen
(plus courier time)

With antibodies
2 hours minimum (dependent on availability of suitable blood)
(plus courier time)

LABELLING REQUIREMENTS

Blood banking standards require STRICT ADHERENCE to the labelling requirements below, as dictated by the Australian and New Zealand Society of Blood Transfusion (ANZSBT) and enforced by the National Association of Testing Authorities (NATA).

This includes blood group, antibody screen, group & hold and blood for crossmatching.

The sample tube MUST be labelled with:

1. Patient's family name (in full)
2. Patient's given name (in full)
3. UR number (hospital patients) and/or Date of Birth
4. Date and time of collection
5. Signature (or initials) of the collector

The request form and sample must match. Please do not use abbreviations or variations of the patient's name.

Samples that do not conform to these labelling requirements will not be processed.

Please note: These procedures also apply to addressograph labels. Addressograph labels must be signed by the collector and the date and time of collection written on the label.

Document Name:	Blood Support Specimen Protocol-MPW Vic Parade		
Document Location:	C:\Marketing and Communications\Blood Support Specimen Protocol (MPW) Freemasons Medical Centre\Blood Support Specimen Protocol-EPW Vic Parade		
Document Number:	XXXXXXX	Version:	29 Aug 2017
Authorised:	Michael Charman	Pages:	1 of 2

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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

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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

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