Plasma
Prothrombin Complex Concentrate
Cryoprecipitate
Fibrinogen concentrate

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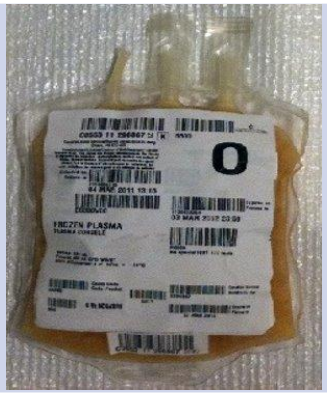
Disclosures

- No relevant financial conflicts of interest
- Acknowledgement – These slides were originally developed by Dr. Callum and have been updated for dissemination this year

Scope

- Interpretation of basic laboratory test values – INR, aPTT, fibrinogen
- Evidence for plasma, PCC, cryoprecipitate and fibrinogen concentrate use
- Limitations of current evidence
- Practical advice to think through real world challenges

- Massive hemorrhage protocols will be covered on day 5

Product	Key Details
Plasma (FP)  	Composed of 90% water, rich in proteins such as coagulation factors, albumin, immunoglobulins ADULT DOSE: 15 mL/kg = 3-5 U PEDIATRIC DOSE: 15 mL/kg
Prothrombin Complex Concentrates (PCC) 	Lyophilized and virally inactivated concentrate of the vitamin K dependent factors (2, 7, 9, 10) ADULT DOSE: 1000 IU-3000 IU dosed by INR (or weight) PEDIATRIC DOSE: 25 IU/kg
Cryoprecipitate and Fibrinogen concentrate   	Fibrinogen concentrate is a lyophilized, virally inactivate concentrate ADULT DOSE: 4g = 4 vials of 1 gram over 5-10 minutes PEDIATRIC DOSE: 50 mg/kg Cryoprecipitate is made from plasma units Thawed in fridge, centrifuged, “supernatant” removed, and refrozen (1 U = 10 mL) Needs to be pooled with sterile technique for use ADULT DOSE: 10 U; PEDIATRIC: 1 U/10 kg to max 10U

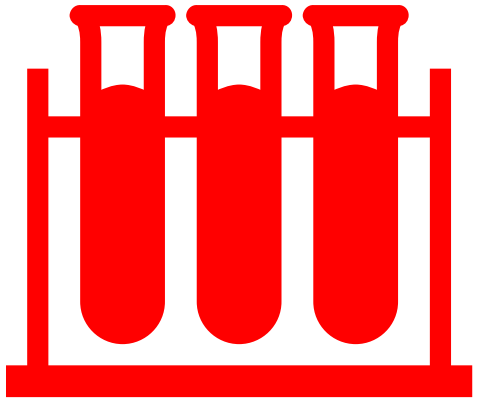
PT/INR and aPTT

Laboratory “coagulation” testing does not…

1. Rule-out bleeding disorder
2. Inform us about bleeding risk

- INR validated for warfarin monitoring
- aPTT can detect Factor VIII (8) <30%, unfractionated heparin & argatroban monitoring

- INR ↑ most commonly from liver disease which is a hypercoagulable state
- aPTT ↑ most common reasons are Lupus anticoagulant and Low Factor XII (12), which are both non-bleeding states



Send laboratory testing in select patients

- Procedures are moderate to high-risk for bleeding or >10% chance of transfusion
- Family history of bleeding
- Personal history of a bleeding tendency systematically assessed
  - As determined by screening with a validated Bleeding assessment tool (BAT)
  - HAS-BLED score >3 or other factors
- Medication monitoring (Warfarin, unfractionated heparin, argatroban)

Plasma

What are the indications for plasma use?

Moderate to severe bleeding

To prevent peri-procedural bleeding in patients with acquired factor deficiency*

Warfarin reversal ONLY if PCC unavailable

Factor replacement if factor concentrate unavailable

Plasmapheresis for Thrombotic thrombocytopenic purpura (TTP)

**** Procedures with high risk of bleeding if*** *INR >1.8 (no liver disease) or >2.5 in those with liver disease*

Transfusion. 2010;50(6):1227-1239
J Vasc interv Radiol 2019; 30:1155-1167

Plasma is NOT indicated in…

- Non-bleeding patients with elevated INR with no planned procedures
- Warfarin reversal if PCC can be used
- Mild bleeding
- Factor replacement when factor concentrates are available

Most plasma transfused is unnecessary

Study	Country	Number of infusions	Patient type	Percent unnecessary
ORBCON electronic audit 2017 (manuscript in review)	Canada	11490	All patients	71% under-dosed 35% inappropriate indication
ORBCON audit (report) audit 2015	Canada	329	All patients	52%
Shih et al Vox Sang 2015	Canada	111	ICU	45%
Tinmouth et al Transfusion 2013	Canada	559	All patients	29%
Stanworth et al. Crit Care 2011	UK	366	ICU	43%*
Stanworth et al Transfusion 2011	UK	3648	All patients (included kids)	58%*
Palo et al. Transfusion 2006	Finland	11590	All patients	66%*

*estimated from tables and texts

Ontario, Canada Plasma use “Failures”

Scenario	% of Plasma used in the Province
Normal INR/PTT	23%
Reversal of warfarin (bleed/procedure)	12%
Reversal of warfarin (no bleed/procedure)	2%
Reversal of other high INR (no bleed/procedure)	6%
Heparin reversal	6%
Direct Oral Anticoagulant reversal	3%

52%

Plasma can be harmful

- TACO and TRALI are the leading causes of transfusion associated mortality
- Plasma has higher risk of both TACO and TRALI compared to other blood products[1]
  - TRALI risk is 7x higher with plasma, compared to RBCs
  - TACO risk is higher with plasma
- Plasma use associated with:
  - higher risk of ventilator-associated pneumonia in critically ill patients[2]
  - higher risk of bleeding in pre-operative patients undergoing non-CV surgery and INR $\geq$ 1.5[3]

1. Transfusion. 2009;49(3):440-52.
2. Crit Care Med. 2008;36(4):1114-8.
3. Lancet Haematol. 2016;3(3):e139-48.

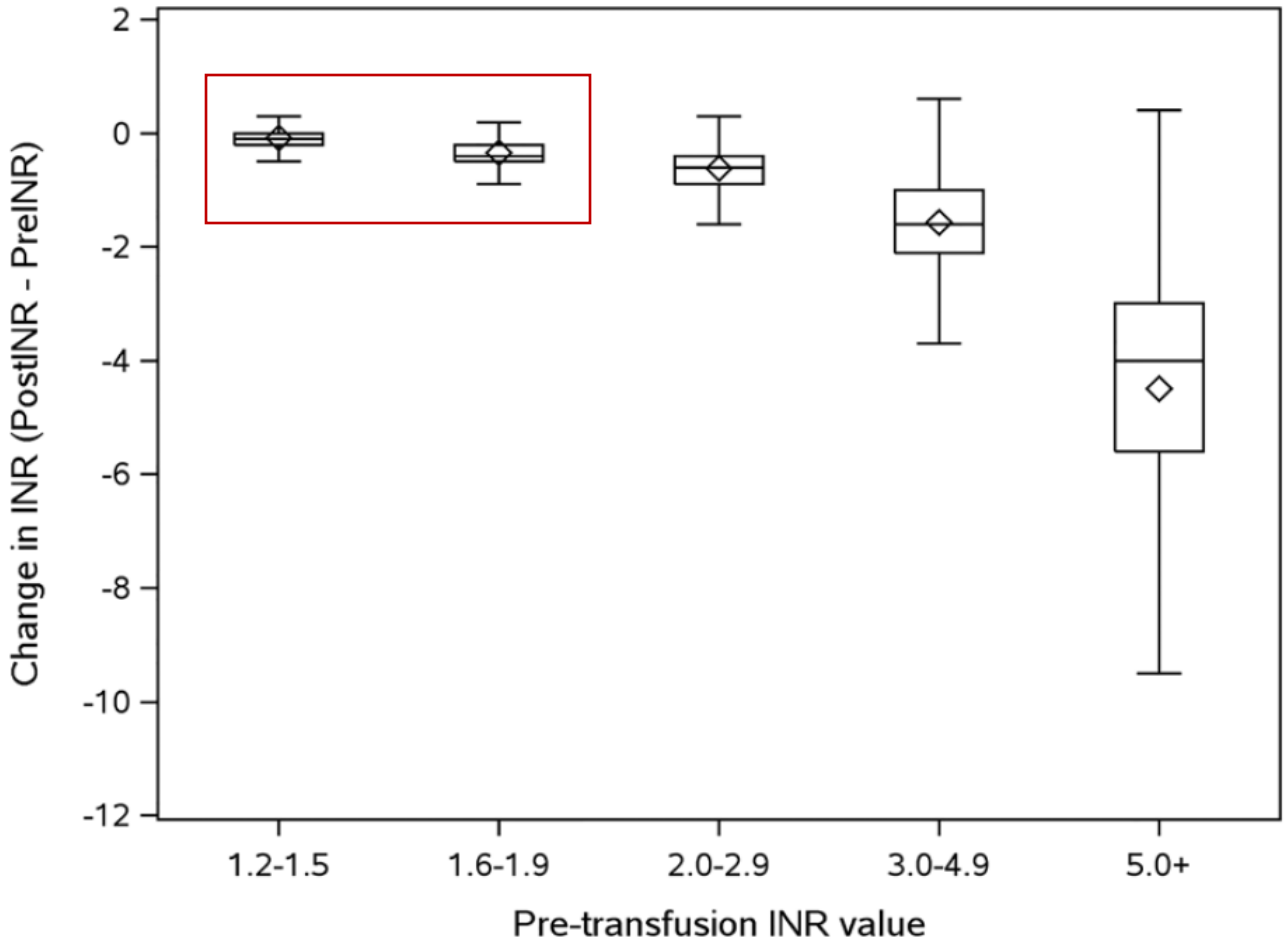
Plasma dose

- Plasma standard dose is 15 mL/kg
  - For a 70 kg individual it is 4 units
  - Decided based on laboratory testing showing increase in factor levels rather than clinical outcomes
- Ideally, factor levels >30% required for reversing coagulopathy
  - 1 in 5 patients with low factors have an increase to >30% [1]
  - strongest effect if INR is >2, minimal change if INR is <1.7[3]
- Decrease in bleeding risk with prophylactic plasma use for elevated INR has not been established[4]

1. Transfusion. 2010;50(6):1227-39
2. Br J Haematol. 2004;125(1): 69-73
3. Am J Clin Pathol. 2006;126(1):133-9
4. Transfus Apher Sci. 2012;46(3):293-8

High INR Procedure/Bleed

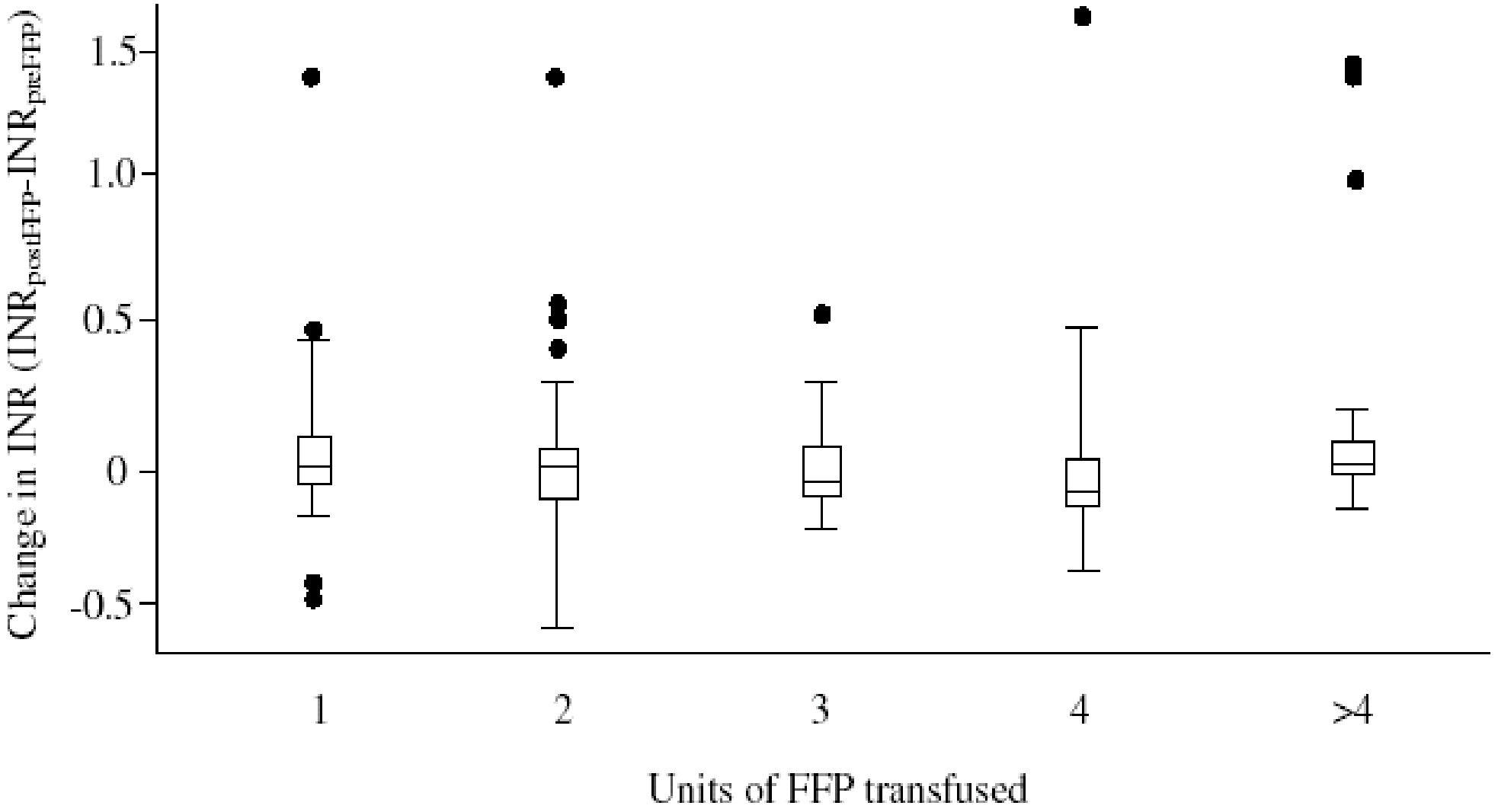
4 units of FFP



N=6779 patients

Warner MA, et al. A & A 2018

Effect of plasma on patients with INR 1.3 to 1.8



Abdel-Wahab OI, et al. Transfusion 2006; 46: 1279-85

Chronic liver disease and coagulopathy

- Re-balanced coagulation seen
  - 50 patients with acute liver injury, mean INR 3.4
  - Endogenous thrombin potential preserved due to decreased protein C
  - Clot lysis had not occurred by 3 hours in 74% of the liver patient samples
  - These patients are in a **pro-thrombotic** state, hence caution when giving FP
- Vascular dilation with nutritional deficiencies leads to more friable tissues
- Thrombocytopenia: platelet function better than the number
- Fibrinolysis: hyperfibrinolysis in severe liver disease

Lisman , J Thromb Haemost 2012; 20: 1312-9.

CSTM SCMT
Canadian Society for Transfusion Medicine
Société canadienne de médecine transfusionnelle

Choosing Wisely Canada™

Don’t transfuse plasma to correct mildly elevated INRs (<1.8) or PTT before a procedure

British Society for Haematology
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The impact of commonly used doses of plasma to correct clotting results, or to reduce the bleeding risk, is very limited particularly when the INR is 1.5–1.9 (Recommendation: 2C)

Liver biopsy and “laboratory coagulation testing”

- Ewe K. Dig Dis Sci 1981;26:388-93.
  - 200 patients undergoing liver biopsy observed
  - No correlation of liver bleeding time and laboratory test results
  - Even patients with INR>3 and platelets <50 x 10^9/L did not bleed more than patients with ‘better’ test results
- Piccinino F et al J of Hepatology 1986; 2: 165-73.
  - A very large series of 68,276 percutaneous biopsies published in 1986 found that major bleeding occurred in only 42 patients.
    - i.e. 1 in 1626 patients
  - no correlation between PT/INR or PLT and bleeding

Random distribution

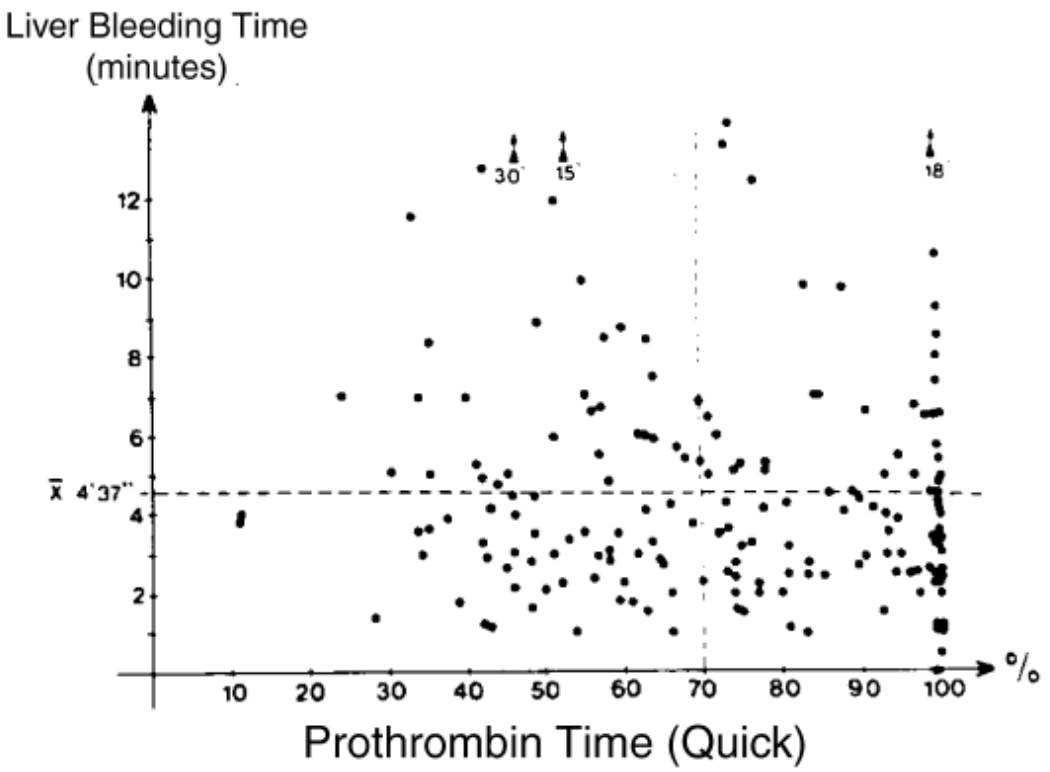

Figure 1-5. Lack of relationship between the liver bleeding time and the preprocedure PT. The time that the liver was directly observed to bleed after biopsy is plotted as a function of the percentage of activity of the PT. Use with permission from Ewe et al.[70]

Ewe K. Dig Dis Sci 1981;26:388-93.

Paracentesis and coagulopathy

- Grabau CM, et al. Hepatology. 2004;40:484-8.
  - 1,100 large volume paracenteses
  - N = 628 pts, 513 had chronic liver disease
  - All procedures were performed without ultrasound guidance and without the transfusion of platelets or plasma
  - The lowest platelet count was 19 x 10^9/L (IQR 42-56) and the highest INR was 8.7 (IQR 1.4-2.2)
  - No significant bleeding in any patient

Grabau CM, et al. Hepatology. 2004;40:484-8.

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Guidelines

- We endorse the liver society recommendations that prophylactic transfusion of FFP and cryoprecipitate is not given in low bleeding risk procedures, such as paracentesis (1C).
- There is no good evidence to support a role for prophylactic FFP to reduce the risk of bleeding from percutaneous liver biopsy. An alternative procedure with a lower bleeding risk, (e.g. transjugular liver biopsy), should be considered instead (2C).

British Journal of Haematology, 2018, **181**, 54–67

CAIR endorsed SIR Guidelines 2019

STANDARDS OF PRACTICE

Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions—Part II: Recommendations

Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe

Indravadan J. Patel, MD, Shiraz Rahim, MD, Jon C. Davidson, MD, Sue E. Hanks, MD, Alda L. Tam, MD, T. Gregory Walker, MD, Luke R. Wilkins, MD, Ravi Sarode, MD, and Ido Weinberg, MD

Procedure related risk

Bleeding risk	Low (<1%)	Moderate to Severe
Vascular procedures	Central line removal Dialysis access IVC filter placement PICC placement Transjugular liver biopsy Subcutaneous port placement Tunneled drainage catheter Venography Venous catheter	Ablation Arterial interventions (sheath >7 Fr) Catheter directed thrombolysis Chemoembolization Complex venous interventions CNS and Spine procedures incl epidural Radioembolization Tunneled venous catheter Urinary tract interventions Uterine fibroid embolization
Non-vascular procedures	Arthrocentesis + joint injection Catheter exchange **Dental extraction (up to 2)** Endoscopy without biopsy Lumbar puncture Pacemaker insertion Paracentesis Peripheral nerve block Superficial aspiration, drainage, skin biopsy Thoracentesis Thyroid biopsy	Ablation Biliary interventions Bone marrow biopsy Complex dental procedures Deep abscess drainage Solid organ biopsy Endoscopy with biopsy Gastrostomy/gastrojejunostomy placement Lymph node biopsy Percutaneous enteric tube (new tract) Spinal procedures

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No routine PT/INR, CBC
INR correct to ≤2.0 – 3.0
PLT transfuse if < 20 x 10^9/L

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Recommended PT/INR, CBC
INR correct to ≤1.5 -1.8
PLT transfuse if < 50 x 10^9/L

Laboratory testing targets

Parameter	Individuals WITHOUT chronic liver disease		Individuals WITH liver disease	
	Low Risk	**High Risk**	**Low Risk**	**High Risk**
INR	Not routinely recommended If on Warfarin, ensure within therapeutic range	< 1.8	N/A	<2.5
PTT (s)	Not recommended	Not recommended	Not recommended	Not recommended
Platelet count ($x10^9$/L)	If checked, transfuse if <20	Transfuse if <50, <70 for neuraxial anesthesia	>20 >30 for liver biopsy	>30
Fibrinogen (g/L)	Not recommended	Not recommended	>1	>1

Prothrombin Complex Concentrate (PCC)

Case

- 83-year-old found with a GCS of 12 at the bottom of the stairs
- Large scalp laceration with substantial blood loss
- Patient on warfarin for atrial fibrillation
- You send a STAT INR – result not back yet!
- Patient in CT – large subdural that needs evacuation
- You have paged neurosurgery
- How do you reverse his warfarin STAT?

Emergency reversal

- Short-term plan (< 6 hours)
  - Prothrombin complex concentrates 1000-3000 IU depending on the INR
    - Lasts 6 hours
    - Contains factors II, VII, IX, and X (Pr C/S, heparin)
    - Only contraindication: HIT (only time you use plasma)
- Long-term plan (after 6 hours)
  - Intravenous vitamin K
    - Intravenous is faster than oral
    - Starts working in 6 hours (prevents rebound)

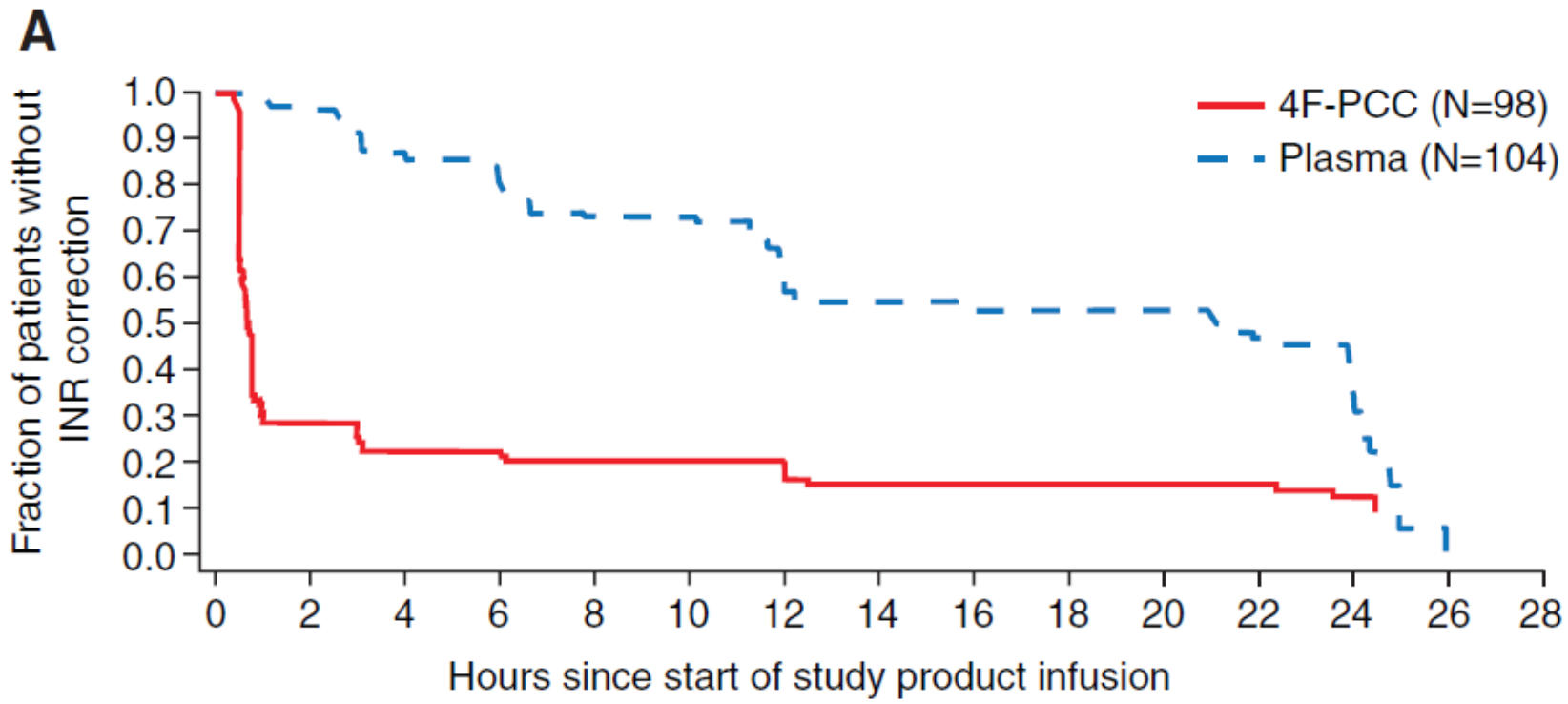
Indications for VKA/warfarin reversal with PCC

- Limb or life-threatening bleeding
  - Intracranial hemorrhage
  - Pericardial bleed
- Emergency surgical procedure within the next 6 hours
  - Traumatic rupture of a spleen, perforated viscous, ruptured aneurysm

Why PCC over Plasma

PCC	Plasma
Pooled, virally inactivated Prion reduction process	Not virally inactivated
Lyophilized Needs to be reconstituted	Needs ABO group (10 min) Needs to be thawed (30 min)
Volume 40 - 80mL Infused over 5 to 10 min (40mL/5min)	Volume 15 mL/kg (~1000 mL) Infused over hours
Lower risk of transfusion reactions	Higher risk of transfusion reactions: TRALI, TACO, anaphylaxis
Only lasts 6-8 hours	

PCC vs. Plasma



Use of PCC showed:

- Faster onset of action
- Lower mortality
- Lower risk of CHF
- Similar thrombosis rates

http://dx.doi.org/10.1160/TH16-04-0266
Thromb Haemost 2016; 116: 879–890

Circulation. 2013;128:1234-1243; originally published online August 9, 2013;

National Advisory Committee on Blood and Blood Products

Dosage: less than the manufacturer's recommended dose

Adult patients:
INR <3 -1000; INR 3-5 – 2000; INR >5 – 3000 IU
Can't wait for the INR – 2000 IU

Maximum total dose: 3000 IU Factor IX activity (adult patients)
Note: listed dose is 50 IU/kg = 3,750 IU for 75 kg patient

Administration: 1000 IU/5 mins; effect is instantaneous!

Weight-based dosing can also be used

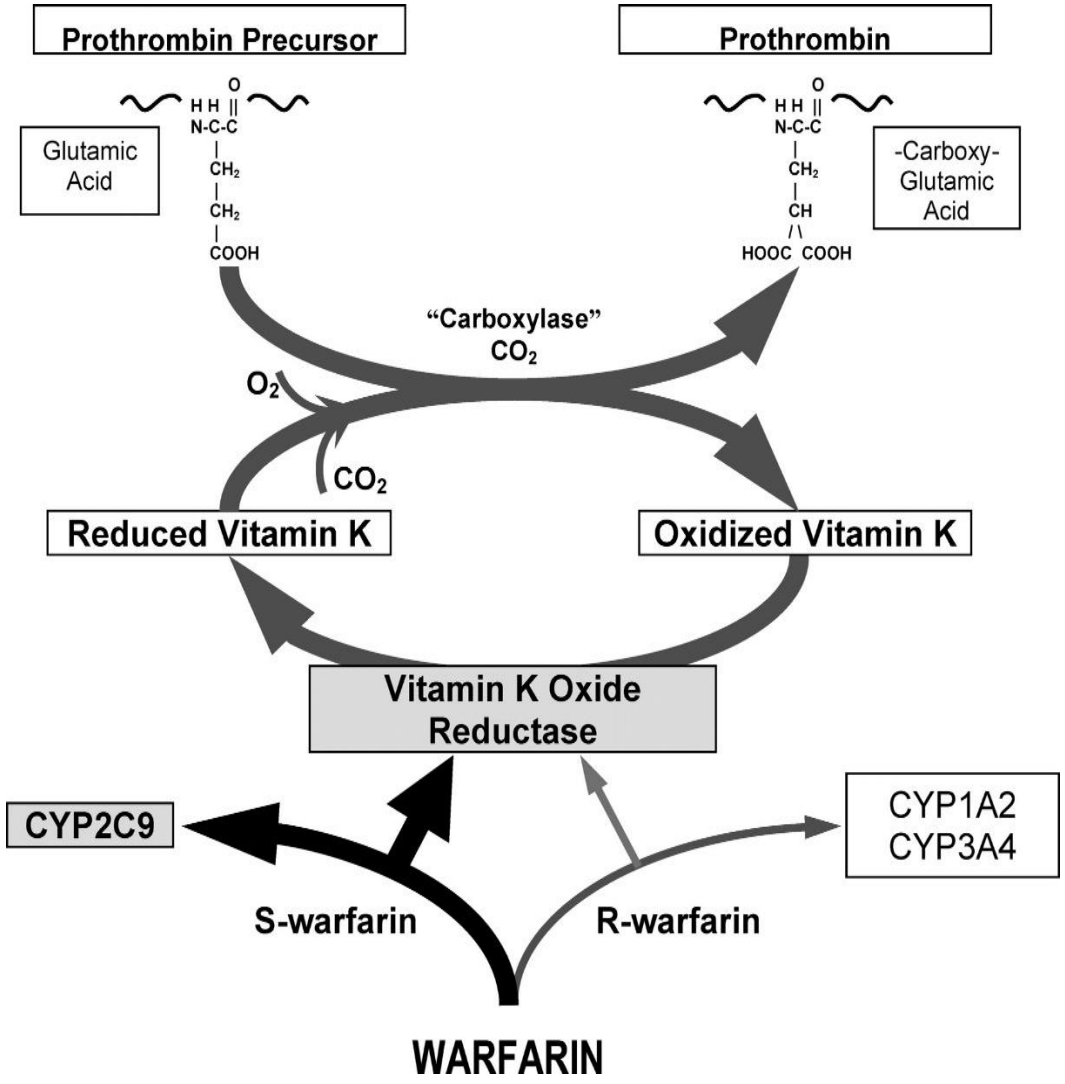
Table 1: Dose of PCC for reversal of anticoagulation

Weight	Dose of PCC
less than 60kg	1500 units
60-75kg	2000 units
76-90kg	2500 units
greater than 90kg	3000 units

Makris, et al. Bleeding guidelines for patients on anticoagulants. BJH 2012.

What about Vitamin K?

- Vitamin K works fast
  - The factors are already synthesized & just need a final conversion step
- Intravenous Vitamin K is safe
  - Historically contained castor oil which lead to increased anaphylaxis
  - Now anaphylaxis risk is 0.04-11/10,000 doses
- DO NOT use subcutaneously or intramuscularly in an emergency setting
- Intravenous formulation can also be given orally



Fiore et al. J Thromb Thrombolysis 2001; 11:175-83

3 situations where vitamin K should suffice

1. Asymptomatic high INRs
   - INR>8-10

   2 mg PO
2. Non-emergency surgery
   - Delay 6 hours

   10 mg IV
3. Non-critical bleeding
   - Epistaxis, dental bleeding etc.

   1 mg IV

1. Tran et al. Med J Austral 2013; 198: 198-9.
2. Holbrook et al. Chest 2012; 141: e152S-184S.
3. Keeling et al. Br J Haematol 2011; 154:311-24
4. Denas et al. J Thromb Thrombolysis 2009;27:340-7

What about DOACs and PCC?

American Journal of Hematology AJH

CRITICAL REVIEW | Free Access

Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum

Adam Cuker, Allison Burnett, Darren Triller, Mark Crowther, Jack Ansell, Elizabeth M. Van Cott, Diane Wirth, Scott Kaatz

First published: 27 March 2019 | https://doi.org/10.1002/ajh.25475 | Citations: 131

Specific reversal agents should be used when available:

- Dabigatran --> Idaracizumab
- Rivaroxaban & Apixaban --> Andexanet alfa (not available in Canada)

If specific agents are not available, 4 factor PCC may be used

- 2000U dose recommended
- Swedish study, N=84, hemostasis effective in 69%, stroke in 2% (Majeed A et al. Blood 2017)
- Canadian study, N=66, hemostasis good in 65% and moderate in 20%, VTE in 8% (Schulman S et al. Thromb Hemost 2018)

Fibrinogen Replacement

Case

- 38-year-old G3P2 immediately post-delivery develops vaginal bleeding
- The bleeding fails to respond to escalating doses of prostaglandins and 2 grams of tranexamic acid
- 4 ***uncrossmatched*** RBCs requested due to transient sBP response to fluid boluses
- Bakri balloon inserted into uterus and en route to OR for hysterectomy
- sBP better at 90, HR 98 after 4 RBCs and bleeding continues – you have ordered 4 more RBCs
- Lab tests pending including Fibrinogen level
- **Should you order/give 4 grams of fibrinogen or 10 units of cryoprecipitate even though no fibrinogen level available?**

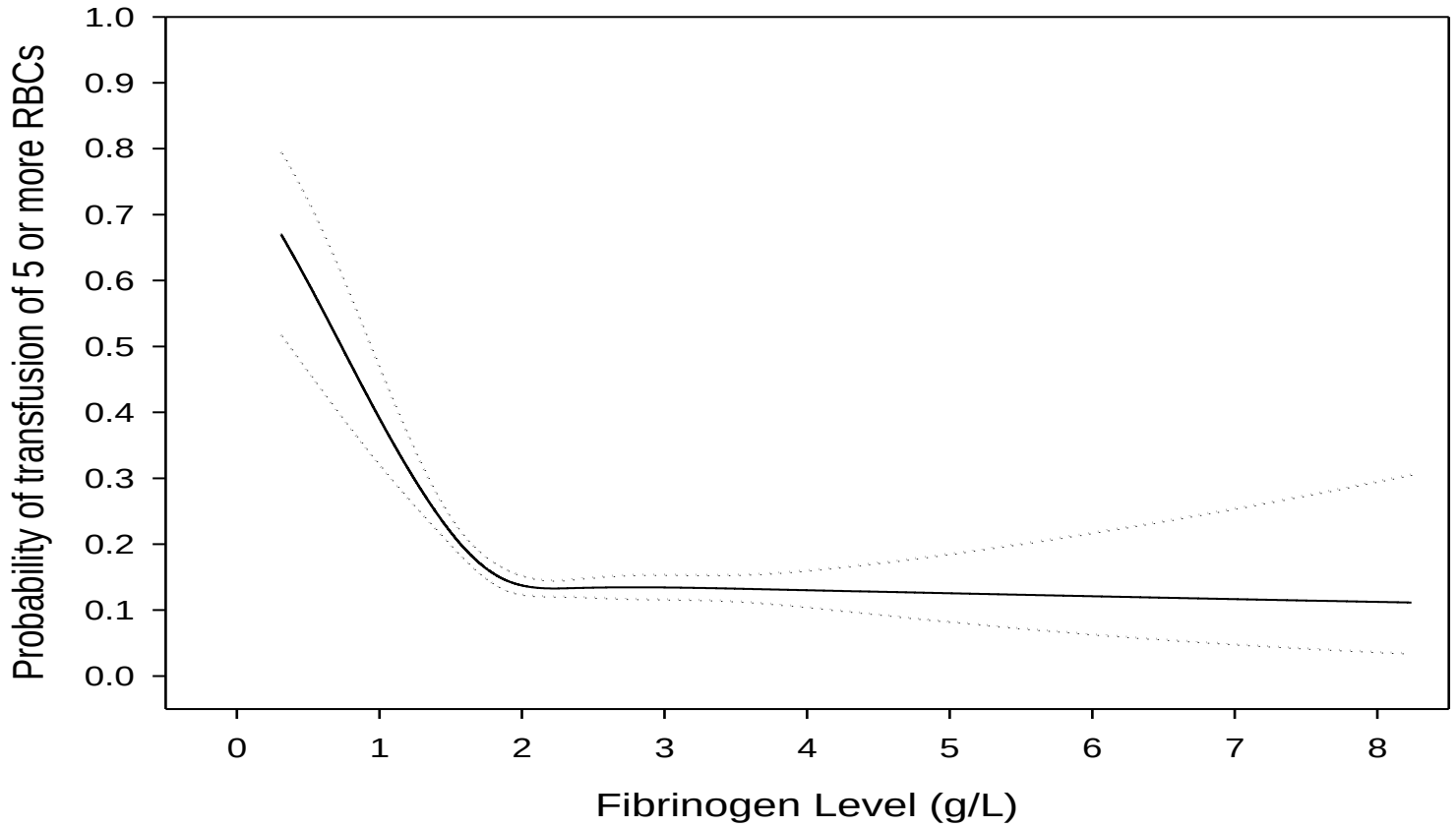
Cryoprecipitate and Fibrinogen Concentrates

- Dosage - 4 grams of fibrinogen (50 mg/kg in kids) or cryoprecipitate 1 unit/10 kg to a max of 10 units (paediatrics)
- The two products are hemostatically equivalent
- ***Measure fibrinogen frequently*** during active bleeding
  - **Call the coagulation lab and ask for it to be added to the INR if you forget**
  - **Transfuse if fibrinogen <1.5 - 2.0 g/L**
- Extreme hemorrhages…don't wait for results…just give it

Guidelines for the bleeding patient

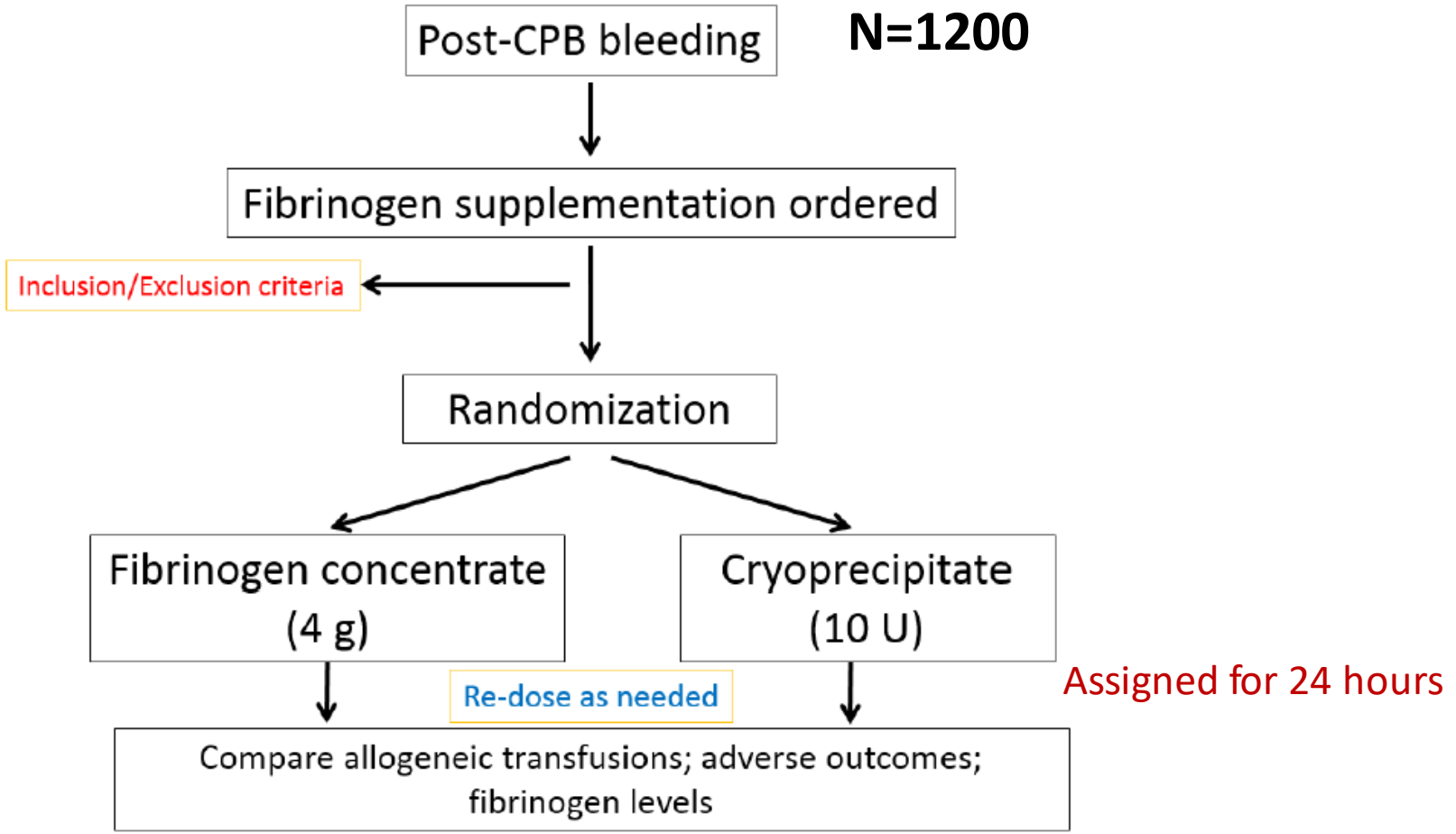
- Cryo or fibrinogen concentrate if fibrinogen <1.5-2.0 g/L
  - European trauma guidelines and European Anesth Guidelines - Rossaint et al. Crit Care 2016 Apr 12;20:100 (<1.5-2.0 /L)
  - British Committee for Standards in Haematology – Haematology management of massive hemorrhage 2015 (<1.5 g/L)

Fibrinogen <2 g/L coming off pump increases risk of excessive blood loss (5u or more) post cardiac surgery



Karkouti et al. Anesth Analg. 2013 May 17

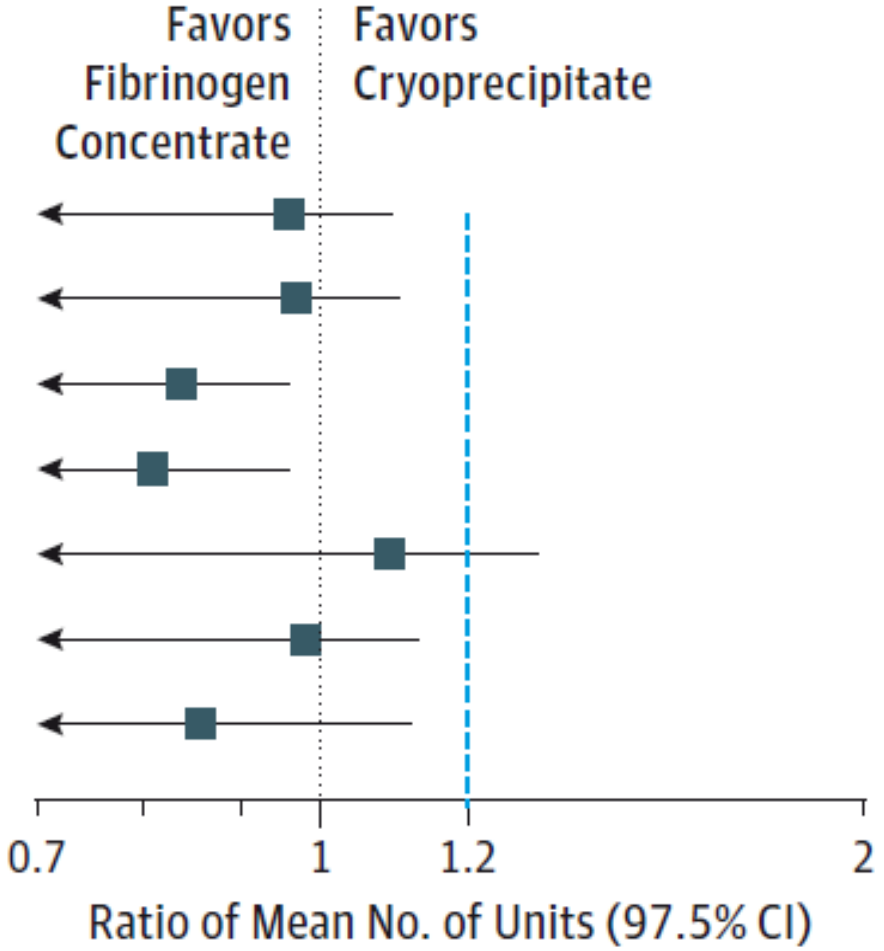
Design



Callum, Karkouti - JAMA. 2019;322(20):1966-1976.

Figure 2. Ratio of Mean Number of Allogeneic Blood Components Transfused in the 24 Hours After Cardiopulmonary Bypass for the Primary Analysis Set, Per-Protocol Analysis Set, and A Priori–Defined Subgroups

Group/Subgroup	Ratio (97.5% CI)
Primary analysis set	0.96 (-∞ to 1.09)
Per-protocol analysis set	0.97 (-∞ to 1.10)
Excluding patients in critical state	0.84 (-∞ to 0.96)
Elective surgery	0.81 (-∞ to 0.96)
Nonelective surgery	1.09 (0 to 1.31)
Complex surgery	0.98 (-∞ to 1.13)
Noncomplex surgery	0.86 (-∞ to 1.12)



Case

- 14-year-old with ALL undergoing induction chemotherapy
- Blood work shows progressive decline in fibrinogen levels due to DIC
- This morning PLT count 14, fibrinogen level 0.8 g/L
- No active bleeding, no oral bleeding
- Scattered petechiae
- No planned procedures
- Should you fix the fibrinogen level?

What do the guidelines recommend if the patient is bleeding in DIC?

Role of plasma, fresh frozen plasma (FFP), coagulation factors, and platelets

Recommendations:

1 The transfusion of platelets is recommended in DIC patients with active bleeding and a platelet count of $<50 \times 10^9$ L^{-1} or in those with a high risk of bleeding and a platelet count of $<20 \times 10^9$ L^{-1} (low quality).

2 The administration of FFP may be useful in patients with active bleeding with either prolonged PT/APTT (>1.5 times normal) or decreased fibrinogen (<1.5 g dL^{-1}). It should be considered in DIC patients requiring an invasive procedure with similar laboratory abnormalities (low quality).

3 The administration of fibrinogen concentrate or cryoprecipitate may be recommended in actively bleeding patients with persisting severe hypofibrinogenemia (<1.5 g L^{-1}) despite FFP replacement (low quality).

Wada et al for ISTH. J Thromb Haemost. 2013 Feb 4.

Acute Lymphocytic Leukemia (not APL)

- N=719 pts with new diagnosis of ALL (not APL) over 15 years at 2 hospitals
  - Hospital 1 'believers' of prophylaxis – 37% of patients given FFP, 68% given cryoprecipitate
  - Hospital 2 didn't believe in prophylaxis – no patients given plasma or cryo
- Prophylaxis did not reduce the risk of thrombosis
- There were no episodes of intracranial hemorrhage at either site
- No benefit, but substantial cost: if hospital 2 had administered FFP and cryo at the same rate as hospital 1 over the 15 years, the cost would have been $238K

Abbott et al. Blood 2009; 114: 5146-51.

Acute Promyelocytic leukemia (APL)

- Maintain platelet count >30-50 (>100 with CNS bleeding)
- Maintain fibrinogen >1.0-1.5 g/L (with cryoprecipitate)

Stein et al. Best Practice and Research Clinical Hematology 2009; 22: 153-63.
Choundhry et al. Am J Hematol. 2012 Jun;87(6):596-603. doi: 10.1002/ajh.23158. Epub 2012 May 2.

Summary – Plasma

- Different patient populations have different INR thresholds for plasma before procedures
  - You must know why the INR is high
- In liver disease, plasma for INRs 1.3 to 1.8 is unlikely to even change the INR let alone patient outcomes
  - Don’t transfuse plasma if INR<1.8 in a patient with liver disease without hemorrhage
- In liver disease, the use of plasma does not reduce bleeding risk before procedures
  - Don’t transfuse plasma if INR elevated before low-risk procedures (PLT>20)
  - limit to high-risk procedures (PLT>30, INR<2.5, FIB>1.0 only)
  - use lower risk techniques (transjugular liver biopsy)

Summary – Prothrombin Complex Concentrate

Emergency reversal

- Vitamin K 10 mg IV
- PCC:
  - INR<3 – 1000IU
  - INR 3-5 – 2000IU
  - INR>5 – 3000IU
  - INR unknown – 2000IU
  - Each 1000IU (5mL) over 5 min

Non-emergency

- Vitamin K only!
- INR > 8 to 10: 2 mg po
- Urgent surgery: 10 mg IV
- Non-critical bleeding: 1 mg IV

Summary – Fibrinogen Concentrate

- Fibrinogen replacement:
  - Transfuse fibrinogen or cryoprecipitate for bleeding patients <1.5-2.0 g/L
  - Acute promyelocytic leukemia patients if fibrinogen<1.5 g/L in acute phase even without bleeding (no other non-bleeding patients)

Your tasks

1. You will perform your next central line, paracentesis or thoracentesis while ignoring the INR
2. You will not give plasma for warfarin reversal when PCC is available
3. When faced with your next hemorrhaging patient, you will measure the fibrinogen so you know if your patient needs replacement