

Transfusion Camp 2021-2022

Day 1: Seminar 1B, September 17, 2021

Plasma, PCC & Fibrinogen Cases, Dr. Aditi Khandelwal

Please start session by asking trainees if they have any questions from the didactic sessions.

Please remind trainees that although one answer is bolded as the correct answer, there may be more than one reasonable answer to the questions. The purpose of the seminar is to promote discussion and explore why certain answers may be more appropriate in certain situations.

Case 1

A 56-year-old man (78 kg) with atrial fibrillation presents to the emergency department with acute onset of severe shortness of breath and pre-syncope with any exertion. He is on warfarin – dose has been stable for 6 months without dose adjustment. He had some chest congestion last week and went to a walk-in clinic where they prescribed Clarithromycin. Heart rate is 130 bpm and blood pressure is 80/30 mmHg. Heart sounds are faint. JVP is grossly distended. Chest-x-ray reveals marked cardiomegaly. Cardiology has been paged for STAT echo for pericardial tamponade from hemorrhage. INR is 10.5 (Normal<1.2). Patient is to undergo the life-saving procedure immediately.

- Which one of the following is the most appropriate management strategy at this time?
 - 1 unit of plasma, vitamin K 10 mg po
 - 4 units of plasma, vitamin K 10 mg IV
 - PCC 3000 IU, vitamin K 10 mg IV**
 - PCC 3000 IU, vitamin K 2 mg po
- How fast should you run the PCCs into the patient?
 - As fast as you can push in by syringe
 - Each 1000 units is run over 1 minute
 - Each 1000 units is run over 5 minutes**
 - Each 1000 units is run over 30 minutes
- The interventional cardiologist wants to know when to expect that the INR will be normalized so that she can do the procedure. Which one of the following is true about warfarin reversal in this case?
 - Collect the INR sample immediately after infusion, proceed with the procedure, and give additional doses of PCC if the post-infusion INR>1.5 and the patient has ongoing bleeding**
 - Recheck the INR after PCCs to determine if additional doses are required before starting the procedure
 - The effect of PCCs will be seen immediately after administration in all patients and there is no need to recheck the INR
 - The effect of the treatment (PCCs and vitamin K) takes 6 hours to normalize the INR, so delay the procedure for 6 hours
- Which of the following is an appropriate indication for PCC administration?
 - Elective reversal of oral anticoagulant therapy before a scheduled invasive procedure.



- B) **Rapid reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding.**
- C) Reversal of warfarin therapy or vitamin K deficiency in patients requiring a surgical procedure within 12-24 hours.
- D) Treatment of INRs over 8-10 without bleeding or need for surgical intervention.

Prothrombin Complex Concentrate (PCC) are lyophilized concentrates of factors 2, 7, 9, and 10 – PCCs are NOT concentrated plasma. They also contain small amounts of heparin, protein C and S, and antithrombin. There are two brands in Canada and the UK (Octaplex and Beriplex) that are used interchangeably. Only 4 factor PCCs are available in Canada. A 3-factor PCC is available in the UK (Cofact) that has lower levels of 7.

PCCs are indicated in patients who are anticoagulated with a vitamin K antagonist (warfarin/coumadin) or who have vitamin K deficiency and:

- Have life or limb threatening bleeding (e.g., intracranial hemorrhage, massive gastrointestinal hemorrhage, pericardial tamponade).
- Require emergency operative procedures that cannot be delayed for medical reasons for more than 6 hours (e.g., perforated bowel, subdural hematoma).

Reversal of anticoagulation with blood products, including PCCs, is not appropriate solely to expedite taking a patient to the operating room or interventional radiology for scheduling reasons (e.g., available operating room for patient needing a non-urgent procedure). It is completely inappropriate to use PCCs for an elective procedure (e.g., colonoscopy) or for reversal of an elevated INR (even if over 10) in the absence of bleeding or a planned procedure.

PCCs cost about \$600 per 1000 IU and approximately 2-4% experience thromboembolic complications (Dentali et al. Thromb Haemost 2011;106:429-38). PCCs are manufactured from human plasma and carry theoretical risks of disease transmission. Informed consent is required. These risks are less than frozen plasma due to the viral inactivation steps during the manufacturing process. However the risk of disease transmission may still occur from manufacturing failures and from emerging pathogens that are resistant to the pathogen reduction strategies (parvovirus, hepatitis A, prions). The risk of TACO is less with PCC vs. plasma due to the much smaller volume required.

The use of frozen plasma is no longer appropriate for management of vitamin K antagonist reversal due to the availability of PCC. (Exception: anticoagulant associated bleeding in patients with heparin induced thrombocytopenia must be treated with frozen plasma, since PCCs contain a small amount of heparin). When surveyed, smaller hospital blood banks are more likely to carry PCC than plasma due to its ease of preparation and longer shelf-life.

The dose recommended is based on the National Advisory Committee recommendations (or the hospital policy). The NAC recommendations for dose are:

- INR 1.5-3.0 give 1000 IU
- INR 3.1-5.0 give 2000 IU
- INR>5.0 give 3000 IU

(<http://www.nacblood.ca/resources/guidelines/PCC-Recommendations-Final-2014-05-16.pdf>). The NAC guidelines are currently undergoing revision.



If the INR is unknown and there is life-threatening hemorrhage, a dose of 2000 IU is recommended and immediately repeat the INR. There is no need to wait 10-60 minutes after the infusion to recheck the INR.

In the UK, the dose recommended by the NHSBT is 25 IU/kg and then repeat the INR. The following table can be used (infuse at 2-3 mL per minute):

Body weight (kg)	Total Dose in IU if 25 IU/Kg	No of vials of 500 IU	mls
Less than 60	1500	3	60
60-75	2000	4	80
75-90	2500	5	100
Greater than 90	3000	6	120

The PCC infusion rate is each 1000 IU (40mL) over 5-15 minutes (Beriplex monograph states can be run at ~8mL/min and Octaplex monograph states can be run at 2-3 mL/min), although most institutions run each 1000 units over 5 minutes as reversal is an emergency therapy. There are case reports of thrombosis from rapid infusion of PCCs (e.g., 3000 IU over 1 minute) and therefore exceeding recommended infusion rate could have adverse consequences (Warren et al. Ann Emerg Med 2009;53:758-61).

The INR should be repeated immediately post-infusion to document correction to an INR of <1.5 (67-100% of patients will have an INR of 1.2-1.3 or less (normal). Also, repeat the INR at 6 hours to ensure no rebound (often due to failure of vitamin K to be administered IV due to an error). For emergency surgery or procedure, surgery should not be delayed waiting for the INR results. The INR should be repeated as soon as possible and additional dosage given intraoperatively if required. There is no maximum daily dose of PCCs, although each infusion should not exceed 3000 IU and additional doses should not be given unless the INR is elevated. If there is poor immediate correction of the INR post-infusion, asking for the lab to add the PTT and fibrinogen on existing blood samples drawn pre- and post-PCC dosing, plus requesting a hematology consultation is warranted to determine if other factors are driving the coagulopathy (e.g., other anticoagulants, inhibitors, coagulopathy of shock).

Vitamin K should always be given for emergency reversal as the effect of PCCs (and plasma) only last 6 hours. This timespan is dependent on the FVII (7) half-life – the shortest of the coagulation factors within PCCs. Vitamin K is the true reversal agent for vitamin K antagonist, and failure to give vitamin K will result in rebounding of the INR. Vitamin K must be given intravenously (IV) as it works considerably faster than oral. The risk of anaphylaxis or other reaction to iv vitamin K is very small and can be reduced by giving as a slow infusion over 10-15 minutes. The appropriate dose of vitamin K for emergencies is unknown but 5-10 mg iv is commonly recommended by expert opinion. Vitamin K should never be given IM (due to risk of hematoma) or SC (due to decreased effectiveness compared to both IV and PO routes) (Mottice et al. Am J Ther 2016 Mar-Apr;23(2):e345-9). Oral vitamin K is appropriate for patients with INR>8-10 in the absence of bleeding or planned procedure (e.g., outpatient) to correct the INR back to therapeutic range of 2-3 (Lubetsky A, et al. Arch Intern Med 2003;163:2469–2473.).

If you see an INR rebounding after initial correction despite ordering intravenous vitamin K, check the nursing documentation to make sure it was administered and to ensure given by the correct route. If IM, SC or PO vitamin K was given in error, administer IV vitamin K immediately (and PCCs if ongoing bleeding).



The important risks of reversal with plasma include: transfusion-associated circulatory overload (TACO), TRALI, allergic reactions, and anaphylaxis. The risk of thromboembolic (TE) complications has not been well studied. Two RCTs of FFP vs. PCC found no difference in the TE rates, but a major reduction in TACO (Goldstein et al. Lancet 385(9982):2077-2087; Sarode et al. Circulation 128:1234-1243). There have been 4 systematic reviews of PCCs vs. plasma (ICH patients, emergency surgery, bleeding and cardiac surgery) and none found an increase in A/VTE events. The immediate risks of reversal with PCC include allergic reactions (rare; rate unknown). The risk of thrombosis has been estimated at 2-4% for both products and plasma (Dentali et al. Thromb Haemost 2011;106:429-38).

The cost difference between plasma and PCC is minimal and therefore using plasma instead of PCC for cost containment is not appropriate. Some physicians order plasma when the reversal is not urgent (ie. They want to reverse the INR by the following day) – this doesn't make sense as the appropriate treatment in this clinical scenario is vitamin K 10 mg IV.

Case 2

A 15-year-old girl (45 kg) presents to the emergency department feeling unwell for 2 weeks with fever, myalgias, malaise and anorexia. She was seen today by her pediatrician who noted jaundice. He promptly sends her to a tertiary care pediatric emergency. She is noted on physical exam to have mild abdominal distention (query ascites) and splenomegaly. She has no bruising except at intravenous puncture sites. On laboratory testing she has markedly elevated liver enzymes (ALT 234, N<40), a bilirubin of 76 (N<20), albumin 24 (N>35), INR of 1.6 (N<1.2), fibrinogen of 1.2 (N>2 g/L). Her platelet count is 65 (N>150). She is seen by hepatology who recommend an urgent liver biopsy to determine the cause and severity of the liver disease. The transjugular liver biopsy is scheduled for in 4 hours. The patient has been eating a full diet for the last month.

5. Which one of the following is the most appropriate transfusion strategy in this patient in lead up to the biopsy?
 - A) **No need for transfusion at this time**
 - B) Transfuse 1000 IU of PCC and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate in the UK)
 - C) Transfuse 1 adult dose of platelets
 - D) Transfuse 3 units (15 ml/kg) of plasma to ensure INR is <1.5 before the procedure

6. The radiologist refuses to perform the procedure until the INR is 1.2 or less. You should:
 - A) Call your staff physician and get direction on how to proceed
 - B) Delay the procedure for 1 day and see if the next radiologist will do it without plasma
 - C) **Page the radiologist performing the procedure to discuss the risks of plasma, explain why plasma is unlikely to lower the INR, and alert them to the 2019 Society for Interventional Radiology Guidelines**
 - D) Transfuse 3 units plasma to ensure the liver biopsy is done

Retrospective large case series of patients with liver disease undergoing common procedures find no increase in bleeding with elevated INRs, compared to patients with normal INRs (van de Weerd EK, et al. Transfusion. 2017;57(10):2512-25). No large randomized trials have been completed, and these trials



are not feasible due to the very low complication rate (numbers needed for the trial would be extremely high to determine if plasma increases or decreases adverse event rates).

Patients with liver disease have widespread derangements (elevated vWF, elevated factor VIII (8), decreased ADAMTS-13, decreased protein C/S, decreased antithrombin, decreased plasminogen, reduced fibrinolysis) (Northup PG, et al. Clin Gastroenterol Hepatol. 2013 Sep;11(9):1064-74; Tripodi A, et al. N Engl J Med. 2011 Jul 14;365(2):147-56). It is possible that this patient is actually balanced in terms of her hemostasis at an INR of 1.6, or even hypercoagulable. Many centres are able to do major surgical procedures on patients with cirrhosis/liver failure, including liver transplantation, without any plasma despite INR>3.0. Therefore, the use of plasma should be restricted to patients undergoing high risk procedures (neurosurgical procedures, high risk interventional radiology procedures) or be reserved for the management of bleeding complications post procedure.

It is unknown what the appropriate INR cut-off should be (if any) for a liver biopsy – there is no relationship between the INR and the risk of bleeding but the recent guidelines from the Society for interventional radiology 2019 guidelines recommend reasonable thresholds for low and high risk of bleeding procedures with liver disease (see detailed powerpoint slides from plasma lecture and charts below; Patel et al. J Vasc Interv Radiol 2019).



SUMMARY OF THE SIR 2019 GUIDELINES:

Decision-making regarding patients on anticoagulants, with underlying coagulopathy, and/or thrombocytopenia prior to invasive procedures in Diagnostic Imaging

(The following is extracted from the **Society of Interventional Radiology Consensus Guidelines for the Peri-procedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions—Part II: Recommendations**. Davidson JC, et al. J Vasc Interv Radiol 2019; 30: 1155-67)

The guidelines divide patients into two procedure categories for decision making (low risk and high risk procedures). The guidelines also divide patients into 3 general categories for types of coagulopathy (anticoagulants, coagulopathy from liver disease, and coagulopathy for all other causes).

Table 1. Low risk and high-risk procedure categorization (if a procedure is not listed estimate risk from similar procedures in procedure list below).

Low risk (common examples)	High risk (common examples)
<ul style="list-style-type: none"> • Catheter exchanges (gastrostomy, biliary, nephrostomy, abscess, including gastrostomy/gastrojejunostomy conversions) • Diagnostic arteriography and arterial interventions: peripheral, sheath < 6 F, embolotherapy • Diagnostic venography and select venous interventions: pelvis and extremities • Dialysis access interventions • Facet joint injections and medial branch nerve blocks (thoracic and lumbar spine) • IVC filter placement and removal • Lumbar puncture • Non-tunneled chest tube placement for pleural effusion • Non-tunneled venous access and removal (including PICC placement) • Paracentesis • Peripheral nerve blocks, joint, and musculoskeletal injections • Sacroiliac joint injection and sacral lateral branch blocks • Superficial abscess drainage or biopsy (palpable lesion, lymph node, soft tissue, breast, thyroid, superficial bone (eg, extremities and bone marrow aspiration)) • Thoracentesis • Transjugular liver biopsy • Trigger point injections including piriformis • Tunneled drainage catheter placement • Tunneled venous catheter placement/removal (including ports) 	<ul style="list-style-type: none"> • Ablations: solid organs, bone, soft tissue, lung • Arterial interventions: > 7-F sheath, aortic, pelvic, mesenteric, CNS • Biliary interventions (including cholecystostomy tube placement) • Catheter directed thrombolysis (DVT, PE, portal vein) • Deep abscess drainage (eg, lung parenchyma, abdominal, pelvic, retroperitoneal) • Deep non-organ biopsies (eg, spine, soft tissue in intraabdominal, retroperitoneal, pelvic compartments) • Gastrostomy/gastrojejunostomy placement • IVC filter removal complex • Portal vein interventions • Solid organ biopsies • Spine procedures with risk of spinal or epidural hematoma (eg, kyphoplasty, vertebroplasty, epidural injections, facet blocks cervical spine) • Transjugular intrahepatic portosystemic shunt • Urinary tract interventions (including nephrostomy tube placement, ureteral dilation, stone removal) • Venous interventions: intrathoracic and CNS interventions



Figure 1. Algorithm for deciding on appropriate management for patients on anticoagulants.

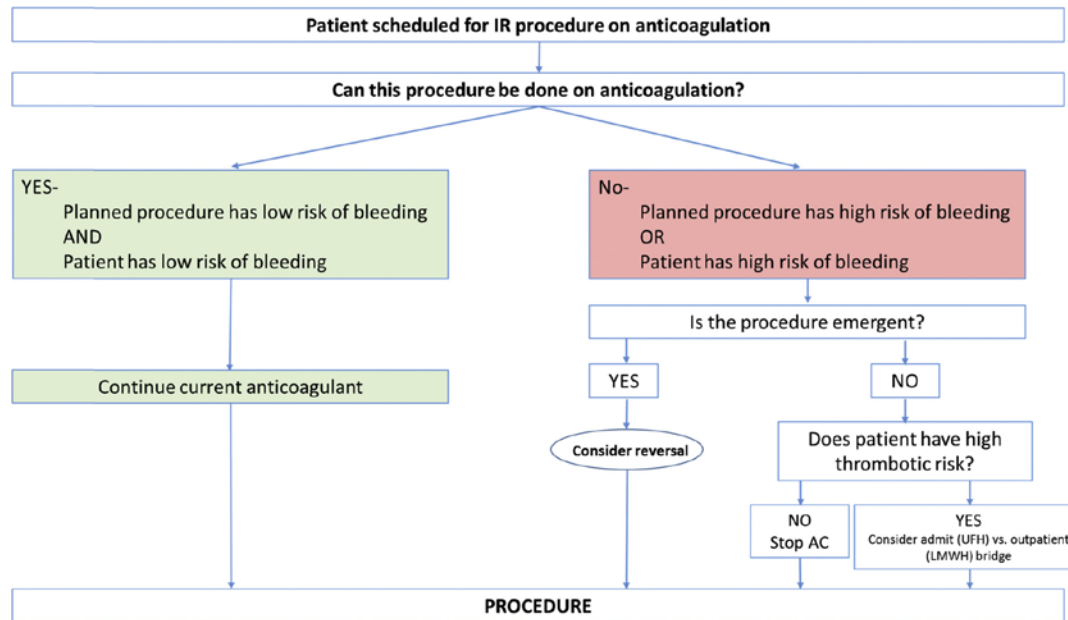


Table 2. Decision making guide for patients with coagulopathy NOT related to an anticoagulant or liver disease (cirrhosis). Low risk and high risk procedure list see Table 1.

Low risk procedure	PT/INR: not routinely recommended <ul style="list-style-type: none"> If INR performed: correct to within range of 2.0–3.0 Platelet count: not routinely recommended <ul style="list-style-type: none"> Transfuse 1 pool of platelets if platelet count < 20x10⁹/L
High risk procedure	PT/INR: routinely recommended <ul style="list-style-type: none"> If INR performed: correct to less than 1.8 Platelet count: routinely recommended <ul style="list-style-type: none"> Transfuse 1 pool of platelets if platelet count < 50x10⁹/L

Table 3. Decision making guide for patients with coagulopathy related to liver disease (cirrhosis). Low risk and high risk procedure list see Table 1.

Low risk procedure	PT/INR: not routinely recommended <ul style="list-style-type: none"> Procedure can be performed at any elevation of the INR Platelet count: routinely recommended <ul style="list-style-type: none"> Transfuse 1 pool of platelets if platelet count < 20x10⁹/L Fibrinogen: routinely recommended <ul style="list-style-type: none"> Transfuse 4 grams of Fibrinogen concentrate if fibrinogen <1.0 g/L
High risk procedure	PT/INR: routinely recommended <ul style="list-style-type: none"> If INR performed: correct to less than 2.5 Platelet count: routinely recommended <ul style="list-style-type: none"> Transfuse 1 pool of platelets if platelet count < 30x10⁹/L Fibrinogen: routinely recommended <ul style="list-style-type: none"> Transfuse 4 grams of Fibrinogen concentrate if fibrinogen <1.0 g/L



Plasma transfusion prior to procedures in the setting of liver disease is discouraged by the AASLD Guidelines, which state the INR should not be used to guide decisions prior to procedures due to its inutility (but that the PLT should be ≥ 50 ; Rockey DC, et al. Hepatology. 2009;49(3):1017-44), and the BCSH guideline for plasma (Green et al. British Journal of Haematology, 2018, 181, 54–67). The CSTM Choosing wisely have stated “DON’T transfuse plasma if < 1.8 ” = therefore do not use plasma below this level in the setting of liver disease. It is inappropriate to EVER give plasma for either a thoracentesis or a paracentesis, no matter how elevated the INR is. The platelet count is a much better predictor of bleeding at the time of a procedure, especially if the platelet count is less than 20.

Note: The cut offs for INR for liver disease vs. other conditions (e.g., warfarin reversal) are different. Do not use the same cut offs for all decisions regarding plasma and PCCs.

Three large retrospective reports have evaluated the change in INR after plasma infusion in patients with mildly elevated INRs (1.3-2.0). The infusion of plasma did not reduce the INR post-infusion. This is likely due to the fact that the effect of plasma does not last very long (4-6 hours) and the INR of frozen plasma is not 1.0 and can be as high as 1.3-1.5 (coagulation factors drop due to the effect of freezing/thawing and then storage at room temperature for up to 5 days).

The major risks include: TACO (1-6%), TRALI (1 in 10,000 per unit), allergic reactions (1 in 100), anaphylaxis (1 in 20,000), and viral risks. Informed consent is required. In a euvolemic patient be very careful to monitor the patient volume status before and during the infusion to mitigate the risk of TACO, especially in non-bleeding patients where the volume may be problematic.

7. The patient subsequently develops a variceal bleed with hypotensive shock. Her INR is now 3.4 ($N < 1.2$) and fibrinogen is 1.6 g/L ($N > 2$). You should:
- A. Transfuse 1 unit of plasma and repeat INR
 - B. Transfuse 5-10 mL/kg of plasma (2 units or 500 mL)
 - C. **Transfuse 15 ml/kg of plasma (3 or 750 mL)**
 - D. Transfuse 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate in the UK)

The correct dose of plasma for an adult patient is 15 mL/kg (adult dose 3-5 units, depending on the patient weight); (Green et al. British Journal of Haematology, 2018, 181, 54–67). The often used dose of “1 unit” or “2 units” is inappropriate for adults and is likely a “carry-over” from the old practice of giving 2 RBCs at a time (and now “1 unit at a time”). The expected rise in coagulation factors from 15 mL/kg (3-5 units) is 20% in clotting factor levels. This patient is 45 kg and thus 675 mL would be required and for adults, this patient should receive 3 units FFP.

If the patient has an in-date group and screen, the preparation time of plasma is a minimum of 25-30 minutes, as the product has to be thawed in a water bath. If the patient has no in-date group and screen, an additional 15 minutes is required to determine the patient ABO blood group. In emergencies, AB plasma will be issued if there is no time to complete the patient blood group (AB plasma lacks anti-A and anti-B and is the “universal” blood donor group for plasma). AB plasma is in chronic short supply and should only be used in emergencies. No matching for Rh-group is required for plasma.

Case 3a

A 35-year-old woman (65 kg) is admitted to the ICU from the ER with endocarditis within 4 hours of presenting to the hospital. She is not bleeding. She is intubated for airway protection and hemodynamically unstable on two inotropes. Her temperature is 39° C. Her blood work is as follows:



Hemoglobin 108 g/L, platelet count 18 (N>150), INR 1.6 (N<1.2), aPTT 42 s (N<36), and fibrinogen 1.3 (N>2.0) g/L. Her peripheral blood smear shows occasional fragments (schistocytes). Blood cultures are positive for gram-positive organism in 2/2 bottles; final culture results are pending. You make the correct diagnosis of sepsis related DIC. She is not bleeding and no procedures are planned in the next 6 hours.

8. Which one of the following is the most appropriate transfusion strategy for this patient?
- A) **No transfusion indicated at this time**
 - B) Transfuse 1 adult dose of platelets
 - C) Transfuse 1 adult dose of platelets and 4 units of plasma
 - D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate in the UK)

In the absence of bleeding or a planned surgical procedure, blood product transfusion is almost never necessary. Plasma has a high rate of adverse reactions and is a large volume (750-1250 mL for an average adult). Its effect starts to diminish after 6 hours and therefore repeated infusions would be required to normalize the INR continuously. Infusions for patients with INRs between 1.3 and 2.0 fail to show an improvement in the INR.

There is no evidence available that suggests fibrinogen replacement is required and guidelines recommend against replacement in patients with DIC (Hunt et al. N Engl J Med 2014;370:847-59; Levi et al N Engl J Med 1999; 341:586-592). The only indication for prophylactic fibrinogen replacement is in patients with APL during the acute presentation until coagulopathy resolves and the high risk period for ICH has passed (this is based on expert opinion as the evidence for this is non-existent; Breen et al. BJH 2012;156:24-36).

Platelet transfusion is not recommended in the case of consumptive thrombocytopenia without active bleeding or pending surgical procedure.

Case 3b

A 17 year old female is seen in the ER with profuse vaginal bleeding and hemorrhagic shock 6 hours after a pregnancy termination. Her BP is 90/50, HR 112, temperature is 38.1° C. Her blood work is as follows: Hemoglobin 65 g/L, platelet count 28 (N>150), INR 1.4 (N<1.2), aPTT 40 s (N<36), and fibrinogen 1.1 g/L (N>2.0). Ultrasound shows retained products of conception. She is hemodynamically unstable and you have ordered 2 units of uncrossmatched (you decide it would imprudent to wait 60 minutes for crossmatched blood) O D-negative and K-negative red cells.

9. Which one of the following is the most appropriate transfusion strategy for this patient in addition to RBCs?
- A) No transfusion indicated at this time
 - B) Transfuse 1 adult dose of platelets
 - C) Transfuse 1 adult dose of platelets and 4 units of plasma
 - D) **Transfuse 1 pool of platelets and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate)**

Platelets are indicated to increase the level to approximately 50 to slow the rate of bleeding until definitive surgical procedure to address the underlying cause of bleeding. Give 1 adult dose of platelets



to increase the platelet count (ideally by at least 25×10^9). Fibrinogen replacement should be given as a source of fibrinogen, and is more effective at raising the fibrinogen level than plasma. Cryoprecipitate and FC have a smaller volume than plasma, and both are rarely reported to be associated with adverse reactions. The European Bleeding guidelines recommend AGAINST using plasma solely for fibrinogen replacement (Spahn et al. Crit Care. 2019 Mar 27;23(1):98). A mildly elevated INR should correct, at least partially, with fibrinogen replacement as well. The standard adult dose of cryoprecipitate is 10 Units (which contains approx. 3-4 grams of fibrinogen) or fibrinogen concentrate 4 g. The target fibrinogen level is unknown, but with severe ongoing bleeding experts recommend raising the fibrinogen level to over 1.5-2 g/L (Rossaint et al. Critical Care2016; 20:100) and above 2 g/L for postpartum hemorrhage. Repeat the CBC, INR and fibrinogen immediately after the platelet and fibrinogen replacement has been administered. A randomized, controlled trial of fibrinogen vs. cryoprecipitate for hemorrhage after cardiac surgery found the latter strategy non-inferior for bleeding control (Callum J et al. JAMA 2019) and its use has superseded cryoprecipitate across Canada due to the reduced risk of pathogen transmission, cryoprecipitate production impacts on platelet production, and concerns regarding inferior outcomes with whole blood filtered RBCs (Hedde N, et al. Lancet Haematology 2016).

Case 3c

A 35-year-old woman is admitted to the hematology service following a diagnosis of acute promyelocytic leukemia (APL). APL is associated with a high rate of early hemorrhagic deaths from ICH. She is afebrile with stable vital signs and her only complaints are fatigue and a petechial rash on her legs. Her blood work is as follows: Hemoglobin 74 g/L, platelet count 18, WBC 63, INR 1.4, aPTT 39 s, and fibrinogen 0.9 g/L. She is to start emergency induction chemotherapy tonight, and is not bleeding.

10. Which one of the following is the most appropriate transfusion strategy for this patient?
- A) No transfusion indicated at this time
 - B) Transfuse 1 unit RBC and 1 adult dose of platelets
 - C) Transfuse 1 unit RBC and 4 grams of fibrinogen (or 10 units of cryoprecipitate)
 - D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen (or 10 units of cryoprecipitate)**

In general, acute leukemia patients do not need plasma or cryoprecipitate for acute leukemia related DIC. A large study compared 2 academic hospitals: hospital A routinely used cryoprecipitate and plasma for patients with coagulopathy/thrombocytopenia; hospital B never used any cryoprecipitate or plasma. There was no difference in the bleeding rates (or thrombosis rates) between the two institutions despite caring for identical patients.

There is one exception, however: patients with APL. Approximately 20-30% of deaths in APL result from hemorrhagic complications (with 7-14% early death rate in large case series). Since APL is highly curable with both non-chemotherapeutic treatments (all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) and chemotherapy, many “expert opinion” reviews recommend keeping $PLT > 50$ and fibrinogen > 1.5 g/L. No recommendations regarding use of FFP appear in recent reviews. It is reasonable at this time to transfuse platelets and fibrinogen in the absence of active bleeding to hit the above listed targets of 1.5 g/L for fibrinogen and > 50 for platelets in the initial presentation of APL. These recommendations are based on expert opinion alone and not based on clinical studies. It is unknown how long into APL treatment fibrinogen replacement is required. Individual patient assessment required – use response to chemo, lab test results over time, and bleeding symptoms in decision to switch from prophylactic to therapeutic treatment strategy.



Cryoprecipitate dosage: 1 unit per 5-10 kg of body weight (most adult centres use a standard pool size of 10 units for all adults; most countries (UK, USA) it comes pre-pooled in groups of 5 units). In a bleeding patient, 1 pool (10 units of cryoprecipitate (Canada); or “2 pools” of 5 units in the UK/USA) would result in a 0.5 g/L rise in fibrinogen. Each cryoprecipitate unit is 5-15 mL of volume. To pool the cryoprecipitate, 10-50 mL of saline is added to reconstitute the fibrinogen. Hence, total volume for 10 units is 150-200 mL. Each unit has a minimum of 0.15 g of fibrinogen (minimum per 10 unit pool = 1.5 grams; although the average measured fibrinogen content is 3-4 grams per pool).

Fibrinogen concentrates is administered as a single dose of 4 grams (pathogen inactivated). Each vial of fibrinogen concentrate is 1 gram reconstituted in 50 mL sterile water. At present, fibrinogen concentrate use for acquired hypofibrinogenemia is considered to be off-label. In the product monograph, where fibrinogen concentrate use is defined for preoperative replacement in patients with congenital hypofibrinogenemia, the recommended rate of infusion is 4 grams over 40 minutes. However, in the setting of bleeding, clinical studies use rapid injection at a rate of 1 gram over 1 minute without complications (Winearls et al. *Trials* 2017; 18:241; Nascimento et al. *Br J Anaesth.* 2016 Dec;117(6):775-782).

Case 4.

You are providing the anesthetic for an 11-year-old girl undergoing scoliosis surgery with a pre-op weight of 39 kg. Pre-op blood work: hemoglobin 118 g/L, MCV 78, Platelet count 288. No INR was done pre-op as her bleeding questionnaire was negative for a bleeding history. At the 2 hour mark of the surgery, she has lost approximately 2500 mL and you have transfused 3 units of RBC. STAT blood work reveals: hemoglobin 78 g/L, PLT count 134 (N>150), INR 2.1 (<1.2), PTT 45 (N<36) and fibrinogen 1.3 (N>2). The surgeon expects to lose another 1000 mL over the next hour. You have not administered any plasma, platelets or fibrinogen yet.

11. Which one of the following is the most appropriate component strategy for this patient?

- A) Transfuse 1 dose platelets (10-15 mL/kg)
- B) Transfuse 2000 IU of PCC
- C) Transfuse 3 units (15 mL/kg) of plasma and 2 grams of fibrinogen (50 mg/kg) or 5 units of cryoprecipitate
- D) Transfuse or 2 grams of fibrinogen or 5 units of cryoprecipitate

There are no “dose” finding studies that guide when to give plasma during active bleeding. In the setting of major hemorrhage that cannot be controlled with surgical hemostasis, administering plasma if the INR is >1.5-1.8 is reasonable, although the medically sound cut-off is thought to be higher by experts in hemostasis.

There are no definitive studies of “dose finding” for fibrinogen replacement. Some guidelines recommend a trigger of 1.0 g/L (BCSH; Green et al. *British Journal of Haematology*, 2018, 181, 54–67) and newer studies have questioned this trigger in postpartum hemorrhage, trauma, and cardiac surgery and have recommended a higher trigger 1.5-2.0 g/L. The truth is we don’t know what the right threshold or target for fibrinogen is! It is reasonable in the setting of mild-moderate hemorrhage to keep fibrinogen >1.0 and in more extreme bleeding situations target a higher level >1.5-2.0 g/L. Repeat the INR and fibrinogen level after infusion. Formula use (1:1 or 2:1) of plasma is not used unless the rate of hemorrhage is extreme (e.g., PPH or gunshot wounds), rate at least 4 RBC units per hour (or expected



transfusion volume of 40 ml/kg for pediatric patients over 24 hours), unable to wait for lab results, and no immediate surgical correction is possible.

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