Transfusion Camp in Rwanda 2023 – Train the Trainer Camp

Seminar 2: Plasma, fibrinogen and prothrombin complex concentrates

***Note: This seminar is to cover transfusions for less severe bleeding or before an invasive procedure and does not cover massive hemorrhage.**

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. Patient is to undergo the life-saving procedure immediately.

1. Which one of the following is the optimal management strategy at this time?
    A) 1 unit of plasma, vitamin K 10 mg po
    B) 4 units of plasma, vitamin K 10 mg IV
    C) 3000 IU of prothrombin complex concentrate, vitamin K 10 mg IV
    D) 3000 IU of prothrombin complex concentrate, vitamin K 2 mg po

2. How fast should prothrombin complex concentrate (PCC) be infused into the patient?
    A) As fast as you can push in by syringe
    B) Each 1000 units is infused over 1 minute
    C) Each 1000 units is infused over 5 minutes
    D) Each 1000 units is infused over 30 minutes

3. The intensivist wants to know when to expect that the INR will be normalized so that she can perform the pericardiocentesis. Which one of the following is true about warfarin reversal in this case?
    A) After infusion, the procedure should be initiated before the result is known; the INR should be rechecked after the PCC is administered to determine if additional doses are required
    B) After infusion, wait for the INR to be rechecked after the PCC is administered to determine if additional doses are required before starting the procedure
    C) The effect of PCCs will be seen immediately after administration in all patients and there is no need to recheck the INR
    D) The effect of the treatment (PCCs and vitamin K) takes 6 hours to normalize the INR, so delay the procedure for 6 hours

4. Which of the following is an appropriate indication for PCC administration?
    A) 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 Concentrates: Indications

There are many brands of prothrombin complex concentrates (PCC) available on the international market, and can be categorized as either 3- or 4-factor concentrates. 3-factor concentrates contain factors 2, 9 and 10 and were originally developed as a source of Factor 9 for patients with hemophilia B. 4-factor concentrates also have factor 7 and, because they are indicated primarily for the replenishment of vitamin K-dependent factors, also contain the vitamin K-dependent anticoagulants proteins C and S. The specific indications for 4-factor concentrates are patients who are anticoagulated with a vitamin K antagonist (warfarin/coumadin) or who have vitamin K deficiency and who either:

- 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).

Risks

PCCs are typically provided as lyophilized products, and because they do not require thawing or pre-transfusion compatibility testing, are faster to prepare than frozen plasma. Like all fractionated plasma products, PCCs have undergone pathogen inactivation, making them less likely to transmit infectious agents than traditional blood components such as plasma. In addition, because they are highly purified, PCCs are also less likely than plasma to cause acute transfusion reactions such as volume overload, acute lung injury, or anaphylaxis.[1,2] Despite the fact that PCCs allow the same quantity of coagulation factors to be infused faster than what is possible with plasma, there is no accompanying increased risk of thrombosis.[3]

For all these reasons, 4-factor PCCs should be considered superior to plasma for the replenishment of vitamin K-dependent coagulation factors, and should be selected whenever available, with the following exceptions:

- Patients with a history of heparin-induced thrombocytopenia (HIT), due to the very small amount of heparin added to each product (this is to prevent in vitro coagulation factor activation, which would greatly increase the potency)
- Patients in whom a global coagulopathy is suspected, eg., if the fibrinogen is also low. This might occur in a patient on warfarin who then develops sepsis

[1] Goldstein et al. Lancet 385(9982):2077-2087
[2] Sarode et al. Circulation 128:1234-1243
[3] Dentali et al. Thromb Haemost 2011;106:429-38

If PCCs are indicated for a patient but are not available (ie., due to their higher cost of approximately $600 per 1000 unit dose), plasma is an acceptable alternative.

Dosing

There are a variety of different dosing regimens for PCCs that are designed to be simpler to use than what is usually recommended by the manufacturer.[4] One example that can be applied to averaged-sized adults is based on the INR and does not require adjustment for weight:

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

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).

Administration

The recommended rate of infusion for a PCC will also vary by product but can often be given slightly faster than what is recommended by the manufacturer: 5-15 minutes for each 1000 units appears to be well-tolerated. However, there are case reports of thrombosis from rapid infusion of PCCs (e.g., 3000 IU over 1 minute)

Whether PCC or plasma is used, it is necessary to recheck the INR immediately after infusion to confirm that it has been adequately corrected, although in emergencies it is not necessary to delay a procedure while waiting for the results.

Vitamin K

It is also true for both PCC and plasma that unless intravenous vitamin K is administered at the same time, rebound anticoagulation may occur 6 hours later, which is when levels of the infused Factor 7 will start to significantly fall off. The dose of vitamin K necessary to reverse the effect of warfarin depends upon how high the INR is at baseline, and how complete the desired reversal is. For emergencies, a dose of 5-10 mg should be adequate for most patients, although checking the INR 6 hours later is still a good practice. Regardless of the dose, intravenous administration is necessary since oral administration will have an onset that is too delayed to prevent rebound. 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. 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).[5]

Finally, it should be emphasized that reversal of anticoagulation with blood products, whether plasma or PCC, 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

[4] https://nacblood.ca/en/resource/recommendations-use-prothrombin-complex-concentrates-canada

[5] Mottice et al. Am J Ther 2016 Mar-Apr;23(2):e345-9

procedure). It is poor quality care to use either plasma or 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. In such cases, holding the warfarin and administering vitamin K is sufficient. 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.[6]

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 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 IU/L), a bilirubin of 76 µmol/L (4.4 mg/dL), hypoalbuminemia (24 g/L), a slightly increased INR (1.6) and decreased fibrinogen of (1.2 g/L). Her platelet count is also marked decreased at 65 x 10^9/L. A plan is made to perform an ultrasound-guided liver biopsy.

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 if fibrinogen unavailable)
    C) Transfuse 1 adult dose of platelets
    D) Transfuse 15 ml/kg of plasma

6. The radiologist refuses to perform the procedure until the INR is 1.2 or less. You should:
    A) Administer 10 mg of IV vitamin K
    B) Delay the procedure for 1 day and see if the next radiologist will do it without plasma
    C) Refer the radiologist to current guidelines on periprocedural hemostasis
    D) Transfuse 15 ml/kg of 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.[7] 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.[8,9] 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

[6] Lubetsky A, et al. Arch Intern Med 2003;163:2469–2473
[7] van de Weerdt EK, et al. Transfusion. 2017;57(10):2512-25
[8] Northup PG, et al. Clin Gastroenterol Hepatol. 2013 Sep;11(9):1064-74
[9] Tripodi A, et al. N Engl J Med. 2011 Jul 14;365(2):147-56

(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.[10]

SUMMARY OF THE 2019 SOCIETY FOR INTERVENTIONAL RADIOLOG GUIDELINES:[11]

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

The guidelines divide patients into two procedures 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)
• 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,	• 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

[10] Patel et al. J Vasc Interv Radiol 2019

[11] Davidson JC, et al. J Vasc Interv Radiol 2019; 30: 1155-67

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)	• 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.

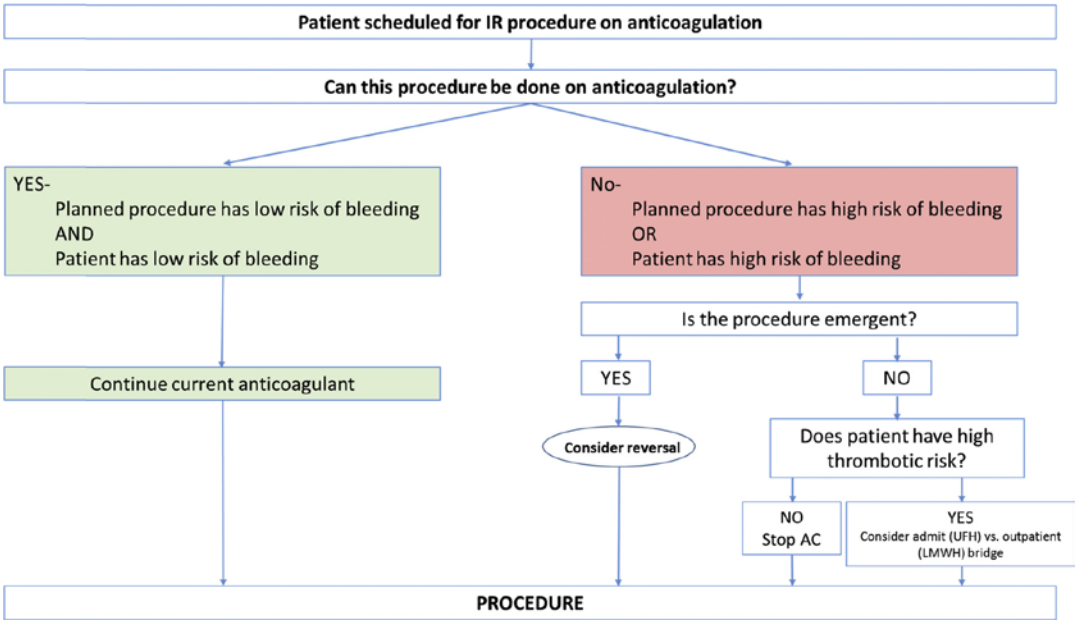

Table 2. Decision making guide for patients with coagulopathy NOT related to an anticoagulant or liver disease (cirrhosis). Low risk and high risk procedure list see Table 1.

Low risk procedure	PT/INR: not routinely recommended • If INR performed: correct to within range of 2.0–3.0 Platelet count: not routinely recommended • Transfuse 1 pool of platelets if platelet count < $20x10^9$/L
High risk procedure	PT/INR: routinely recommended • If INR performed: correct to less than 1.8 Platelet count: routinely recommended • Transfuse 1 pool of platelets if platelet count < $50x10^9$/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 • Procedure can be performed at any elevation of the INR Platelet count: routinely recommended

	• Transfuse 1 pool of platelets if platelet count < $20x10^9$/L Fibrinogen: routinely recommended • Transfuse 4 grams of Fibrinogen concentrate if fibrinogen <1.0 g/L
High risk procedure	PT/INR: routinely recommended • If INR performed: correct to less than 2.5 Platelet count: routinely recommended • Transfuse 1 pool of platelets if platelet count < $30x10^9$/L Fibrinogen: routinely recommended • Transfuse 4 grams of Fibrinogen concentrate if fibrinogen <1.0 g/L

Plasma transfusion prior to procedures in the setting of liver disease is also discouraged by both the guidelines from the American Association for the Study of Liver Diseases,[12] which state the INR should not be used to guide decisions prior to procedures due to its inutility (but that the platelet count should be ≥50 x 10^9/L), and the British Committee for Standards in Hematology guideline for plasma.[13] The Canadian Standards for Transfusion Medicine Choosing Wisely[14] campaign states "DON'T transfuse plasma if <1.8", i.e 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 of plasma transfusion 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 and fibrinogen is 1.6 g/L. You should:
    A. Transfuse 15 ml/kg of plasma and repeat INR
    B. Transfuse 5-10 mL/kg of plasma
    C. Transfuse 15 ml/kg of plasma
    D. Transfuse 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate if fibrinogen unavailable)

[12] Rockey DC, et al. Hepatology. 2009;49(3):1017-44
[13] Green et al. British Journal of Haematology, 2018, 181, 54–67
[14] https://www.transfusion.ca/Education/Choosing-Wisely

The correct dose of plasma for an adult patient is 15 mL/kg (adult dose 3-5 units, depending on the patient weight).[13] 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 of plasma.

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 10.8 g/dL, platelet count 18 x 10^9/L, INR 1.6, aPTT 42 s, and fibrinogen 1.3 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 if fibrinogen unavailable)

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.[15,16] The only indication for prophylactic fibrinogen replacement is in patients with acute promyelocytic leukemia 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).[17]

Platelet transfusion is not recommended in the case of consumptive thrombocytopenia without active bleeding or pending surgical procedure, even if platelet count < 10.

[15] Hunt et al. N Engl J Med 2014;370:847-59
[16] Levi et al N Engl J Med 1999; 341:586-592
[17] Breen et al. BJH 2012;156:24-36

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 mmHg, HR 112 bpm, temperature is 38.1° C. Her blood work is as follows: Hemoglobin 6.5 g/dL, platelet count 28 x 10^9/L, INR 1.4, aPTT 40 s, and fibrinogen 1.1 g/L. 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) group 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 adult dose of platelets and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate if fibrinogen unavailable)

Platelets are indicated to increase the level to approximately 50 x 10^9/L 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 (the expected increment will be approximately 25 x 10^9/L). Fibrinogen replacement should be given as a source of fibrinogen, and is more effective at raising the fibrinogen level than plasma. Cryoprecipitate and fibrinogen concentrate 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.[18] 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[19] 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.[20] In Canada, use of fibrinogen concentrate now supersedes cryoprecipitate due to the reduced risk of pathogen transmission, the detrimental effects of cryoprecipitate production impacts on platelet production, and concerns regarding inferior outcomes with whole blood filtered RBCs.[21]

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 intracranial hemorrhage. 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 7.4 g/dL, platelet count 18 x 10^9/L,

[18] Spahn et al. Crit Care. 2019 Mar 27;23(1):98
[19] Rossaint et al. Critical Care2016; 20:100
[20] Callum J et al. JAMA 2019
[21] Heddle N, et al. Lancet Haematology 2016

WBC 63 x 10^9/L, 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 if fibrinogen concentrate not available)
    D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen (or 10 units of cryoprecipitate if fibrinogen concentrate not available)

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 the platelet count >50 x 10^9/L and fibrinogen >1.5 g/L. No recommendations regarding use of plasma appear in recent reviews. For the patient in this case, it is reasonable at this time to transfuse platelets and fibrinogen even in the absence of active bleeding to hit the above listed targets. 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 to decide when to switch from a 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; and in many countries it is provided to the hospital pre-pooled in groups of 5 units). In a bleeding patient, 1 pool (ie., 10 units of cryoprecipitate, or "2 pools" of 5 units) should result in a 0.5 g/L rise in fibrinogen. Each cryoprecipitate unit is 5-15 mL of volume, and following the addition of 10-50 mL of saline for reconstitution, the total volume for 10 units is 150-200 mL, typically containing a total of 3-4 grams of fibrinogen.

Fibrinogen concentrate is administered as a single dose of 4 grams, with each 1 gram vial reconstituted in 50 mL sterile water. In the product monograph, where fibrinogen concentrate use is indicated 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 describe rapid injection at a rate of 1 gram over 1 minute without complications.[22,23]

[22] Winearls et al. Trials 2017; 18:241
[23] 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 11.8 g/dL, MCV 78 fL, platelet count 288 x 10^9/L. 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 7.8 g/dL, platelet count 134 x 10^9/L, INR 2.1, PTT 45s and fibrinogen 1.3 g/L. The surgeon expects to lose another 1000 mL of blood 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 adult dose platelets
    - B) Transfuse 2000 IU of PCC
    - C) Transfuse 15 mL/kg of plasma and either 2 grams of fibrinogen (50 mg/kg) or 5 units of cryoprecipitate
    - D) Transfuse either 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,[13] while 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), with transfusion occurring at a rate of at least 4 RBC units per hour (or expected transfusion volume of 40 ml/kg for pediatric patients over 24 hours), with inability to wait for lab results, and no immediate surgical correction is possible.