Transfusion Camp Rwanda
June 4th 2022
Seminar 1: Triggers for RBC and platelet transfusions

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 70 year old male is admitted to the ICU with respiratory failure due to pneumococcal pneumonia. His past medical history is significant for coronary artery disease but he has been asymptomatic since undergoing bypass operation approximately 5 years ago. He is on antibiotics and is hemodynamically stable. He is intubated and ventilated (PS10, PEEP 8, FiO2 0.5, oxygen saturation 94%). There is no evidence of bleeding or hemolysis. However, over the last few days his hemoglobin concentration has drifted down to 7.9 g/dL.

1) Which of the following represents the most appropriate RBC transfusion strategy for this patient?
   - A) Transfuse RBCs if Hgb <10 g/dL
   - B) Transfuse RBCs if Hgb <9 g/dL
   - C) Transfuse RBCs if Hgb <8 g/dL
   - D) Transfuse RBCs if Hgb <7 g/dL

This patient does not currently require an RBC transfusion. Red blood cells are transfused to increase oxygen delivery to the tissues. Studies have healthy volunteers show hemoglobin levels as low as 5 g/dL are well tolerated so long as perfusion (ie., intravascular volume) was maintained. The ability to tolerate anemia depends on the patient's age, co-morbidities and clinical situation. Symptoms of tissue hypoxia are non-specific and may include: fatigue, lightheadedness, chest pain, shortness of breath and presyncope. Assessment of tissue hypoxia may be challenging in a critically ill patient.

The results of the TRICC (Transfusion Requirements in Critical Care) randomized controlled trial are directly applicable to this patient.[1] In this study, 838 euvolemic ICU patients with hemoglobin < 9 g/dL were randomized to two different transfusion strategies: restrictive (transfuse only if Hgb < 7 g/dL) versus liberal (transfuse only if Hgb < 10 g/dL). There was no difference in 30 day mortality (18.7 vs 23.3%), suggesting that the restrictive strategy was safe. In fact, patients randomized to a restrictive transfusion strategy had a lower likelihood of dying before discharge (22.2 vs 28.1%, p = 0.05).

Important exclusion criteria for the TRICC trial were patients with active bleeding, and patients who were admitted after a routine cardiac procedure. In addition, while subgroup analysis did not reveal any

[1] Hébert PC, Wells G, Blajchman MA, et al A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999 Feb 11;340(6):409-17. Erratum in: N Engl J Med 1999 Apr 1;340(13):1056.

advantage of a liberal transfusion strategy in patients with a history of cardiac disease, such patients represented only a quarter of those who were enrolled. Therefore, caution should be exercised in generalizing the findings of the TRICC trial to patients with chronic anemia, active bleeding, or cardiac disease. Subsequent studies of a restrictive transfusion strategies in these populations have therefore sometimes used a higher transfusion threshold of 7.5 or 8 g/dL. However, the results of the great majority of these trials have still shown that a restrictive strategy is at least as safe as a liberal approach

The literature on different Hgb thresholds for RBC transfusion is well summarized in the recent evidence-based AABB[2] and ICC-PBM[3] guidelines (Mueller et al, JAMA 2019):

- The following restrictive RBC transfusion thresholds are recommended as per AABB guidelines:
  - Transfusion is not indicated until the hemoglobin level is 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients
  - For patients undergoing orthopedic or cardiac surgery and those with preexisting cardiovascular disease, use transfusion threshold of 80 g/dL
  - These recommendations do not apply to patients with acute coronary syndrome, severe thrombocytopenia (patients treated for hematological or oncological reasons who are at risk of bleeding), and chronic transfusion–dependent anemia

- The following restrictive RBC transfusion thresholds are recommended as per the ICC-PBM guidelines:

Table 2. Clinical Recommendations: Red Blood Cell Transfusion Thresholds

Clinical Recommendation	Level of Evidence
CR5—Restrictive RBC transfusion threshold (hemoglobin concentration <7 g/dL) in critically ill but clinically stable intensive care patients	Strong recommendation, moderate certainty in the evidence of effects
CR6—Restrictive RBC transfusion threshold (hemoglobin concentration <7.5 g/dL) in patients undergoing cardiac surgery	Strong recommendation, moderate certainty in the evidence of effects
CR7—Restrictive transfusion threshold (hemoglobin concentration <8 g/dL) in patients with hip fracture and cardiovascular disease or other risk factors	Conditional recommendation, moderate certainty in the evidence of effects
CR8—Restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding	Conditional recommendation, low certainty in the evidence of effects

Abbreviations: CR, clinical recommendation; RBC, red blood cell.

  - Further research on RBC transfusion support in patients with hematologic and oncologic diseases, coronary heart diseases, noncardiac or nonorthopedic surgery, or brain injury is ongoing. Note that a recently published randomized controlled trial of RBC transfusion in patients with thrombocytopenia in the setting of stem cell transplantation did not find that maintaining a higher hemoglobin level through liberal transfusion helped decrease the risk of bleeding.[4]

[2] Carson JL, Guyatt G, Heddle NM et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016 Nov 15;316(19):2025-2035
[3] Mueller MM, Van Remoortel H, Meybohm P, et al with the ICC PBM Frankfurt 2018 Group. Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference. JAMA. 2019 Mar 12;321(10):983-997
[4] Tay J, Allan DS, Chatelain E, et al. Liberal Versus Restrictive Red Blood Cell Transfusion Thresholds in Hematopoietic Cell Transplantation: A Randomized, Open Label, Phase III, Noninferiority Trial. J Clin Oncol. 2020 May 1;38(13):1463-1473.

Another important exclusion from the TRICC trial was patients with chronic anemia. Subsequently published RCTs have suggested that in these patients, even a hemoglobin less than 7 g/dL can be well tolerated. The World Health Organization recommends not performing transfusions in African children hospitalized for uncomplicated severe anemia (hemoglobin level of 4 to 6 g/dL and no signs of clinical severity), a strategy supported by a recently published randomized controlled trial.[5] Most of the children in this study had malarial anemia; patients with sickle cell disease were excluded. Given the complexity and risk of transfusion decisions in patients with hemoglobinopathies, transfusions should only be ordered for this population in consultation with a hematologist.

In general, given the cost, risk and scarcity of blood, an RBC transfusion should only be pursued if the patient truly requires an increase in their hemoglobin, and an RBC transfusion is the only option to accomplish that.

2) Which of the following strategies may minimize the patient's need for future RBC transfusion?
   A) Minimize unnecessary diagnostic phlebotomy
   B) Start an erythropoiesis stimulating agent
   C) Start B12 supplementation
   D) Start iron supplementation

Anemia is common in critically ill patients and is frequently treated with RBC transfusions, even in the absence of bleeding. In a 2004 study of 4 892 patients admitted to ICUs in the United States, for example, 44% of patients received at least one RBC transfusion while they were admitted, with only 24% transfused to treat active bleeding. This patient's anemia is likewise not apparently due to bleeding and is likely a result of both frequent phlebotomies for laboratory testing and inhibited erythropoiesis from inflammation and malnutrition. The ICU team may therefore consider the following strategies: reduce unnecessary phlebotomies, prescribe an erythropoiesis-stimulating agent (ESA) such as erythropoietin, or provide increased nutritional support (ie., iron, B12, or folate supplements)

The benefits of ESA therapy in critically ill patients are marginal. A 2007 meta-analysis of 9 randomized controlled trials did find that critically ill patients prescribed an ESA had their risk of transfusion decreased by approximately 25%; however, the average number of RBCs transfused was only 0.41 units less than amongst patients not prescribed an ESA.[6] Had these patients all been managed with a restrictive transfusion strategy, the benefit of ESA would likely have been even smaller. Given the cost and potential risk of thrombosis, ESA treatment is rarely indicated in critically ill patients.

There is little evidence that iron supplementation is of benefit in this setting as well. In a randomized controlled trial of IV iron in 150 patients with anemia in the setting of traumatic critical illness, no effect was observed on hemoglobin levels or transfusion requirements, despite the fact that the majority had

[5] Maitland K, Kiguli S, Olupot-Olupot P, Engoru C, Mallewa M, Saramago Goncalves P, Opoka RO, Mpoya A, Alaroker F, Nteziyaremye J, Chagaluka G, Kennedy N, Nabawanuka E, Nakuya M, Namayanja C, Uyoga S, Kyeyune Byabazaire D, M'baya B, Wabwire B, Frost G, Bates I, Evans JA, Williams TN, George EC, Gibb DM, Walker AS; TRACT Group. Immediate Transfusion in African Children with Uncomplicated Severe Anemia. N Engl J Med. 2019 Aug 1;381(5):407-419

[6] Zarychanski R, Turgeon AF, McIntyre L, et al. Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. CMAJ 2007; 177(7):725-34

evidence of iron-restricted erythropoiesis.[7] Given the cost and increased risk of infection that accompanies IV iron therapy,[8] its use cannot be advocated in critically ill patients. Importantly, however, less than 2% of patients enrolled in this study had serum ferritin levels < 28 µg/L, indicating true iron deficiency. In such patients, iron repletion therapy may still be of some benefit. B12 deficiency is so rare in critically ill patients that routine supplementation cannot be justified.[9]

Preventing iatrogenic anemia is therefore the best course of action and A is thus the best answer. Multiple studies have shown that patients admitted to hospital routinely lose 50 mL or more of blood per day to samples drawn for laboratory testing.[10] Strategies that have been shown to decrease the amount of phlebotomy losses include the use of devices that return blood from testing or flushing lines to the patient, and transition to small volume tubes for lab tests. These tubes are of the same size and cost the same; however they have less vacuum and as a result, draw 25-50% less blood into the tube.[11] The most effective strategy, however, is to avoid the reflexive ordering of laboratory testing which is unlikely to provide new or useful information fir the management of the patient.

3) You review the patient's laboratory results and notice that his troponin is significantly elevated. Troponin was ordered to further investigate an episode of rapid atrial fibrillation and ST changes earlier in the morning. Which one of the following represents the best transfusion strategy for this patient?

   A) No transfusion is needed at this time
   B) Transfuse 1 unit RBC rapidly
   C) Transfuse 1 unit RBC over 3 hours
   D) Transfuse 2 units RBC rapidly

The impact of red blood cell transfusion on outcomes in patients with acute coronary syndrome is controversial. A 2018 systematic review examined the association between blood transfusion and the risk for all-cause mortality and reinfarction, drawing data from 17 observational studies, 2 525 550 subjects, and follow-up period ranging from 30 days to 5 years.[12] Red blood cell transfusion (compared with no blood transfusion) was associated with higher short- and long-term all-cause mortality as well as reinfarction rates (adjusted RR 2.23 and 2.61, respectively). In hemoglobin-stratified analyses, a graded association between red blood cell transfusion and mortality was observed, transfusion and risk of all-cause mortality was borderline significant at hemoglobin levels below 8 g/dL (RR 0.52), and was associated with an increased risk of mortality at a hemoglobin above 10 g/dL (RR 3.34). The authors

[7] Pieracci FM, Stovall RT, Jaouen B, Rodil M, Cappa A, Burlew CC, Holena DN, Maier R, Berry S, Jurkovich J, Moore EE. A multicenter, randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness*. Crit Care Med. 2014 Sep;42(9):2048-57
[8] Shah AA, Donovan K, Seeley C, Dickson EA, Palmer AJR, Doree C, Brunskill S, Reid J, Acheson AG, Sugavanam A, Litton E, Stanworth SJ. Risk of Infection Associated With Administration of Intravenous Iron: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Nov 1;4(11):e2133935
[9] Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. J Crit Care. 2001 Mar;16(1):36-41
[10] Shander A, Corwin HL. A Narrative Review on Hospital-Acquired Anemia: Keeping Blood where It Belongs. Transfus Med Rev. 2020 Jul;34(3):195-199.
[11] Whitehead NS, Williams LO, Meleth S, et al. Interventions to prevent iatrogenic anemia: a Laboratory Medicine Best Practices systematic review. Crit Care. 2019 Aug 9;23(1):278
[12] Wang Y, Shi X, Du R, Chen Y, Zhang Q. Impact of red blood cell transfusion on acute coronary syndrome: a meta-analysis. Intern Emerg Med. 2018 Mar;13(2):231-241

concluded that transfusion had beneficial or neutral effects on mortality at hemoglobin levels below 8 g/dL, and harmful effects above 10 g/dL. This review suggests that there is no absolute threshold and the optimal, evidence-based approach has not been yet determined. The recently published RCT REALITY has shown that in patients with AMI restrictive transfusion strategy (Hgb 8 g/dL or below) was non-inferior to liberal strategy (Hgb 10 g/dL or below).[13] A large definitive randomized controlled trial addressing this issue is underway (MINT): 3 500 patients with AMI randomized to restrictive strategy (Hgb less than 8 g/dL) versus liberal strategy (Hgb less than 10 g/dL).

A reasonable approach in this situation would be to transfuse when Hgb <8 g/dL, one unit of RBC at a time and at a slow rate to prevent volume overload while frequently reassessing symptoms. Transfusion of RBC beyond hemoglobin of 10 g/dL may be harmful.

Case 2

25 year old female with no significant past medical history, is seen in the emergency room with "a critically abnormal laboratory result", a hemoglobin of 6 g/dL. She has a long-standing history of menorrhagia and was sent to the ER by her family MD. On questioning, she endorses fatigue and reduced stamina but remains active and continues working full time. Her CBC reveals Hgb 6 g/dL, MCV 65 fL, platelets 487 x 10^9/L, coagulation studies are normal.

4) Which of the following represents the <u>least</u> appropriate intervention?
   A) Intravenous iron
   B) Oral iron
   C) Referral to gynecology
   D) Transfusion of RBC

This patient likely has iron deficiency anemia related to her menorrhagia. Because of the chronicity of the problem, she is only minimally symptomatic. Diagnosis of IDA can be confirmed by ordering iron studies. IDA is the most common nutritional deficiency anemia, and an estimated 10-40% of women are iron deficient.

This patient does not require a transfusion. In addition to usual risks associated with transfusion, consider the risk of RBC antigen alloimmunization in a young, potentially child-bearing woman; and volume overload since her anemia is euvolemic. Do not transfuse RBC unless clear and worrisome symptoms of anemia (tachycardia, hypotension, chest pain, shortness of breath, pre-syncope).

She should be referred to hematology for anemia management and perhaps to rule out a bleeding disorder, and to gynecology to manage her menorrhagia. She should receive iron – either oral or intravenous. The advantages of oral iron are reduced cost and ability to take at home, but absorption is poor (only 10% of the elemental iron taken by mouth is actually absorbed), meaning that replenishment is very slow.

[13] Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial. JAMA. 2021 Feb 9;325(6):552-560

Oral iron also causes gastrointestinal side effects, which is a common cause of non-compliance. Newer oral iron formulations appear to be inferior to older ferrous salt formulations. Ferrous salts improve hemoglobin up to 2 g/dL more with one in five more attaining iron deficiency anemia resolution at 3-months. Evidence that newer formulations have less adverse effects is also inconsistent and not supported by published literature.[14]

Intravenous iron has the advantage of much more rapid treatment – depending on the formulation used, a total target dose of 1 gram of iron can be administered over 1 to 3 infusions. However, it is more expensive than oral iron and requires a healthcare worker to administer and monitor. Side effects include[15]

- Metallic taste, headache, nausea, vomiting, diarrhea, abdominal pain, back pain, muscle cramps, arthralgias, infusion site reactions
- Fishbane reaction (facial flushing, myalgia, arthralgia, chest pain)
- Hypersensitivity reaction including anaphylaxis

Case 3

A 2 year-old female is seen because of pallor and her mother feels that she is less active than the other toddlers. Nutritional history indicates that the child is no longer breast feeding and her diet consists primarily of maize porridge. There is no history of fever and no splenomegaly on examination. CBC shows hemoglobin 7.9 g/dL, MCV 72 fL, WBC 7.9 x 10^9/L, platelets 475 x 10^9/L.

5) Which of the following is the most appropriate management of this child's anemia?
   A) Empiric treatment of malaria, followed by IV iron weekly for 6 weeks
   B) Resume breastfeeding
   C) Provide nutritional consultation and oral iron supplementation
   D) Transfuse a weight-based dose of RBCs

Iron deficiency in children is very common in many parts of Africa, and has been estimated to affect approximately 1 in 5 children under age two in Southern Rwanda.[16] Studies show that iron deficiency in children is associated with learning disabilities. Causes include poor diet, low iron content in the soil where crops are grown, and malabsorption secondary to intestinal parasites, or chronic inflammation (eg., recurrent malaria). Improving dietary iron (eg., introduction of fish or other animal protein sources) and providing iron supplements, typically at a dose of 3-6 mg/kg per day of elemental iron for 3 months, is the preferred treatment. A meta-analysis found little evidence that augmenting oral iron intake increases the risk of malaria in children living in endemic areas.[17] Whether or not the same is true for intravenous infusions of iron, the cost and inconvenience of arranging them is probably not justified in this case. Similarly, while transfusing RBCs will result in the most rapid increase in hemoglobin of all the above options, the cost and risk is not justified for this degree of anemia. Finally, while breastmilk is

[14] https://www.cadth.ca/sites/default/files/pdf/htis/jan-2016/RC0735%20Oral%20Iron%20Final.pdf and http://campaign.r20.constantcontact.com/render?m=1126690796893&ca=8fe7f43e-95dc-4dea-b378-f734e4d72c11
[15] Lim W, Afif W, Knowles S, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. Vox Sang. 2019 May;114(4):363-373
[16] Lemoine A, Tounian P. Childhood anemia and iron deficiency in sub-Saharan Africa - risk factors and prevention: A review. Arch Pediatr. 2020 Nov;27(8):490-496
[17] Gera T, Sachdev HS, Boy E. Effect of iron-fortified foods on hematologic and biological outcomes: systematic review of randomized controlled trials. Am J Clin Nutr. 2012 Aug;96(2):309-24.

an important source of iron for newborns, and is much superior to cow's milk, it is generally insufficient to meet nutritional needs after 6 months of age and cannot be relied upon as a treatment of this child's iron deficiency.[18]

Case 4

A 27 year-old man with acute myeloid leukemia is admitted for induction chemotherapy. He is afebrile. He denies bleeding but examination reveals numerous petechiae on his lower extremities and a few large ecchymoses on his extremities and trunk. Morning CBC reveals Hgb 7.3 g/dL and platelets 5 x 10^9/L. Review of his recent CBC results indicates that his platelet count has not been above 10 for the past two weeks, despite being transfused platelets two to three times per week.

6) In addition to investigating the cause of the patient's high platelet transfusion requirements, which one of the following is the most appropriate transfusion strategy for this patient?
   A) Only transfuse platelets in the presence of active bleeding
   B) Start the patient on tranexamic acid
   C) Transfuse 1 adult dose of platelets today
   D) Transfuse 2 adult doses of platelets today

Platelet transfusion guideline is provided below:

Platelet count (x 10^9/L)	*Clinical Setting*	*Recommendation*
< 10	Hypoproliferative (eg., not ITP, DIC, etc)	Transfuse 1 adult dose
< 20	Procedures not associated with significant blood loss (eg., central line placement)	Transfuse 1 adult dose
< 30	Patients on anticoagulants that must remain at full dose (eg., proximal leg DVT < 30 days ago)	Transfuse 1 adult dose
20 - 50	Procedures not associated with significant blood loss (eg., central line placement)	Have 1 adult dose on hand but only transfuse if significant bleeding
< 50	1. Significant bleeding, or 2. Prior to major surgical procedures	Transfuse 1 adult dose immediately pre-procedure
< 50	Immune thrombocytopenia	Transfuse 1 adult dose only if life-threatening bleeding
< 100	1. Neurosurgical procedure 2. Traumatic brain injury/intracranial hemorrhage	Transfuse 1 adult dose
Any	Platelet dysfunction with significant hemorrhage (eg., post-cardiopulmonary bypass)	Transfuse 1 adult dose

In the above table, one adult dose of platelets refers to a pool of platelet concentrates obtained from 4-6 whole blood donations, or a platelet product collected by apheresis. Either way, the total number of platelets in an adult dose is typically 3 x 10^{11}/L in approximately 300 mL of plasma. The majority of these recommendations are based on expert opinion and are not evidence based.

[18] Tounian P, Chouraqui JP. Fer et nutrition [Iron in nutrition]. Arch Pediatr. 2017 May;24(5S):5S23-5S31. French.

However, randomized controlled trials have established that in patients with hypoproliferative thrombocytopenia (ie., not due to immune thrombocytopenia), transfusing platelets prophylactically whenever the platelet count is < 10 x 10^9/L decreases the risk of spontaneous bleeding, and the risk of spontaneous bleeding increases the longer the platelet count is below this threshold.[19] Therefore, unless this patient's platelet count is expected to increase on its own in the next few days, withholding platelet transfusion is likely to increase the risk of bleeding; in certain circumstances, such as the presence of fungal pneumonia, this bleeding may be fatal.[20] On the other hand, several trials have shown that there is no clinical benefit in prophylactically transfusing hypoproliferative thrombocytopenia at thresholds higher than 10 x 10^9/L, or with using larger than standard doses of platelets.[21] Tranexamic acid may be considered an alternative to platelet transfusions in thrombocytopenic patients for whom platelet products are unavailable. However, there is no evidence to date that this results in equivalent hemostasis; in fact, adding tranexamic acid to prophylactic platelet transfusions doesn't appear to provide any increment benefit.[22]

7) You suspect that he has developed platelet transfusion refractoriness due to antiplatelet antibodies. Which one of the following investigations is <u>least</u> likely to help you determine the cause of the refractoriness?

A) Bone marrow aspirate and biopsy
B) HLA antibody screen
C) Panculture to look for occult infection
D) Platelet count measured one hour post platelet transfusion

Platelet refractoriness is a persistent lack of response to platelet transfusion. It may result from non-immune factors (majority of cases: sepsis, splenomegaly, medications, thrombosis, DIC, bleeding) vs. immune factors (minority of cases: alloimmunization to human leukocyte antigens (HLA), human platelet antigens (HPA), or both, or other platelet antigens). To distinguish which is occurring, the preferred investigation is to select a relatively fresh (eg., less than 4 days from time of collection) and ABO identical platelet product and then measure the patient's platelet increment no more than hour after transfusion. Even when removing the confounding effects of ABO group and product age, the observed increment will still vary depending on how many platelets are transfused and the patient's body surface area, and the formula for a corrected count increment incorporates for those factors. However, an average adult-dose of platelets transfused to an average adult patient should cause the platelet count to increase by at least 10 10^9/L. If the platelet count hasn't increased by at least this much even an hour after transfusion, it is very likely that the patient has immune-mediated platelet refractoriness, due to either autoantibodies (ie., immune thrombocytopenia) or alloantibodies to HLA or HPA antigens. A variety of methods are available to detect these antibodies, but are rarely available at the local hospital and will therefore need to be referred out. Once confirmed, the blood supplier may be able to select platelet products that are matched for those antibodies. However, the entire process may take a week or longer, and therefore investigations should start as soon as refractory thrombocytopenia is observed.

[19] Stanworth SJ, Estcourt LJ, Powter G, et al. N Engl J Med. 2013 May 9;368(19):1771-80.
[20] Wandt H, Schaefer-Eckart K, Wendelin K,. Lancet. 2012 Oct 13;380(9850):1309-16.
[21] Kumar A, Mhaskar R, Grossman BJ, et al. Transfusion. 2015 May;55(5):1116-27.
[22] Gernsheimer TB, Brown SP, PhD, Triulzi DJ, MD, Blood 2020.136 (Supp 1): 1–2

8) The patient is transitioned to ABO-identical, fresh platelets and on two occasions the 1-hour increment in platelet count was < 10 10^9/L. A sample of patient plasma is sent to a referral laboratory to assess for anti-HLA antibodies, and the blood supplier is notified that HLA-matched platelets may be required, if available. Which one of the following is the <u>least</u> appropriate management strategy while awaiting arrival of HLA-selected platelets?

A) Give IVIg 1g/kg daily
B) Give oral tranexamic acid to treat minor bleeding
C) Transfuse pooled, ABO compatible and freshest available platelets
D) Transfuse platelets only to treat clinically significant bleeding

Patients with alloimmune refractoriness should be managed with HLA selected platelets. Often HLA selected platelets are referred to as HLA matched platelets but these two products are different. HLA selected platelets are antigen negative for the HLA antibodies which the patient has developed, and not necessarily HLA matched for the patient's HLA phenotype, and may therefore provoke the appearance of other antibodies. However, they are often easier to source than HLA-matched platelets and should be selected if that is the only product available. If even HLA-selected products aren't selected, the best odds of avoiding the patient's HLA antibodies are to select products pooled from several donors, while also minimizing the clearance that accompanies ABO-mismatched or older platelet products. If these continue to produce even a short-term increment in platelet count, then there is no point in transfusing prophylactically, and platelet transfusion should be attempted only for treatment of serious bleeding. Minor bleeding may be managed with tranexamic acid. Immunomodulation with IVIG, steroids, etc. to manage alloimmune refractoriness is ineffective and is not recommended, unless there is suspicion that the patient has an autoantibody (ie, immune thrombocytopenia)

Case 5a

A 69 year old male is admitted via ER with acute subdural hematoma following a fall. He is known to have liver cirrhosis due to alcohol. His CBC revealed Hgb 12.5 g/dL and platelets 75 x 10^9/L. His INR was 1.3. He is scheduled for a burr hole surgery later this evening.

9) Which one of the following represents the most appropriate transfusion strategy?

A) No need for platelet transfusion
B) Transfuse 1 adult dose of platelets and repeat CBC
C) Transfuse 1 adult dose of platelets only if significant intra-operative bleeding
D) Transfuse 2 adult doses of platelets

See answer to question 1, case 1 above. Even though not based on evidence, usually platelet transfusion is recommended for patients going for neurosurgical procedures/intracerebral bleeding to maintain platelet count above 100 x 10^9/L. Transfuse 1 adult dose of platelets and monitor clinically for bleeding and with regular CBC. In this situation, the platelet count may not increase, or may decrease very rapidly, due to the presence of splenomegaly from the patient's portal hypertension. If this is observed, it may not be necessary to repeatedly transfuse platelets to achieve a platelet count of 100 x10^9/L,

especially since the platelets sequestered in an enlarged spleen are often still viable and can be released back into circulation (eg., in response to epinephrine), where they can contribute to hemostasis.[23]

Case 5b

An 80 year-old male on aspirin and clopidogrel presents with spontaneous ICH. His GCS is 15 and no surgical intervention is planned. His platelet count is 249 x 10^9/L and INR and aPTT are normal.

10) Which one of the following is the most appropriate therapy?
   A. 1 adult dose of platelets
   B. 2 adult doses of platelets
   C. PCC 50IU/kg IV and Vitamin K 10 mg IV
   D. None of the above

Platelet transfusion can be used to reverse the effects of anti-platelet drugs. Clopidogrel is an oral pro-drug and its active metabolite irreversibly binds and inhibits the ADP receptor $P2Y_{12}$ thus blocking platelet activation. The plasma half-life of this drug is 7-8 hours while the half-life of its active metabolite is less than 1 hour.[24] However, its antiplatelet effect can last for up to 5 days. There are no reliable, readily available tests to diagnose Clopidogrel-associated platelet dysfunction. There are also no clinical studies examining efficacy of platelet transfusions to manage bleeding in the setting of a platelet dysfunction due to antiplatelet agents. Most studies to date have assessed the effect of antiplatelet agents by measuring in vitro platelet function pre and post transfusion of normal donor platelets, and it is not clear if these results translate to in vivo clinical outcomes. The PATCH trial, in fact, has shown that transfusing platelets to reverse the effect of drug-induced thrombasthenia can actually worsen outcomes.[25] In this randomized controlled trial, patients on antiplatelet medications with spontaneous intracerebral hemorrhage, actually had a higher rate of bleeding (25% vs 14%) as well as thrombotic complications (4% vs 1%) if they were transfused platelets, results that were accompanied by an overall worse functional status and mortality rate. . In view of this trial, routine transfusion of platelets in this situation is not recommended. Although this study was limited to patients with spontaneous intracranial hemorrhage, caution should be exercised when transfusing platelets to thrombasthenic patients with other types of bleeding (eg., peptic ulcers in patients taking NSAID therapy). Whenever possible, surgical control of bleeding should be prioritized in these patients.

[23] Bakovic D, Pivac N, Eterovic D, et al. Clin Physiol Funct Imaging. 2013 Jan;33(1):30-7
[24] Scharbert G, Wetzel L, Schrottmaier WC, Kral JB, Weber T, Assinger A. Comparison of patient intake of ticagrelor, prasugrel, or clopidogrel on restoring platelet function by donor platelets. Transfusion. 2015 Jun;55(6):1320-6.
[25] Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, Nederkoorn PJ, de Haan RJ, Roos YB; PATCH Investigators. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet. 2016 Jun 25;387(10038):2605-2613.

Transfusion Camp Rwanda
June 4th 2022
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.

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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.

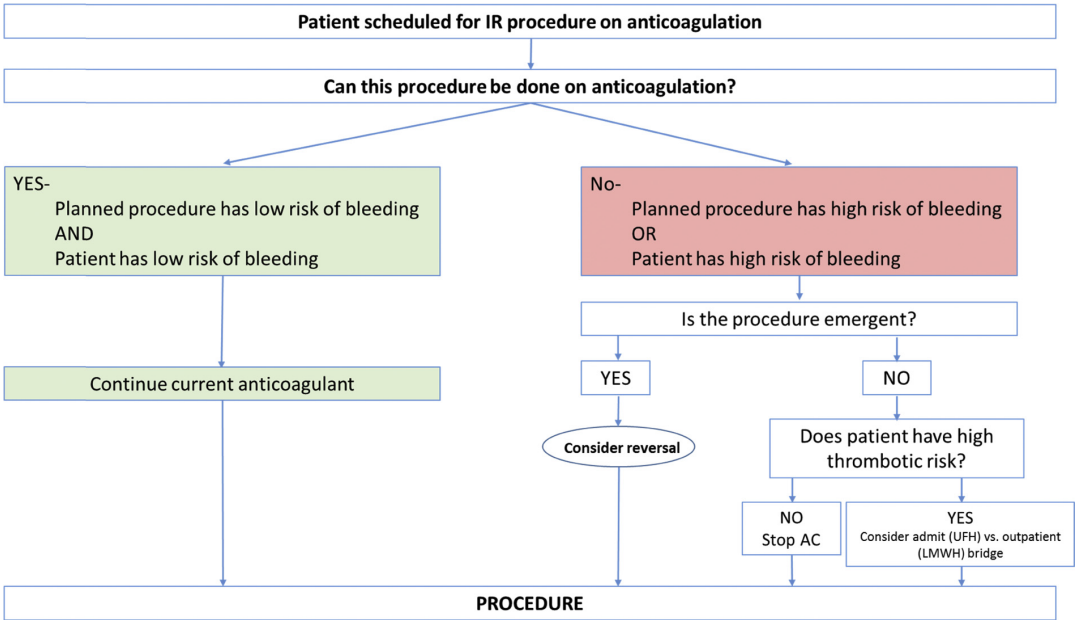

Table 2. Decision making guide for patients with coagulopathy NOT related to an anticoagulant or liver disease (cirrhosis). Low risk and high risk procedure list see Table 1.

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.