Transfusion Camp 2021-2022
Day 1: Seminar 1A, September 17, 2021
Triggers for RBC and platelet transfusions, Dr. Katerina Pavenski

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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

27 yo male 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 Hb 73g/L and platelets $5x10^9$/L. Review of his recent CBC results indicates that his platelet count has not been above 10 for at least a week, despite daily or sometimes twice daily platelet transfusions.

1) **In addition to investigating the lack of post-transfusion platelet count increment, which one of the following is the most appropriate transfusion strategy for this patient?**
   - **A) No point in transfusing him as platelet count doesn't go up**
   - **B) Order a slow drip of platelets to continue throughout the day**
   - **C) Transfuse 1 adult dose of platelets today**
   - **D) Transfuse 2 adult doses of platelets today**

Platelet transfusion guideline is provided below:

<10	Hypoproliferative (non-immune) thrombocytopenia	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 should not be stopped	Transfuse 1 adult dose
20-50	Procedures not associated with significant blood loss	1 adult dose on hold, transfuse only if significant bleeding
<50	Significant bleeding Pre-major surgery, lumbar puncture, epidural anaesthesia	Transfuse 1 pool immediately before procedure
<50	Immune thrombocytopenia	Transfuse platelets only with life-threatening bleeding
<100	CNS surgery, ICH, TBI	Transfuse 1 adult dose
Any	Platelet dysfunction *and marked bleeding* (e.g. post cardiopulmonary bypass, aspirin, or other antiplatelet agents)	Transfuse 1 adult dose

The majority of these recommendations are based on expert opinion and are not evidence based. For patients with hypoproliferative thrombocytopenia, a trigger of 10 is as safe as a trigger of 20 (Rebulla et al 1997). Platelets are ordered for these patients only when the platelet count drops into the single digit range (recent platelet guidelines: AABB Kaufmann et al 2015; ICTMG Nahirniak et al 2015; BSH Estcourt et al 2016).

What is meant by 1 adult dose? 1 adult dose of platelets may come in the form of 1 pooled platelet (from 4 donor units in 1 bag) or 1 apheresis unit.

2) **You suspect that he has developed platelet transfusion refractoriness. 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.

Platelet refractoriness 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).

Lack of or inadequate platelet count increment (definitions vary; may use absolute increment of $<20x10^9$/L) following transfusion of one fresh (freshest available, <4 days old), ABO identical adult platelet dose (1 BC pool or 1 apheresis concentrate) is consistent with platelet refractoriness. Both ABO platelet incompatibility and older product age have been associated with worse increments. Investigation to rule out non-immune factors should be performed (panculture, imaging for splenomegaly, review medications, etc.). To investigate for alloimmunization, send patient's sample to TM laboratory for platelet antibody screen (HLA antibodies (at Canadian Blood Services, performed by Luminex flow cytometry); HPA antibodies (at Canadian Blood Services, ELISA or MAIPA).

Poor one hour post platelet count increment is suggestive of immune refractoriness.

3) **His investigations are consistent with alloimmune refractoriness and you request HLA-selected platelets. 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 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, and not necessarily HLA matched. HLA typing and collection of HLA selected platelets may take up to 7 days. In the meantime, the patient may be supported with ABO identical, freshest available platelets. It is also reasonable to stop prophylactic transfusions and limit platelet transfusions to management of significant bleeding. Minor bleeding may be managed with tranexamic acid. Immunomodulation with IVIG, steroids, etc. to manage alloimmune refractoriness is ineffective and is not recommended.

Case 2a

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 125g/L and platelets 75x10^9/L. His INR was 1.3. He is scheduled for a burr hole surgery later this evening.

4) 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 100x10^9/L. Transfuse 1 adult dose of platelets and monitor clinically for bleeding and with regular CBC.

Case 2b

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.

5) 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 (Scharbert et al Transfusion 2015). 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. To reverse the effect of clopidogrel, use of higher platelet doses (2-5 adult platelet doses) has been suggested (Hansson et al BJH 2014, Vilahur et al JTH 2006). Clopidogrel has no effect on transfused platelet function (Scharbert et al Transfusion 2015).

Until recently, the recommendation was to transfuse 2 adult doses of platelets and monitor clinically (or radiographically) for ongoing bleeding. However, PATCH RCT (Lancet 2016) has shown that in patients on antiplatelet medications and who present with a spontaneous intracerebral hemorrhage, transfusion of platelets was associated with inferior outcomes. In view of this trial, routine transfusion of platelets in this situation is not recommended.

Case 3

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 CABG approximately 5 years ago. He is on antibiotics and 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 79 g/L.

6) **Which of the following represents the most appropriate RBC transfusion strategy for this patient?**
   - **A) Transfuse RBCs if Hgb <100 g/L**
   - **B) Transfuse RBCs if Hgb <90 g/L**
   - **C) Transfuse RBCs if Hgb <80 g/L**
   - **D) Transfuse RBCs if Hgb <70 g/L**

Does this patient require RBC transfusion? No.

Red blood cells are transfused to increase oxygen delivery to the tissues. Normal healthy volunteers may tolerate hemoglobin levels as low as 50 g/L. 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.

TRICC RCT trial findings are directly applicable to this patient (Hebert et al. NEJM 1999; 340: 409-417. A multicenter, randomized, controlled clinical trial of transfusion requirements in critically ill patients). 838 ICU patients were randomized to two different transfusion strategies: restrictive (transfuse only if Hgb < 70 g/L) versus liberal (transfuse only if Hgb < 100 g/L). There was no difference in 30 d mortality (18.7 vs 23.3%), suggesting that restrictive strategy was safe. However, patients with severe cardiac disease were less often enrolled in the trial so this study may not be generalizable to patients with active coronary ischemic syndromes.

The discussion on triggers is well summarized in the recent evidence-based AABB guidelines (Carson et al 2016) and ICC-PBM guidelines (Mueller et al, JAMA 2019):

- The following **restrictive** RBC transfusion thresholds are recommended as per AABB guidelines (Carson et al 2016):
  - Transfusion is not indicated until the hemoglobin level is **70g/L** 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 **80g/L**
  - 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 (Mueller et al, JAMA 2019):

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.

7) 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

What is the likely cause of his anemia?

About 65% of patients in critical care units are anemic (Hgb<120g/L) and 40-50% of these patients are transfused. About 90% of transfusions in the ICU are given to non-bleeding patients (Holst 2013). This patient's anemia is likely iatrogenic (multiple phlebotomies for blood work in the ICU), but may also be exacerbated by anemia of chronic disease and bone marrow suppression by infection.

ICU team may consider the following: reduce unnecessary phlebotomies, diagnose and treat anemia, start hematinics (iron, B12, folate) and/or ESA. Of note, evidence for ESA in critically

ill patients is controversial (ESA reduces odds of transfusion and number of units transfused but effects are minimal – systematic review by Zarychanski et al CMAJ 2007). Iron supplementation is also controversial – efficacy, safety and cost. B12 supplementation will only work if patient is Vitamin B12 deficient. Preventing iatrogenic anemia is the best course of action. A is thus the best answer. Another approach may involve different test tubes. For example, some hospitals have implemented 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.

8) 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

Impact of red blood cell transfusion on acute coronary syndrome: a meta-analysis. Wang et al Intern Emerg Med 2018. The impact of red blood cell transfusion on outcomes in patients with acute coronary syndrome is controversial. This systematic review examined the association between blood transfusion and the risk for all-cause mortality and reinfarction. It included 17 observational studies, 2,525,550 subjects, and follow-up period ranging from 30 days to 5 years.

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; 95% CI 1.47-3.39; HR 1.93; 95% CI 1.12-3.34; RR 2.61; 95% CI 2.17-3.14, 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 80g/L (RR 0.52; 95% CI 0.25-1.06), and was associated with an increased risk of mortality at a hemoglobin above 100g/L (RR 3.34; 95% CI 2.25-4.97). The authors concluded that transfusion had beneficial or neutral effects on mortality at hemoglobin levels below 80g/L, and harmful effects above 100g/L.

This review suggests that there is no absolute threshold and the optimal, evidence-based approach has not been yet determined. A reasonable approach would be to transfuse when Hgb<80g/L, 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 100g/L may be harmful.

The recently published RCT REALITY has shown that in patients with AMI restrictive transfusion strategy (Hgb 80g/L or below) was non-inferior to liberal strategy (Hgb 100g/L or below) (Ducrocq et al JAMA 2021). A large definitive randomized controlled trial addressing this issue is underway (MINT): 3500 patients with AMI randomized to restrictive strategy (Hgb less than 80g/L) versus liberal strategy (Hgb less than 100g/L).

Case 4

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 60g/L. 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 with her weekly spinning classes. Her CBC reveals Hgb 60 g/L, MCV 65fL, platelets 487 x 10(9)/L; coagulation studies are normal.

9) 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 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.

Oral iron supplement	Dose, mg	Elemental mg	Cost (2020), $
Ferrous gluconate	300	35	0.13
Ferrous sulfate	300	60	0.03
Ferrous fumarate	300	100	0.13-0.43
Iron Polysaccharide (Feramax, Triferex)	150	150	0.71-0.92
Heme Iron (Proferrin, Optifer)	398	11	0.86-1.03

- Oral iron:
  - Advantages: inexpensive (over the counter), available
  - Disadvantages: absorption only 10% of elemental Fe, takes a long time to correct anemia and replenish iron stores
  - Adverse effects: GI side effects -> non-compliance

Newer oral iron formulations appear to be inferior to older ferrous salt formulations. Ferrous salts improve hemoglobin up to 20g/L more with one in five more attaining IDA resolution at 3-months. Evidence that newer formulations have less adverse effects is also inconsistent and not supported by published literature (References: 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 Accessed 2020 July)

IV Iron Supplement	Iron sucrose (Venofer)	Iron isomaltoside (Monoferric)
MW (kDa)	43	150
Plasma ½ life	6 hours	1 to 4 days
Max single dose	300 mg	20mg/kg (up to 1500mg)
Test dose	No	No
Cost	$37.50 (100mg)	$48.60 (100mg)
Life threatening ADE	0.6 per 10^6	

IV iron:

- Adverse effects (for more reading, see Lim et al Vox Sanguinis 2019; **https://doi.org/10.1111/vox.12773**)
  - 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
- Disadvantages: cost, availability, need for a hospital visit
- Advantages: rapidly effective

Case 5.

A 2.5 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 a fussy eater and continues to drink as many as 6 bottles of homogenized milk per day. CBC shows hemoglobin 79 g/L, MCV 72 fL, WBC 7.9 x 10^9/L, platelets 475 x 10^9/L.

10) Which of the following is the most appropriate management of this child's anemia?

A) Administer IV iron weekly for 6 weeks
B) Increase dietary iron intake
C) Provide nutritional intervention and oral iron supplementation
D) Transfuse a weight-based dose of RBCs

- No different than adult management except
    - Liquid supplementation and dose is 6mg/kg elemental iron
    - Get rid of bottle
    - Limit milk intake to 10-18 ounces per day
- Studies show that iron deficiency in children is associated with learning disabilities.