Transfusion Camp 2023-24
Day 1: Seminar 1A, September 22, 2023
Triggers for RBC and platelet transfusions, Dr. Sebastian Vuong & Dr. Shuoyan Ning

---

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

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.

1) **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 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.

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

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.

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

In patients with ACS (including MI), a reasonable approach is a threshold of 80g/L, although there is no absolute evidence-based threshold in this patient population.

The recently published REALITY trial (Ducrocq et al JAMA 2021), a non-inferiority RCT, randomized 668 adults with AMI to a restrictive (<80g/L) vs liberal (<100g/L) arms. For the primary outcome of MACE including death after 30 days, restrictive was non inferior to liberal strategy; the outcome occurred in 11% of patients in the restrictive arm, compared to 14% of patients in the liberal arm. The study was not powered to evaluate superiority. A large study called Myocardial Ischemia and Transfusion (MINT) is currently underway which is evaluating 3500 patients with ACS (80g/L vs 100g/L groups) and is powered to evaluate superiority. Previously published systematic reviews based on less robust evidence suggests that transfusion to Hb > 100 may be harmful (Wang et al. Intern Emerg Med 2018).
Note that the latest AABB guidelines for RBC transfusions was published in 2016 and did not include the results/recommendations from the REALITY trial.

Case 2

27 yo patient with acute myeloid leukemia is admitted for induction chemotherapy. The patient is afebrile. The patient denies bleeding but examination reveals numerous petechiae on the lower extremities and a few large ecchymoses on the extremities and trunk. Morning CBC reveals Hb 73g/L and platelets $5x10^9$/L. Review of recent CBC results indicates that the platelet count has not been above 10 for at least a week, despite daily or sometimes twice daily platelet transfusions.

4) **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 the patient 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. Some of the cutoffs are controversial and vary between institutions – for example, < 80 is used by some centers for epidural anaesthesia as opposed to 50 as indicated in the table above. 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). A recently published trial (van Baarle et al. NEJM 2023), randomizing patients receiving CVC lines (plt count 10-50) reported that no PLT transfusion did not meet non inferiority compared to transfusion prior to line placement. Grade 2-4 catheter related bleeding occurred in 11.9% versus 4.8% of non transfused and transfused patients, respectively); risks were highest for tunneled catheters and among hematology patients. In subgroup analysis, the relative risk of bleeding was higher in the no transfusion group in subclavian vein insertion group (vs. no difference in internal jugular site) and hematology ward patients (vs no difference in ICU patients).

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 for non pathogen reduced platelets, and 7 donors pooled for pathogen reduced platelets which is then split into 2 individual platelet doses) or 1 apheresis unit. Educational materials are available on ProfEdu

(https://professionaleducation.blood.ca/en/transfusion/clinical-guide/pathogen-reduced-platelets).

In this case, it is still not yet clear if the cause of platelet refractoriness is non-immune or immune without additional investigations. Trial of an additional platelet transfusion (ABO identical, fresh platelet) while conducting additional investigations (discussed in question 2) is reasonable in a patient with hypoproliferative thrombocytopenia < 10, and petechiae/ecchymosis.

5) **You suspect that the patient has developed platelet transfusion refractoriness. Which of the following investigations is NOT required to help you establish 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 within the first 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. Pathogen reduced platelets may yield lower count increments than non pathogen reduced platelet transfusions. 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.

6) **The investigations are consistent with alloimmune refractoriness and you request HLA-selected platelets. Please select the management strategythat would be least appropriate 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.

Other potential therapeutic options include tranexamic acid, although efficacy may be limited.The a-TREAT trial published in 2022 by Gernsheimer et al. was an RCT that randomized 337 patients with hematologic malignancy and platelet count < 30 to prophylactic TXA or placebo for the prevention of bleeding. Trial reported no difference at 30 days in the mean number of platelet transfusions, WHO grade 2+ bleeding, thrombotic events or deaths due to serious bleeding. Patients also received platelet transfusions if counts are less than 10. This study was not designed/powered to evaluate the efficacy of TXA in patients with active bleeding, or in cases of platelet transfusion refractoriness. Immunomodulation with IVIG, steroids, etc. to manage alloimmune refractoriness is ineffective and is not recommended.

Case 3a

69 year old patient is admitted via ER with acute subdural hematoma following a fall. The patient is known to have liver cirrhosis due to alcohol. CBC revealed Hgb 125g/L and platelets 75x10^9/L. The INR was 1.3. The patient is scheduled for a burr hole surgery later this evening.

7) 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 4, case 2 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. This came from a 1972 study that simply looked at bleeding time vs platelet count, and they found that at >100, there was normal bleeding time. Transfuse 1 adult dose of platelets and monitor clinically for bleeding and with regular CBC.

Case 3b

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

8) 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, including clopidogrel. 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. There are limited clinical studies. The PATCH RCT (Lancet 2016), showed that patients on antiplatelet medications who present with a spontaneous intracerebral hemorrhage with platelet count > 100, transfusion of platelets was associated with inferior neurological outcomes at 3 months. It should be noted that that over 75% of these patients were on ASA alone. In view of this trial, routine transfusion of platelets in this specific situation is currently not recommended (2022 AHA guidelines).

For other clinical situations (anti-platelet related bleeding, anti-platelet therapies prior to emergency surgery) platelet transfusions can be provided on a case-by-case basis. There are variability in terms of timing of dose, degree of platelet inhibition, half-life, and reversibility between drugs. Clopidogrel is an oral pro-drug and its active metabolite irreversibly binds and inhibits the ADP receptor P2Y12. Clopidogrel has no effect on transfused platelet function (Scharbert et al Transfusion 2015). Ticagrelor is not reversible with platelet transfusions because of its mechanism of action involving binding to the ADP receptor on the platelet surface. There is no universal guidance on the dosing of platelet transfusions in these settings; one adult platelet transfusion is reasonable in most situations, while two has been suggested in some situations (eg. for individuals requiring urgent neurosurgery) (Swan et al. Blood Reviews 2020).

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 is NOT an appropriate initial 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 patient; and volume overload since her anemia is euvolemic. If this patient had hemodynamic instability or evidence of end-organ ischemia secondary to severe anemia (e.g. tachycardia, hypotension, chest pain, shortness of breath, pre-syncope), RBC transfusion would be indicated.

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 choice between oral and IV iron depends on many factors such as acuity of anemia, malabsorptive issues, cost, availability, and tolerance. Many patients with mild iron deficiency could be trialed on with oral formulations. IV iron can be provided in patients who are unresponsive to or intolerant of oral iron replacement therapy, who are anticipated to have poor absorption of oral iron (eg. gastric bypass), or for patients for whom rapid iron replacement (for example, preoperative ID or symptomatic anemia) is desired.

The typical response to oral repletion starts with rapid resolution of pagophagia, if present. Within a few days of treatment, patients may experience improved well-being, restless legs should abate or resolve, and a reticulocytosis may start/increase. The hemoglobin will slowly rise starting at 1-2 weeks after treatment. With IV iron, hemoglobin will similarly start to rise at around 1 week but can increase at a faster rate. Iron-dependent maturation from erythroblasts to differentiated RBCs takes 4-6 days, therefore a therapeutic effect from IV iron can be expected to be seen in 5-7 days (Besarab et al, Oncologist 2009).

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 toddler is seen because of pallor and the child's 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.

Dietary factors are the most common cause of IDA in infants and children and include insufficient iron intake, introduction of unmodified (nonformula) cow's milk before the age of 12 months, occult blood loss from cow's milk protein-induced colitis, and obesity.

For infants less than 12 months, avoid feeding unmodified (nonformula) cow's milk or goat's milk. For children 1-5 years of age, Canadian nutrition guidelines recommend limiting cow's milk consumption to no more than 500 mL per day. This is because cow's milk has low iron content and low bioavailability. Children should be transitioned from bottle to cup as prolonged bottle feeding has been shown to be a significant contributor to high milk consumption and resultant IDA.