Transfusion Camp 2019-2020
Morning Seminar on Day 1, July 19, 2019

Triggers for RBC and platelet transfusions

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 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 is based on expert opinion and is not evidenced 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).

2) **You suspect that he has developed platelet refractoriness. Which one of the following investigations is least 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 one hour post platelet transfusion**

Platelet refractoriness is a persistent lack of response following 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 (<48 hrs 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).

3) **His investigations are consistent with alloimmune refractoriness and you request HLA-selected platelets. Which one of the following is the least appropriate management strategy while awaiting 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 if there is 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.

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 at a dose of 50IU/kg IV and Vitamin K 10 mg IV**
- **D. None of the above**

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), especially when the active metabolite is present in the circulation (Tanaka et al BJA 2014). Of note, 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, a recent RCT (PATCH, 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.

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 asymptomaticsince 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 70 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**

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.

Does this patient require RBC transfusion? Justify your answer.

Red blood cells are transfused to increase oxygen delivery to the tissues. Normal healthy volunteers tolerate hemoglobin levels as low as 50 g/L. Patients without a history of ischemic heart disease generally tolerate hemoglobin levels as low as 70 g/L. Symptoms of tissue hypoxia are non-specific and may include: fatigue, lightheadedness, chest pain, shortness of breath and presyncope. In an intubated, sedated patient, one may look at EKG or laboratory evidence of ischemia. Newer non-invasive technologies such as Near Infra-Red Spectroscopy (NIRS) to assess tissue/cellular oxygenation or cerebral oxymetry to measure cerebral oxygen saturation may be helpful but unfortunately are not widely available and are still poorly studied.

Re: RBC transfusion triggers, TRICC trial findings may be 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%); no

difference in overall mortality for patients with history of ischemic heart disease (20.5 vs. 22.9%) and reduced in-hospital mortality (22.2 vs. 28.1%). It should be noted that 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.

Would your answer change if he had evidence of septic shock?

RBC transfusions to patients with sepsis have been advocated to prevent tissue hypoxia and prevent MOSF. It appears that in patients with septic shock oxygen delivery may increase following RBC transfusion but expected increase in oxygen consumption does not occur. Possible explanations include heterogeneous perfusion (stagnant hypoxia) in early sepsis, storage lesion of transfused RBC, mitochondrial changes (cytopathic hypoxia). Moreover, a recent RCT (TRISS), confirmed no benefit of liberal over restrictive transfusion trigger in septic patients.

30 day Mortality in Restrictive vs. Liberal Transfusion Triggers

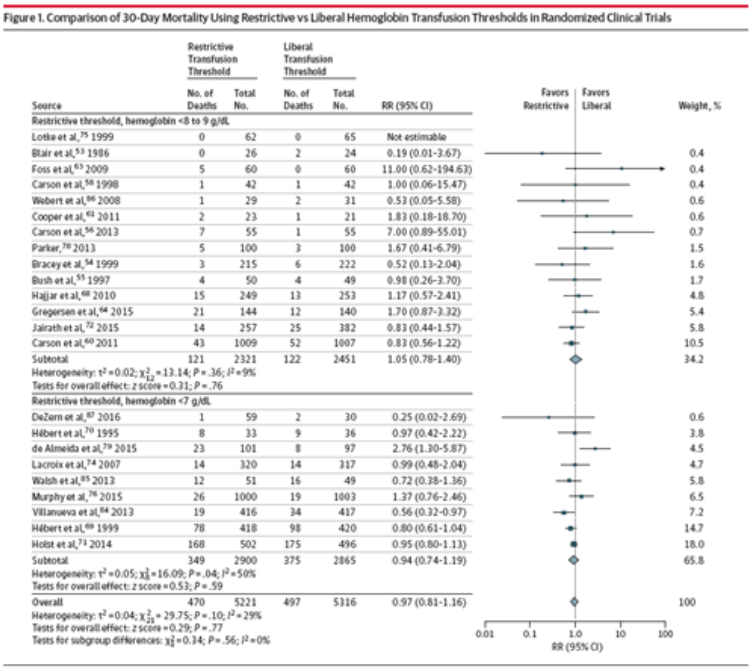

Figure 1. Comparison of 30-Day Mortality Using Restrictive vs Liberal Hemoglobin Transfusion Thresholds in Randomized Clinical Trials

Source	Restrictive Transfusion Threshold No. of Deaths	Restrictive Transfusion Threshold Total No.	Liberal Transfusion Threshold No. of Deaths	Liberal Transfusion Threshold Total No.	RR (95% CI)	Weight, %
Restrictive threshold, hemoglobin <8 to 9 g/dL						
Lotke et al,[75] 1999	0	62	0	65	Not estimable	
Blair et al,[53] 1986	0	26	2	24	0.19 (0.01-3.67)	0.4
Foss et al,[63] 2009	5	60	0	60	11.00 (0.62-194.63)	0.4
Carson et al,[58] 1998	1	42	1	42	1.00 (0.06-15.47)	0.4
Webert et al,[86] 2008	1	29	2	31	0.53 (0.05-5.58)	0.6
Cooper et al,[61] 2011	2	23	1	21	1.83 (0.18-18.70)	0.6
Carson et al,[56] 2013	7	55	1	55	7.00 (0.89-55.01)	0.7
Parker,[78] 2013	5	100	3	100	1.67 (0.41-6.79)	1.5
Bracey et al,[54] 1999	3	215	6	222	0.52 (0.13-2.04)	1.6
Bush et al,[55] 1997	4	50	4	49	0.98 (0.26-3.70)	1.7
Hajjar et al,[60] 2010	15	249	13	253	1.17 (0.57-2.41)	4.8
Gregersen et al,[64] 2015	21	144	12	140	1.70 (0.87-3.32)	5.4
Jairath et al,[72] 2015	14	257	25	382	0.83 (0.44-1.57)	5.8
Carson et al,[60] 2011	43	1009	52	1007	0.83 (0.56-1.22)	10.5
Subtotal	121	2321	122	2451	1.05 (0.78-1.40)	34.2
Heterogeneity: $\tau^2=0.02$; $\chi^2_{12}=13.14$; $P=.36$; $I^2=9\%$						
Tests for overall effect: z score $=0.31$; $P=.76$						
Restrictive threshold, hemoglobin <7 g/dL						
DeZern et al,[67] 2016	1	59	2	30	0.25 (0.02-2.69)	0.6
Hébert et al,[70] 1995	8	33	9	36	0.97 (0.42-2.22)	3.8
de Almeida et al,[79] 2015	23	101	8	97	2.76 (1.30-5.87)	4.5
Lacroix et al,[74] 2007	14	320	14	317	0.99 (0.48-2.04)	4.7
Walsh et al,[85] 2013	12	51	16	49	0.72 (0.38-1.36)	5.8
Murphy et al,[76] 2015	26	1000	19	1003	1.37 (0.76-2.46)	6.5
Villanueva et al,[84] 2013	19	416	34	417	0.56 (0.32-0.97)	7.2
Hébert et al,[69] 1999	78	418	98	420	0.80 (0.61-1.04)	14.7
Holst et al,[71] 2014	168	502	175	496	0.95 (0.80-1.13)	18.0
Subtotal	349	2900	375	2865	0.94 (0.74-1.19)	65.8
Heterogeneity: $\tau^2=0.05$; $\chi^2_8=16.09$; $P=.04$; $I^2=50\%$						
Tests for overall effect: z score $=0.53$; $P=.59$						
Overall	470	5221	497	5316	0.97 (0.81-1.16)	100
Heterogeneity: $\tau^2=0.04$; $\chi^2_{24}=29.75$; $P=.10$; $I^2=29\%$						
Tests for overall effect: z score $=0.29$; $P=.77$						
Tests for subgroup differences: $\chi^2_1=0.34$; $P=.56$; $I^2=0\%$						

Favors Restrictive | Favors Liberal

0.01 0.1 1.0 10 100

RR (95% CI)

Carson et al 2016

The discussion on triggers is well summarized in the recent 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 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 phlebotomy
B) Start an erythropoiesis stimulating agent
C) Start B12 supplementation
D) Start iron supplementation

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 were minimal – systematic review by Zarychanskiet et al CMAJ 2007). Iron supplementation is also controversial – efficacy, safety and cost. B12 supplementation will only work if patient is Vitamin B12 deficient. A is probably the best answer. 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.

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 continues to run for 30-45 minutes three

times per week before work. Her CBC reveals Hgb 60 g/L, MCV 65fL, platelets 487 x 10(9)/L; coagulation studies are normal.

8) Which of the following represents the least 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 alloimmunization in a young, potentially child-bearing woman; 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, $
Ferrous gluconate	300	35	0.02
Ferrous sulfate	300	60	0.06
Ferrous fumarate	300	100	0.12-0.21
Iron Polysaccharide (Feramax, Triferex)	150	150	0.46
Heme Iron (Proferrin, Optifer)	398	11	0.50

- 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 iron formulations appear 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 inconsistent and likely cannot be supported (http://campaign.r20.constantcontact.com/render?m=1126690796893&ca=8fe7f43e-95dc-4dea-b378-f734e4d72c11)

IV Iron Supplement	Iron sucrose (Venofer)	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
  - Metallic taste, headache, nausea, vomiting, diarrhea, abdo pain, back pain, muscle cramps, arthralgias, infusion site reactions
  - Allergic reaction
  - Hypotension (due to free iron)
- Disadvantages: cost, availability, need for a hospital visit
- Advantages: rapidly effective

Case 4a

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.

9) 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

Case 5.

You are on medical consults and are called to the orthopedics ward to assess an 85 year old female with Hb of 75g/L. The patient had ORIF of Right hip fracture 3 days ago and is convalescing. She has a history of coronary artery disease. Her vital signs are BP 145/90 mmHg, HR 88, and oxygen saturation 96% on room air.

10) **Which one of the following represents an evidence-based transfusion strategy for this patient?**
    - **A) No transfusion is needed**
    - **B) Order oral iron supplementation**
    - **C) Transfuse 1 unit RBC now**
    - **D) Transfuse 2 units RBC now**

In general:

In general, a decision to transfuse should be based on the patient's clinical status rather than any particular hemoglobin level. If the patient is comfortable, not actively bleeding and hemodynamically stable, RBC transfusion may not be warranted. On the other hand, presence of exertional chest pain or objective evidence of ischemia suggests that the patient is not able to tolerate anemia and may need a transfusion. Furthermore, a very recent publication also suggests that age-related transfusion thresholds should be considered. This is because few transfusion trials have been exclusive to older adults, anemia is associated with worse outcomes in older adults and cardiac output declines with age, impacting oxygen delivery potential (Simon et al TMR 2019). In conflict with this hypothesis was a 6 month followup analysis of patients in the TRICS III trial in cardiac surgery (Mazer et al NEJM 2018) which demonstrated a trend towards improved outcomes in the older age groups (75 years and above) with a restrictive transfusion strategy (Hb < 75 g/L).

If she is asymptomatic

FOCUS Trial. Carson et al. NEJM 2011;365;2453-62. A multicenter, randomized, controlled clinical trial of 2016 pts with history of or risk factor for cardiac disease after hip-fracture surgery. Randomized to restrictive transfusion strategy (transfuse if Hgb < 80 g/L or symptoms) versus liberal (transfuse if Hgb < 100 g/L). This was a randomized controlled clinical trial to test the hypothesis that higher blood transfusion threshold improves functional recovery and reduces morbidity and mortality. The primary outcome was a composite outcome of death and inability to walk across room without assistance at 60 days. The most important secondary outcome was postoperative unstable angina, myocardial infarction or death. There were no differences between the groups in any of the outcomes.

If she is symptomatic and/or has evidence of ischemia?

When you go to assess the patient pre-transfusion, she looks unwell. She is complaining of chest pressure that ensued following a shower. EKG is showing ST depressions in anterior leads. You page Cardiology on call.

11) **Which one of the following represents an evidence-based 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 2016

The impact of red blood cell transfusion on outcomes in patients with acute coronary syndrome is controversial. We conducted a systematic review with meta-analysis of studies assessing the association between blood transfusion and the risk for all-cause mortality and reinfarction. The search yielded 17 observational studies, of 2,525,550 subjects, during a study follow-up period, ranging from 30 days to 5 years.

Red blood cell transfusion compared with no blood transfusion is 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 8.0 g/dL (RR 0.52; 95% CI 0.25-1.06), and was associated with an increased risk of mortality at a hemoglobin above 10 g/dL (RR 3.34; 95% CI 2.25-4.97).

Red blood cell transfusion was associated with an increased risk of short- and long-term mortality as well as myocardial reinfarction. However, transfusion appeared to have beneficial or neutral effects on mortality at hemoglobin levels below 8.0 g/dL, and harmful effects above 10 g/dL. A large definitive randomized controlled trial addressing this issue is urgently required and is underway (MINT).

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.