Blood Product Utilization

A Mythbusters! Style Review

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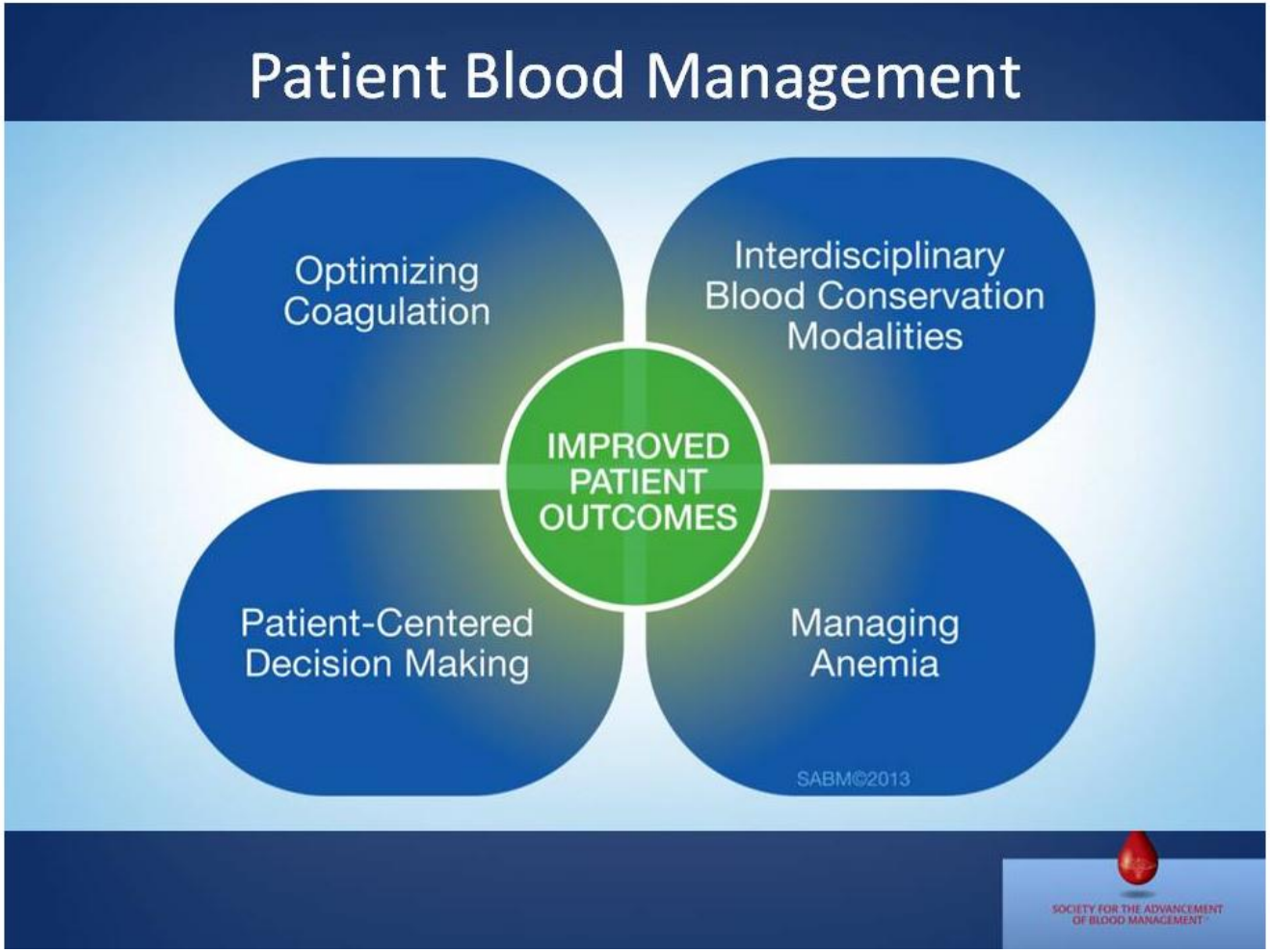
4/28/18

Objectives

- Describe concepts in Patient Blood Management
- Review common misconceptions surrounding blood transfusion
- Summarize current evidence for appropriate utilization of red blood cells, platelets, and cryoprecipitate

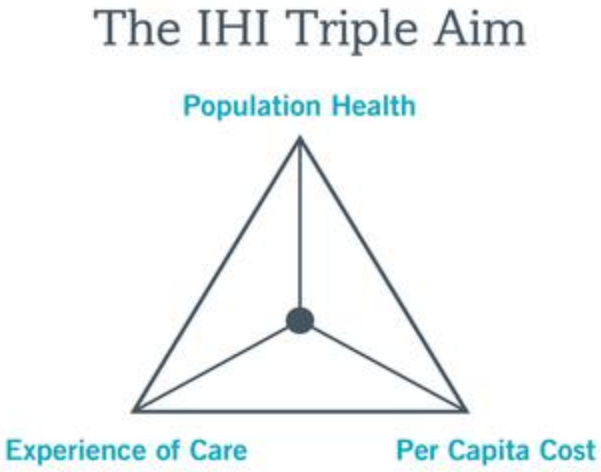


PBM definition: “the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcomes”

-Society for the Advancement of Blood Management

The IHI Triple Aim

- IHI Triple Aim is a framework developed by the Institute for Healthcare Improvement
  - Improving the patient experience of care (including quality and satisfaction);
  - Improving the health of populations; and
  - Reducing the per capita cost of health care.



Why Patient Blood Management?

- Agency for Healthcare Research and Quality reported in 2013 that the most frequent procedure performed during hospitalization in 2010 was blood transfusion
  - 11% of hospital stays with a procedure received transfusion
  - 126% increased incidence compared to 1997
- The Joint Commission and American Medical Association identified “over-transfusion of red blood cells,” as one of five target areas to reduce “instances of overuse”
- Anemia is common
  - 9% females age 20-49
  - 18.6 % of nursing home residents
  - 12.8% at hospital discharge
  - May exceed 50% in patients hospitalized with CHF or pneumonia

Risks of allogeneic blood exposure

Direct causal risks:

- Viral exposure
- Bacterial contamination
- Citrate exposure:
  - acidosis, hypocalcemia
- Hyperkalemia
- Mistransfusion
- Volume overload
- Transfusion reactions

Indirect plausible risks:

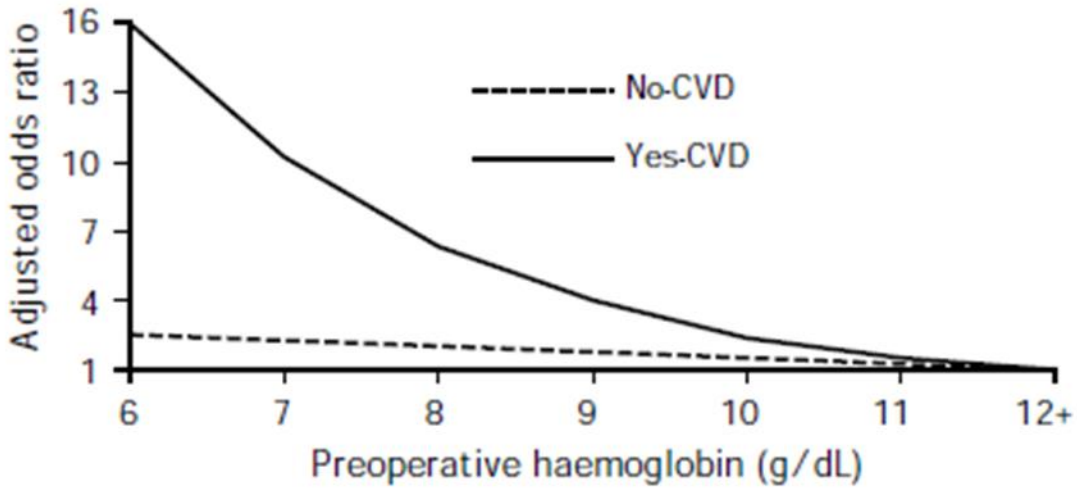
- Immunomodulation
- Infection
- Pneumonia
- Slowed wound healing
- Prolonged ventilator use

- Increased length of stay
- Increased cost
- Increased morbidity and mortality

Decreased exposure = increased safety and decreased cost

Risks of anemia

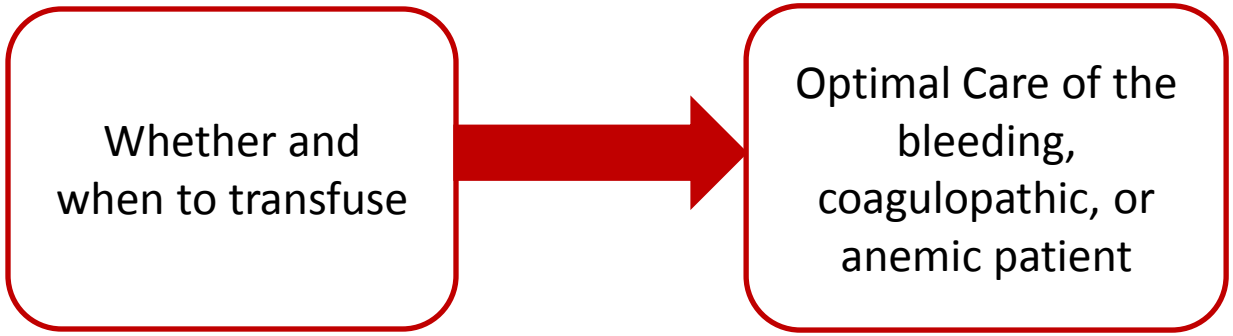
- Independent association with mortality in multiple patient populations
- Especially in patients with cardiovascular disease



30day mortality in adult Jehovah's witness patients undergoing non-cardiac surgery

From Product Focus to Patient Focus

- = the transformational next step



MYTH 1

- Patients should be transfused to a hemoglobin of 10 g/dL or hematocrit of 30% (the “10/30 rule”)

Evidence for Red Blood Cell Transfusion

- Restrictive vs Liberal Transfusion Randomized Controlled Trials (RCT)
  - Over 7000 patients enrolled in various trials
  - Many are small but three have >900 patients
  - Results consistently suggest that restrictive transfusion approach is safe
  - No adequately powered RCT in acute coronary syndrome

- A restrictive approach appears safe and is often associated with decreased morbidity and mortality.

Restrictive vs Liberal RBC Transfusion

RCT	n	PATIENTS	RESTRICTIVE	LIBERAL	OUTCOME	RESULT
TRICC	838	ICU	7	10	30day mort	Not Signif
TRACS	512	CABG/Valve	8	10	30day mort or organ failure	Not Signif
FOCUS	2016	Hip fracture & CV disease	8	10	60day mort or inability to walk 10’	Not Signif
CRIT	45	ACS	8	10	30day mort, MI, revasc	Favor Restrictive
MINT	110	ACS or CAD with PCI	8	10	30day mort, MI, revasc	Not Signif
Villanueva	921	UGI bleed	7	9	45day mort	Favor Restrictive
Robertson	200	TBI	7	10	6 month GCS	Not signif
TRISS	998	Septic shock	7	9	90 day mort, ischemia, life support	Not signif

MYTH 1

- Patients should be transfused to a hemoglobin of 10 g/dL or hematocrit of 30% (the “10/30 rule”)

BUSTED

MYTH 2

- But, really, cardiac patients should have a hemoglobin of 10 g/dL or hematocrit of 30% (the “10/30 rule”)

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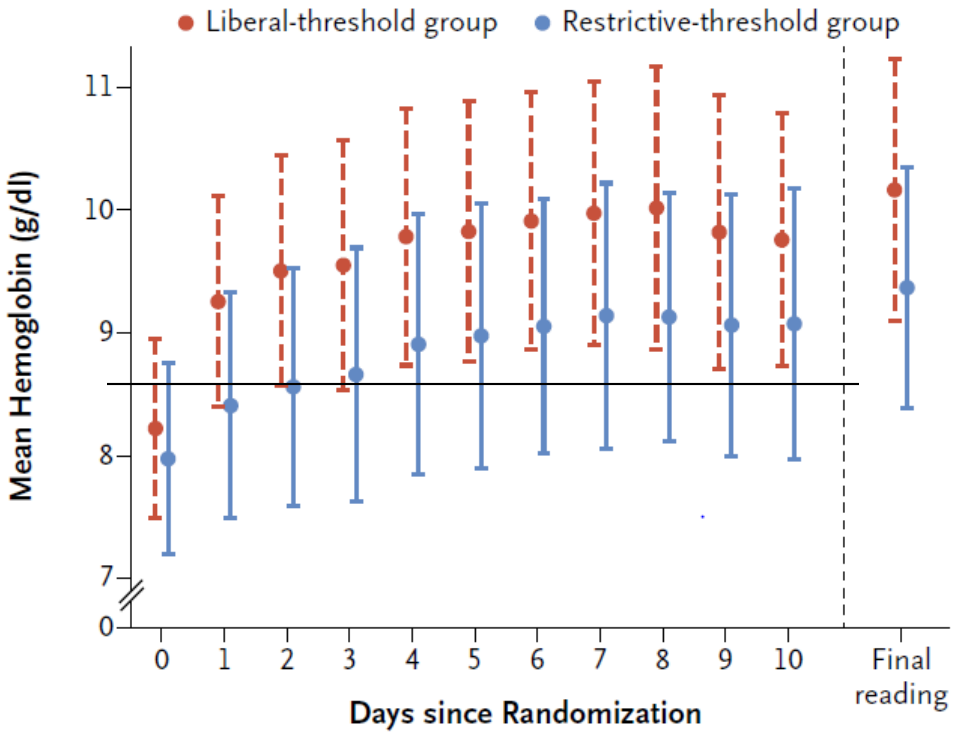
Liberal or Restrictive Transfusion after Cardiac Surgery

Gavin J. Murphy, F.R.C.S., Katie Pike, M.Sc., Chris A. Rogers, Ph.D., Sarah Wordsworth, Ph.D., Elizabeth A. Stokes, M.Sc., Gianni D. Angelini, F.R.C.S., and Barnaby C. Reeves, D.Phil., for the TITRe2 Investigators*

- n=1000 restrictive (Hgb 7.5 g/dL), n=1003 liberal (Hgb 9 g/dL))
- 53.4% in restrictive group and 92.2% in liberal group received transfusion
- Primary outcome – composite of serious infection (sepsis or wound infection) or an ischemic event (permanent stroke, MI, gut infarct, AKI) within 3 mos. after randomization
  - Primary-outcome reached in 35.1% in restrictive group and 33.0% in liberal group
  - Serious postop complications outside the primary-outcome occurred in 35.7% in restrictive group and 34.2% in liberal group
  - BUT more deaths in restrictive group (4.2%) than liberal (2.6%) p=0.045

Type of Transfusion	Restrictive Transfusion Threshold (N = 1000)	Liberal Transfusion Threshold (N = 1003)	Odds Ratio (95% CI)	P Value
	number (percent)			
≥1 Units of red cells transfused before randomization — no. of patients (%)†	250 (25.0)	264 (26.3)		
Units of red cells transfused after randomization‡				
Total units transfused — no.	1494	2494		
Median — no.	1.0	2.0		
Interquartile range	0–2.0	1.0–3.0		
Distribution — no. of patients (%)			0.58 (0.54– 0.62)§	<0.001
0 units	466 (46.6)	78 (7.8)		
1 unit	193 (19.3)	341 (34.0)		
2 units	152 (15.2)	262 (26.1)		
3 units	66 (6.6)	141 (14.1)		
4 units	50 (5.0)	62 (6.2)		
≥5 units	73 (7.3)	119 (11.9)		
Transfused red cells during entire index admission — no. of patients (%)¶	637 (63.7)	952 (94.9)		
Other transfusions — no. of patients (%)¶				
Fresh-frozen plasma	297 (29.7)	284 (28.3)	1.08 (0.88–1.33)	0.45
Platelets	376 (37.6)	362 (36.1)	1.08 (0.89–1.31)	0.42
Cryoprecipitate	99 (9.9)	102 (10.2)	0.99 (0.72–1.35)	0.95
Activated factor used — no. of patients (%)¶	7 (0.7)	5 (0.5)	1.41 (0.45–4.45)	0.56
Human blood coagulation factor IX used — no. of patients (%)¶	52 (5.2)	48 (4.8)	1.21 (0.73–2.03)	0.46
Severe nonadherence — no. of patients (%)‖	97 (9.7)	62 (6.2)		
Any nonadherence — no. of patients (%)**	300 (30.0)	453 (45.2)		

- After randomization, the difference in hemoglobin between groups was only 1 g/dL



- An assessment of causes of death or of serious adverse events that preceded death did not suggest any specific cause-and-effect relationship (analysis limited by small number of deaths n= 68 and also by reality that cardiac surgical deaths typically occur after a sequence of adverse events)

MYTH 2

- But, really, cardiac patients should have a hemoglobin of 10 g/dL or hematocrit of 30% (the “10/30 rule”)

PLAUSIBLE

MYTH 3

- Old blood is bad (the “storage lesion”)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age of Transfused Blood in Critically Ill Adults

Jacques Lacroix, M.D., Paul C. Hébert, M.D., Dean A. Fergusson, Ph.D., Alan Tinmouth, M.D., Deborah J. Cook, M.D., John C. Marshall, M.D., Lucy Clayton, M.Sc., Lauralyn McIntyre, M.D., Jeannie Callum, M.D., Alexis F. Turgeon, M.D., Morris A. Blajchman, M.D., Timothy S. Walsh, M.D., Simon J. Stanworth, F.R.C.P., Helen Campbell, D.Phil., Gilles Capellier, M.D., Pierre Tiberghien, M.D., Laurent Bardiaux, M.D., Leo van de Watering, M.D., Nardo J. van der Meer, M.D., Elham Sabri, M.Sc., and Dong Vo, B.Eng., for the ABLE Investigators and the Canadian Critical Care Trials Group*

- n=1211 fresh-blood (6.1 ± 4.9 days), n=1219 standard blood (22.0 ± 8.4 days))
- 96.4% in fresh group and 97.1% in standard group received transfusion
- Primary outcome – 90-day all-cause mortality
- Secondary outcomes – major illnesses; duration of respiratory, hemodynamic, or renal support; LOS; transfusion reactions

The results of our trial are consistent with those of seven randomized, controlled trials that compared various durations of red-cell storage. Five pilot trials did not detect clinically important clinical consequences of prolonged red-cell storage.[10,11,19-21] Moreover, in two larger trials, transfusion of fresh red cells, as compared with standard-issue red cells, did not reduce the complications of prematurity in very-low-birth-weight infants[22] or reduce the rates of organ failure or adverse events among 1098 patients undergoing elective cardiac surgical procedures.[23,24]

MYTH 3

- Old blood is bad (the "storage lesion")

BUSTED

Physiology Overview

- The primary way that oxygen is delivered in the body is via hemoglobin-binding within our erythrocytes.
- Anemia is associated with a compensatory increase in cardiac index and, when severe, may decrease tissue oxygenation.
- Packed red blood cells (RBC) consist of erythrocytes concentrated from whole blood donations by centrifugation *OR* collected by apheresis.
- Transfusing PRBC in an anemic patient may improve tissue oxygenation in some situations, but, in many situations, the risk of transfusing PRBC may be greater than the probability of benefit.

Red Blood Cell Transfusion Overview

In non-hemorrhaging patients:

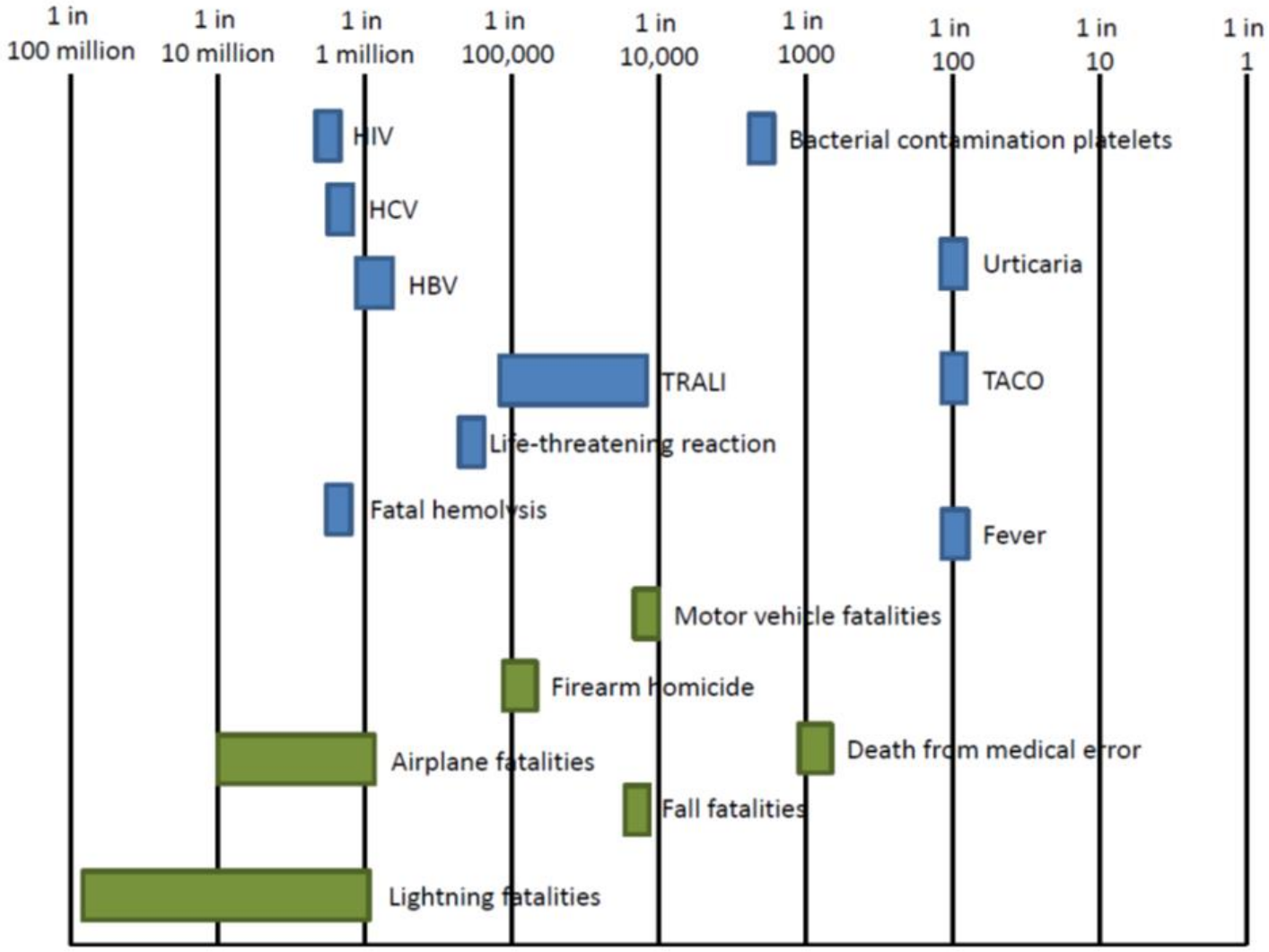
- RBC transfusion should not be considered until the hemoglobin is less than 7-8 g/dL.
  - Caveats: lack of adequately powered RCT in ACS and higher end of spectrum for post-CPB
- The decision to transfuse should be based on clinical assessment after correction of hypovolemia (i.e. not solely on hemoglobin).
- Transfusions should be ordered one unit at a time, followed by repeat clinical evaluation.

Clinical Assessment

- Common signs and symptoms of anemia may include:
  - Shortness of breath
  - Fatigue
  - Tachycardia
- Hypovolemia can mimic symptomatic anemia, and it is important to correct, which can often be accomplished with crystalloids.

Transfusion Mechanics

- In a stable, non-bleeding or hemolyzing adult transfused with compatible PRBC:
  - Hemoglobin equilibrates in 15 mins after transfusion
  - One PRBC unit will increase Hgb by 1 g/dL and Hct by 3%
- Infusion rate: as patient can tolerate, generally over 75 mins-4 hrs (maximum)
- All PRBC in all GHS hospitals are leukoreduced.



Adverse effects of transfusion contrasted with other life risks. Estimates of the current risk per unit of red blood cell transfused (or per platelet transfused, as designated), in blue, are contrasted against risk for fatality per year for various life events, in green. Risk is depicted on a logarithmic scale. HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload. (Adapted from Carson JL, Grossman BJ, Kleinman S, et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. Ann Intern Med, 2012;157:49-58.)

Risks of Transfusion

The greatest risks of transfusion are not always causally linked to known transfusion reactions.

- Villanueva et al showed a 4% absolute increase in mortality in patients with upper GI hemorrhage when they were transfused to a target hemoglobin of 9 g/dL (rather than 7 g/dL)
- Recent meta-analysis (Rhode JM, et al) showed a 5% increase in the pooled risk of serious infection in patients who were liberally transfused.

Considerations for Future Transfusion Avoidance

- Anemia diagnosis and management
  - Anemia labs
  - Parenteral iron, B12, folate, ESAs
  - Patient education
  - Treat anemia prior to elective surgery
  - Opportunity to manage anemia while patient in the hospital
- Avoid excessive phlebotomy (e.g. “daily” labs)
- Arrest bleeding promptly – don’t wait
- Optimize coagulation

MYTH 4

- My hem/onc patient has special circumstances XYZ over everyone else, so give prophylactic platelet transfusions to keep platelets >20,000

To give or not to give, that is the question

Summary of moderate quality evidence:

- Three RCTs compared bleeding outcomes in inpatients with radiation and/or chemotherapy-associated hypoproliferative thrombocytopenia assigned to receive or not receive prophylactic platelet transfusions
  - Outcomes: prophylactic transfusions significantly reduced risk for spontaneous grade 2 or greater bleeding

Evidence for Platelet Transfusion

Summary of moderate quality evidence:

- Four RCTs examined the threshold platelet count at which platelets should be transfused prophylactically in inpatients with therapy-induced hypoproliferative thrombocytopenia
  - Outcomes: the 10,000/µL threshold was associated with fewer number days bleeding, lower platelet usage, and fewer transfusion reactions and a 20,000/µL or 30,000/µL threshold was not associated with statistically lower incidence of grade 2 or greater bleeding

MYTH 4

- My hem/onc patient has special circumstances XYZ over everyone else, so transfuse platelets to 20,000

BUSTED

MYTH 5

- When my patient's platelet count is low, I should give two units of platelets

Evidence for Platelet Transfusion

Summary of moderate quality evidence:

- Two RCTs compared high-dose platelets (defined as two apheresis units) to standard dose of one unit
  - Outcomes: prophylactic transfusion of high-dose platelets did not reduce the risk for bleeding compared with standard-dose

Evidence for Platelet Transfusion

Summary of moderate quality evidence:

- Four RCTs examined whether prophylactic transfusion of low-dose platelets (defined as one-half apheresis unit) would provide hemostasis equal to standard dose of one unit in patients with therapy-induced hypoproliferative thrombocytopenia
  - Outcomes: no difference in grade 2 or greater bleeding between standard and low-dose

MYTH 5

- When my patient's platelet count is low, I should give two units of platelets

BUSTED

Platelet Overview

- Platelets are obtained by two different methods: platelet concentrates from whole blood or apheresis platelets
  - GHS uses only apheresis platelets at all sites

- Unlike other blood components, platelets must be stored at room temperature, limiting the shelf life to 5 days because of the risk for bacterial growth during storage

- Platelet transfusion risks include allergic/anaphylactoid, febrile non-hemolytic, sepsis, and transfusion-related acute lung injury
  - Sepsis from a bacterially contaminated platelet represents the most frequent infectious complication from any blood product

Platelet Overview

- Most platelet transfusions are given prophylactically to reduce the risk for spontaneous bleeding in thrombocytopenic patients

- Transfusions should be ordered one unit at a time, followed by repeat platelet count and clinical evaluation.
  - Greater doses are not effective and lower doses, equal to one-half of a standard apheresis unit, are equally effective

Platelet Transfusion Mechanics

- Measure platelet count from 10-60 minutes after transfusion
  - One apheresis platelet will increase platelet count by 30,000-60,000/µL in average-sized adults
  - In neonates and infants, a dose of 5-10 mL/kg will increase platelet count by 50,000-100,000/µL
- Response to platelet transfusion is adversely affected by fever, sepsis, splenomegaly, severe bleeding, consumptive coagulopathy, HLA alloimmunization, and certain medications (e.g. amphotericin B)
- All apheresis platelets are inherently leukoreduced

Evidence for Platelet Transfusion

- Evidence supporting prophylactic transfusion for invasive procedures is based on:
  - 8 observational studies of CVC placement
  - 7 observational studies of LP in children
  - 1 series on 167 invasive procedures including 29 major surgeries and 24 moderately invasive procedures
  - Meta-analysis of 6 RCTs and a single pilot study on cardiac surgical patients
- Evidence supporting platelet transfusion and platelet inhibitor drugs can be found in 6 observational studies

Platelet transfusion considerations

- Consider consult with Laboratory Medicine if bleeding persists
- Consider whether additional clinical factors are contributing to the risk of bleeding (renal failure, medications, end-organ dysfunction, coagulopathy). If renal failure, consider DDAVP.
- Platelets are contraindicated in patients with thrombotic thrombocytopenic purpura (TTP) and heparin-induced thrombocytopenia (HIT) unless life-threatening hemorrhage

MYTH 6

- Cryoprecipitate is off the market in many European countries in lieu of fibrinogen concentrate

Cryoprecipitate Overview

- Cryoprecipitate was originally developed as therapy for hemophilia A, due to the factor VIII content
- With the advance in recombinant factor development, cryoprecipitate is no longer used for its original purpose but is instead used for acquired coagulopathy, such as in clinical settings associated with hemorrhage

Cryoprecipitate Overview

- The usual recommendation of cryoprecipitate transfusion to supplement fibrinogen when fibrinogen level is <100 mg/dL is empiric and not based on solid clinical evidence
  - Randomized controlled trials are needed to determine the clinical efficacy of cryoprecipitate, compared with the efficacy of alternative preparations
- The development of fibrinogen concentrate, along with safety concerns related to TRALI and transfusion-transmitted infection, has led to the withdraw of cryoprecipitate from the market in many European countries

MYTH 6

- Cryoprecipitate is off the market in many European countries in lieu of fibrinogen concentrate

CONFIRMED