Overview of Transfusion guidelines

Sai Karan Vamsi Guda D.O.
OSU IM - PGYIII

Overview

- Background
- Methods
- Results
- Discussion
- Limitation
- AABB guideline recommendations
- Massive Transfusion Protocol (MTP)
- Thromboelastography (TEG)
- Transfusion trend changes a OSUMC

Background

Background

- 100 million units PRBC obtained worldwide/ year
- 13 million in the USA
- There remains substantial variation in the practice of transfusing patients.
- Physicians often use either hemoglobin level or the symptoms of anemia to decide when to transfuse.

Background

- Transfusion guidelines are to be designed to *optimize clinical outcomes* and to *avoid non-clinically indicated transfusions*
- The criticisms of the guidelines released by AABB in 2012 were that the RCTs were **small studies** (median: 120 patients; range: 22 - 2016 patients; total n=6264 in 19 RCT) and had **high risk of bias**.
- Since then however there has been a tremendous increase in the RCT assess PRBC guidelines.

Background

Table 1. Approximate Risk Per-Unit Transfusion of Red Blood Cells (RBCs)

Adverse Event	Approximate Risk Per-Unit Transfusion of RBCs
Febrile reaction[11]	1:60[a] ★
Transfusion-associated circulatory overload[12,13]	1:100[b] ★
Allergic reaction[14]	1:250 ★
Transfusion-related acute lung injury[15]	1:12 000 ★
Hepatitis C virus infection[16]	1:1 149 000
Hepatitis B virus infection[17]	1:1 208 000 to 1:843 000[c]
Human immunodeficiency virus infection[16]	1:1 467 000
Fatal hemolysis[18]	1:1 972 000

- Relative safety of transfusion reactions is described in (Table 1).
- Unnecessary transfusion expose patients to increased risk and costs without benefit.
- A liberal strategy is to be utilized if there's evidence for improvement in outcomes.

Methods

Methods

- **AIM:** These guidelines provide recommendations for the clinicians caring for hospitalized adult patients who are hemodynamically stable and are candidates for RBC transfusions.
- The committee members had no substantial conflicts of interest, who included:
- Former members of the AABB clinical transfusion medicine committee, experts appointed by professional organizations as subject matter experts (American Association for the Surgery of Trauma; Society of Critical Care Medicine; American College of Cardiology; American Society of Anesthesiologists; and American Society of Hematology), a patient representative. The physician panel included primarily pathologists, hematologists, anesthesiologist, cardiologist, internist, critical care medicine physician, trauma or acute care surgeon, and a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist

Methods

- The guidelines were developed based on separately published up-dated systematic reviews of the literature on transfusion thresholds
- Literature searches of RCTs evaluating transfusion thresholds from 1950 through May 2016
- The systematic review included RCTs in which the transfusion groups were assigned on the basis of a *clear transfusion trigger* or *threshold*, which was described as *hemoglobin or hematocrit level* that had to be reached before a RBC transfusion was administered.
- Trials of patients treated surgically, medically, as those involving adults or children (but not neonates) were included.

Methods

- The primary outcome was mortality
  - 30-day mortality for transfusion thresholds
- Secondary outcomes for transfusion thresholds included
  - *Morbidity*, *hemoglobin levels* (the timing of measurement varied among trials) and the *number* of PRBC units transfused.
    - Nonfatal myocardial infarction,
    - Pulmonary edema or congestive heart failure
    - Stroke
    - Thromboembolism
    - Renal failure
    - Infection
    - Re-bleeding
    - Mental confusion

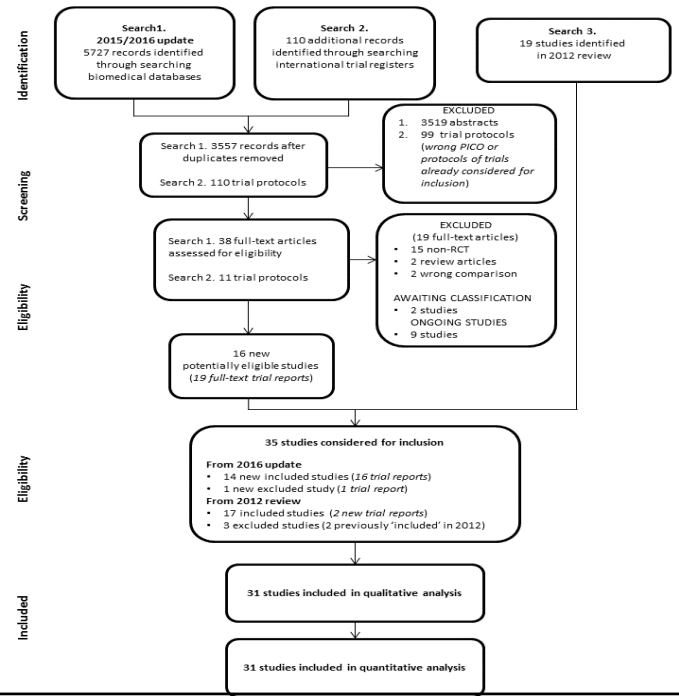
Methods

- Each RCT was assessed for the risk of bias for **sequence generation**, **allocation concealment**, **blinding**, and **incomplete outcome data**
- Statistical heterogeneity was assessed using both I^2 and χ^2 tests.

Methods

- When the evidence suggested **no harm** from withholding transfusion, the committee was prepared to make a **strong recommendation** for a **restrictive threshold**.
- When evidence regarding **harm was uncertain**, the committee elected **not to make** a recommendation.
- "When deciding to transfuse an individual patient, it is good practice to consider not only the hemoglobin level, but the overall clinical context and alternative therapies to transfusion."
- Variables to take into consideration include the *rate of decline* in *hemoglobin level*, *intravascular volume status*, *shortness of breath*, *exercise tolerance*, *light headedness*, *cardiac chest pain*, *hypotension* or *tachycardia* unresponsive to fluid challenge, and *patient preferences*.

Results



- 3557 records were evaluated
- 3519 – only abstracts were removed
- 38 full text articles with 11 trial protocols were further evaluated and after removing all non RCT studies ended up with **31 RCTs** which included both **Qualitative and Quantitative Data analysis.**
- **12587 patients**

Results

Table 2. Evidence for the Association Between Hemoglobin Transfusion Thresholds and Clinical Outcomes in Hospitalized Adult Patients Who Are Hemodynamically Stable and in Need of a Red Blood Cell Transfusion[a]

Quality Assessment[b]						No./Total (%) of Patients by Hemoglobin Transfusion Threshold		Effect		
No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Restrictive (7-8 g/dL)	Liberal (9-10 g/dL)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Quality of RCTs
Primary Outcome: 30-d Mortality										
23	Not serious	Not serious	Not serious	Serious[c]	None detected	470/5221 (9.0)	497/5316 (9.3)	0.97 (0.81-1.16)	3 fewer deaths per 1000 (15 fewer deaths to 18 more per 1000)	Moderate
Secondary Outcomes										
Myocardial Infarction (MI)										
16	Not serious	Not serious	Not serious	Not serious	None detected	78/4156 (1.9)	69/4147 (1.7)	1.08 (0.74-1.60)	1 more MI per 1000 (4 fewer MIs to 10 more per 1000)	High
Pulmonary Edema (PE) or Congestive Heart Failure (CHF)										
12	Serious[d]	Not serious	Not serious	Serious[e]	None detected	87/3132 (2.8)	114/3125 (3.6)	0.78 (0.45-1.35)	8 fewer PEs or CHFs per 1000 (13 more PEs or CHFs to 20 fewer per 1000)	Low
Stroke or Cerebrovascular Accident (CA)										
13	Not serious	Not serious	Not serious	Not serious	None detected	49/3675 (1.3)	62/3668 (1.7)	0.78 (0.53-1.14)	4 fewer strokes or CAs per 1000 (2 more strokes or CAs to 8 fewer per 1000)	High
Rebleeding										
6	Not serious	Serious[f]	Not serious	Serious[g]	None detected	215/1489 (14.4)	264/1619 (16.3)	0.75 (0.51-1.10)	41 fewer events per 1000 (16 more events to 80 fewer per 1000)	Low
Pneumonia										
14	Not serious	Not serious	Not serious	Not serious	None detected	239/3140 (7.6)	256/3137 (8.2)	0.94 (0.80-1.11)	5 fewer cases of pneumonia per 1000 (9 more cases to 16 fewer per 1000)	High
Thromboembolism										
10	Not serious	Not serious	Not serious	Not serious	None detected	16/2010 (0.8)	21/2009 (1.0)	0.77 (0.41-1.45)	2 fewer thromboembolisms per 1000 (5 more thromboembolisms to 6 fewer per 1000)	High

- Transfusion strategy did not influence the risk of cardiovascular events, including myocardial infarction, congestive heart failure, or stroke.

Results - Primary Outcome

- Thirty-day mortality is the primary outcome, and 23 trials reported data (N = 10,537 participants).
  - There was **no difference** in the 30-day mortality between restrictive and liberal transfusion strategies
- **Subgroup analysis of 30-day mortality: restrictive threshold of 8 g/dL to 9 g/dL versus 7 g/dL**
  - 14 trials, with 4772 participants, used a restrictive threshold of **8 g/dL to 9 g/dL**.
  - 9 trials, with 5765 participants, used a **7 g/dL** restrictive thresh- old.
  - The test for subgroup differences was not significant (p= 0.56), indicating that there was no difference in the mortality risk between the two thresholds.

Results – Subgroup analysis

- **Subgroup analyses of 30-day mortality: clinical specialty**
- The clinical specialty used in the trials: cardiac surgery, orthopedic surgery, vascular surgery, acute blood loss or trauma, gastrointestinal (GI) bleeding, critical care, acute myocardial infarction, or hematological malignancies.
- In two trials that reported mortality at 30 days in 2221 participants with **acute blood loss or trauma (GI bleeding)**, the **mortality** was **significantly lower** using the **restrictive strategy** compared with the liberal strategy
- Two trials recruited 154 participants who had **acute myocardial infarction** and evaluated mortality after random allocation; for this subgroup, the **mortality risk** was **higher** in the **restrictive strategy** group than in the liberal strategy group

Results – Clinical Outcomes

- **No difference** between the restrictive and liberal transfusion strategies
  - Cardiac events: 9 trials; 4849
  - Myocardial infarction (fatal and non-fatal):16 trials; 8303
  - Congestive heart failure: 12 trials; 6257
  - Cerebrovascular accident: 13 trials; 7343
  - Rebleeding: 6 trials; 3108. The risk of developing recurrent bleeding associated with restrictive transfusion was about half that of liberal transfusion.

Results – Clinical Outcomes

- **No difference** between the restrictive and liberal transfusion strategies
  - Infection:
    - Sepsis/bacteremia: 7 trials; 3963
    - Pneumonia: 14 trials: 6277
    - Pneumonia or wound infection: 14 trials; 9574
  - Thromboembolism: 10 trials; 4019
  - Renal failure: 10 trials; 5929
  - Mental confusion: 6 trials; 1344
  - Functional recovery: 4 trials reported functional outcomes in orthopedic surgery participants.

Discussion

Discussion

- The results of the meta-analyses indicated that restrictive transfusion strategies led to a reduction of more than one-third (43%) in the number of participants receiving at least one unit of blood.
- Most importantly, the meta-analyses provided no evidence that restrictive transfusion policies harmed the participants or that they benefited from the use of liberal transfusion policies, within the parameters defined in the trials.
- Across *nearly* all subgroups, the results indicated that risk of death and other adverse events were not impacted by either liberal or restrictive transfusion thresholds.

Discussion

- In acute blood loss **and** those with acute myocardial infarction, mortality was influenced by a liberal or restrictive transfusion strategy – 30-day mortality between the subgroups was not significant (P = 0.13).
  - Participants enrolled with acute myocardial infarction demonstrated different results for 30-day mortality.
  - Two small trials "**Liberal Versus Restrictive Transfusion Thresholds For Patients With Symptomatic Coronary Artery Disease**" and "**the CRIT Randomized Pilot Study**" included these participants (N = 154) for which the 30-day mortality was **3.88 times higher** in the restrictive transfusion group than in the liberal transfusion group
- In participants with gastrointestinal bleeding a restrictive transfusion strategy was associated with a 35% lower risk of 30- day mortality than a liberal transfusion strategy.

Discussion

- The compared the risk of infection was analyzed in three ways but *did not find* evidence of a reduced risk of infection associated with restrictive transfusion.
- These results varied significantly from previous analyses provided by Rohde et al in 2014 where a restrictive strategy was attributed to decreasing the risk of infection.
- The studies evaluating functional capacity were not analyzed equally as they did not use the same measure for functional capacity

Limitations

- Assigning a single level of bias to multiple outcomes was not possible because of variable methods
- Some studies were not appropriately blinded, while others demonstrated allocation bias
- There is subjective interpretation of severity of cardiovascular events
- All these trials evaluated patients receiving PRBC inpatient where endpoints are different compared to outpatient.
- Pathophysiological application of hbg concentration as a marker for tissue oxygenation is inadequate.

Recommendations

Recommendations

- The AABB recommends a **restrictive** RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is **7 g/dL** for hospitalized adult patients who are hemodynamically stable, including **critically ill patients**, rather than a liberal threshold when the hemoglobin level is **10 g/dL;** (**strong recommendation, moderate quality evidence**).
  - 6 trials (TRICC/TRISS) conducted with critical care patients
  - Threshold for restrictive was 7 g/dL; liberal 9 – 10 g/dL

Recommendations

- For patients undergoing **orthopedic surgery** or **cardiac surgery** and those with **preexisting cardiovascular disease**, the AABB recommends a restrictive RBC transfusion threshold hemoglobin level of **8 g/dL;** (**strong recommendation, moderate quality evidence**).
  - Orthopedic: 10 trials; Restrictive threshold was 8; Liberal threshold 10 g/dL
  - There was no difference in ability to walk, multiple measures of function, fatigue, and length of hospital stay
  - CVD: 5 trials; Restrictive threshold was 8; Liberal threshold 10 g/dL
  - TRICS III currently in process is evaluating threshold of 7.5 g/dL

Recommendations

- These recommendations apply to all but the following conditions for which the evidence is insufficient for any recommendation: **acute coronary syndrome**, **severe thrombocytopenia** (patients treated for hematological or oncological disorders who at risk of bleeding), and **chronic transfusion–dependent anemia**.

Massive Transfusion Protocol

Massive Transfusion Protocol

- Definition:
  - Replacement of one entire blood volume within 24 h
  - Transfusion of >10 units of packed red blood cells (PRBCs) in 24 h
  - Replacement of 50% of total blood volume (TBV) within 4 h.
  - Greater than 150 cc/min blood loss

Massive Transfusion Protocol

Class of haemorrhagic shock				
	I	II	III	IV
Blood loss (mL)	Up to 750	750–1500	1500–2000	> 2000
Blood loss (% blood volume)	Up to 15	15–30	30–40	> 40
Pulse rate (per minute)	< 100	100–120	120–140	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (per minute)	14–20	20–30	30–40	> 35
Urine output (mL/hour)	> 30	20–30	5–15	Negligible
Central nervous system/mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

Recommendations

Recommendations

- It is recommended that *institutions develop* Massive Transfusion Protocols (MTP) that included dose, timing and ratio of blood component therapy for use in trauma patients with, or at risk of, critical bleeding requiring massive transfusion (Grade C)
- In Patients with critical bleeding requiring massive transfusion, hemoglobin concentration should be interpreted in the context of hemodynamic status, organ perfusion and tissue oxygenation (PP).
- The patient having a critical bleed is to be adequately resuscitated and surgical interventions sought out.

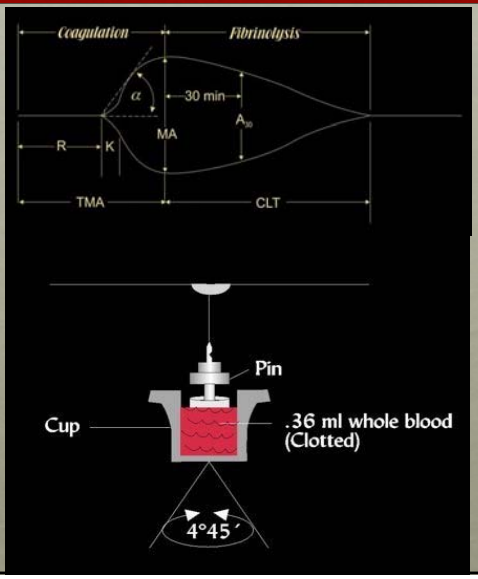
Recommendations

- The routine use of rFVIIa in trauma patients with critical bleeding requiring massive transfusion is not recommended because of its lack of effect on mortality (Grade B) and variable effect on morbidity (Grade C)
  - rFVIIa should be used only after surgical hemostasis ad component therapy have failed to control critical bleeding
  - If is to be used an initial dose of 90 ug/kg is reasonable
- In trauma patients with critical bleeding requiring massive transfusion, an RBC: FFP ratio of </= 2:1 is associated with reduced mortality
  - 4 level III studies examined the effect of FFP or platelet transfusion on mortality/morbidity; ? Survivor bias; Need to see use of fibrinogen or cryoprecipitate

Thromboelastography

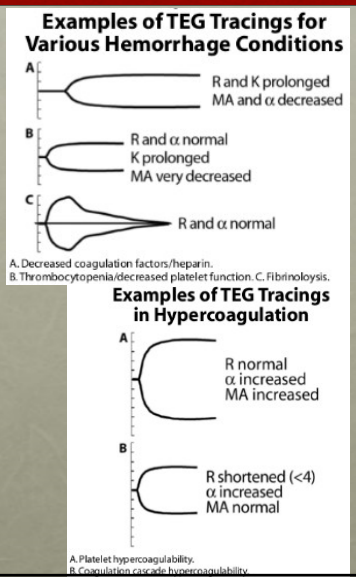
Thromboelastography

- In critically bleeding patients requiring massive transfusion, there is insufficient evidence to identify an INR (PT/APTT), fibrinogen level or platelet count to trigger a blood component transfusion
  - There is unavoidable delay in provision of laboratory result there is an increase in the use of *thromboelastography* (TEG).
- TEG is a method of testing efficiency of coagulation in blood.
- It was designed to overcome the static nature of other assessments such as INR/PT/PTT/Fibrinogen/D-Dimer
- Typically used during obstetric, cardiac and liver transplant surgeries



Thromboelastography

- Parameters of measurements
  - *R-time*: time of latency from initiation of test to initial fibrin formation
  - *K-time*: time taken to achieve certain level of clot strength
  - *alpha-angle*: measures speed of fibrin build up and cross linking
  - *Maximum amplitude (MA)*: measure ultimate strength of the fibrin clot.
- Deficient coagulation factors: prolonged *r, k times* and *decreased MA and alpha angle*
- Hypercoagulable states: *k, r times* are decreased with increase of *MA and alpha angle*.



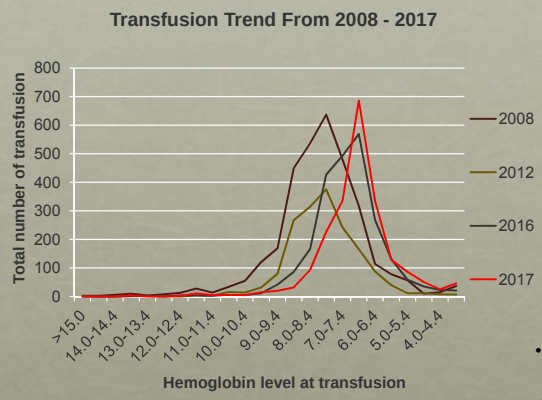
Recommendations

Recommendations

- Recommended dose of blood components:
  - FFP: 15mL/kg
  - Platelets: 1 adult therapeutic dose
  - Cryoprecipitate: 3 – 4 g
  - rVIIa: 90 ug/kg
- In trauma patients with or at risk of significant hemorrhage, tranexamic acid should be considered
  - Loading dose: 1 g over 10 minutes
  - Followed by infusion of 1g over 8 hrs

OSU Transfusion trend

OSU PRBC Transfusion trends



AIM: The goal is to improve inpatient, non-operative PRBC transfusion by 20% utilizing 2012 guidelines by December 2016 and 2017.

Total Number Of PRBC Transfusions, Hb 8-12 g/dL From 2012 To 2017

	2012	2013	2014	2015	2016	2017
11.5-11.9	4	2	1	4	4	11
11.0-11.4	3	5	5	3	3	5
10.5-10.9	16	4	6	5	6	6
10.0-10.4	14	10	18	22	5	5
9.5-9.9	32	46	37	23	12	15
9.0-9.4	80	86	87	73	42	20
8.5-8.9	267	227	219	184	86	32
8.0-8.4	314	274	316	345	166	93

- Since the implementation of the review process, PRBC transfusions have decreased by 49% in 2016 and by 71% in 2017 in patients with hemoglobin 8-12 g/dL.
- The total number of transfusions performed in 2016 and 2017 was lower.
- The case-mix index was utilized to assess the complexity of the patient and was found no not a significant contributor.

Conclusion

Summary

- A 2 distinct tiers of hemoglobin triggers for RBC transfusions: hemoglobin concentration of less than 7 g/dL for stable, adult inpatients including those in the intensive care unit, and hemoglobin concentration of less than 8 g/dL for a select group of post-surgery patients or those with preexisting cardiac disease.
- It is recommended that institutions develop Massive Transfusion Protocols (MTP) that included dose, timing and ratio of blood component therapy for use in trauma patients with, or at risk of, critical bleeding requiring massive transfusion.
- Blood component transfusion recommendations are:
  - FFP: 15mL/kg
  - Platelets: 1 adult therapeutic dose
  - Cryoprecipitate: 3 – 4 g

References

- **1**. WorldHealthOrganization.Bloodsafetyand availability. http://www.who.int/mediacentre /factsheets/fs279/en/. Accessed January 25, 2016.
- **2**. Whitaker BI, Rajbhandary S, Harris, A. *The 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey Report*. Bethesda, MD: AABB; 2015.
- **3**. RaoSV,ChiswellK,SunJL,etal.International variation in the use of blood transfusion in patients with non-ST-segment elevation acute coronary syndromes. *Am J Cardiol*. 2008;101(1):25-29.
- **4**. RogersMA,BlumbergN,SaintS,LangaKM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: a cohort study. *BMC Med*. 2009;7:37.
- **5**. Bennett-GuerreroE,ZhaoY,O'BrienSM,etal. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA*. 2010;304(14): 1568-1575.
- **6**. FrankSM,SavageWJ,RothschildJA,etal. Variability in blood and blood component utilization as assessed by an anesthesia information management system. *Anesthesiology*. 2012;117(1): 99-106.
- **7**. KwokCS,SherwoodMW,WatsonSM,etal. Blood transfusion after percutaneous coronary intervention and risk of subsequent adverse outcomes: a systematic review and meta-analysis. *JACC Cardiovasc Interv*. 2015;8(3):436-446.
- **8**. Vuille-LessardE,BoudreaultD,GirardF,RuelM, Chagnon M, Hardy JF. Red blood cell transfusion practice in elective orthopedic surgery: a multicenter cohort study. *Transfusion*. 2010;50 (10):2117-2124.
- **9**. Practiceguidelinesforbloodcomponent therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology*. 1996;84(3):732-747.
- **10**. NapolitanoLM,KurekS,LuchetteFA,etal; American College of Critical Care Medicine of the Society of Critical Care Medicine; Eastern