Objectives

• Review definition of anemia, common causes in ICU, and potential problems
• Discuss up to date evidence on PRBC transfusion guidelines in critical care
• Discuss indications for other blood product administration (FFP, platelets, cryoprecipitate)
• Discuss complications of blood product administration
• Discuss use of thromboelastogram (TEG)
Anemia

- Decrease in oxygen carrying capacity of blood
- O2 carrying capacity is function of total volume of circulating blood cells → Decrease in total red cell volume.
- Anemia itself does not compromise tissue oxygenation as long as intravascular volume is maintained.
Anemia

- Clinicians use Hb/Hct as definition of anemia.
- Problematic since plasma volume is highly influential on Hb/Hct concentration.
- Plasma volume changes in critically ill pts.
  - Hemodynamically unstable
  - Fluid shifts
  - Hypoalbunemia
  - IVF
  - Diuretics

- Hb/Hct are not reliable indicators of anemia in critically ill patients.
Causes of Anemia in ICU

• Systemic Inflammation
  – Inflammatory cytokines can inhibit erythropoietin release
  – Decreased marrow response to erythropoietin
  – Iron sequestration in macrophages
  – Increased destruction of RBCs

• Phlebotomy
  – 40ml – 70 ml daily
  – 4 times higher in ICU patients

• Acute blood loss
Use of Hct/Hb in Acute Blood Loss

• Change in Hb/Hct show poor correlation of blood volume and RBC deficits
• Acute blood loss is whole blood loss
  – Proportional decreases blood/plasma
  – Eventual decrease in Hct/Hb due to sodium and water conservation (renin-angiotensin system)
• Decrease in Hct/Hb is usually due to volume resuscitation
Compensatory Response to Anemia

• VO2 = CO x 13.4 x Hb x (SaO2 - SvO2)

• In anemia VO2 remains constant due to
  – Increase cardiac output
    • Decreased blood viscosity (reduced afterload)
    • Sympathetic nervous system activation
  – Increase in peripheral O2 extraction
    • Decrease in Hct → Decrease in DO2 → counterbalanced by increased O2 extraction
**Compensatory Response to Anemia**

- When Hct falls below 10%, the increased O2 extraction can no longer match the decreased DO2 therefore VO2 falls as well.

- O2 extraction = (SaO2-SvO2)
  - 50% or higher inadequate tissue oxygenation
  - Associated with elevated lactate

- Progressive isovolemic anemia will not decrease tissue oxygenation until Hct/Hb very low.
  - Hct 10, Hb 3g/dL (animal studies)
  - Hb 5g/dL (healthy adult study)
Hypovolemic anemia

- Circulatory system is a volume responsive pump
- Compensatory response to acute blood loss anemia
  - Transcapillary refill: 15% of blood volume
  - Activation of renin-angiotensin system
  - Sodium and water conservation
  - Increased production of RBCs in bone marrow
Acute Blood Loss Anemia

• Four classes of blood loss
  – Class I: ≤ 15% loss blood volume
    • Transcapillary refill
    • Clinical findings minimal
  – Class II: 15-30% loss blood volume
    • Orthostatic changes in heart rate and BP
    • Sympathetic vasoconstriction maintain BP and perfusion
    • UOP falls 20-30 mL/hr.
    • Splanchnic flow may me compromised
      -risk of intestinal barrier breakdown and translocation
Acute Blood Loss Anemia

– Class III: 30-40% blood volume loss
  • Decompensated hypovolemic shock
  • Vasoconstriction response can no longer maintain BP and organ perfusion
  • UOP 5-15/hr.

– Class IV: >40% blood volume loss
  • Severe hypotension
  • Oliguria
  • Changes may be irreversible
A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care (Herbert, PC et al.)

- **Background:**
  - Restrictive vs liberal RBC strategy in critically ill patients
  - Compare rates of death and severity of organ dysfunction

- **Methods:**
  - Enrolled 838 euvolemic critically ill pts w/ Hb <9.0g/dL w/in 72 hrs. of admission
  - Random assignment of 418 pts to restrictive strategy (Hb <7.0), maintained at 7.0-9.0 g/dL
  - Random assignment of 420 pts to liberal strategy (Hb <10.0), maintained at 10.0-12.0 g/dL
A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care (Herbert, PC et al.)

Results:
- Overall 30-day mortality similar: 18.7% restrictive vs. 23.3% liberal (P=0.11)
- Restrictive group mortality lower in patients who were less acutely ill: 8.7% restrictive vs. 16.1% liberal (P=0.03)
- Restrictive group mortality less at age 55 and below: 5.7% restrictive vs 13.0% liberal (but not w/sig cardiac dx)
- Restrictive group in-hospital mortality significantly lower: 22.2% restrictive vs. 28.1% liberal (P=0.05)

Conclusion:
- Restrictive transfusion is at least as effective if not superior to liberal transfusion strategies in critically ill patients with possible exception of pts w/ MI and unstable angina.
• Red Blood Cell Transfusion: A Clinical Practice Guideline From the American Association of Blood Banks Carson, JL et al.
  – Description: Guideline to provide clinical recommendations regarding Hb thresholds and other clinical variables that trigger RBC transfusion in hemodynamically stable pts
  – Methods:
    • Systematic review of randomized clinical trials evaluating transfusion thresholds
    • Literature search 1950-Feb 2011
    • Examined patients who received any RBC and how many RBC to describe effect of restrictive strategy on RBC use
    • Examined restrictive clinical consequences regarding overall mortality, non-fatal MI, cardiac events, pulm edema, stroke, thromboembolism, renal failure, infection, hemorrhage, confusion, functional recovery, and length of hospital stay
• Recommendations:
  – Restrictive transfusion strategy of Hb 7.0-8.0 g/dL in hospitalized, stable patients
  – Restrictive strategy of Hb >8.0 g/dL in hospitalized pts with preexisting CV disease; consider transfusion for pts w/symptoms (CP, orthostatic hypotension, tachycardia unresponsive to fluid, CHF)
  – Cannot recommend for or against liberal or restrictive transfusion strategies for hospitalized, hemodynamically stable pts with ACS
  – Transfusion decisions to be influenced by symptoms as well as Hb concentrations
• Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery (Carson, JL et al.)

  — Background
  • Randomized trial to determine if higher threshold for transfusion would improve recovery after hip surgery for hip fracture.

  — Methods
  • 2016 patients enrolled age 50 or older
  • History or risk factors of cardiovascular disease
  • Hb 10.0g/dL or lower after hip surgery
  • Random assignment to liberal transfusion (>10.0g/dL) and restrictive transfusion strategy (<8.0 g/dL)
  • Primary outcome defined as death or inability to walk across room without human assistance on 60 day follow-up.
Results

- Primary outcome rate of 35.2% in liberal strategy group.
- Primary outcome rate of 34.7% in restrictive strategy group.
- In hospital acute coronary syndrome or death for liberal group 4.3% and 5.2% for restrictive group.
- Rates of death on 60 day follow up were 7.6% (liberal) and 6.6% (restrictive).
- Rates of other complications similar.

Conclusions

- Liberal transfusion strategy did not reduce rate of death or inability to walk.
- Did not reduce in-hospital morbidity in elderly patients at high cardiovascular risk.
Transfusion Review

• Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease Carson, JL et al.

  – Background
    • Investigates whether patients with acute coronary syndrome benefit from higher Hb levels.

  – Methods
    • Pilot trial in 110 patients with acute coronary syndrome or stable angina undergoing cardiac catheterization and Hb level < 10.0 g/dL
    • Liberal transfusion strategy received one or more units to raise Hb >10.0 g/dL.
    • Restrictive transfusion strategy received blood for symptoms from anemia or for Hb <8.0 g/dL.
    • Primary outcome defined as death, myocardial infarction, or unscheduled revascularization 30 days post randomization.
Transfusion Review

Results

- Mean number of units transfused 1.6 in liberal and 0.6 in restrictive.
- Primary outcome 10.9% in liberal group and 25.5% in restrictive group.
- Death at 30 days less frequent in liberal group compared to restrictive group.

Conclusions

- Liberal transfusion strategy associated with trend in fewer major cardiac events and deaths than in more restrictive strategy.
Clinical practice guideline: Red blood cell transfusion and critical care (Napolitano et al.)

- **Objective:**
  - To develop practice guideline for RBCs in trauma and CC

- **Methods:**
  - Developed by joint task force of Eastern Association for Surgery and Trauma (EAST) and American College of Critical Care Medicine (AACM) of SCCM
  - Comprehensive literature review
  - Used scientific grading methods employed by Canadian and US Preventative Task force
    - Grading of Evidence: Class I, II, III
    - Grading of Recommendations: Level I, II, III
Transfusion Review

• Questions:
  – What are the risks and benefits of RBC transfusion in critically ill and injured patients?
  – What are the indications for RBC transfusion? During resuscitation, during hospitalization?
  – What are the alternatives to RBC transfusions?
  – What practices are useful in decreasing need for RBC transfusions?
• Recommendations regarding indications for RBC Transfusion:
  – RBC tx recommended in hemorrhagic shock (Level 1)
  – RBC tx may be indicated for pts w/ evidence of acute hemorrhage and hemodynamic instability or inadequate D02 (Level 1)
  – A “restrictive” transfusion strategy (Hb <7.0) is as effective as “liberal” strategy (Hb <10.0) in critically ill patients w/hemodynamically stable anemia, except in pts w/MI or unstable myocardial ischemia. (Level 1)
  – The use of only Hb as a ‘transfusion trigger’ should be avoided. Tx should be based on intravascular volume, evidence of shock, duration/extent of anemia, cardiopulmonary physiologic parameters. (Level 2)
  – In absence of acute hemorrhage, RBC should be given as single units. (Level 2)
Recommendations regarding indication for RBC transfusion:

- Consider transfusion if Hb is <7.0 g/dL in critically ill pts requiring mechanical ventilation. No benefit of liberal tx in mechanically ventilated patients. (Level 2)
- Consider transfusion if Hb <7.0 g/dL in resuscitated critically ill trauma patients. No benefit to liberal transfusion strategy. (Level 2)
- Consider transfusion if Hb is <7.0 g/dL in critically ill patients with stable cardiac disease. No benefit of liberal transfusion strategy. (Level 2)
- RBC transfusion should not be considered as an absolute method to improve tissue oxygen consumption (VO2) in critically ill patients. (Level 2)
- RBC transfusion may be beneficial in patients with acute coronary symptoms who are anemic (Hb <8.0 g/dL) on hospital admission. (Level 3)
Transfusion Review With Concomitant Disease

• **RBC Transfusion in Sepsis**
  - No sufficient data to support Level 1 recommendations.
  - Transfusion needs must be assessed individually given there are no known optimal transfusion triggers in sepsis and no clear evidence that blood transfusion increases tissue oxygenation (VO2). (Level 2)

• **RBC Transfusion in Patients at risk for or with ALI or ARDS**
  - No sufficient data to support Level 1 recommendations.
  - All efforts should be made to avoid RBC transfusion after completing resuscitation. (Level 2)
  - All efforts should be made to diagnose and report transfusion related ALI (TRALI) to blood bank as it has emerges as leading cause of transfusion associated morbidity and mortality. (Level 2)
  - RBC transfusion should not be considered as a method to facilitate weaning MV. (Level 2)
Transfusion Review With Concomitant Disease

- **RBC Regarding Patients with Neurologic Injury and Diseases**
  - No Level 1 recommendations.
  - No benefit to ‘liberal’ transfusion strategy in patients with moderate to severe traumatic brain injury. (Level 2).
  - Decisions must be assessed individually in patients with SAH as there is no clear evidence that blood transfusion is associated with improved outcomes. (Level 3)
Transfusion Review

- Recommendations regarding RBC Transfusion Risks
  - Insufficient data to support Level 1 recommendations.
  - RBC transfusion is associated with nosocomial infection (wound, PNA, sepsis) rates independent of other factors. (Level 2)
  - RBC transfusion is an independent risk factor for sepsis or MOF and SIRS. (Level 2)
  - RBC transfusion are associated with longer ICU and hospital LOS, increased complications, and increased mortality. (Level 2)
  - There is a relationship between transfusion and ALI and ARDS. (Level 2)
• Alternatives to RBC transfusion
  – Insufficient Level 1 data recommendations.
  – Recombinant human erythropoietin administration improves reticulocytosis and hematocrit and may decrease overall transfusion requirements. (Level 2)
  – Hemoglobin based oxygen carriers. (Level 2)

• Reduction of RBC Transfusion
  – Insufficient Level 1 data recommendations.
  – Use of low adult volume or pediatric tubes to reduce phlebotomy volume. (Level 2)
  – Use of blood conservation devices for re-infusion of waste blood. (Level 2)
  – Intraoperative and post-operative blood salvage. (Level 2)
  – Reduction of diagnostic and laboratory testing. (Level 2)
• Acute Hemolytic Reaction
  – Caused by transfusion ABO incompatibility
    • Antibodies of recipient bind to ABO surface antigen of donor RBC ensuing lysis of donor cells
    • Incites systemic inflammatory response
  – Symptoms include fever, dyspnea, chest pain, low back pain, hypotension.
  – Treatment
    • Immediately stop transfusion
    • If hypotensive infuse volume. Colloids may be beneficial d/t rapid volume expansion.
    • May require vasopressors. Supportive care.
    • Blood samples and blood back to blood bank for repeat typing and cross matching, direct antiglobulin, and plasma free hemoglobin.
Febrile Nonhemolytic Reaction

- 1 per 200, 0.5% of RBC transfusions
- Result of antibodies in recipient to leukocytes in donor RBC
- Fever 1 to 6 hours after transfusion (fever later than acute hemolytic reactions)

Treatment

- Same as hemolytic reaction if severe
- More than 75% will not experience fever with future transfusions.
- If fever recurs may require leukocyte poor red cell preparations.
Transfusion Risks and Complications

- Allergic reactions
  - Caused by presence of foreign donor proteins
    - Sensitization to proteins in prior transfusions
    - Patients with IgA deficiency are particularly prone
  - Symptoms
    - Pruritis
    - Urticaria
    - Usually not associated with fever
  - Treatment
    - May continue if no fever.
    - Antihistamines for symptomatic relief.
    - Possible washed cell (plasma removal) for subsequent transfusions for severe allergic reactions.
Transfusion Risks and Complications

• Blood born bacterial infections and viruses
  – Bacterial: 1 per 500,000
  – Hepatitis B: 1 per 220,000
  – Hepatitis C: 1 per 1.6 million
  – HIV: 1 per 1.9 million
Transfusion Risks and Complications

• Acute Lung Injury
  – TRALI
    • Inflammatory lung injury: during or within first 6 hours after start of transfusion
    • 1 per 5,000
    • Antileukocyte antibodies in donor blood bind to circulating granulocytes in recipient blood and promote leukocyte sequestration in pulmonary microcirculation
    • Presents as Acute Respiratory Distress Syndrome
    • Leading cause of death from blood transfusions.
  • Symptoms
    – Dyspnea
    – Hypoxemia
    – CXR eventually shows diffuse pulmonary infiltrates
- TRALI continued
  • Treatment
    - Intubation and mechanical ventilation often required.
    - Usually resolves in one week.
    - Supportive care.
    - Stop transfusion if still infusing at time of respiratory compromise.
Transfusion Risks and Complications

• Immunomodulation
  – Increased incidence of nosocomial infections
  – Promotion of immunosuppression
    • Mechanisms unknown
    • Possibly antigenic substances or leukocytes in transfused blood persist in the recipient and down-regulate immune system
Transfusion Risks and Complications

• **Volume overload**
  – Expansion of intravascular volume may cause pulmonary edema
  – Pts with decreased cardiac and renal function at risk
  – FFP more prone to causing pulmonary edema

• **Hypothermia**
  – Blood products are stored at cold temperatures
  – Coagulopathy
    – Cardiac irritability, peripheral vasoconstriction

• **Coagulopathy**
  – Hemodilution with massive transfusion of RBCs
  – Acidosis from shock-induced tissue hypoxia

• **Citrate toxicity**
  – May not be metabolized in massive transfusion, hypocalcemia
Transfusion Guidelines

• Think about every unit of blood you give your patients.
• Weigh risks and benefits of each PRBC administered.
• Instill Transfusion Protocols and Guidelines
No active Bleeding without known cardiac disease or risk factors:

- **Hb < 7 g/dl**: Transfuse 1 units PRBCs and reassess patient’s clinical status and Hb level. Maintain Hb level at 7-9 g/dl. Reassess Hb after administration.

- **Hb 7 to 9 g/dl**: Limit transfusions unless known cardiac disease or inadequate tissue O2 delivery is documented (i.e., new onset tachycardia, hypotension, SvO2<60, elevated lactate).

- **Hb > 9**: RBC transfusion is not indicated.

No active bleed with known active cardiac disease (possibly those with high risk of cardiac disease):

- **Hb < 9 g/dl** with evidence of cardiac ischemia, new onset tachycardia, shortness of breath/chest pain, or decline in O2 saturation: Transfuse 1 units PRBC’s and reassess patient’s clinical status and Hb level. Maintain Hb level at 9-10 g/dl. Reassess Hb after administration.
Transfusion Guidelines

• **Active Bleeding:**

  • **Rapid acute hemorrhage w/o control**: Transfuse PRBC. May need un-crossmatched or type specific blood.

  • **Estimated blood loss >30-40% or >1.5 – 2 L**: Transfuse PRBC. May need un-crossmatched or type specific blood.

  • **Estimated blood loss 25 - 30% or 1 – 1.5 L**: Crystalloid/colloid resuscitation, proceed to PRBC’s if recurrent signs of hypovolemia.

  • **Presence of co-morbid factors** – Consider transfusion with lesser degrees of blood loss.
• **FFP**: Separated from freshly drawn blood, Frozen for storage, must be used within 24 hours of thawing

• **Indications**
  – Inadequate hemostasis, active bleeding
  – Benefit of correcting hemostasis outweigh plasma risks
  – Massive transfusion: decrease dilution deficiency of coagulation factors
  – Prior to invasive procedures with high risk of bleeding
  – Should not be used to reverse supra-therapeutic INR from warfarin unless active bleeding or invasive procedure

• **Expected Response**
  – INR of plasma is ~1.3-1.5
  – Less effective in patients with lower INR
  – Patients with severe factor deficiencies are more responsive
Cryoprecipitate

- **Cryo**: Collected by thawing FFP and collecting the white precipitate
  - Rich in von Willebrand factor, Factor VIII, Factor XIII, and fibrinogen
  - Allows these factors to be replaced at much lower volume than FFP.

- **Indications:**
  - von Willebrand disease
  - Hemophilia
  - Hypfibrinogenemia
  - Massive transfusion
  - DIC

- In bleeding patient may follow fibrinogen levels and thromboelastogram (TEG).

- May raise fibrinogen 70 mg/dL per 10 bag cryoprecipitate.
Platelets

• Indications
  – Stop active hemorrhaging
  – Prophylactic
    • <10,000 to prevent spontaneous hemorrhage
    • <50,000 with active bleeding, scheduled invasive procedure, platelet disorder
    • <100,000 central nervous system injury (TBI), trauma, neurosurgery
    • Normal platelet count with ongoing bleeding and reason for platelet dysfunction

• Expected Response
  – Expected raise in platelet count 5,000 – 10,000 per unit administered
Thromboelastogram

- **Coagulation**
  - Kinetics of clot development
  - Reaction time, first significant clot formation
  - Achievement of certain clot firmness

- **Fibrinolysis**
  - Angle
  - Maximum amplitude – maximum strength of clot
  - Percent lysis 30 minutes after MA
  - LY
  - LY30

Image: bloodcmecenter.org
## Thromboelastogram

### Thromboelastography definitions

<table>
<thead>
<tr>
<th>Clot phase</th>
<th>Parameter</th>
<th>Measurement</th>
<th>TEG® abbreviation</th>
<th>ROTEM® abbreviation</th>
<th>Enzymatic stage</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clot initiation</td>
<td>Clotting time</td>
<td>Time from start of sample to 2 mm clot amplitude</td>
<td>Reaction time (R)</td>
<td>Clot time (CT)</td>
<td>Early activation of clotting cascade resulting in initial thrombin burst</td>
<td>Prolonged by clotting factor deficiencies, anticoagulants, and hypofibrinogenemia. Shortened in hypercoagulable states.</td>
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<td></td>
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</tr>
<tr>
<td>Clot kinetics</td>
<td>Clot formation time</td>
<td>Time from 2 mm to 20 mm clot amplitude</td>
<td>Clot formation time (K)</td>
<td>Clot formation time (CFT)</td>
<td>Clot potentiation by activation of platelets and thrombin-mediated cleavage of soluble fibrinogen</td>
<td>Prolonged by clotting factor deficiencies, hypofibrinogenemia, thrombocytopenia, and platelet dysfunction. Abnormally low in clotting factor deficiencies, hypofibrinogenemia, thrombocytopenia, and platelet dysfunction.</td>
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<tr>
<td></td>
<td>Angle</td>
<td>Angle of tangent line from 2 mm to 20 mm clot formation</td>
<td>Alpha angle</td>
<td>Alpha angle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clot strength</td>
<td>Maximal clot strength</td>
<td>Amplitude measured at peak clot strength</td>
<td>Maximal amplitude (MA)</td>
<td>Maximal clot firmness (MCF)</td>
<td>Maximal clot strength achieved via GP IIb/IIIa-mediated platelet-fibrin interactions</td>
<td>Abnormally low in hypofibrinogenemia, thrombocytopenia, or platelet dysfunction. Abnormally high in platelet hypercoagulability.</td>
</tr>
<tr>
<td></td>
<td>Clot viscoelasticity</td>
<td>Calculated from maximal amplitude</td>
<td>G</td>
<td>Maximal clot elasticity (MCE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clot lysis</td>
<td>Clot lysis</td>
<td>Percentage of loss of amplitude at fixed time after maximal amplitude</td>
<td>Lysis at 30 min (LY30), estimated percentage of lysis (EPL)</td>
<td>Lysis index at 30 min (LI30), maximal lysis (ML)</td>
<td>Activation of fibrinolytic system</td>
<td>Abnormally high in enzymatic or mechanical hyperfibrinolysis.</td>
</tr>
</tbody>
</table>

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Transfusion Guidelines

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