Transfusion and Blood Component Therapy: When, What, and Who

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No financial disclosures
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Learning Objectives

• At the conclusion of the activity participants should be able to:
  – Discuss the risks and benefits of transfusion of red blood cells and the appropriate trigger for transfusion
  – Discuss the available alternatives to blood transfusion
  – Discuss the importance of teamwork in developing a bloodless surgery strategy
Outline Of Presentation

• Overview of blood transfusion
• Transfusion trigger controversy
  – Risks of anemia
  – Blood transfusion studies
• Risks of “old blood”
• Alternatives to blood transfusion
• Blood substitutes
• Blood component therapy
• Massive transfusion
Blood Transfusion in The United States

- 15 million units collected
- 14 million units transfused
- 2/3 used perioperatively or in the ICU
- Studies estimate that up to 50% of transfusions are inappropriate
- Cost of $300 - $1,000 per unit
- Increasing blood shortages
  - Decreasing donations
  - Increasing age of the population
When Should We Transfuse?

**Transfusion trigger:** The hemoglobin concentration at which the benefits of transfusion exceed the risks of transfusion.
It’s all about oxygen
Hemoglobin And Oxygen Delivery

\[ \text{DO}_2 = \text{CO} \times \text{CaO}_2 = \text{CO} \times 1.37 \times \text{Hgb} \times \text{SaO}_2 \]

Critical oxygen delivery (COD) is the \( \text{DO}_2 \) below which \( \text{VO}_2 \) decreases.
Hemoglobin And Oxygen Delivery

\[ DO_2 = CO \times CaO_2 = CO \times 1.37 \times Hgb \times SaO_2 \]

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Critical oxygen delivery (COD) is the DO\textsubscript{2} below which VO\textsubscript{2} decreases.
Hemoglobin And Oxygen Delivery

\[ \text{DO}_2 = \text{CO} \times \text{CaO}_2 = \text{CO} \times 1.37 \times \text{Hgb} \times \text{SaO}_2 \]

Critical oxygen delivery (COD) is the DO\(_2\) below which VO\(_2\) decreases
The highest value of oxygen delivery occurs at which of the following hematocrit values?

1. 60%
2. 50%
3. 40%
4. 30%

4. 30%
Tolerance Of Anemia

- Decreased viscosity: ↑CO, ↑SV
  - \( \text{DO}_2 \) increased at 30% hematocrit and normal at 20% hematocrit
- COD = 8-10 ml/kg/min (hemoglobin 4, \( \text{PvO}_2 \) 35 mm Hg)
- Acute hemodilution to hemoglobin 5 g/dL in healthy patients in volunteers
  - Weiskopf, JAMA 1998; 279:217
Limitations of Anemia

• Increased CO requires avoidance of hypovolemia
• Increased metabolic demands
Limitations Of Anemia

• Increased CO requires avoidance of hypovolemia
• Increased metabolic demands
  – Sepsis
Early Goal-Directed Therapy

  - 263 patients with severe sepsis and septic shock
  - Randomized to standard therapy or early goal-directed therapy (EGDT)
  - Standard therapy
    - Crystalloid boluses for CVP 8-12
    - Vasopressors/vasodilators for MAP 65-90
    - Urine output $\geq 0.5$ ml/kg/h
EGDT Protocol

• EGDT
  – Catheter for measurement of central venous oxygen saturation (ScvO2)
    • If ScvO2 < 70%
      – RBC transfusion to hematocrit > 30%
      – Dobutamine up to 20 μg/kg/min
      – Sedation and mechanical ventilation
What Was Done During the First 6 Hours?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Goal-Directed</th>
<th>Standard</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids</td>
<td>4981 mL</td>
<td>3499 mL</td>
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<tr>
<td>RBCs</td>
<td>64%</td>
<td>18%</td>
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<tr>
<td>Inotropes</td>
<td>14%</td>
<td>0.8%</td>
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</tr>
</tbody>
</table>

EGDT Decreased Mortality

Limitations Of Anemia

• Increased CO requires avoidance of hypovolemia
• Increased metabolic demands
• Coronary circulation
  – Increased coronary blood flow required to compensate for anemia
  – Increased ischemia at hematocrit < 28%
Do Benefits of Transfusion Outweigh the Risks?
Audience Response Question

The largest number of deaths per year related to blood transfusion occurs from which of the following complications?

1. ABO mismatched transfusion
2. Transfusion-related acute lung injury (TRALI)
3. Hepatitis B
4. Hepatitis C
5. Bacterial contamination
Risks of Blood Transfusion

- Fatal hemolytic reaction (1:500,000)
- HIV (1:7,800,000), HCV (1:1,935,000), HBV (1:350,000)
- Other infections (CMV, Yersinia, malaria, West Nile, vCJD, human herpesvirus-8)
- Febrile reactions (1%)
- TACO (transfusion-associated circulatory overload)
- TRALI (1:5,000)
- Immunosuppression
  - Perioperative infection
- Problem of “old blood”
TRALI

- Marik, Crit Care Med 2008; 36:3080
  - Leading cause of transfusion-related deaths
    - Markedly underdiagnosed
  - Two distinct types of TRALI
TRALI

• Classic TRALI
  – Acute onset (< 6 hours), complete resolution (< 96 hours), 5-10% mortality
  – Incidence 1/5,000 RBC, 1/2,000 FFP, 1/400 platelet concentrates
  – Due to antileukocyte antibodies in donor plasma
  – Increased incidence with multiparous female donors
    • Marked decrease with exclusive use of male donors (1:170,000)
TRALI

- Delayed TRALI
  - Onset 6-72 hours, course similar to ARDS
  - Mortality 35-45%
  - Related to multiple units (lipid mediators or cytokines)
  - High incidence in ICU patients (2-hit hypothesis)
    - 40-50% incidence with massive transfusion
Transfusion and Perioperative Infection

• Hill, J Trauma 2003; 54:908
  – Meta-analysis of 20 perioperative studies
  – Increased odds ratio (OR = 3.45) for postoperative bacterial infection
Are patients sick because they get transfused, or are they transfused because they are sick?
Blood Transfusion in The ICU

  – 838 ICU patients with Hgb < 9 within 72 hours of admission
  – Randomized to transfusion Hgb trigger of 7 or 10 (restrictive vs. liberal)
Trial Results (I)

• Decreased blood transfusions in the restrictive (Hgb 7) group
  – 2.6 vs. 5.6 units (54% reduction)
  – No transfusions in 33% of restrictive group
Trial Results (II)

- All results favored the restrictive (Hgb 7) strategy
Trial Results (III)

- Subgroup analyses
  - Decreased 30 day mortality in less severely ill patients (9% vs. 16%)
  - Decreased 30 day mortality in patients < 55 years (6% vs. 13%)
  - Equal mortality in patients with cardiac disease (21% vs. 23%)
Transfusion Requirements After Cardiac Surgery (TRACS) Study

• Hajjar, JAMA 2010; 304:1559
  – RCT of Hct 24 vs. 30%; n = 502
  – Percent of patients transfused: 47% vs. 78%
  – Units transfused: 258 vs. 613
  – Composite endpoint of death, cardiogenic shock, ARDS, renal replacement therapy
  – Identical outcome in the two groups (11% vs. 10%)
FOCUS Trial

- Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair
  - 2,016 patients with cardiovascular disease
    - 40% CAD, 17% CHF, 11% PVD, 24% prior CVA/TIA
    - Median age of 82
  - Randomized to Hgb transfusion trigger of 10 vs. symptoms (optional transfusion at 8)
  - Outcome was the ability to walk 10 feet without assistance
  - Percentage transfused: 42% vs. 97%
  - Units transfused: 652 vs. 1866
  - Identical morbidity and mortality
Transfusion Threshold

  - RCT of 921 patients with acute upper GI bleed
  - Transfusion threshold of 7 vs. 9 g/dL
  - 14% vs. 51% transfused
  - 1.5 vs. 3.7 units transfused
  - Death HR 0.55
Less is More in MI

• Chatterjee, AMA Intern Med 2013; 173:132
  – Meta-analysis of 10 studies of blood transfusion strategy in anemia associated with myocardial infarction
  – Increased mortality with a strategy of blood transfusion vs. no (18% vs 10%)
  – Higher risk for mortality independent of baseline hemoglobin level, nadir hemoglobin level, and change in hemoglobin level during the hospital stay
Transfusion Threshold

• Carson, Cochrane Database Syst Rev 2012; CD002042
  – 19 RCTs, 6,264 patients
  – Restrictive transfusion strategy
    • 39% decrease in risk of transfusion
    • 1.19 less units per patient
    • Decreased hospital mortality (RR 0.77)
    • No adverse effects
• 2009 SCCM guidelines recommend hemoglobin 7 g/dL for hemodynamically stable patients
Specific Patient Populations

- Ischemic heart disease
  - Limited data but hemoglobin 8 g/dL for transfusion
- Severe sepsis and septic shock
  - ? Threshold of 10 g/dL during the first 6 hours of resuscitation
- Neurological patients
  - No data to recommend aggressive transfusion
- Elderly patients
  - Trend towards increased mortality with aggressive transfusion (hemoglobin 9 g/dL) (Walsh, CCM 2013; 41:2354)
• Koch, N Engl J Med 2008; 358:1229
  – Retrospective study of cardiac surgery patients receiving old (> 14 days) or new (≤ 14 days) blood
  – All complications increased in patients receiving old blood
Adverse Effects Of Blood Storage

• Decreased RBC deformability
  – Decreased RBC ATP
Age of Blood

Scanning electron micrographs of red blood cells isolated from stored blood on Day 1, Day 21, and Day 35. During storage, the shape of RBCs changed gradually from normal discoid to echinocytes (dented or shriveled red cells).

Adverse Effects Of Blood Storage

- Decreased RBC deformability
- Decreased 2,3 DPG
- Decreased SNO-hemoglobin
- Increased red cell death with increased age of blood (25% at 24 hours in expiring blood)
- Cytokine release during storage and increased inflammation with transfusion
Blood Transfusion In The ICU

• Marik, JAMA 269:3024, 1993
  – 23 patients with sepsis
  – Transfused with 3 units PRBC
  – Oxygen delivery but not oxygen consumption increased
  – pH$i$ decreased proportional to the age of the blood
  – pH$i$ always decreased if blood > 15 days old
Red Cell Storage

• Kor, Am J Respir Crit Care Med 2012; 185:842
  – RCT (n = 100) of fresh (≤ 5 days) vs. standard blood in ventilated ICU patients
  – 4 vs. 26 days of storage
  – No difference in lung function or immunologic or coagulation studies
Red Cell Storage

- Fergusson, JAMA 2012; 308:1443
  - RCT of 377 premature infants with very low birth weight
  - Randomized to RBC < 7 days vs. standard RBCs
  - 5.1 vs. 14.6 days of storage
  - Identical rates (53%) of nosocomial infection
Ongoing Studies

• Red Cell Storage Duration and Outcomes in Cardiac Surgery (Cleveland Clinic)
  – Patients undergoing CABG with or without valve (n = 2800)
  – Randomized to newer blood (< 14 days) or older blood (> 20 days)

• ABLE (Age of Blood Evaluation)
  – Canadian Institute of Health Research
  – ICU patients who require transfusion (n = 2510)
  – Randomized to newer blood (< 8 days) or control leukoreduced blood

• RECESS (Red Cell Storage Duration Study)
  – NHLBI
  – Patients undergoing complex cardiac surgery (n=1750)
  – Randomized to newer leukoreduced blood (≤ 10 days) or older leukoreduced blood (≥21 days)
Alternatives To Blood Transfusion

- Lower transfusion trigger
- Erythropoietin (especially preoperative)
- Predeposited autologous donation
- Intraoperative acute normovolemic hemodilution
- Intraoperative RBC salvage
- Blood substitutes
- Decreased phlebotomy

- Blood management involves an approach, not a technique
EPO Mechanism of Action

1. Kidney senses hypoxia and increases endogenous EPO production.
2. EPO acts on the erythroid progenitor cells in the bone marrow to produce new red blood cells.
3. Kidney senses increased tissue oxygenation.
### Erythropoietin And Elective Surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>EPO Total Dose (U/kg)</th>
<th>EPO Duration (Days)</th>
<th>% of Patients Who Received Allogeneic-Blood Transfusions</th>
<th>P Value*</th>
<th>No. of Patients</th>
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<tr>
<td>Autologous blood donors</td>
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<tr>
<td>With no anemia</td>
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<td>21</td>
<td>19</td>
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<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients not donating autologous blood</td>
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<tr>
<td>Canadian Orthopedic Peri-operative Erythropoietin Study Group(^{27})</td>
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<td>14</td>
<td>42</td>
<td>24</td>
<td>&lt;0.001</td>
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<td></td>
<td>2700</td>
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<tr>
<td></td>
<td>1500</td>
<td>14</td>
<td></td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

*Goodnough NEJM 1997; 336:933*
EPO 3 Study

- 1460 patients
- No decrease in blood transfusions (46 vs. 48%; 4.5 vs. 4.3 units)
- Increased thrombotic events in patients not receiving heparin
Alternatives To Blood Transfusion

• Lower transfusion trigger
• Erythropoietin (especially preoperative)
• Preoperative autologous donation
• Intraoperative acute normovolemic hemodilution
• Intraoperative RBC salvage
• Decreased phlebotomy
• Blood substitutes
Predeposited Autologous Donation

• Henry, Cochrane Database of Systematic Reviews, 2004
• Meta-analysis of 8 trials with 1,119 patients
  – PAD decreased preoperative Hgb by 1.23 g/dL
  – PAD increased total transfusion (RR 1.29)
  – PAD decreased allogeneic transfusion (RR 0.37)
  – Poor methodology (unblinded, no transfusion protocol)
  – No outcome benefit demonstrated
Alternatives To Blood Transfusion

• Lower transfusion trigger
• Erythropoietin (especially preoperative)
• Predeposited autologous donation
• Intraoperative acute normovolemic hemodilution: Rarely useful
• Intraoperative RBC salvage
• Blood substitutes
• Decreased phlebotomy
Mathematics of ANH

Weiskopf, Anesthesiology 2001;94:439
Acute Normovolemic Hemodilution

  - 130 patients undergoing major hepatic resection randomized to ANH vs. no ANH
  - Baseline hemoglobin 13.3
  - Hemodilution to hemoglobin 8
    - Median 2250 ml ANH
  - Strict transfusion protocol (hemoglobin 7 intraoperatively, 8 postoperatively)
  - Average savings of 0.29 units per patient (p = .067)
Alternatives To Blood Transfusion

- Lower transfusion trigger
- Erythropoietin (especially preoperative)
- Predeposited autologous donation
- Intraoperative acute normovolemic hemodilution
- Intraoperative RBC salvage: Limited recovery
- Decreased phlebotomy
- Blood substitutes
Cell Saver in Cardiac Surgery

- Cholette, Ped Crit Care Med 2013; 14:137
  – 106 infants undergoing cardiac surgery
Alternatives To Blood Transfusion

• Lower transfusion trigger
• Erythropoietin (especially preoperative)
• Predeposited autologous donation
• Intraoperative acute normovolemic hemodilution
• Intraoperative RBC salvage: Limited recovery
• Decreased phlebotomy (41 ml/day)
• Blood substitutes
Alternatives To Blood Transfusion

- Lower transfusion trigger
- Erythropoietin (especially preoperative)
- Predeposited autologous donation
- Intraoperative acute normovolemic hemodilution
- Intraoperative RBC salvage
- Decreased phlebotomy
- Blood substitutes: Not ready for prime time
Blood Substitutes

• Perfluorocarbon solutions
• Stroma-free hemoglobin solutions
Blood Substitutes

• Perfluorocarbon solutions
  – No longer in development as blood substitutes

• Stroma-free hemoglobin solutions
Hemoglobin Solutions

• Natanson, JAMA 2008; 299:2304
  – Meta-analysis of 16 trials (5 products)
  – Increased mortality: OR 1.30 (1.05, 1.61)
  – Increased myocardial infarction: OR 2.71 (1.67, 4.40)
  – NO binding results in decreased blood flow, increased mediator production, increased platelet activation, all producing thrombosis
Polyheme and Trauma

- Moore, J Am Coll Surg 2009; 208:1
- RCT (n = 714) of Polyheme begun at scene with up to 6 units
- Primary endpoint of 30 day mortality
  - Polyheme 13%
  - Control 10%
Final Word On Blood Substitutes

“Blood is still the best thing in our veins”

—Woody Allen
Blood Component Therapy

• Fresh frozen plasma and concentrates
• Platelets
• Cryoprecipitate
• Treatment for massive coagulopathy
  – Recombinant activated factor VIIa
  – FEIBA
Risks Of Blood Components

- Viral transmission
- Allergic reactions
- TRALI
- Fluid overload
- Mismatched transfusions
## Cross-Matching

<table>
<thead>
<tr>
<th>Blood type</th>
<th>A (40%)</th>
<th>B (11%)</th>
<th>AB (4%)</th>
<th>O (45%)</th>
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<tbody>
<tr>
<td><strong>RBC antigens</strong></td>
<td>A</td>
<td>B</td>
<td>AB</td>
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<td><strong>Plasma antibodies</strong></td>
<td>Anti-B</td>
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<td>AB</td>
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<tr>
<td><strong>RBC recipient</strong></td>
<td>A, O</td>
<td>B, O</td>
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<tr>
<td><strong>Plasma donor</strong></td>
<td>A, O</td>
<td>B, O</td>
<td>Universal</td>
<td>O</td>
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</tbody>
</table>
Compatibility Testing

• Type & Screen
  – Verification of ABO-Rh of donor & recipient blood
  – Screening test for unexpected antibodies
    • Commercially supplied RBCs (selected for panel of antigens) are mixed with the recipient serum to screen for antibodies

• Type & Cross match
  – Cross match between donor RBCs and recipient serum
Acute Hemolytic Transfusion Reaction

- Fever
- Chills/rigors
- Chest pain
- Respiratory distress
- Nausea/vomiting
- Urticaria

- Hypotension
- DIC/coagulopathy
- Hemoglobinuria
- Acute renal failure
Fresh Frozen Plasma

• Clotting factors present in whole blood
• Use within 24 hours of thawing
• Risk of viral transmission
  – Solvent-Detergent (SD) FFP is pooled from multiple donors
    • Octaplas approved by FDA in 2013
  – Techniques for viral inactivation of single units being developed
• Risk of TRALI
  – Marked reduction with exclusion of female donors
Fresh Frozen Plasma

• Approximately half the FFP usage is inappropriate
• Poor correlation between FFP and INR
  – 20% factors = INR 3
  – 30% factors = INR 2
  – 40% factors = INR 1.6
• INR does not predict clinical bleeding, especially if INR < 1.7
• FFP does not correct moderate prolongations of the INR (1.5)
• Prophylactic FFP does not decrease bleeding if INR < 1.7
• No evidence of prophylactic or therapeutic use of FFP in 80 RCTs (Yang, Transfusion 2012; 52:1673)
Audience Response Question

Which of the following is the most appropriate intervention for the patient with intracranial hemorrhage and an INR of 7 due to warfarin therapy?

1. Intravenous vitamin K
2. Subcutaneous vitamin K
3. Fresh frozen plasma
4. 3-factor prothrombin complex concentrate
5. 4-factor prothrombin complex concentrate

*Answer: 5.*
Prothrombin Complex Concentrates

- Bebulin VH, Profilnine SD, Proplex T
- Used for rapid reversal of warfarin with major bleeding or intracranial hemorrhage since more rapid reversal than either vitamin K or FFP
- Preparations of either 3 factors (2, 9,10) or 4 factors (2, 7, 9, 10); 4-factor preferred for warfarin reversal
- TRALI antibodies removed during preparation
- 1-2 ml/kg (vs. 15 ml/kg for FFP)
- Can produce thrombosis (DVT, CVA, MI)
- Can reverse rivaroxaban (factor Xa inhibitor) but not dabigatran (thrombin inhibitor)
Platelets

- Single unit increases count by 7,500-10,000/mm$^3$
  - Replaced by apheresis platelets (8 units)
- Viral transmission
- Risk of bacterial contamination
  - Stored at room temperature
  - 5 day maximum storage
Platelets

- Thresholds are poorly defined
  - 100,000 for neurosurgery
  - 50,000 for major surgery
  - 5,000 - 10,000 to prevent spontaneous bleeding
Cryoprecipitate

- Cold insoluble portion of FFP
  - Pooled in bags of 10-20 units
  - Total volume of 200-300 ml
- Concentrated source of fibrinogen, factor VIII, factor XIII and vWF
- Fibrinogen content > 10 mg/mL (FFP 2-4)
- Indications
  - Fibrinogen <80-150/200 mg/dL in bleeding patients
  - Correction of presumed hypofibrinogenemia in massively transfused patients
  - Second-line therapy for bleeding patients with von Willebrand’s disease (DDAVP) or Hemophilia A (factor VIII concentrate)
Massive Transfusion
Massive Transfusion

• Transfusion of at least 10 units of PRBCs within 24 hours

• Hemorrhage is the second leading cause of death from trauma
  – 1–3% of civilian trauma patients require massive transfusion
  – 20% of deaths from hemorrhage are preventable
Changing Landscape in Trauma

- Early trauma-induced coagulopathy (ETIC)
- Point-of-care coagulation assays (TEG)
- Massive transfusion protocols
Early Trauma-induced Coagulopathy

• Old paradigm considered coagulopathy as due to dilution
• New data suggest primary coagulopathy due to ischemia and inflammation
  – Exacerbated by hypothermia and acidosis
• Pre-determined ratio of PRBC:FFP:platelets (similar to whole blood) with cryoprecipitate added
Resuscitation in Massive Trauma

- Borgman, J Trauma 2007; 63:805
Resuscitation in Massive Trauma

Fibrinogen in Massive Trauma

- Stinger, J Trauma 2008; 64(2 Suppl):S79
Grady Memorial Hospital Massive Transfusion Protocol

<table>
<thead>
<tr>
<th>Package</th>
<th>RBCs</th>
<th>Plasma</th>
<th>PLTs</th>
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</tr>
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<td>6</td>
<td>6 units</td>
<td>6 units</td>
<td></td>
<td>10 units</td>
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</table>

Shaz, Transfusion 2010; 50:49
Increased Coagulation Products Improves Survival
Complications of Massive Transfusion

- Hypothermia
- Hyperkalemia (1 meq/L/day of storage)
- pH changes (initial acidosis; later alkalosis)
- Citrate toxicity (decreased ionized calcium)
- Increased Hgb-O₂ affinity
Activated Factors

- Recombinant activated VII (NovoSeven)
- FEIBA (Factor Eight Inhibitor Bypassing Activity)
  - Activated VII plus II, VIII, IX, and X
  - Heat used for viral inactivation
- Approved for hemophilia but extensively used for coagulopathy
- Cost of rFVIIa approximately $1/mcg or $5,000 - $25,000 per patient
Meta-analysis of rFVIIA

• Simpson, Cochrane Database Syst Rev 2012; CD005011
  – 16 RCTs of prophylactic use
    • No change in mortality (RR 1.04)
    • Decreased blood loss (-297 ml)
  – 13 RCTs of therapeutic use
    • No statistically significant effects
    • Trend towards decreased mortality (RR 0.91; 95% CI 0.78 – 1.06)
    – Increased arterial thromboembolic events (RR 1.45)
    – “effectiveness of rFVIIA as a more general haemostatic drug, either prophylactically or therapeutically, remains unproven...use outside current licensed indications should be restricted to clinical trials”
Safety of rFVIIa

• Levi, NEJM 2010; 363:1791
  – Analysis of 35 RCT for off-label use
  – No increase in venous thromboembolic events
  – Increased arterial events: 5.5% vs. 3.2%
    • Synergistic effect of age on arterial events
      → ≥ 75 years: 10.8% vs. 4.1%
Use Of rFVIIa

- Individualize for specific settings
- Requires platelets, fibrinogen, normothermia, and reversal of acidosis
Summary (I)

• Anemia is well-tolerated in the majority of patients

• The appropriate transfusion trigger is likely a hemoglobin $\leq 7$ in the majority of patients

• The lack of benefit of blood transfusion may be related to “old blood”
Summary (II)

• Blood substitutes remain a hope for the future
• Future red blood cells may come from transgenic animals, stem cells, or “in vitro” bone marrow
• Role of administration of activated factor 7, FFP, platelets, and fibrinogen in massive trauma requires continued definition
THANK YOU!