Blood Conservation: Current concepts in transfusion medicine

Andrew Shaw MB FRCA FCCM
Department of Anesthesiology
Duke University Medical Center
Andrew.shaw@duke.edu
Goals

- Review risks of transfusion
- Review data supporting liberal strategy
- Discuss minimum acceptable hemoglobin levels
- Review data supporting conservative strategy
Why the Blood Supply Is an Issue

- Disease transmission
- Decreased availability of blood donors
Goal of Red Blood Cell Transfusion

- Increase hemoglobin concentration
- Improve oxygen delivery to tissues
Transfusion Risks

The known risks of transfusion-transmitted diseases are estimated as follows:

- HIV (type 1) 1:2,100,000
- Hepatitis C 1:1,935,000
- Hepatitis B 1:200,000
- HTLV-1 1:2,993,000

HTLV = Human T cell lymphotrophic virus.

## Transfusion Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hives</td>
<td>1:500</td>
</tr>
<tr>
<td>Fever</td>
<td>1:1000 to 10,000</td>
</tr>
<tr>
<td>Bacterial contamination/shock</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>1:900 to 2000</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>&lt; 1:1,000,000</td>
</tr>
<tr>
<td>Acute hemolysis</td>
<td>1:19,000</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1:100,000</td>
</tr>
<tr>
<td>TRALI (Transfusion-related acute lung injury)</td>
<td>1:100,000</td>
</tr>
<tr>
<td>Graft versus host disease (selected recipients) (without IRRADIATION)</td>
<td>1:700 to 5000</td>
</tr>
<tr>
<td>ABO hemolysis (FATAL)</td>
<td>1:250,000 to 600,000</td>
</tr>
</tbody>
</table>

[http://www.anemiaclinic.org/patient/blood_safety_supply_alternatives/what_are_the_risks_of_a_blood_transfusion](http://www.anemiaclinic.org/patient/blood_safety_supply_alternatives/what_are_the_risks_of_a_blood_transfusion)
Transfusion Risks

- Citrate toxicity
- Volume overload
- Hyperkalemia
- Immunomodulation
- Creutzfeldt-Jakob disease
- Inflammation
- Immunosuppression
- Decreased cell-mediated immunity
- Altered lymphocyte subsets
- Accelerated cancer growth
Immunosuppression

- Allogeneic transfusion may enhance tumor recurrence following colorectal cancer resection (Heiss MM, J Clin Oncol 1994)
- Allogeneic transfusion associated bacterial infection (↑35%) and pneumonia (↑52%) (Carson JL, Transfusion 1999)
- Length of storage of transfused RBCs was associated with postoperative pneumonia following CABG surgery, 5% per unit (Vamvakas EC, Transfusion 1999)
- Allogeneic transfusion is associated with prolonged hospital LOS (Vamvakas EC, Transfusion 2000)
Inflammation

• Immunogenic effects of allogeneic transfusions include:
  – Induction of HLA antibodies
  – Generation of pro-inflammatory cytokines
  – Allergic reactions (3% of transfusions)
  – Contact activation with bradykinin release
  – Passive transfer of donor antibodies (TRALI)

• Platelet transfusions are most immunogenic

Novotny VJM, Blood 1995
Consequences of Prolonged Blood Storage

- Corpuscular changes
  - Depletion of adenosine triphosphate
  - 2, 3 diphosphoglycerate
  - low P50 (O2 dissociation)
  - Loss of deformability
Consequences of Prolonged Blood Storage

• Changes in media
  – Release of cytokines, bioreactive substances
  – Decrease pH
  – Release of free hemoglobin
Duration of Red-Cell Storage and Complications after Cardiac Surgery

- Transfusion of cells stored > 14 days assoc with signif inc risk of postop complications
- Decreased survival
- Prolonged intubation
- Renal failure
- Sepsis and MOF
- 2872 patients received > 8000 units

Koch et al, NEJM 2008;358:1229-39
Factors Influencing Decision to Correct Anemia

Factors

- Chronicity of Anemia
- Metabolic Needs
- Ongoing Blood Loss
- Hemoglobin Level
- Comorbid Diseases
- Age
- Cost
- Cause
Low HCT and Adverse Outcome

• CPB HCT of <14% in low risk patients and <17% in high risk patients associated with doubling of mortality risk (Fang WC, Circulation 1997)
• Below 23%, CPB HCT is inversely related to mortality (Defoe GR, Ann Thorac Surg 2001)
• Low hematocrit was associated with renal (Swaminathan M et al., Ann Thorac Surg 2003)
• Preop anemia and polycythemia are associated with an increased 30-day mortality and cardiac events in patients for noncardiac surgery (Wu W et al., JAMA 2007)
• Preop anemia in noncardiac surg - strongly and indep assoc with postop mortality (Beattie-Anesthesiology, V 110, March 2009)
Blood Product Purchase Costs / Unit
Northeast USA Hospital: FY 2005

- LR-PRBCs = $227
- RBCs = $227
- Whole blood, autologous = $397
- Platelets = $72
- Pheresis platelets = $545
- FFP = $49
- Cryoprecipitate = $54
How Low Can the Hgb go?

- Mortality due to anemia increases with Hgb $\leq 5.0$ gm/dL in Jehovah’s Witness patients (Viele MK, Transfusion 1995)
- >95% mortality if Hgb $< 3.0$ gm/dL in Jehovah’s Witness patients (Spence RK, Am Surg 1992)
How Low Can the Hgb go

• Hgb of 5.0 gm/dL does not compromise global tissue oxygenation in conscious, healthy, resting humans (Weiskopf RB, JAMA 1998; Hopf HW, Arch Surg 2000)

• Cognitive function impaired at Hgb between 5.0 and 6.0 gm/dL reversible with supplemental oxygen (Weiskopf RB, Anesthesiology, 2000)
Hebert et. al, *NEJM*, Feb 1999

- A multicenter randomized, controlled clinical trial of transfusion requirements in critical care
- Designed to compare a restrictive vs. a liberal strategy for blood transfusions in critically ill patients
Methods: Hebert et. al

• 838 patients with euvolemia after initial treatment who had hemoglobin concentrations < 9.0g/dl within 72 hours of admission were enrolled

• 418 pts: Restrictive arm: transfused for Hgb<7.0

• 420 pts: Liberal arm: transfused for Hgb< 10.0
## Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>Restrictive group</th>
<th>Liberal group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of death at 30 days</td>
<td>18.7%</td>
<td>23.3</td>
</tr>
<tr>
<td>Mortality rates</td>
<td>22.2%</td>
<td>28.1</td>
</tr>
</tbody>
</table>
A. All Patients

- Survival (%)

- Days

- Restrictive-transfusion strategy

- Liberal-transfusion strategy

- P = 0.10

Graph showing survival over days for two strategies.
Patients with APACHE II Score ≤20

Survival (%)
0  5  10  15  20  25  30
Days

Restrictive-transfusion strategy
Liberal-transfusion strategy

P = 0.02
Low HCT and Improved Outcome

• With exception of coronary ischemia patients, restricted RBC transfusion (Hgb trigger of 7 vs 10) associated with lower 30-day mortality in ICU patients (Hebert PC, NEJM 1999)
Transfusion and Outcome

- European study of anemia in ICU setting
- Prospective, observational study in 1999
- 3534 patients from 146 ICUs
- Propensity score variables: age, sex, admission type, diagnosis on admission, SOFA score, Apache II score, day 1 Hgb, recent h/o anemia, recent acute blood loss, shock on ICU admission, hospital LOS
- Overall mortality rate 29.0% for transfused patients vs 14.9% for non-transfused patients

Vincent et al, JAMA 2002
Vincent et al, JAMA 288:1499-1507, 2002
Transfusion and Outcome

- Retrospective, study of long-term outcome in 1,915 patients after primary CABG

- 5-year mortality twice as high in transfused patients

- After correction for comorbidity, 5-year mortality remained 70% higher in transfused group (p<0.001)

Fig 3. Kaplan-Meier estimates of survival based on equal propensity scores of any transfusion (XFN) versus no transfusion (No XFN). (CABG = coronary artery bypass grafting.)

Engoren et al, Ann Thorac Surg 74:1180-6, 2002 (p<0.001)
Blood Transfusion in Elderly Patients with Acute Myocardial Infarction

- Retrospective study of data on 78,974 Medicare beneficiaries 65 years old or older who were hospitalized with acute myocardial infarction
- **Conclusions** Blood transfusion is associated with a lower short-term mortality rate among elderly patients with acute myocardial infarction if the hematocrit on admission is 30.0 % or lower and may be effective in patients with a hematocrit as high as 33.0% on admission

*Wen-Chih Wu, M.D, NEJM, 2001;345:1230-1236*
Relationship of Blood Transfusion and Clinical Outcomes in Patients With Acute Coronary Syndromes

- 24,112 enrollees in 3 large international trials of patients with acute coronary syndromes (the GUSTO IIb, PURSUIT, and PARAGON B trials)

**Conclusions** Blood transfusion in the setting of acute coronary syndromes is associated with higher mortality, and this relationship persists after adjustment for other predictive factors and timing of events

Association of Hemoglobin Levels With Clinical Outcomes in Acute Coronary Syndromes

- Examined the association between baseline hemoglobin values and major adverse cardiovascular events through 30 days in 39,922 patients enrolled in clinical trials of ACS

- **Conclusions**—*Anemia* is a powerful and independent predictor of *major adverse cardiovascular events* in patients across the spectrum of ACS

Marc S. Sabatine, MD, *Circulation*. 2005;111:2042-2049
What is “Standard of Care?”
ASA Guidelines

- ASA published guidelines in 1996 and 2006 for transfusion therapy
- Outlines provided indications for packed RBC and component therapy in an attempt to curtail unnecessary transfusion
- Generally accepted
Effect of Guidelines

- Inappropriate use of blood products has not been curtailed in spite of guidelines
- Conventional lab tests too slow
- Point-of care testing and protocol-driven therapy necessary to decrease inappropriate use of products

Goodnough, Transfus Sci 1998
So what is the answer?

- Very low hemoglobin is harmful
- Low hemoglobin may be harmful in the presence of co-morbidity
- Unnecessary transfusion is harmful
- The best answer is to prevent low hemoglobin in the first place
Strategies for Blood Conservation

- Preop optimization
- Aprotinin vs. anti-fibrinolytic therapy
- Cell salvage
- Intraoperative autologous donation
- Adopting physiologic “transfusion triggers”
- Protocol-driven care
Preoperative Optimization: Erythropoietin Therapy

- Recombinant human erythropoietin stimulates erythropoiesis similar to the endogenous hormone
- Proven to increase Hb and decrease allogeneic transfusion when given prior to major orthopedic surgery in randomized, controlled trials
  
  Goldberg MA, 1996; de Andrade JR, 1996; Faris PM, 1996

- Reticulocytosis develops in 5-9 days followed by average rise of 1 gm/dL Hb each week
- May require iron supplementation
- F.D.A. Warning Is Issued on Anemia Drugs’ Overuse – NYT March 2007
Medicare-Approved Indications for Epoetin Alfa

- Non-cardiac, non-vascular surgery
- Preoperative hemoglobin level > 10 and ≤ 12 g/dL
- Anticipated perioperative blood loss of ≥ 2 units of whole blood
- Not a candidate for autologous predonation
- Anemia is due to chronic disease responsive to epoetin alfa
- Pre-treatment hemoglobin must be obtained within one week of initial epoetin alfa dose
- Epoetin alfa, 600 U/kg q week x 3 and on day of surgery or 300 U/kg daily x 10 days
Intervention to Limit Bleeding

- Treatment with ε-aminocaproic acid, tranexamic acid and aprotinin decreased bleeding and increased transfusion avoidance
- No increase in perioperative MI
- Aprotinin *decreased* mortality 45% compared with placebo (1999)
Antifibrinolytics: Lysine Analogues

- ε-amino-caproic acid and tranexamic acid block binding of plasminogen, tPA and plasmin to lysine sites on fibrin
- Much less expensive than aprotinin
- Likely as effective as aprotinin in low-risk patients (Despotis, Ann Thorac Surg 2001)
Aprotinin

• “The association between aprotinin and serious end-organ damage indicates that continued use is not prudent.”¹
• “These findings indicate that in addition to the previously reported acute renal and vascular safety concerns, aprotinin use is associated with an increased risk of long-term mortality following CABG surgery.”²
• “Patients who received aprotinin alone on the day of CABG surgery had a higher mortality than patients who received aminocaproic acid alone.”³
• “Patients who received aprotinin had a higher mortality rate and larger increases in serum creatinine levels than those who received aminocaproic acid or no antifibrinolytic agent.”⁴

1. Mangano DT. NEJM 2006; Volume 354:353-365
4. Shaw A. NEJM 2008; Volume 358:784-793
Cell-Saver

- Unknown whether microemboli correlate with long-term neurocognitive outcome
- Effective at salvaging RBCs but removes platelets and plasma proteins
- Increased cost?
Perioperative Cell Salvage

- Meta-analysis of 29 studies in cardiac or orthopedic surgery with avoidance of allogeneic RBCs as outcome
- Cell salvage decreased risk of exposure for orthopedic patients (RR 0.39, 0.3-0.51)

Huet C et al., Anesth Analg 1999
Autologous Normovolemic Hemodilution

• What’s involved?
• Can significantly reduce RBC transfusion requirements (Helm RE, Ann Thorac Surg 1996)
• Avoidance benefit requires large volume of autologous blood (Bryson GL, Anesth Analg 1998)
• ANH similar to PAD and PAD+EPO (Monk et al, Anesthesiology. 1999 Jul;91(1):24-33)
Autologous Normovolemic Hemodilution
ANH

- Procedure results in:
  - $\downarrow$ $O_2$ carrying capacity
  - $\downarrow$ Blood viscosity
  - $\uparrow$ SNS stimulation
  - $\uparrow$ VR, stroke volume, cardiac output
  - $\downarrow$ Number of RBCs lost during surgery
Acute Normovolemic Hemodilution: Potential Patient Selection Criteria

- Estimated blood loss $\geq 1500$ mL
- Preoperative Hb concentration $\geq 12$ g/dL after correction of normovolemia
- Normal cardiovascular function (ie, no ischemic signs, no ST-segment changes)
- Absence of
  - Renal, lung, or other disease or infection
  - Untreated hypertension and liver cirrhosis
  - Coagulation abnormalities
- Patients who have a type and crossmatch for surgery

Perioperative Blood Conservation: Normovolemic Hemodilution

- RCT 78 patients for major liver resection
- Hemodilution to HCT 24% or control
- Minimum HCT 20%
- Avoidance at 72 hrs
- Significant (p <0.05) reduction in allogeneic exposure

Matot I et al., Anesthesiology 2002
Point of Care Testing

- TEG monitoring lowered the incidence of transfusion and decreased the rate of mediastinal re-exploration (predictive value >90%)
  - Spiess et al, J Cardiothorac Vasc Anesth, 1995
- Postoperative and total transfusion rates were significantly reduced in a prospective, randomized trial of a transfusion algorithm combined with thromboelastography.
  - Shore-Lesserson et al, Anesth Analg, 1999
Lowering Transfusion Trigger

• Prospective, randomized trial of 428 consecutive primary CABG patients
• Changed “institutional transfusion trigger” from 9 gm/dL to 8 gm/dL in study group
• Significant difference in transfusion rate
• No difference in objective or subjective clinical outcome
• Saves resources; cuts cost
  – Bracey et al, Transfusion, 1999
The Future

• Trend toward less allogeneic blood use in surgery likely driven by consumer
• Care to avoid severe anemia
• Blood supply increasingly restricted
• As yet unidentified infectious agents may contaminate blood supply
• Protocol-driven Tx with physiologic triggers
• Oxygen therapeutic research successful within five years
Conclusions

• Overwhelming evidence revealing problems with transfused blood
• Only one good RCT to date
• “Nothing Better” available
• Poor practice guidelines and protocols
• Surgical sabotage!