Risks of Transfusion: Outcome
The BIG Questions!

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Can we talk transfusion?
You went to work expecting a normal day!
Disclosures

• Bayer Pharmaceuticals
• Synthetic Blood International
• The Medicines Company
• McSPI Hematology Sub-Group Director (Past)
Mark Twain: Speaks the Truth

• It ain’t what you don’t know that gets you into trouble.
• It’s what you know for sure that just ain’t so!
Let’s Learn Something!

• “I have not failed. I’ve just found 10,000 ways that won’t work.” Thomas Alva Edison

• “An expert is a man who has made all the mistakes which can be made in a very narrow field.” Niels Bhor
Transfusion Practice is Bizarre!

- Wide variability.
- No one knows what is “best”.
- Everyone thinks they do!

Scarcity—Could We as a Group Change this?

- 1990-US imported 2% of its blood supply (France and Western Europe)
- 5% decrease in donations from 1994-97
- CJD, European travel restrictions will decrease immediately donations by estimates 7-9% reduction
- Aging population-donor-recipient shift
- Elective Surgery Halted
- Effects of Sept 11, 2001 ???
- FFP no longer from multiparous donors-TRALI.
- Leukoreduction
Most blood is used in a smaller number of patients (cardiac).
The **BIG** Questions

- Does transfusion improve or worsen outcome?
- Are the findings real or just associations?
- What mechanisms might be responsible?
- When should we, or must we transfuse?
- Are we damned if we do, damned if we don’t?
- What about those not transfused-JW?
- **We cannot let people bleed to death!**
Blood is Mystical!

“RIVETING.” — NEW YORK TIMES

THE BASIS
for the
PBS SERIES
RED GOLD

DOUGLAS STARR
Enculturation of Transfusion

- Blood is a “life-giving force”
- Poster child for Blood Banks
- 1-800-Save A Life
- “For the life of a creature is in the blood…” (Leviticus 17:11)
Some decisions are easy!
Transfusion is emotional!

CLOSE TO HOME / BY JOHN MCPHERSON

"Oh, brother. Not THIS anesthesiologist again!"
A Few Words About Risks

- Known Risks - We should avoid!
- Unknown risks we must deal with but not be overwhelmed and surprised!
Risk/ Benefit

• Risks
  ➢ Decreased O₂ delivery
  ➢ Immune Modulation
  ➢ TRALI
  ➢ White Cells
  ➢ Adverse Outcomes
  ➢ ABO-Rh
  ➢ Emerging Viruses
  ➢ Costs
  ➢ Allergy
  ➢ Etc. (Hypotension, myocardial dysfunction.)
  ➢ Infectious-HIV/Hep, Malaria, Parasites

• Benefits
  – Fresh Blood
  – Pediatric Heart
  – Historical-Fresh Blood
  – Trauma
  – Massive Transfusion
Transfusion Trigger: History

- 1900-1925: 3-5gm/dl - cardiac failure/critical DO$_2$
- 1925-1939: 5-7gm/dl - focus on prophylaxis
- 1930: Nobel Prize in Medicine: Landsteiner for histocompatibility

- 1937-1987: 10gm/dl - John Lundy, MD

- 1987-2006: 7-10gm Consensus Conference, ASA, ACS etc.

The Religion of 10
Only 1 Randomized Trial-Ever!

- 838 critically ill in ICU
- 10.0 g/dl vs. 7.0 g/dl trigger
### Hebert et al. Mortality and Outcomes at 30 days

<table>
<thead>
<tr>
<th></th>
<th>Restrictive</th>
<th>Liberal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>18.7 vs 23.3</td>
<td>P= 0.10</td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>8.7 vs. 16.1</td>
<td>P=0.03</td>
<td></td>
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<tr>
<td>&lt;55yo</td>
<td>5.7 vs. 13.0</td>
<td>P=0.02</td>
<td></td>
</tr>
<tr>
<td>Cardiac Dx</td>
<td>20.5 vs.22.9</td>
<td>P= 0.69</td>
<td></td>
</tr>
<tr>
<td>Death(Hosp)</td>
<td>22.2 vs. 28.1</td>
<td>P= 0.05</td>
<td></td>
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</table>
Hebert et al. Complications in Hospital (%/P value)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Restrictive</th>
<th>Liberal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0.7</td>
<td>2.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>5.3</td>
<td>10.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Angina</td>
<td>1.2</td>
<td>2.1</td>
<td>0.28</td>
</tr>
<tr>
<td>ARDS</td>
<td>7.7</td>
<td>11.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Infectious</td>
<td>10.0</td>
<td>11.4</td>
<td>0.38</td>
</tr>
</tbody>
</table>
• Medical Error Perspective
  – Having the wrong plan.
  – Failure in execution of the right plan (human error)

➤ Blood industry has done a great job on the execution part, but may be perfectly delivering a lethal product.
TRALI/ TACO Very Common

- TRALI: 1/73 to 1/193 patients transfused. 50% mortality!
- 1/4000 units Tx.
- TACO: 1/50 patients transfused. 20% mortality
- 25-50,000 deaths per year!

Fresh-Frozen Plasma and Platelet Transfusions Are Associated With Development of Acute Lung Injury in Critically Ill Medical Patients

Hassat Khan, MD, Jon Belsher, MD, Murat Yilmaz, MD, Bekete Atetta, MD, FCCP, Jeffrey L. Winters, MD, S. Brandon Moore, MD, Rolf D. Hübmayr, MD, FCCP, and Ognjen Cajic, MD, FCCP

Background: Transfusion has long been identified as a risk factor for acute lung injury (ALI/ARDS). No study has formally evaluated the transfusion of specific blood products as a risk factor for ALI/ARDS in critically ill medical patients.

Methods: In this single-center retrospective cohort study, 541 consecutive critically ill patients were studied for the development of ALI/ARDS. Patients who received blood product transfusions were compared with those who did not, in univariate and multivariate propensity analyses. Results: Two hundred ninety-eight patients (55%) received blood transfusions. Transfused patients were older (mean ± SD age, 67 ± 17 years vs 62 ± 10 years; p = 0.001) and had higher acute physiology and chronic health evaluation (APACHE) III scores (74 ± 32 vs 56 ± 23; p < 0.001) than those who had not received transfusion. ALI/ARDS developed more commonly (25% vs 16%; p = 0.025) in patients exposed to transfusion. Seventeen patients received massive RBC transfusions (i.e., > 10 U of blood transfused within 24 h), of whom 13 also received fresh-frozen plasma (FFP) and 11 received platelet transfusions. When adjusted for the probability of transfusion and other ALI/ARDS risk factors, any transfusion was associated with the development of ALI/ARDS (odds ratio [OR], 2.14; 95% confidence interval [CI], 1.24 to 3.75). Among those patients receiving individual blood products, ALI/ARDS was more likely to develop in patients who received FFP transfusions (OR, 2.48; 95% CI, 1.29 to 4.74) and platelet transfusions (OR, 3.99; 95% CI, 1.20 to 13.02) than in those who received only RBC transfusions (OR, 1.39; 95% CI, 0.79 to 2.43).

Conclusion: Transfusion is associated with an increased risk of the development of ALI/ARDS in critically ill medical patients. The risk is higher with transfusion of plasma-rich blood products, FFP, and platelets, than with RBCs.

Key words: cohort study; fresh-frozen plasma; platelets; pulmonary-renal; risk factor; transfusion-related acute lung injury

Abbreviations: ALI = acute lung injury; APACHE = acute physiology and chronic health evaluation; CI = confidence interval; CPE = cardiogenic pulmonary edema; DIC = disseminated intravascular coagulation; FFP = fresh-frozen plasma; INR = international normalized ratio; ICU = medical ICU; OR = odds ratio; RBC = red blood cell; TRALI = transfusion-related acute lung injury

FFP and Plt. Tx. Causes Pulmonary Dysfunction
Tx and A-Fib: Inflammatory Effect?

- Transfusion is associated with new onset AF: Tx. 46%, No Tx. 38% P< 0.001
- Odds ratio: 1.22-1.25 depending whether on or off pump

Tx Increases Septicemia, Wound Infections

- 15,592 CPB Procedures at Cleveland Clinic 1998-2003
- 55% Tx. Rate
  - Multivariate Association with Tx
- Septicemia/bacteremia \( p<0.0001 \)
- Superficial infection \( p<0.0007 \)
- Deep infection \( p<0.0001 \)

Influence of Transfusion and Infection in Cardiac Surgery


Percentage

Units of Blood

Severe Infection
Mediastinitis
Pneumonia
Sepsis

n = 738
EFFECT OF RED CELL TRANSFUSION ON MORTALITY

van de Watering 1998 (n = 914)

Wallis 2002 (n = 597)

Bilgin 2004 (n = 496)

Fung 2004 (n = 1146)

**Mortality (%)**

CABG/valve

* p<0.05, † p = 0.11 (need to enroll 1174 pts to detect an 80% decrease)

£ Non-randomized trial
Effect of Transfusion on Long-term Survival

Factors Associated with Increased Mortality

<table>
<thead>
<tr>
<th>Risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative Transfusion</td>
<td>2.4</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>1.9</td>
</tr>
<tr>
<td>COPD</td>
<td>2.2</td>
</tr>
<tr>
<td>NYHA FC IV</td>
<td>1.5</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Quality of Life

• 1995-1999 – 12,536 Pts. Cleveland Clinic
• Duke Activity Status Index, 6 and 12 months

• Quality of life was incrementally worse the more perioperative red cells transfused (P<0.0001), platelets (P<0.02).

Effect of Transfusion on Long-term Survival

We treat women badly!

• 380 pt cohort study- U of Rochester.
• Primary CABG or Valve
• Women more likely to be Tx. ODs ratio-21.6 (95% CI 3.8-124.2)
• Women 4.4 X more likely to develop infection
• Women more likely: infection p=0.005, pulmonary dysfunction p=0.005, mortality p=0.007

Transfusion is associated with increased risk of ventricular failure, inability to wean from bypass, and use of two or more inotropes.

Prior work from this same group claimed it was low-Hct that was associated with adverse events.

Renal Injury, Hemodilution and Transfusion

- Retrospective 1760 Pts
- Single center
- 31% female
- CABG with CPB
- Major Outcome: Delta Creatinine
- Renal Injury = Delta Creatinine > 50%
- Acute Renal Failure = 100% increase in Creatinine and > 2.1mg/dl.
- Anemia associated with renal failure

Propensity Analysis: Tx and Cr Change

- % Change Cr. 0.0029
- %Cr-Clearance 0.0043
- Renal Injury 0.0030
- ARF 0.0010
- LOS 0.0027

Tx. and Infection

- Intra-Op Tx. 6.8% (yes)/3.1% (no) 0.001
- Post-Op Tx. 7.7% (yes)/2.2% (no) 0.001
- Both 9.7% (yes)/3.0% (no) 0.001
- Any 6.5% (yes)/2.0% (no) 0.001

Editorial

• Spiess BD. Choose One: Damned if you do/Damned if you don’t. Critical Care Medicine 2005.
• Both Low Hct and Tx are implicated in adverse events.
• Tx makes it worse, not better.
• Blood Conservation is the Answer!

Evolution of adverse changes in stored RBCs

PNAS | October 23, 2007 | vol. 104 | no. 43 | 17063–17068
Blood Storage

RBC Shape Change During Storage

Day 1
Day 21
Day 35

Hovav T et al. Transfusion 1999;39:277
Cell Changes

**Figure 21-1.** Scanner electron micrograph showing red blood cells taken from the patient preoperatively.

**Figure 21-5.** Homologous red blood cells stored for 15 days.
Aged Blood Increases Shock!

• “Intestinal oxygen consumption and mesenteric venous P02 were restored with only fresh blood. Intestinal microvascular P02 improved only with transfusion of fresh blood”.

Animal Model of Tx?

**TRANSFUSION PRACTICE**

Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions

Arnold G. Tran, Pedro Cabalides, and Marcus Intaglia

**BACKGROUND:** Transfusions are intended to augment oxygen-carrying capacity. The ability of fresh and stored red blood cells (RBCs) to maintain microvascular perfusion and oxygen delivery to the tissues has not been directly measured.

**STUDY DESIGN AND METHODS:** Microvascular responses to exchange transfusion with fresh and stored RBCs after acute isoosmotic hemodilution with a plasma expander were investigated with the hamster window chamber model. In vivo functional capillary density, (FCDs), blood flow, and high-resolution oxygen distribution in microvascular networks were measured by image-analytic methods.

**RESULTS:** Exchange transfusion with an RBC suspension after a 50 percent isovolemic hemodilution with dextrans 70/35 MM + 70 KDa resulted in a hematocrit of 10 percent (opt 0.12 g/dl, hemoglobin [Hb]). All other systemic variables were unchanged. Stored RBCs (7 days in citrate-phosphate-dextrose-adenine-1) preserved in fresh human plasma matched to the iso- and Hb concentration were exchanged transfused until 75 percent of the circulating RBCs were stored RBCs. Stored RBCs reduced microvascular flow and FCD by 63 and 54 percent, respectively, of the level achieved when fresh RBCs were exchanged transfused. Microvascular oxygen extraction by the stored RBCs was 54 percent lower than that of the fresh RBCs. The tissue oxygen levels were 5.5 and 14.4 mmHg for the stored and fresh RBCs, respectively.

**CONCLUSION:** Circulation of stored RBCs in a hemodiluted animal resulted in significantly microvascular and underestimated microcirculation that was not detectable at the systemic level.

**ABBREVIATIONS:** FCD = functional capillary density, Hb = hemoglobin, MAP = mean arterial pressure, 400 = arterial oxygen partial pressure.

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Received for publication April 1, 2001; revision received June 5, 2001; accepted June 26, 2001.

**TRANSFUSION** 2001;41:1628-1631.
Tissue O$_2$ Delivery is the Key!

- 400% Reduction in O$_2$ Delivery with Tx.
- Arterial and Venous Blood Gases do not Reflect the Lack of Delivery!
- Perhaps they will only at DO$_{2}$crit ?
Tx. Does Not Increase Oxygen Delivery?

- This should be a sentinel article!
- Tx blood increased calculated $O_2$ delivery
- Tissue $O_2$ unchanged by 1 or 2 units RBC’s

- **Tissue $O_2$ Doubled with 100% FiO$_2$**
Intracellular Changes

- ATP - 3.9-2.5 umol/gm-Hg
- 2,3,DPG - 13.7-1.2 umol/gm/HG
- 5-24 hours for 2,3 DPG regeneration
2,3 DPG in Stored Blood

Figure 6.1. ATP and 2,3-DPG levels of blood collected in citric dextrose solutions containing 5 mM adenine. The numbers indicate the pH levels of the preservative solution into which the blood was drawn. (From Beutler, E., et al. Depletion and regeneration of 2,3-diphosphoglyceric acid in stored red blood cells. Transfusion 1969;9:109–114. Used by permission.)
2,3 DPG Rejuvenation?

Figure 6.5. Regeneration of 2,3-DPG in red cells transfused into three patients. The patients’ own red cells were labeled with $^{51}$Cr; the transfused red cells were recovered by differential agglutination, and correction for any agglutinable cells made using the $^{51}$Cr label. (From Beutler E, Wood L. The in vivo regeneration of red cell 2,3-diphosphoglyceric acid [DPG] after transfusion of stored blood. J Lab Clin Med 1969;74: 500–504. Used by permission.)
Platelets Associated with Worse Outcomes

• Spiess BD et al. Platelet transfusions during coronary artery bypass grafting surgery are associated with serious adverse outcomes. Transfusion 2004;44:1143-1148

• Bayer Aprotinin database, N-1720

• 284 received Plts.
McSP Epi-II: Blood Tx is Really Bad!

Morbid Risks of Unnecessary Red Blood Cell Transfusion in Stable Coronary Artery Bypass Graft Patients.

Patrick Moehlme, MD,1,2, Stephanie A. Snyder-Russen, MD,3,4,* \nY-S. Wang, ScD,5, Alexander Kellner, MD,6,7, Bernd W. Boeckiger, MD,5,4, \nShirley Wang, ScD,5,7, Jack Levin, MD,8, and Dennis T. Mangan, PhD, MD,6,4,*

1 Multicenter Study of Perioperative Ischemia Research Group (McSP), 2 Ischemia Research and Education Foundation, San Francisco, CA, 3 Department of Anesthesiology, Ludwig-Maximilans University, Munich, Germany, 4 Department of Anesthesiology, University of Heidelberg, Heidelberg, Germany, 5 Department of Anesthesiology and Intensive Care Medicine, Medical University, Graz, Austria, 6 University of California School of Medicine, San Francisco.

Abstract

The persistent variability in red blood cell transfusion practice in coronary artery bypass graft (CABG) patients, despite established guidelines, suggests inappropriate use. Our objective was to determine the impact of postoperative red blood cell (RBC) transfusion in entirely stable CABG patients. We investigated a cohort of 940 stably transfused CABG patients from the 5,065 patients enrolled in the Multicenter Study of Perioperative Ischemia Epidemiology II (EPIC II) Study with (1) low to
Peri-operative Blood Transfusion & Blood Conservation in Cardiac Surgery
The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Practice Guideline Series

A Report from the Society of Thoracic Surgeons Workforce on Evidence-Based Medicine
In Collaboration with the Society of Cardiovascular Anesthesiologists Special Taskforce on Blood Transfusion

From the University of Kentucky Chandler Medical Center, Lexington, KY, USA (VAF, SPF, SPS, and EAH), University of Florida, Jacksonville, FL (CKH), University of Pennsylvania Health System, Philadelphia, PA, USA (CRB), Harefield Hospital, London, UK (DR), Rush Presbyterian St. Lukes’ Medical Center, Chicago, IL (RSDH), Washington University Medical Center, St. Louis, MO, USA (GD), and Center for the Evaluative Clinical Sciences, Dartmouth Medical School, Lebanon, NH (JRB)

*Bruce D. Spiess, MD, FAHA (SCA Task Force Chair), Linda Shore-Lesserson, MD, Mark Stafford-Smith, MD, C. David Mazer, MD, Elliott Bennett-Guerrero, MD, Steven E. Hill, MD, Simon Body, MB,ChB, MPH.. Mount Sinai School of Medicine of New York University New York, NY, USA (LS-L), Duke University Medical Center, Durham, NC, USA, (MS-S, EB-G, SEH). St. Michael’s Hospital Toronto, Ontario, Canada, (DM), and Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA (SB).

Ann Thorac Surg 2007; 83:S27-86
Guidelines

- 59 specific recommendations!
- I will not review them all in this lecture!
JCAHO 2007

- 2-5-07 JCAHO stakeholders meeting.
- Universal agreement that blood management performance measures will need to be included in their accreditation process!
- Attendees included: NIH, FDA Society for Critical Care Medicine, SABM and American Association of Orthopedic Surgeons
What to Do? - Research!

“Back to Square One!”
Lead or Follow/
Learn/Question: What is the Truth?