Reengineering transfusion and cellular therapy processes hospitalwide: ensuring the safe utilization of blood products
Brooks, Transfusion 2005;45S

• “Blood donor centers have done a remarkable job of making the blood in the bag safer than it has ever been.”
• “The actual process of transfusion, however, is an area that has languished while public attention and healthcare resources have been focused on blood centers.”
• “The most significant risks associated with blood transfusion reside with the transfusion process rather than the unit of blood.”
• “If blood safety is to improve, reengineering must occur at the hospital level.”

The mantra of blood safety: time for a new tune?
Farrugia, Vox Sanguinis 2004;86

• “Optimal blood usage should be viewed as an essential component of the complex nexus of blood safety measures.”
  — European Commission ‘Kiruth Initiative’
• “It is important that the blood safety focus shifts from the product considerations which underlie the traditional ‘Safety Tripod’ concept and focus more strongly on blood product usage as part of the transfusion medicine process.”
What is Blood Management?

• Blood management is a comprehensive, multidisciplinary process that is designed to promote the optimal use blood products throughout the hospital.
• The goal of blood management is ensure the safe and efficient use of the many resources involved in the complex process of blood component therapy.

Is Blood Utilization Efficient?
Variation in Transfusion Practice- Cardiac Surgery

• Primary CABG patients at 24 institution
• Transfusion rates:
  – RBC 27- 92%
  – Platelets 0- 36%
  – FFP 0- 36%
  – Cryo 0- 17%

Why does this occur?
Stover et al, JCTVA 2000;14

Anemia Management vs.
Transfusion Management

• Although mild anemia is well tolerated in most patients, moderate to severe anemia appears to be harmful in high risk patients, particularly in those with significant cardiovascular disease
• Logically, the traditional treatment of anemia has been blood transfusions, which carry their own set of risks
• What physicians are making is an individualized trade-off decision between the risks of anemia vs. the risks and benefits of transfusion
**Does transfusion practice affect mortality in critically ill patients?**

*Hebert- Am J Respir Crit Care Med 1997;155*

- Prospective observational cohort of 4470 critically ill patients (~20% CV disease)
- In patients with cardiac disease, there was a trend toward an increased mortality when hemoglobin values were < 9.5 g/dL.
  - Increasing hemoglobin values in anemic cardiac patients was associated with improved survival.
- "We conclude that anemia increases the risk of death in critically ill patients with cardiac disease. Blood transfusions appear to decrease this risk."

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**Adverse effects of low hematocrit during CPB in the adult: Should current practice be changed?**

*Habib-JTCVS 2003;125*

- Nadir HCT < 22% on CPB was independently associated with:
  - Increased operative mortality.
  - Increased ICU and hospital LOS.
  - Increased total costs.
  - Decreased long-term survival.
- "Changes to several areas of practice in CPB patients can alter the level of hemodilution... (including) freer use of transfusions to maintain HCT at predetermined levels."

---

**“Confounding By Indication”**

Habib, JTCVS 2003;125
Do Transfusions Improve Outcomes in Anemic Patients?

A multicenter, randomized controlled clinical trial of transfusion strategies in critical care
Hebert et al, NEJM 1999;340(6)

- Prospective, randomized multicenter Canadian study with 838 critically ill ICU patients
- Liberal transfusion strategy (Hb 10.0 g/dL) vs restrictive strategy (Hb 7.0 g/dL)
  - Restrictive transfusion group had a mean Hgb of 8.5 and received 2.6 +/- 4.1 units
  - Liberal transfusion group mean Hgb 10.7 and received 5.6 +/- 5.3 units

Overall, the adjusted multi-organ dysfunction score and in-hospital mortality were significantly higher in the liberal transfusion group than in the restrictive transfusion group
- No sub-group of these critically ill patients demonstrated an added benefit of higher Hgb levels, and most patients in the liberal transfusion group had worse outcomes.
Hebert et al. Outcomes and Morbidity

<table>
<thead>
<tr>
<th></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>Pulm 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>Infections</td>
<td>10.0</td>
<td>11.4</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Hebert et al. Outcomes and Mortality at 30 days

<table>
<thead>
<tr>
<th></th>
<th>Restrictive (%)</th>
<th>Liberal (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>18.7</td>
<td>23.3</td>
<td>0.10</td>
</tr>
<tr>
<td>APACHE ≤20</td>
<td>8.7</td>
<td>16.1</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;55yo</td>
<td>5.7</td>
<td>13.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac Dx</td>
<td>20.5</td>
<td>22.9</td>
<td>0.69</td>
</tr>
<tr>
<td>Death (Hosp)</td>
<td>22.2</td>
<td>28.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

“A restrictive strategy of red cell transfusions is at least as effective as and possibly superior to a liberal strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction or unstable angina.”

Hebert et al, NEJM 1999;340(6)
Role of hemodilutional anemia and transfusion during CPB in renal injury after CABG


- Retrospective review of 1760 CABG patients
- Impact of nadir HCT, CPB time and transfusion on renal dysfn using multivariate analysis and propensity scores
- Nadir HCT <24% assoc with renal dysfn and ARF
- Transfusion increased renal injury at HCT < 24%
  - Renal inj 14.4%-> 26.0%
  - ARF 3.4% -> 12.0%
  - LOS 6.3d -> 8.1d
  - Mortality 1.4% -> 3.8%

“This need (to test the efficacy of methods aimed at minimizing CPB hemodilution) is amplified by growing evidence, including from this study, of the adverse effects and ineffectiveness of packed RBC transfusions as a means to avoid excessive hemodilutional anemia.”


Why Don’t Transfusions Necessarily Improve Outcomes in Anemic Patients?
Stored allogeneic blood is different than endogenous hemoglobin!

- **Storage Defects**
  - Impaired tissue oxygen delivery due to storage defects
- **Transfusion Complications**
  - Adverse effects and immune system changes as a consequence of allogeneic transplantation

### Storage Defects and Microvascular Perfusion

- Decreased 2,3- DPG, ADP
- Poor deformability
- Build-up of cytokines, free hemoglobin, K+

![Graph showing concentration over time](Image)

Kristiansson, Acta Anesth Scand 1996; 40

![Microvascular perfusion with stored RBCs](Image)

Tsai, Transfusion 2004; 44

- Hamster model of hemorrhagic shock and resuscitation with fresh or 28 day stored RBCs
- Hamster window chamber model to measure functional capillary density, microvascular blood flow and O2 distribution
- Stored RBC resulted in malperfused and under-oxygenated microvasculature (75% reduction) that was not detected at the systemic level
Effect of stored blood transfusion on oxygen delivery in patients with sepsis
-Bone, Marik, Sibbald- JAMA 1993:269(23)

- 33 ICU patients with sepsis
- Transfusion of 3U PRBC for Hb <10g/dL
- ↑SVR, ↑PVR
- DO2 increased
- VO2 unchanged
- Lactate increased
- Gastric pH decreased for RBC> 15 days

Adverse Effects of Allogeneic Blood (“Excess Baggage”)

- Infectious Complications
  - Viral, bacterial contamination of platelets (1:3000), other (nvCJD, West Nile, Chagas)
- Febrile and allergic reactions
- Hemolytic transfusion reactions (clerical)
  - Leading cause of morbidity and mortality
- Other
  - TRALI, ARDS, GVH, SIRS, TACO
  - Microchimerism

Perioperative Adverse Events and Platelet Transfusions
-Spiess, Transfusion 2004:44

- Retrospective review of aprotinin data base- 1720 CABG patients
- Stepwise multiple regression to account for confounding factors
- Platelet transfusions independently associated with increased risk of:
  - pulmonary injury
  - infection
  - stroke
  - death
Transfusion Related Immunomodulation (TRIM)

- Dose-dependent alterations in immune function
  - Upregulation of humoral immunity
  - Decreases in NK cell and macrophage activity, activation of T-suppressor cells (anergy)
  - Effect has been known and well-documented for years
- 7-10 fold increase in postoperative infection rates leading to increased LOS, resource consumption, total hospital costs
- Increased cancer recurrence rates in transfused patients, increased 5 year mortality in CABG
- A linear dose-response curve of adverse clinical effects is well documented with large studies using multivariate analysis
Dose Response for Post-injury Multiple Organ Failure

Moore et al, Arch Surg 1997;(132)

Dose Response for Mortality and Transfusion in Critical Care

Vincent et al, JAMA 2002; 288(12)

Dose Response for Length of Stay in Critical Care

Shapiro et al, J Trauma 2003;55
Are we using this hazardous therapy wisely?

*Can four hours a year of committee time adequately develop, promote and monitor appropriate blood utilization practices throughout the hospital?*

Variation in Transfusion Practice- Orthopaedics

- Review of transfusion practice for hip fractures at 19 institutions
- RBC transfusion rate varied from 31.2% to 54.0%

*Poses et al, Am J Medicine 1998;105(3)*

*Corwin- Crit Care Med 2004;32(1)*
“Blood use decisions are probably more akin to those applied to common antibiotics than to those applied to specialized medicines like chemotherapy agents or seizure-control medications.”

“… it is perhaps not surprising that many transfusion decisions are ill informed, outdated, or, simply incorrect.”
America's Blood Centers
Safety Measures and Average Red Blood Cell Service Fees
1984 - 2003

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 Ab Test</td>
<td>HCV 2.0 Test</td>
<td>HBc and ALT Tests</td>
<td>HTLV-I Test</td>
<td>HCV 1.0 Test</td>
<td>FDA cGMP Guidelines</td>
<td>HIV-1/2 Test</td>
<td>HIV-1 P24 Antigen Test</td>
<td>Universal Leukoreduction</td>
<td>West Nile NAT</td>
<td>Licensed HIV/HCV NA</td>
<td></td>
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</tbody>
</table>

RBCs $42 | $43 | $43 | $46 | $49 | $53 | $58 | $61 | $64 | $69 | $73 | $73 | $75 | $76 | $77 | $85 | $92 | $101 | $119 | $140 |

RBCs, LR $111 | $115 | $116 | $117 | $116.7 | $121 | $126 | $134 | $151 | $169.5 |

Cost/Unit (2004 $)*

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Facilities</th>
<th>Study Technique</th>
<th>Acquisition Cost %</th>
<th>Patient Sample</th>
<th>Cost/Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forbes, 1991 (1)</td>
<td>19 Teaching Hospitals with Level I or II Trauma</td>
<td>Survey of blood related charges</td>
<td>37%</td>
<td>Mixed Population</td>
<td>$485</td>
</tr>
<tr>
<td>Mohandas, 1999 (12)</td>
<td>Outpatient Cancer Center</td>
<td>Review of blood related charges for 219 patients</td>
<td>26%</td>
<td>Solid Tumors</td>
<td>$660</td>
</tr>
<tr>
<td>Cantor, 1998 (13)</td>
<td>Outpatient Cancer Center</td>
<td>Survey of blood related cost activities</td>
<td>10%</td>
<td>Solid Tumors Hematologic Tumors</td>
<td>$512</td>
</tr>
<tr>
<td>Crémieux, 2000 (14)</td>
<td>Outpatient Cancer Center</td>
<td>Cost activities recorded for 517 patients</td>
<td>59%</td>
<td>Complex Patients</td>
<td>$538</td>
</tr>
</tbody>
</table>

*2004 Medical Services CPI, base acquisition cost $178

Hospital Resource Variable Costs

<table>
<thead>
<tr>
<th>Hospital Resource</th>
<th>Variable Cost (2004$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating-room variable time</td>
<td>$1730 - $2880/ hour</td>
</tr>
<tr>
<td>Postoperative hospital day</td>
<td>$1260/ day</td>
</tr>
<tr>
<td>ICU day</td>
<td>$5480/ day</td>
</tr>
<tr>
<td>ICU day ventilated patient</td>
<td>$6480/ day</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>$10,500</td>
</tr>
<tr>
<td>Serious postoperative infection- orthopedic surgery patient</td>
<td>$17,500 - $18,800</td>
</tr>
<tr>
<td>Postoperative deep sternal infection-cardiac surgery patient</td>
<td>$25,600</td>
</tr>
<tr>
<td>Post procedure bleeding, Percutaneous Coronary intervention</td>
<td>$15,700</td>
</tr>
<tr>
<td>Respiration for bleeding- Cardiac surgery patient</td>
<td>$20,500 - $20,600</td>
</tr>
<tr>
<td>Red blood cell transfusion-variable cost per unit</td>
<td>$1780 - $2950/ unit</td>
</tr>
</tbody>
</table>
## Applied Blood Management

**Management goals - Woody Allen’s Law**
- Avoid/ minimize anemia
- Avoid/ minimize transfusions
- Efficient utilization of resources

**Stewardship**

**Organizational principles**
- Attention to detail
- Utilization of evidence-based guidelines and clinical best practices
- Multidisciplinary teams
- Proactive approach

---

**Trust… but verify.**

-Ronald Reagan

**Speak softly… and carry a big stick.**

-Theodore Roosevelt
**Peer Blood Utilization Profiling**

LR RBC Use in DRG 105 (Cardiac Valve & Other Major CT Proc W/O Cardiac Cath)

- Mean = 5.5 units
- Path Norm = 6.5

**Multidisciplinary Team - Cardiac Surgery**
- Cardiac surgeons
- Anesthesiologists
- Perfusion
- Nurses - Preop/OR/CR/ CVPV Ward
- Physician’s Assistants
- Pharmacists
- Laboratory/ Blood Bank
- Administrators
  - Supervisory
  - Purchasing
  - Quality
  - Financial

**Blood Management Opportunities - CABG**

- **Preoperative**
  - Risk stratification and intervention
  - Anemia management
  - Introgeneic blood loss (cath lab)
  - Cessation of drugs that increase bleeding
- **Intraoperative**
  - Avoidance of hemodilution
  - Heparin management protocols
  - Pump prime volumes
  - Pump circuit coatings
  - Perfusion/ autotransfusion techniques
- **Intraoperative (cont)**
  - Surgical techniques
  - Anesthetic techniques
  - Pharmacologic therapies
  - Topical hemostatic agents
  - Point of care
    - Hemoglobin
    - Coagulation status
    - Coagulation management protocols
    - Rewarming protocols
- **Postoperative**
  - Point of care
  - Postoperative autotransfusion
  - Evidence-based guidelines
Variation in transfusion rates among institutions is the end result of the actions or inactions of organizations to manage the series of events that ultimately lead to blood transfusions.

Further, this series of events is largely predictable and to a great extent is controllable.

Final Thoughts:
Transfusion Committee vs. Blood Utilization Committee

Which do you have?

Blood Management Issues and Opportunities- Summary
- Blood products are increasingly scarce and increasingly expensive
- Blood component therapy is inherently hazardous
- Blood utilization is less than optimal
- Better management of blood resources presents a tremendous opportunity for patients, physicians, hospitals and communities

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www.BloodManagement.com


8. Tsai AG, Cabrales P, Intaglietta M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. Transfusion 2004;44:1626-34.


