Evidence-Based Transfusion Practice: RBCs & Plasma

Richard LeBlond, MD, MACP
Chief Quality and Safety Officer
Billings Clinic

Primum Non Nocere
First Do No Harm

"given an existing problem, it may be better not to do something, or even to do nothing, than to risk causing more harm than good"
Disclosure

Royalties Received from McGraw-Hill
It ain’t what you don’t know that gets you in trouble. It’s what you know for sure that just ain’t so.

Mark Twain

Belief is difficult to overcome with evidence:

--H. pylori and duodenal ulcer
--Beta-blockers for heart failure
Learning Objectives: First Do No Harm

- Challenge longstanding beliefs
- Overcome habits not supported by evidence
- Look for the evidence
- Understand the adverse effects of transfusion
- Recognize and report transfusion associated adverse events
- Practice evidence-based transfusion medicine
- Protect patients from unnecessary transfusion
Blood Management Is Important

• Safety
  – Transfusion is an immunosuppressant
  – Transfusion is a Tissue Transplant
  – Transfusion process is inherently hazardous

• Optimal use of blood products
  – The supply is limited
  – The resource is expensive

• Regulatory
  – Joint Commission and AABB requirements
The Changing Transfusion Paradigm

- Blood bank blood is normal blood
- Transfusions are good for patients
- Oxygen delivery is improved
- If some is good, more is better
- Treat numbers: H&H
The Changing Transfusion Paradigm

- Blood bank blood is normal blood
- Transfusions are good for patients
- Oxygen delivery is improved
- If some is good, more is better
- Treat numbers: H&H

- Banked blood is a degraded blood product
- RBC transfusion harms all patients
- Tissue oxygenation may be worse
- Give the minimum amount necessary
- Treat the patient
Indication Creep

• When and why was transfusion developed?
• World War II: to treat large volume blood loss.
• How are physicians taught to use blood products?
• How are they used now?
  – RBC: volume replacement, “symptomatic anemia”
  – FFP: treat elevated PT/INR to lower “bleeding risk”
• What evidence would we want today to introduce transfusion into medical practice?
• Evaluate the evidence as a test of non-inferiority.
Indication Creep

• When and why was transfusion developed?
• World War II: to treat large volume blood loss.
• How are physicians taught to use blood products?
• How are they used now?
  – RBC: volume replacement, “symptomatic anemia”
  – FFP: treat elevated PT/INR to lower “bleeding risk”
• What evidence would we want today to introduce transfusion into medical practice?
• Evaluate the evidence as a test of non-inferiority.
Acute Upper GI Bleeding

**A** Survival, According to Transfusion Strategy

- **Restrictive strategy**
- **Liberal strategy**

<table>
<thead>
<tr>
<th>Days</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>45</td>
<td>55</td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Restrictive strategy</th>
<th>Liberal strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>444</td>
<td>445</td>
</tr>
<tr>
<td>5</td>
<td>429</td>
<td>428</td>
</tr>
<tr>
<td>10</td>
<td>412</td>
<td>407</td>
</tr>
<tr>
<td>15</td>
<td>404</td>
<td>407</td>
</tr>
<tr>
<td>20</td>
<td>401</td>
<td>397</td>
</tr>
<tr>
<td>25</td>
<td>399</td>
<td>393</td>
</tr>
<tr>
<td>30</td>
<td>397</td>
<td>386</td>
</tr>
<tr>
<td>35</td>
<td>395</td>
<td>383</td>
</tr>
<tr>
<td>40</td>
<td>394</td>
<td>378</td>
</tr>
<tr>
<td>45</td>
<td>392</td>
<td>372</td>
</tr>
</tbody>
</table>

**B** Death by 6 Weeks, According to Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Restrictive Strategy</th>
<th>Liberal Strategy</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>23/444 (5)</td>
<td>41/445 (9)</td>
<td>0.55 (0.33–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Patients with cirrhosis</td>
<td>15/139 (11)</td>
<td>25/138 (18)</td>
<td>0.57 (0.30–1.08)</td>
<td>0.08</td>
</tr>
<tr>
<td>Child-Pugh class A or B</td>
<td>5/113 (4)</td>
<td>13/109 (12)</td>
<td>0.30 (0.11–0.85)</td>
<td>0.02</td>
</tr>
<tr>
<td>Child-Pugh class C</td>
<td>10/26 (38)</td>
<td>12/29 (41)</td>
<td>1.04 (0.45–2.37)</td>
<td>0.91</td>
</tr>
<tr>
<td>Bleeding from varices</td>
<td>10/93 (11)</td>
<td>17/97 (18)</td>
<td>0.58 (0.27–1.27)</td>
<td>0.18</td>
</tr>
<tr>
<td>Bleeding from peptic ulcer</td>
<td>7/228 (3)</td>
<td>11/209 (5)</td>
<td>0.70 (0.26–1.25)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
A multicenter, randomized controlled clinical trial of transfusion triggers in critical care

Prospective, randomized multicenter Canadian study with 838 critically ill ICU patients

Liberal transfusion: hg 10.0 g/dl
Restrictive transfusion: hg 7.0 g/dl
A multicenter, randomized controlled clinical trial of transfusion triggers in critical care

- 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.

<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>ARDS</td>
<td>7.7</td>
<td>11.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Angina</td>
<td>1.2</td>
<td>2.1</td>
<td>0.28</td>
</tr>
<tr>
<td>Infections</td>
<td>10.0</td>
<td>11.4</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Hébert et al, NEJM 1999;340(6)

Prospective, randomized multicenter Canadian study with 838 critically ill ICU patients

Liberal transfusion: hgb 10.0 g/dl
Restrictive transfusion: hgb 7.0 g/dl
Stratified analyses showed a protective effect of transfusion in patients with nadir hemoglobin \(< 8 \text{ g/dL}\) (adjusted HR 0.13, 95% CI 0.03 to 0.65, \(p = 0.013\)). By contrast, transfusion was associated with increased mortality in patients with nadir hemoglobin \(>8 \text{ g/dL}\) (adjusted HR 2.2, 95% CI 1.5 to 3.3; \(p < 0.0001\)). Similar results were obtained for the composite end point of death/MI/heart failure (\(p\) for interaction = 0.04).

In conclusion, RBC transfusion in patients with acute MI and hemoglobin \(< 8 \text{ g/dL}\) may be appropriate.

The increased mortality observed in transfused patients with nadir hemoglobin above 8 g/dL underscores the clinical difficulty of balancing risks and benefits of RBC transfusion in the setting of ACS.
Mortality in **Acute Myocardial Infarction**: Relationship to Hemoglobin >8.0 and Transfusion

![Graph showing cumulative probability of mortality over time for transfusion vs. no transfusion with Log Rank P < 0.0001](image)
OBJECTIVES: We sought to examine the short- and long-term outcomes of blood transfusion in patients presenting with ST-segment elevation myocardial infarction (STEMI).

METHODS: We evaluated 30-day, 6-month, and 1-year all-cause mortality among 4,131 STEMI patients enrolled in the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) IIb trial. Patients were categorized according to whether they received a blood transfusion during hospitalization. Cox proportional hazards survival models with transfusion as a time-dependent covariate were conducted for the whole and for the propensity-matched groups. Additionally, a series of sensitivity analyses assessed the magnitude of hidden bias that would need to be present to explain the associations actually observed.

Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction.
JACC Cardiovasc Interv 2009 Jan;2(1):46-53 (ISSN: 1876-7605)

Shishehbor MH; Madhwal S; Rajagopal V; Hsu A; Kelly P; Gurm HS; Kapadia SR; Lauer MS; Topol EJ
Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio 44195, USA.
**RESULTS: Death** at 30 days (13.7% vs. 5.5%), 6 months (19.7% vs. 6.9%), and 1 year (21.8% vs. 8.7%) was significantly higher for transfused patients than for nontransfused patients, respectively. After adjusting for over 25 baseline characteristics, nadir hemoglobin, and propensity score for transfusion, and using transfusion as a time-dependent covariate, transfusion remained significantly associated with increased risk of mortality at 30 days (hazard ratio [HR]: 3.89, 95% confidence interval [CI]: 2.66 to 5.68, p < 0.001), 6 months (HR: 3.63, 95% CI: 2.67 to 4.95, p < 0.001), and 1 year (HR: 3.03, 95% CI: 2.25 to 4.08, p < 0.001). Similar results were observed in the propensity-matched patients.

**CONCLUSIONS:** Blood transfusion is associated with increased short- and long-term mortality in the setting of STEMI.
Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction.

JACC Cardiovasc Interv 2009 Jan;2(1):46-53  (ISSN: 1876-7605)

Shishehbor MH; Madhwal S; Rajagopal V; Hsu A; Kelly P; Gurm HS; Kapadia SR; Lauer MS; Topol EJ
Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio 44195, USA. shishem@gmail.com.
Conclusions—Red blood cell transfusion in patients having cardiac surgery is strongly associated with both infection and ischemic postoperative morbidity, hospital stay, increased early and late mortality, and hospital costs. (Circulation. 2007;116:2544-2552.)
Cardiac Surgery Outcomes Related to RBC Transfusion: Australia

After correction for comorbidities and other factors, transfusion was still associated with a 66% increase in mortality.

Adverse Outcomes Related to Intraoperative PRBC Transfusion

941,496 Surgical Procedures
Patients Matched by Registry Data

Figure. Unadjusted mortality and composite morbidity rates by number of units of packed red blood cells (PRBCs) received in intraoperative blood transfusion.

National Surgery Quality Improvement Program (NSQIP)
American College of Surgeons
NSQIP: Outcomes with one unit PRBC day of surgery or first two postoperative days

Table 3. Outcome Comparisons Between Propensity-Matched Groups

<table>
<thead>
<tr>
<th>Postoperative Complication</th>
<th>No Transfusion (n=11,855)</th>
<th>Transfusion (n=11,855)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, %</td>
<td>5.2</td>
<td>6.1</td>
<td>.005</td>
</tr>
<tr>
<td>Wound problems, %</td>
<td>9.7</td>
<td>11.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulmonary, %</td>
<td>11.7</td>
<td>15.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal, %</td>
<td>5.5</td>
<td>6.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CNS, %</td>
<td>1.3</td>
<td>1.3</td>
<td>.91</td>
</tr>
<tr>
<td>Cardiac, %</td>
<td>2.0</td>
<td>2.4</td>
<td>.06</td>
</tr>
<tr>
<td>Sepsis, %</td>
<td>8.2</td>
<td>10.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Return to OR, %</td>
<td>11.4</td>
<td>12.1</td>
<td>.09</td>
</tr>
<tr>
<td>Composite morbidity, %</td>
<td>30.1</td>
<td>34.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postoperative length of stay, mean (SD), d</td>
<td>10.3 (14.3)</td>
<td>11.8 (14.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Adverse Effects of Blood Component Therapy

- Febrile and allergic reactions
- Hemolytic transfusion reactions
- Infection: SSI, CLA-BSI, VAP, UTI
- Transfusion-Related Acute Lung Injury (TRALI)
  - Unexplained acute lung injury within 6 hours of transfusion
  - Mortality rate 5% to 20%
  - Incidence 1:1000 to 1:5000 transfusion
- Transfusion-Associated Circulatory Overload (TACO)
  - Volume overload leading to CHF and pulmonary edema
- Transfusion-Related Immunomodulation (TRIM)
  - Alter immune system → more susceptible to bacteria, viruses, and tumor cells
  - Results in higher hospital acquired infection rates, cancer recurrence rates, and mortality rates
Adverse Effects of Blood Component Therapy

• Febrile and allergic reactions
• Hemolytic transfusion reactions
• Infection: SSI, CLA-BSI, VAP, UTI

• Transfusion-Related Acute Lung Injury (TRALI)
  – Unexplained acute lung injury within 6 hours of transfusion
  – Mortality rate 5% to 20%
  – Incidence 1:1000 to 1:5000 transfusion

• Transfusion-Associated Circulatory Overload (TACO)
  – Volume overload leading to CHF and pulmonary edema

• Transfusion-Related Immunomodulation (TRIM)
  – Alter immune system → more susceptible to bacteria, viruses, and tumor cells
  – Results in higher hospital acquired infection rates, cancer recurrence rates, and mortality rates

Toy- CritCareMed 2005;33(4)
BENEFICIAL EFFECT OF OPERATION-DAY
BLOOD-TRANSFUSIONS ON HUMAN
RENAL-ALLOGRAFT SURVIVAL

C. R. Stiller            B. L. Lockwood
N. R. Sinclair          R. A. Ulan
R. R. Sheppard          J. A. Sharpe
P. Hayman

Nephrology and Transplantation Unit, Department of
Medicine, University Hospital, London, Ontario, Canada

Summary        In 56 patients the 1-year renal-graft sur-
                vival was significantly better (71% vs
                40%) in those who had received blood before operation,
                confirming previous observations. In addition, trans-
                fusion on the day of operation proved to have been
                beneficial, both in those previously transfused (82% vs
                64%) and in those never previously transfused (71% vs
                28%). Irrespective of pretransplant transfusion, 1-year
                graft survival was significantly better (79% vs 44%) in
                those transfused on the day of operation.
Effect of operation-day transfusion on graft survival.

- ● - Transfused on day of surgery;
- ○ - Not transfused on day of surgery.
PEROPERATIVE BLOOD-TRANSFUSIONS
IMPROVE CADAVERIC RENAL-ALLOGRAFT
SURVIVAL IN NON-TRANSFUSED RECIPIENTS

A Prospective Controlled Clinical Trial

K. A. Williams
M. E. French

A. Ting
D. Oliver

P. J. Morris

Nuffield Department of Surgery, University of Oxford, John
Radcliffe Hospital, Oxford

Summary  The effect of peroperative transfusion
was studied in 27 patients who had
never had a blood-transfusion or been pregnant and who
were receiving their first cadaver renal allograft. 13 pa-
tients in the treatment group were given 2 units of whole
stored blood at transplantation, whereas 14 patients in
the control group were given no blood. Actuarial anal-
ysis after 2 years showed a graft survival of 85% at 1 year
in the treated group compared with 34% at 1 year in the
control group (p=0.03). Transfusion of non-transfused
patients during transplantation may be as effective as
pregraft transfusion.

THE LANCET, MAY 24, 1980
Fig. I—Actuarial analysis of graft survival of unsensitised recipients in peroperative transfusion trial.

A = 2 peroperative transfusions: treatment group
B = 0 peroperative transfusions: control group
C = overall first cadaver allograft survival in the Oxford unit, for comparison with A and B (n=175, over five years).
Association Between Blood Transfusion and Infection Risk

Figure 3. Association between blood transfusion and the risk of infectious complications (odds ratio [OR] and 95% confidence interval [CI]). ICU, intensive care Unit.
# Association Between Blood Transfusion and Infection Risk

<table>
<thead>
<tr>
<th>Hospital Acquired Condition</th>
<th>Transfusion Odds Ratio</th>
<th>Comments (2010$ costs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious preventable event-massive air embolism</td>
<td></td>
<td>Can occur with rapid transfusions or improper cell saver</td>
</tr>
<tr>
<td>Serious preventable event-blood incompatibility</td>
<td></td>
<td>1:16,000 transfused patients receive the wrong unit of blood¹</td>
</tr>
<tr>
<td>Reoperation for bleeding after CABG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinitis after CABG</td>
<td>2.0²</td>
<td>$34,000 event</td>
</tr>
<tr>
<td>Vascular catheter associate infection</td>
<td>2.8- 5.0³</td>
<td>$20,000 event</td>
</tr>
<tr>
<td>Catheter associated urinary infection</td>
<td>4.2⁴</td>
<td></td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>3.5- 5.3⁵</td>
<td>$23,000 event</td>
</tr>
<tr>
<td>Ventilator acquired pneumonia</td>
<td>1.9⁶</td>
<td>$19,500 event</td>
</tr>
</tbody>
</table>

*Odds ratio of 2 doubles risk of occurrence
Association Between Blood Transfusion and ARDS

Figure 4. Association between blood transfusion and the risk of developing adult respiratory distress syndrome (odds ratio [OR] and 95% confidence interval [CI]). ICU, intensive care unit.
RESULTS: A total of 116 consecutive patients were analyzed. Of these, 32 patients in the PAD group and 42 patients in the ICS group had follow-up of at least 4.75 years. There was a significantly higher rate of biochemical failure (34.4% vs. 9.5%; \( p = 0.02 \)) and metastases (12.5% vs. 0%; \( p = 0.03 \)) in the PAD group versus the ICS group; there was no significant difference in mortality (9.4% vs. 0%; \( p = 0.08 \)).

CONCLUSION: ICS appears to be a safe and effective method of allogeneic blood conservation in patients undergoing RP. The findings suggest that there is no increased risk of biochemical failure, disease dissemination, or mortality at 5 years post-RP as a result of ICS use.

Blood Product Issues: Storage Defects and Microvascular Perfusion

- Build-up of cytokines, free Hgb, K+, debris (BRMs) \(^1,2\)
- Decreased 2,3- DP, ADP, NO
- Poor deformability leading to decreased oxygen exchange\(^3\)

Kristiansson- ActaAnesthScand 1996;40
Fransen- Chest 1999;116
Hovav- Transfusion 1999; 39
Perfusion
RBC Transfusion & Tissue Oxygenation

• RBC transfusion does not improve tissue oxygen consumption consistently in critically ill patients, either globally or at the level of the microcirculation.
• RBC transfusion is not associated with improvements in clinical outcome in the critically ill and may result in worse outcomes in some patients.
• Specific factors that identify patients who will improve from RBC transfusion are difficult to identify.
• Lack of efficacy of RBC transfusion likely is related to storage time, increased endothelial adherence of stored RBCs, nitric oxide binding by free hemoglobin in stored blood, donor leukocytes, host inflammatory response, and reduced red cell deformability.

AABB Recommendations 2013

- **Recommendation 1:** The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

- **Recommendation 2:** The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).

- **Recommendation 3:** The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).

- **Recommendation 4:** The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).

AABB Recommendations 2013

- **Recommendation 1:** The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

- **Recommendation 2:** The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).

- **Recommendation 3:** The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).

- **Recommendation 4:** The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).
AABB Recommendations 2013

• **Recommendation 1:** The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

• **Recommendation 2:** The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).

• **Recommendation 3:** The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).

• **Recommendation 4:** The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).

AABB Recommendations 2013

- **Recommendation 1:** The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

- **Recommendation 2:** The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).

- **Recommendation 3:** The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).

- **Recommendation 4:** The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).

Indication Creep

• When and why was transfusion developed?
• World War II: to treat large volume blood loss.
• How are physicians taught to use blood products?
• How are they used now?
  – RBC: volume replacement, “symptomatic anemia”
  – FFP: treat elevated PT/INR to lower “bleeding risk”
• What evidence would we want today to introduce transfusion into medical practice?
• Evaluate the evidence as a test of non-inferiority.
PRBC Indications

- < 7 g/dL (< 21% HCT)
- Hematocrit ≤ 24% or hemoglobin ≤ 8 g/dL in acute coronary syndrome (STEMI, NSTEMI, unstable angina) or congestive heart failure
- Acute hemorrhage: (> 1500-2000 mL), not responding to volume resuscitation
- BMT/Leukemia: ≤ 8 g/dL (≤ 24% HCT)
- Sepsis: SvO2 < 70% and HCT < 30% within first 6 hours of therapy
- Tachycardia, hypotension not corrected by volume replacement

Transfuse 1 unit, then reassess!
34% reduction in administrations
## Blood Administrations

<table>
<thead>
<tr>
<th>Year</th>
<th>OR Total</th>
<th>SICU Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>9997</td>
<td>4975</td>
</tr>
<tr>
<td>2009</td>
<td>11411</td>
<td>4352</td>
</tr>
<tr>
<td>2010</td>
<td>10209</td>
<td>3638</td>
</tr>
<tr>
<td>2011</td>
<td>9340</td>
<td>3546</td>
</tr>
<tr>
<td>2012</td>
<td>7538</td>
<td>2966</td>
</tr>
</tbody>
</table>

**OR** 28% Reduction  
**SICU** 31% Reduction
Summary of UIHC Impact
18 months of data

• Better use of a limited resource
• Better use of nursing, pathology, and laboratory time.
• The estimated savings through March 2013: $12,625,541
  – Purchase savings of $875,565
  – Transfusion cost savings of $2,358,462
  – Adverse event avoidance of $9,390,434.
Questions on Red Cell Transfusion?
Plasma Learning Objectives

• Review relationship of INR to normal hemostasis

• Plasma transfusion myths
  – PT and PTT predict bleeding risk
  – PT/INR is normalized with plasma transfusion
  – Plasma transfusion is safe

• Review plasma transfusion indications
Plasma Learning Objectives

• Review relationship of INR to normal hemostasis

• Plasma transfusion myths
  – PT and PTT predict bleeding risk
  – PT/INR is normalized with plasma transfusion
  – NOT TRUE NOT TRUE NOT TRUE NOT TRUE

• Review plasma transfusion indications
Figure 1-7. Zones of response to bleeding risk at the time of invasive procedures. The x-axis is meant to depict the product of both platelet number and functional activity. Patients with normal laboratory values are represented by the smallest rectangle. A large number of patients with mild-to-moderate abnormalities of preprocedure laboratory tests are in the zone of physiologic reserve and are not likely to derive any benefit from preprocedure transfusion therapy.
Which of the following is not an anticoagulant?

- Unfractionated heparin
- LMWH
- Warfarin
- Dabigatran
- Hirudin
- Rivaroxaban
Which of the following is not an anticoagulant?

- Unfractionated heparin  anti-Xa
- LMWH  anti-Xa
- Warfarin
- Dabigatran  thrombin-inhibitor
- Hirudin  thrombin-inhibitor
- Rivaroxaban  anti-Xa
Which of the following is not an anticoagulant?

- Warfarin is a hypo-coagulant. By lowering the levels of factors I, VII, IX, X, protein S & C. Notice that it lowers the anticoagulant factors (proteins S & C). Warfarin does not block an ongoing coagulation cascade, coagulation is adequate just slower. The other drugs STOP and activated coagulation cascade; they are anti-coagulants.

- In advanced liver disease patients are most often hypercoagulable for this reason (NEJM 365;2:147 July 14, 2011)
**Figure 2** Change in international normalized ratio (INR) per unit of plasma transfused. See Equation 1

**Toward Rational Fresh Frozen Plasma Transfusion**

The Effect of Plasma Transfusion on Coagulation Test Results

Lorne L. Holland, MD, and Jay P. Brooks, MD, MBA

*Am J Clin Pathol* 2006;126:133-139
FFP Fails to Correct INR

• 22 ICU subjects with PT or aPTT > 1.5 were given FFP
• Factor analysis showed that 10/22 subjects had adequate factor levels, despite abnormal tests
• Impact on coagulopathy was dose-related:
  – 12 mL/kg: 1 of 5 corrected
  – 33.5 mL/kg: 7 of 7 corrected

**FFP Fails to Correct INR**

- 22 ICU subjects with PT or aPTT > 1.5 were given FFP
- Factor analysis showed that 10/22 subjects had adequate factor levels, despite abnormal tests
- Impact on coagulopathy was dose-related:
  - 12 mL/kg: 1 of 5 corrected
  - 33.5 mL/kg: 7 of 7 corrected  \(2500 \text{ mL} > 10 \text{ units!}\)

Does the PT/INR Predict Bleeding Risk?

- Central venous catheterization
- Paracentesis
- Thoracentesis
- Liver Biopsy
Central Venous Catheterization in Liver Disease

- 658 Procedures
- SC (n=352); IJ (n=306)
- Median INR
  - SC: 2.4
  - IJ: 2.7
- Complications
  - Major = 1 (INR 1.5, plt 68; arterial puncture)
  - Minor = Risks were high INR (>5), low plt, IJ site

Bleeding Risk of Paracentesis

- Complications in 1% (abdominal wall hematomas) despite abnormal PT in 71% (Runyon BA: Arch Intern Med 1986; 146:2259)

- In 4729 paracenteses, 9 had bleeding complications, 8 with renal failure; (Pache I: Aliment Pharmacol Ther 2005; 21:525)

- 1100 large-volume paracenteses, no hemorrhage, despite (Grabou CM: Hepatology 2004; 40:484):
  - No FFP
  - Platelet count as low as 19,000
  - INR as high as 8.7 (75% were > 1.5)

- Of Hepatologists attending a conference of coagulopathy of liver disease, 50% said they never give FFP or only if INR>2.5 (Caldwell SH: Hepatology 2006; 44:1039)
US-Guided Thoracentesis

Real-time ultrasound during catheter insertion

<table>
<thead>
<tr>
<th>INR</th>
<th>Number</th>
<th>Hemorrhage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>555</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>267</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>139</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 2.5</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 3.0</td>
<td>32</td>
<td>0</td>
</tr>
</tbody>
</table>

Patel MD, et.al: AJR 2011; 197:W164
Liver Biopsy

- 200 subjects with cirrhosis, fatty liver, or metastatic disease
- No exclusions based on pre-procedure tests; no prophylactic transfusions
- Needle biopsy via laparoscope
- Bleeding at site directly visualized, timed
- No correlation with INR or platelets

Ewe K: Dig Dis Sci 1981; 26:388
Why Doesn’t INR Predict Risk for Post-Procedure Bleeding?

• Clinical hemostasis:
  – vessel; cellular blood elements; platelet number and function; fibrin formation; fibrinolysis

• INR and aPTT:
  – fibrin formation (in response to an artificial stimulus)

HEMOSTASIS

A. Vasoconstriction
- Endothelium
- Basement membrane
- Arteriole smooth muscle

Site of injury
- Reflex vasoconstriction
- ECM (collagen)

Endothelin release causes vasoconstriction

B. Primary Hemostasis
1. Platelet adhesion (ADP, TXA2)
2. Shape change
3. Granule release
4. Recruitment
5. Aggregation (hemostatic plug)

C. Secondary Hemostasis
1. Tissue factor
2. Phospholipid complex expression
3. Thrombin activation
4. Fibrin polymerization

D. Antithrombotic Counter-Regulation
- Release of:
  - t-PA (fibrinolysis)
  - thrombomodulin (blocks coagulation cascade)

- Trapped neutrophil
- Trapped red blood cells
- Polymerized fibrin
Factor levels equal or greater than 30% produce normal hemostasis.
Transfusion-Associated Circulatory Overload: TACO

- 51 of 901 (6%) of transfused patients developed TACO (median age 73)
- Cases had a more positive fluid balance and were transfused a greater volume of plasma (0.4L)
- Risk factors:
  - LV dysfunction
  - FFP ordered to reverse anticoagulant

Li G, et.al: Transfusion 2011; 51:338
Transfusion-Associated Acute Lung Injury: TRALI

- 115 ICU patients with INR > 1.5
- FFP transfused in 38.3%
- INR corrected in 36%
  - Median FFP dose
    - Not corrected: 10 mL/kg
    - Corrected: 17 mL/kg (6 units)
- New bleeding episodes: no difference
- New-onset ALI: 18 v 4% (p=0.21)
Summary of Plasma Use

• INR poorly predicts factor adequacy
• INR does not predict bleeding from procedures
• Bleeding usually follows vascular injury
• FFP is not indicated before procedures when INR is modestly elevated (<2) and perhaps not even when more elevated
• FFP use strongly associated with TRALI and TACO
Indications for Plasma Transfusion

• Bleeding patient with inherited or acquired coagulopathy due to factor deficiency and specific factor replacement is not available
• Bleeding patient who requires replacement of multiple coagulation factors (DIC, liver failure)
• Bleeding and need for massive transfusion protocol
• Bleeding patient on warfarin for whom reversal with vitamin K will be too slow
Indications for Plasma Transfusion

- **Bleeding** patient with inherited or acquired coagulopathy due to factor deficiency and specific factor replacement is not available
- **Bleeding** patient who requires replacement of multiple coagulation factors (DIC, liver failure)
- **Bleeding** and need for massive transfusion protocol
- **Bleeding** patient on warfarin for whom reversal with vitamin K will be too slow
UIHC Plasma Transfusion Policy

<table>
<thead>
<tr>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent reversal of warfarin</td>
</tr>
<tr>
<td>INR &gt;1.8 and significant hemorrhage</td>
</tr>
<tr>
<td>INR &gt;2.0 and planned invasive procedure</td>
</tr>
<tr>
<td>Protocol (e.g., ECMO, liver transplant, pediatric cardiac, exchange transfusion)</td>
</tr>
<tr>
<td>Unlisted (other): Specify in comments</td>
</tr>
</tbody>
</table>
In trauma patients, and perhaps others, accelerated fibrinolysis is likely more important than reduction in coagulation factors.

Strong evidence supports use of tranexamic acid as soon as possible after major trauma.
Reduction in plasma transfusion after enforcement of transfusion guidelines

Maria Tavares, Pamela DiQuattro, Norma Nolette, Gina Conti, and Joseph Sweeney

TRANSFUSION 2011;51:754-761.

INTERDICTING THE TRANSFUSION OF FFP

Fig. 2. Patient mean case mix index per calendar year. The error bars are ±1 SEM.
Evidence-Based Transfusion Practice: RBCs & Plasma

Richard LeBlond, MD, MACP
Chief Quality and Safety Officer
Billings Clinic

QUESTIONS?

"given an existing problem, it may be better not to do something, or even to do nothing, than to risk causing more harm than good"