Seuils transfusionnels en 2016

Philippe Van der Linden MD, PhD
Conflict of Interest Disclosure

In the past 5 years, I have received honoraria or travel support for consulting or lecturing from the following companies:
Fresenius-Kabi GmbH
CSL Behring GmbH
Janssen-Cilag SA
Transfusion Practices in Critically Ill Patients

Myocardial infarction

- 55-year-old man
- Major vascular surgery (AAA)
- POD4: retrosternal chest pain
- ECG: anterior wall myocardial infarction: ICU admission
- No other complication
- No evidence of a volume deficit

Transfusion Practices in Critically Ill Patients

The “Transfusion” Dilemma

Risks associated with anemia

Effectiveness of blood transfusion

Risks associated with blood transfusion
Intraoperative Anemia & Postoperative Morbi-mortality After Cardiac Surgery

Intraoperative Anemia & Postoperative Morbi-mortality After Cardiac Surgery

Blood Transfusion & Postoperative Morbidity-Mortality After Cardiac Surgery

Objectives:

To compare the benefit and harm of restrictive versus liberal transfusion strategies to guide RBCs transfusions.

Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis

31 trials – 9,813 patients

✓ Results: restrictive transfusion strategies

- ↓ risk of receiving RBC transfusion (RR: 0.54; 95% CI: 0.47 to 0.63)
- ↓ volume of transfused RBCs (MD: -1.43; 95% CI: -2.01 to -0.86)
- No impact on mortality (RR:0.86; 95% CI: 0.74 to 1.01)
- No impact on morbidity (RR:0.98; 95% CI: 0.85 to 1.12)
- No impact on fatal or non-fatal MI (RR: 1.28; 95% CI: 0.66 to 2.49)

A 15% relative risk reduction or increase in overall morbidity with restrictive transfusion strategies could be excluded

Red Blood Cell Transfusion Threshold & Storage


<table>
<thead>
<tr>
<th>Source</th>
<th>Restrictive Transfusion Threshold</th>
<th>Liberal Transfusion Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>Total No.</td>
</tr>
<tr>
<td>Lotke et al, 1999</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>Blair et al, 1986</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Foss et al, 2009</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Carson et al, 1998</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Weber et al, 2008</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>Cooper et al, 2011</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Carson et al, 2013</td>
<td>7</td>
<td>55</td>
</tr>
<tr>
<td>Parker, 2013</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Bracey et al, 1999</td>
<td>3</td>
<td>215</td>
</tr>
<tr>
<td>Bush et al, 1997</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Hajjar et al, 2010</td>
<td>15</td>
<td>249</td>
</tr>
<tr>
<td>Gregersen et al, 2015</td>
<td>21</td>
<td>144</td>
</tr>
<tr>
<td>Jairath et al, 2015</td>
<td>14</td>
<td>257</td>
</tr>
<tr>
<td>Carson et al, 2011</td>
<td>43</td>
<td>1009</td>
</tr>
<tr>
<td>Subtotal</td>
<td>121</td>
<td>2321</td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 0.02; \chi^2 = 13.14; P = .36; \hat{\rho} = 9%$
Tests for overall effect: $z$ score = 0.31; $P = .76$

<table>
<thead>
<tr>
<th>Source</th>
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<th>Liberal Transfusion Threshold</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>Total No.</td>
</tr>
<tr>
<td>DeZern et al, 2016</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>Hébert et al, 1995</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>de Almeida et al, 2015</td>
<td>23</td>
<td>101</td>
</tr>
<tr>
<td>Lacroix et al, 2007</td>
<td>14</td>
<td>320</td>
</tr>
<tr>
<td>Walsh et al, 2013</td>
<td>12</td>
<td>51</td>
</tr>
<tr>
<td>Murphy et al, 2015</td>
<td>26</td>
<td>1000</td>
</tr>
<tr>
<td>Villanueva et al, 2013</td>
<td>19</td>
<td>416</td>
</tr>
<tr>
<td>Hébert et al, 1999</td>
<td>78</td>
<td>418</td>
</tr>
<tr>
<td>Holst et al, 2014</td>
<td>168</td>
<td>502</td>
</tr>
<tr>
<td>Subtotal</td>
<td>349</td>
<td>2900</td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 0.05; \chi^2 = 16.09; P = .04; \hat{\rho} = 50%$
Tests for overall effect: $z$ score = 0.53; $P = .59$

Overall

<table>
<thead>
<tr>
<th>Source</th>
<th>Restrictive Transfusion Threshold</th>
<th>Liberal Transfusion Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>Total No.</td>
</tr>
<tr>
<td></td>
<td>470</td>
<td>5221</td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 0.04; \chi^2 = 79.75; P = .10; \hat{\rho} = 29%$
Tests for overall effect: $z$ score = 0.29; $P = .77$
Tests for subgroup differences: $\chi^2 = 0.34; P = .56; \hat{\rho} = 0%$
Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

☑ Prospective randomized controlled trial:
  • Restrictive transfusion strategy: Hb < 7 g/dl (N=461)
  • Liberal transfusion strategy: Hb < 9 g/dl (N=460)

☑ 1 outcome:
  45-day mortality

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Prospective randomized controlled trial:
- Restrictive transfusion strategy: Hb < 7 g/dl (N=461)
- Liberal transfusion strategy: Hb < 9 g/dl (N=460)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Restrictive Strategy (N=444)</th>
<th>Liberal Strategy (N=445)</th>
<th>Hazard Ratio with Restrictive Strategy (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause within 45 days — no. (%)</td>
<td>23 (5)</td>
<td>41 (9)</td>
<td>0.55 (0.33–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Further bleeding — no. of patients/total no. (%)</td>
<td>45/444 (10)</td>
<td>71/445 (16)</td>
<td>0.62 (0.43–0.91)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adverse events — no. (%)†</td>
<td>179 (40)</td>
<td>214 (48)</td>
<td>0.73 (0.56–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Transfusion reactions</td>
<td>14 (3)</td>
<td>38 (9)</td>
<td>0.35 (0.19–0.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>12 (3)</td>
<td>16 (4)</td>
<td>0.74 (0.35–1.59)</td>
<td>0.56</td>
</tr>
<tr>
<td>Transfusion-associated circulatory overload</td>
<td>2 (&lt;1)</td>
<td>16 (4)</td>
<td>0.06 (0.01–0.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>1 (&lt;1)</td>
<td>6 (1)</td>
<td>0.16 (0.02–1.37)</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiac complications§</td>
<td>49 (11)</td>
<td>70 (16)</td>
<td>0.64 (0.43–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Acute coronary syndrome¶</td>
<td>8 (2)</td>
<td>13 (3)</td>
<td>0.61 (0.25–0.49)</td>
<td>0.27</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>12 (3)</td>
<td>21 (5)</td>
<td>0.56 (0.27–1.12)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Liberal or Restrictive Transfusion after Cardiac Surgery

- Multicenter parallel-group trial (postoperative period):
  - Restrictive transfusion strategy: Hb < 7.5 g/dl (N=1000)
  - Liberal transfusion strategy: Hb < 9 g/dl (N=1003)

- 1 outcome: 90-day mortality + morbidity

Blood Transfusion Strategy in Patients With Symptomatic Coronary Artery Disease

✔ Pilot trial: 110 ACS patients or stable angina undergoing cardiac catheterization and a Hb < 10 g/dl
  • Liberal strategy: Hb < 10 g/dl (N=55)
  • Restrictive strategy: symptoms of anemia or Hb < 8 g/dl (N=55)

✔ Primary outcome: composite of death, MI or unscheduled revascularization 30 days post randomization

Transfusion Medicine

« It is unlikely that any level of hemoglobin can be used as a universal threshold for transfusion ».

Transfusion Thresholds

« The decision to transfuse should be guided by an assessment of individual patient on the basis of a combination of symptoms, signs, lab measures and not by a single hemoglobin level ». 
Blood Transfusion Strategy in High-Risk Patients after Hip Fracture Surgery

✓ Prospective randomized trial: patients ≥ 50 years of age with a history or risk factors for CVD with Hb < 10 g/dl after surgery

✓ Transfusion strategy:
  • Liberal Hb threshold of 10 g/dl
  • Restrictive: symptoms of anemia or for Hb < 8g/dl

✓ RBC transfused unit by unit

✓ Primary outcome: death or inability to walk across room without human assistance on 60-day follow-up

Blood Transfusion Strategy in High-Risk Patients after Hip Fracture Surgery

Age of the patients: 82 ± 10 y

Age of de blood: 22 ± 10 days

Leukoreduction: 90%

Primary outcome: death or inability to walk across room without human assistance on 60-day follow-up: 35.2 % vs 34.7%

Blood Transfusion Strategy in High-Risk Patients after Hip Fracture Surgery: 3 Years Survival

<table>
<thead>
<tr>
<th>Causes</th>
<th>Total deaths (n=841)</th>
<th>Deaths in the liberal transfusion group (n=432)</th>
<th>Deaths in the restrictive transfusion group (n=409)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>278 (33%)</td>
<td>141 (33%)</td>
<td>137 (34%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>103 (12%)</td>
<td>54 (13%)</td>
<td>49 (12%)</td>
</tr>
<tr>
<td>Infection</td>
<td>78 (9%)</td>
<td>41 (9%)</td>
<td>37 (9%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>57 (7%)</td>
<td>27 (6%)</td>
<td>30 (7%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>108 (13%)</td>
<td>56 (13%)</td>
<td>52 (13%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>58 (7%)</td>
<td>29 (7%)</td>
<td>29 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>147 (17%)</td>
<td>79 (18%)</td>
<td>68 (17%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (1%)</td>
<td>5 (1%)</td>
<td>7 (2%)</td>
</tr>
</tbody>
</table>

Data are n (%).

Transfusion Triggers

- Dyspnea
- Tachycardia
- Hypotension
- ST-T Abnormalities
- \( \text{PvO}_2, \text{SvO}_2, \text{O}_2\text{ER} \)
- Central venous \( \text{O}_2 \) saturation?
- Others (lactate)?
Central Venous O₂ Saturation as a Physiologic Transfusion Trigger

O₂ER = VO₂ / DO₂
≈ (SaO₂ − SvO₂) / SaO₂
≈ 1 − SvO₂

SvO₂ normal range: 68-77%
Central venous O2 saturation (ScVO₂): 5% above

Sensitivity: 82%
Threshold value for ScVO₂ with the best sensitivity and specificity: = 69.5%
Specificity: 76%

Randomized noninferiority trial: children with a Hb concentration ≤ 5 g/dL and a lactate level ≥ 5 mmol/L

Pre-storage leukoreduced RBC transfusion (10-20 ml/kg)
- Long storage RBC units (32 [30-34] days; N=145)
- Short storage units (8 [7-9] days; N=145)

From Dhabangi A et al. JAMA doi:10.1001/jama.2015.13977
Randomized noninferiority trial: children with a Hb level ≤ 5 g/dL and a lactate level ≥ 5 mmol/L

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From Dhabangi A et al. JAMA doi:10.1001/jama.2015.13977
Change in Stored Red Blood Cell Characteristics Over Time

Blood Transfusion: "Storage Effects"

✓ Decreased 2, 3 - diphosphoglycerate (~ 0 after 15 days)
  ► Increased affinity of hemoglobin for oxygen

✓ Decreased in red blood cell ATP
  ► Change in RBC shape (discoid to spherocytic)
  ► Reduced cellular deformability

Decreased tissue oxygen availability

Endothelial swelling and tissue edema in sepsis reduce capillary luminal diameter
Effects of Allogeneic Blood Transfusion on VO2

3 units PRBCs: hemoglobin 9.0 ± 0.8 to 11.9 ± 0.9 g/dl

Red Blood Cell Transfusion Threshold & Storage

✓ RBC storage duration: 13 RCTS; 5,515 patients

Red Blood Cell Transfusion Threshold & Storage


Transfusion threshold
31 RCTS
12,587 patients
Relationship of Erythrocyte Transfusion With Short & Long-term Mortality

✓ Population-based cohort study through analysis of administrative databases. Patients undergoing elective hip or knee surgery from 1999 to 2008 in Ontario (N=162,190 patients)

Transfusion rate:
Quartile 1: 12.7%
Quartile 2: 17.5%
Quartile 3: 23.7%
Quartile 4: 37.0%

Mortality (%)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Hospitals</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>39,859</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>41,678</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>39,033</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>41,620</td>
</tr>
</tbody>
</table>

Hospital-specific Transfusion Quartile

<table>
<thead>
<tr>
<th>Quartile</th>
<th>30-day Mortality</th>
<th>1-yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>HR 1.06 (95% CI, 0.83–1.35; P = 0.66)</td>
<td>HR 1.05 (95% CI, 0.91–1.22; P = 0.50)</td>
</tr>
<tr>
<td>2</td>
<td>HR 1.07 (95% CI, 0.81–1.40; P = 0.65)</td>
<td>HR 0.99 (95% CI, 0.87–1.13; P = 0.88)</td>
</tr>
<tr>
<td>3</td>
<td>HR 1.11 (95% CI, 0.82–1.50; P = 0.50)</td>
<td>HR 1.02 (95% CI, 0.82–1.26; P = 0.88)</td>
</tr>
<tr>
<td>Highest</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Association of Blood Transfusion With Mortality: Cause or Confounding?

- Retrospective study of patient data (2002-8; N=2599 patients)
- Risk factors associated with in-hospital mortality

- Chest tube drainage was the strongest independent predictor of mortality while blood transfusion was not

Association Between Blood Transfusion & Morbidity-Mortality After Major Surgery

Is transfusion the causal event leading to worse outcome or rather a marker for a sicker patient population that is more likely to undergo transfusion for many reasons?
Indications for RBC transfusion:  
- To maintain a predefined hematocrit on bypass  
- To treat perioperative blood loss and/or inadequate oxygen delivery  

Hypothesis: indication for RBC transfusion may impact the effects of transfusion on postoperative morbi-mortality in pediatric cardiac surgery  

Indications For Red Cell Transfusion In Pediatric Cardiac Surgery: Effects on Outcome

✓ Retrospective cohort study (2006-2009; N=855)

Indications For Red Cell Transfusion In Pediatric Cardiac Surgery: Effects on Outcome

✓ Retrospective cohort study (2006-2009; N=855)

✓ Transfused children (N=568)
  • Maintenance on-bypass hct of 24% (CPB driven: N=358)
  • Hemorrhage or O₂ delivery increase (therapeutic: N= 210)

Hematocrit ≥ 24%, depending on clinical conditions: degree of hemorrhage, arterial hypoxemia, low cardiac output syndrome...

✓ Standardized anesthetic, CPB and surgical techniques

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  • Hemorrhage or O_2 delivery increase (therapeutic: N=210)

✓ Primary outcome: composite measure including either hospital death and/or the presence of at least 2 of the following events:
  • Pulmonary failure (mechanical ventilation duration > 75th percentile)
  • Prolonged inotropic support (inotropes > 5 µg/kg.min for more than 48h)
  • Renal failure (reduction of postop creat clearance ≥ 75% from baseline)

Indications For Red Cell Transfusion In Pediatric Cardiac Surgery: Effects on Outcome

- Retrospective cohort study (2006-2009; N=855)

* p<0.05 CPB versus therapeutic transfusion group

Indications For Red Cell Transfusion In Pediatric Cardiac Surgery: Effects on Outcome

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Indications For Red Cell Transfusion In Pediatric Cardiac Surgery: Effects on Outcome

- Transfused children (N=568)
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  - Hemorrhage or $O_2$ delivery increase (therapeutic: N=210)

- Adjusted multivariate analysis (age, gender, preop weight, redo-surgery, RACHS-1 score, and RBC transfusion volume)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA score</td>
<td>3.06 [1.50-6.23]</td>
<td>0.002</td>
</tr>
<tr>
<td>Indication for transfusion</td>
<td>1.90 [1.13-3.19]</td>
<td>0.016</td>
</tr>
<tr>
<td>PRISM II score</td>
<td>1.09 [1.04-1.13]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative SaO2 (%)</td>
<td>1.03 [1.01-1.05]</td>
<td>0.006</td>
</tr>
<tr>
<td>Total intraoperative blood loss (ml/lkg)</td>
<td>1.01 [1.00-1.02]</td>
<td>0.002</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>1.01 [1.00-1.02]</td>
<td>0.014</td>
</tr>
<tr>
<td>Total blood loss (ml/kg)</td>
<td>1.01 [1.00-1.01]</td>
<td>0.021</td>
</tr>
</tbody>
</table>
Indications For Red Cell Transfusion In Pediatric Cardiac Surgery: Effects on Outcome

Transfused children (N=568)
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- Hemorrhage or O2 delivery increase (therapeutic: N=210)

Indications For Red Cell Transfusion In Pediatric Cardiac Surgery: Effects on Outcome

The indication for transfusion per se influences the effect of RBC transfusion on postoperative morbi-mortality. This parameter should be considered in further research on the effects of blood transfusion on outcome.
Does RBC Transfusion Transfused on Bypass Affect Outcome In Pediatric Cardiac Surgery

✓ RBC transfusion during CPB to maintained a predefined hct

✓ Hypothesis: on-bypass RBC transfusion does not affect postoperative morbi-mortality in pediatric cardiac surgery

Does RBC Transfusion Transfused on Bypass Affect Outcome In Pediatric Cardiac Surgery

✓ Retrospective cohort study (2006-2012; N=1215)

Excluded patients were moribund (ASA5) or Jehovah’s witness patients

Does RBC Transfusion Transfused on Bypass Affect Outcome In Pediatric Cardiac Surgery

✓ Retrospective cohort study (2006-2012; N=1215)

✓ Studied population (N=854)
  • No transfusion (N=439)
  • Transfused to maintain an on-bypass hct of 24% (N= 415)

✓ Primary outcome: composite measure including either hospital death and/or the presence of at least 2 of the following events:
  • Pulmonary failure (mechanical ventilation duration > 75th percentile)
  • Prolonged inotropic support (inotropes > 5 µg/kg.min for more than 48h)
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  • No transfusion (N=439)
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✓ Statistics: a propensity score analysis, using genetic matching followed by a logistic regression for binary outcomes variables and weighted least squares linear regression for continuous outcomes

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  • No transfusion (N=439)
  • Transfused to maintain an on-bypass hct of 24% (N=415)

![Composite primary outcome (%)](image)

P=0.538

There is no evidence that on-bypass RBC transfusion affect outcome in pediatric cardiac surgery.
The real impact of RBC transfusion on postoperative morbidity-mortality remains to be determined.
Transfusion (%)

- Transfusion practice largely individualized for each patient
- Transfusion policy based on a “one by one unit” strategy

Perioperative Transfusion Trigger

Development of a patient’s blood management program:
- Optimization of preoperative RBC mass
- “Restrictive” blood loss strategy
Merci de votre attention
Patient Blood Management

☑ Defined as “the appropriate use of blood and blood components with a goal of minimized their use”.

☑ Encompasses an evidence-based medical and surgical approach that is multidisciplinary (transfusion medicine specialists, surgeons, anesthesiologists, and critical care specialists) and multiprofessional (physicians, nurses, pump technologists, and pharmacists)

Patient Blood Management: Motivation

- Known (and unknown) risk associated with blood products
- Constraints from escalating costs
- Preservation of the national blood inventory
  - Decreased donors' population
  - Increased demand of products
  - Mismatch between recipients and donors regarding ABO blood groups (i.e. sickle cell disease)