The appropriate use of blood transfusion in critically ill children

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Sainte-Justine Hospital
Université de Montréal
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- **ABLE study:**
  - CIHR grant #177453.
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- **Health Technology Assessment, National Institute for Health Research (United Kingdom).**
- Sanquin (Netherland)

- **Research program on blood products:**
  - FRSQ grant #24460.
What determines red blood cell (RBC) transfusions in PICU?

Anemia, Blood Loss, and Blood Transfusions in North American Children in the Intensive Care Unit

Scott T. Bateman¹, Jacques Lacroix², Katia Boven³, Peter Forbes⁴, Roger Barton⁵, Neal J. Thomas⁶, Brian Jacobs⁷, Barry Markovitz⁸, Brahm Goldstein⁹, James H. Hanson¹⁰, H. Agnes Li¹¹, and Adrienne G. Randolph¹², for the Pediatric Acute Lung Injury and Sepsis Investigators Network*


**TABLE 4. REASON FOR FIRST TRANSFUSION BY ORDERING PHYSICIAN (n = 476)**

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<th>Mean Pretransfusion Hemoglobin, g/dl (SD [median])</th>
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- Threshold hemoglobin (Hb).

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What determines red blood cell (RBC) transfusions in PICU?

- Threshold hemoglobin (Hb).
- Acute blood loss:
  - Hemorrhage & bleeding.
  - Blood collection.
- Cardiovascular/respiratory insufficiency.
- What about goal-directed transfusion therapy?
Structure of this lecture

- **Goal-directed** red blood cell (RBC) transfusion therapy.

- **Hemoglobin** (Hb): threshold for RBC transfusion:
  - Threshold Hb in **stable** patients:
    - All patients enrolled in TRIPICU study.
    - Severity of illness (planned TRIPICU subgroup analysis).
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Goal-directed RBC transfusion therapy

Goal-directed RBC transfusion therapy is frequently advocated.

Basic principle: a RBC transfusion is given aiming to attain a given “physiological” goal.

Many goals are suggested:

- Goals related to O$_2$ delivery and/or O$_2$ consumption (VO$_2$):
  - Global markers: DO$_2$, VO$_2$, blood lactate, Sv’O$_2$ (mixed venous O$_2$ saturation), ScvO$_2$, (central venous SO$_2$), O$_2$ extraction rate, etc.
  - Regional (tissular) markers: near-infrared spectroscopy (NIRS), StO$_2$ (tissular SO$_2$), regional O$_2$ extraction rate, etc.

- Other goals: heart rate variability, plethysmographic variability, vascular endothelial growth factor, etc.
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Early goal-directed therapy: ScvO$_2$ (Rivers et al. N Engl J Med)

- **Site:** one emergency room.
- **Patients:** 266 adults in severe sepsis or septic shock.
- **Randomization (goal vs no goal):** central venous O$_2$ saturation (ScvO$_2$) $\geq$ 70% vs no ScvO$_2$ measurement.
  - Rationale of the goal: providing enough O$_2$ delivery (DO$_2$) should prevent more cellular insult.
- **Intervention:** early (< 6 hr) protocolized therapy.
  - Mechanical ventilation.
  - Up to 80 mL/kg of fluid.
  - Dobutamine and vasoconstrictive therapy.
  - Red blood cell transfusion if ScvO$_2$ still < 70%.
- **Conclusion:** mortality was 30.5% with early goal-directed therapy vs 46.5% in controls.
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**Goal:**

\[
\text{ScvO}_2 \geq 70\%.
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Early goal-directed therapy: ScvO$_2$ (Rivers et al. N Engl J Med)

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Many large RCTs are presently on-going to see if these results can be repeated.
Goal-directed therapy: ScvO$_2$

- Sites: 2 Brazilian hospitals (emergency room, PICU).
- Patients: 102 children in severe sepsis or fluid refractory shock.
- Randomization (goal vs no goal): central venous O$_2$ saturation (ScvO$_2$) $\geq$ 70% vs no ScvO$_2$ measurement.
- Intervention: idem Rivers’ study (first 6 hours).
  - More crystalloid (28 (20–40) vs. 5 (0–20) ml/kg, $p < 0.0001$).
  - More inotropic drugs (29.4% vs. 7.8%, $p = 0.01$).
  - More RBC transfusions (45.1% vs. 15.7%, $p = 0.002$).
- Conclusion: mortality was 11.8% with ScvO$_2$ driven early goal-directed therapy vs 39.2% in controls.
  - The role of RBC transfusion is unclear.
Goal-directed RBC transfusion therapy: conclusion

- Goal-directed RBC transfusion therapy might be the right clinical approach.
  - However, there are good data only for ScvO₂, and the role of RBC transfusion in ScvO₂-directed goal therapy is unclear.
  - There are no data supporting the use of other possible goals.
- Actually, there is...
  - no consensus on what should be the first choice goal (maybe ScvO₂ in patients in severe sepsis),
  - nor any consensus on what threshold should be used for these goals.
- Presently, the best available hard data in PICU are about 3 determinants: severity of illness (stable vs unstable), threshold Hb and case-mix (cardiac vs non-cardiac children).
Structure of this lecture

- Goal-directed red blood cell (RBC) transfusion therapy.
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We suggest taking into account if a patient is stable or not in the decision making process to give a RBC transfusion to a critically ill child. Why?

- Because most available data come from the TRIPICU study, a randomized clinical trial that included only stable or stabilized patients.
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The NEW ENGLAND JOURNAL of MEDICINE

Transfusion Strategies for Patients in Pediatric Intensive Care Units

Jacques Lacroix, M.D., Paul C. Hébert, M.D., James S. Hutchison, M.D., Heather A. Hume, M.D., Marisa Tucci, M.D., Thierry Ducruet, M.Sc., France Gauvin, M.D., Jean-Paul Collet, M.D., Ph.D., Baruch J. Toledano, M.D., Pierre Robillard, M.D., Ari Joffe, M.D., Dominique Biarent, M.D., Kathleen Meert, M.D., and Mark J. Peters, M.D., for the TRIPICU Investigators, the Canadian Critical Care Trials Group, and the Pediatric Acute Lung Injury and Sepsis Investigators Network
Stable patients: definition

- Stable/stabilized patients: definition in TRIPICU study.
  - The mean arterial pressure is not less than 2 standard deviations below normal mean for age…
  - and the cardiovascular support (pressors/inotropes and fluids) has not been increased for at least 2 hours.

- Note that the respiratory and neurological status are not taken into account.
Basic design of TRIPICU study

**Eligible:** Hb ≤ 9.5 g/dL (95 g/L) within 7 days post entry into PICU
Basic design of TRIPICU study

Eligible: Hb $\leq 9.5$ g/dL (95 g/L) within 7 days post entry into PICU

Liberal group: transfusion if Hb $\leq 9.5$ g/dL

Restrictive group: transfusion if Hb $\leq 7.0$ g/dL
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**Targeted Hb post-transfusion:** 8.5-9.5 g/dL

Only pre-storage leukocyte-reduced packed RBC units were used.
## RCT: threshold Hb in pediatric ICU cases (TRIPICU study)

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* New/progressive MODS (multiple organ dysfunction syndrome) was the primary outcome measure of the TRIPICU study; all deaths were considered cases of progressive MODS.
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Can we apply these results to subgroups of patients enrolled in TRIPICU?
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Severity of illness in stable patients (data from TRIPICU)

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<th>PRISM score</th>
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<th>P value</th>
</tr>
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<tbody>
<tr>
<td>0 (lowest quartile)</td>
<td>+1.5 (–6.3 to +9.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>1-4 (second quartile)</td>
<td>–0.3 (–7.9 to +7.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>5-7 (third quartile)</td>
<td>–2.2 (–13.0 to +8.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>≥8 (highest quartile)</td>
<td>+2.4 (–11.1 to +15.9)</td>
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These results suggest that there is no justification to give more RBC transfusions to stable critically ill children even when their severity of illness is higher.
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Sepsis subgroup, including 34 cases of septic shock: outcomes

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<th>Liberal (68)</th>
<th>P-value</th>
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<tr>
<td>New/progressive MODS †</td>
<td>13</td>
<td>13</td>
<td>0.97</td>
</tr>
<tr>
<td>Highest daily PELOD score</td>
<td>14.9 ±16.4</td>
<td>12.6±14.2</td>
<td>0.33</td>
</tr>
<tr>
<td>PICU mortality</td>
<td>5</td>
<td>2</td>
<td>0.44</td>
</tr>
<tr>
<td>28th day mortality</td>
<td>7</td>
<td>2</td>
<td>0.08</td>
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### Subgroup of post-operative care of non-cardiac surgery

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<th>Liberal (64)</th>
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<tr>
<td>New/progressive MODS †</td>
<td>5 (8.3%)</td>
<td>6 (9.4%)</td>
<td>0.83</td>
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<tr>
<td>Highest PELOD score</td>
<td>7.4 ±9.6</td>
<td>7.6 ±8.8</td>
<td>NS</td>
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<td>PICU mortality</td>
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† Absolute risk reduction: 1.1% (95%CI: –8.9%, +11%).
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    - Trauma and neurological cases (unplanned TRIPICU subgroup analysis).
  - **Threshold Hb in unstable patients (guidelines):**
    - Acute blood loss (guidelines).
    - Other unstable patients (guidelines).
  - **Threshold Hb in the post-operative care of cardiac surgery:**
    - Uncyanotic cardiac cases (planned TRIPICU subgroup analysis).
    - Cyanotic cardiac cases (trial of Cholette et al. PCCM 2011;12:39-45).
RBC transfusion and new/progressive MODS (N/P MODS) in children with respiratory problem

<table>
<thead>
<tr>
<th>Condition</th>
<th>Restrictive strategy</th>
<th>Liberal strategy</th>
<th>Absolute risk reduction (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Total</td>
<td>320</td>
<td>317</td>
<td></td>
</tr>
<tr>
<td>N/P MODS</td>
<td>38</td>
<td>39</td>
<td>+0.4% (–4.6, 5.5)</td>
<td>NI</td>
</tr>
<tr>
<td>Respiratory dysfunction</td>
<td>Patients (n)</td>
<td>234</td>
<td>246</td>
<td></td>
</tr>
<tr>
<td>N/P MODS</td>
<td>33</td>
<td>35</td>
<td>+0.1%</td>
<td>NS</td>
</tr>
<tr>
<td>ALI</td>
<td>Patients (n)</td>
<td>38</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>N/P MODS</td>
<td>10</td>
<td>7</td>
<td>–6.3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Giving more RBC transfusions to stable critically ill children with respiratory problems enrolled in TRIPICU did not decrease the incidence of new/progressive MODS (N/P MODS).
Structure of this lecture

- Goal-directed red blood cell (RBC) transfusion therapy.
- Hemoglobin (Hb): threshold for RBC transfusion:
  - Threshold Hb in **stable** patients:
    - All patients enrolled in TRIPICU study.
    - Severity of illness (planned TRIPICU subgroup analysis).
    - Patients with sepsis (planned TRIPICU subgroup analysis).
    - Post-operative care of non-cardiac surgery (planned subgroup analysis).
    - Acute lung injury (unplanned TRIPICU subgroup analysis).
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    - Cyanotic cardiac cases (trial of Cholette et al. PCCM 2011;12:39-45).
Data from TRIPICU suggest that giving RBC transfusions to stable PICU children with neurological dysfunction and/or severe trauma do not improve their outcome if Hb is > 7 g/dL.
Structure of this lecture

- Goal-directed red blood cell (RBC) transfusion therapy.
- Hemoglobin (Hb): threshold for RBC transfusion:
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    - Uncyanotic cardiac cases (planned TRIPICU subgroup analysis).
    - Cyanotic cardiac cases (trial of Cholette et al. PCCM 2011;12:39-45).
Unstable patients with active blood loss

- Hemorrhagic shock: RBC transfusion is mandatory.
- Goal of RBC transfusion: blood loss replacement.
  - Volume of bleeding may be difficult to estimate in PICU.
    - Hb level is unreliable because it takes a few hours to fall.
    - Some bleedings are difficult to measure (chest drainage, chylous effusion, bleeding in the abdomen, etc).
  - Methods to estimate blood loss from bleeding are not well validated in PICU:
    - WHO bleeding score (Slichter et al, 2004)
    - GEMINA bleeding score (Zumberg et al, 2002), etc.
- What blood loss should prompt a RBC transfusion?
  - No consensus, unless the patient is in hemorrhagic shock.
Unstable critically ill children without blood loss

- Examples of unstable patients without hemorrhagic shock: other cause of uncontrolled shock, uncontrolled intracranial hypertension, ECMO, etc.

- Threshold Hb in unstable children without hemorrhagic shock: unknown.
  - Intensivists believe that a higher threshold may be required in unstable patients (Laverdière et al. Pediatr Crit Care Med).
  - However, no hard data support this point of view.

- Recommendation: use your clinical judgment.
Structure of this lecture

- Goal-directed red blood cell (RBC) transfusion therapy.
- Hemoglobin (Hb): threshold for RBC transfusion:
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    - Uncyanotic cardiac cases (planned TRIPICU subgroup analysis).
    - Cyanotic cardiac cases (trial of Cholette et al. PCCM 2011;12:39-45).
Survey on stated practice in post-op of pediatric cardiac surgery†

- Objective of the survey: to characterize the stated practice pattern of practitioners involved in ICU-care after a pediatric cardiac surgery, with respect to the transfusion of red blood cell (RBC) units.
- Population: Canadian intensivists, cardiac surgeons and cardiologists.
- Time: October to December 2009.
- Response rate: 63% (60/95).
- Number of filled questionnaires: 35.

Stated practice pattern: non-cyanotic heart disease

Hb below which MD would transfuse

<table>
<thead>
<tr>
<th>Hemoglobin (Hb) value (g/dL)</th>
<th>Number of MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>0</td>
</tr>
<tr>
<td>&lt;8</td>
<td>0</td>
</tr>
<tr>
<td>&lt;9</td>
<td>0</td>
</tr>
<tr>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
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</tr>
<tr>
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<td>0</td>
</tr>
</tbody>
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Arterial switch, 6 days
Atri-ventricular canal, 5 months

Stated practice pattern: non-cyanotic heart disease

Hb below which MD would transfuse

- Arterial switch, 6 days
- Atri-ventricular canal, 5 months

Hemoglobin (Hb) value (g/dL)

TRIPICU: threshold Hb in non-cyanotic cardiac cases*

<table>
<thead>
<tr>
<th>Threshold Hb (g/dL)</th>
<th>7.0</th>
<th>9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>New/progressive MODS (n)</td>
<td>8</td>
<td>4 †</td>
</tr>
<tr>
<td>Deaths (n)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Median blood lactate (mmol/L)</td>
<td>1.6 ± 1.0</td>
<td>1.5 ± 0.9</td>
</tr>
</tbody>
</table>

* Patients less than 28 days of age were excluded.  † P value: 0.36.
MODS: multiple organ dysfunction syndrome.

Thus, in TRIPICU, giving more RBC transfusions to cardiac non-cyanotic stable critically ill children do not improve their outcome if Hb is > 7 g/dL.
Stated practice pattern: cyanotic heart disease

Hb value below which MD would transfuse

- Glenn (Fallot) 6 days
- Glenn (hypoplastic left heart, 5 months)

Hemoglobin (Hb) value (g/dL)

- <7
- <8
- <9
- <10
- <11
- <12
- <13
- <14

Stated practice pattern: cyanotic heart disease

Hb value below which MD would transfuse

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<tr>
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<td>10</td>
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Glenn (Fallot) 6 days
Glenn (hypoplastic left heart, 5 months)

RCT: threshold Hb in pediatric cyanotic cardiac cases

<table>
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<tr>
<th>Threshold Hb (g/dL)</th>
<th>9.0</th>
<th>13.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n) *</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>New/progressive MODS (n)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Deaths (n)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Median blood lactate (mmol/L)</td>
<td>1.4 ± 0.05</td>
<td>1.4 ± 0.04</td>
</tr>
<tr>
<td>Peak blood lactate (mmol/L)</td>
<td>3.1 ± 1.5</td>
<td>3.2 ± 1.3</td>
</tr>
<tr>
<td>$O_2$ extraction (%)</td>
<td>31 ± 7</td>
<td>26 ± 6 †</td>
</tr>
</tbody>
</table>

These data suggest that giving more RBC transfusions to cardiac cyanotic critically ill children do not improve their outcome if their Hb is > 9 g/dL.

*33 cases of Glenn and 27 Fontan. †P value: 0.013.

Conclusion
## Conclusion: stable patients

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<tr>
<th>TRIPICU groups</th>
<th>Planned?</th>
<th>#</th>
<th>Absolute risk reduction</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td>Yes</td>
<td>637</td>
<td>0.4%</td>
<td>-4.6 to +5.5</td>
</tr>
<tr>
<td>PRISM score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (1st quartile)</td>
<td>Yes</td>
<td>128</td>
<td>+1.5% (-6.3 to +9.4)</td>
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</tr>
<tr>
<td>1-4 (2nd quartile)</td>
<td>Yes</td>
<td>239</td>
<td>-0.3% (-7.9 to +7.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>5-7 (3rd quartile)</td>
<td>Yes</td>
<td>121</td>
<td>-2.2% (-13.0 to +8.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>≥ 8 (4th quartile)</td>
<td>Yes</td>
<td>149</td>
<td>+1.5% (-6.3 to +9.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cases of sepsis</td>
<td>Yes</td>
<td>137</td>
<td>+0.3%</td>
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</tr>
<tr>
<td>Pediatric surgery</td>
<td>Yes</td>
<td>124</td>
<td>+1.0%</td>
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</tr>
<tr>
<td>Non-cyanotic cardiac surgery</td>
<td>Yes</td>
<td>125</td>
<td>+6.3%</td>
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<td>No</td>
<td>480</td>
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<td>ALI</td>
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<td>73</td>
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<td>ARDS</td>
<td>No</td>
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**Conclusion:** stable patients
### Conclusion: stable patients

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<td>Head trauma</td>
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Data from TRIPICU study show great consistency of results in all these planned and unplanned subgroup analyses.

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<td>Head trauma</td>
<td>No</td>
<td>30</td>
<td>+2.3%</td>
<td></td>
</tr>
<tr>
<td>Severe trauma</td>
<td>Yes</td>
<td>40</td>
<td>–5.8</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

- In spite of this consistency, prudent interpretation of these results is mandatory:
  - Subgroup analyses must be considered as hypothesis-generating only.
  - Multiple comparisons.
  - Small number of subjects in many comparisons.

- Notwithstanding this, the available data support the point of view that the main recommendation of the TRIPICU study (to consider RBC transfusions in stable critically ill children only if their Hb is < 7 g/dL) is applicable to all the following subgroups:
  - High severity of illness (this was measured with PRISM score in TRIPICU).
  - Respiratory dysfunction, ALI, ARDS.
  - All septic states, once stabilized.
  - Neurological dysfunction, severe head trauma.
  - Severe trauma and all pediatric surgeries, including cardiac surgery of noncyanotic patients who are older than 28 days of age.
Decision tree for red blood cell transfusion in PICU

**Critically ill cardiac children**

- **Hemorrhagic shock:** RBC transfusion must be given.
- **No hemorrhagic shock:**
  - **Post-operative care of a cardiac surgery**
    - **Stable**: if Hb > 70 g/L, no RBC; RBC can be useful in some cases if Hb < 70 g/L.
    - **Unstable**: clinical judgment.
  - **Stable†**: if Hb > 70 g/L, no RBC; RBC can be useful in some cases if Hb < 70 g/L.
    - **Unstable**: clinical judgment.

**Not a case of cardiac surgery**

- **Hemorrhagic shock:** RBC transfusion must be given.
- **Post-operative care of a cardiac surgery**
  - **Stable†, non-cyanotic**:
    - a) < 28 days of age: clinical judgment.
    - b) > 28: no RBC if Hb > 70 g/L?
  - **Post-operative, cyanotic**: 
    - a) < 28: clinical judgment.
    - b) > 28: no RBC if Hb > 90 g/L?
**Decision tree for red blood cell transfusion in PICU**

**Critically ill cardiac children**
- Hemorrhagic shock: RBC transfusion must be given.
- Not a case of cardiac surgery: if Hb > 70 g/L, no RBC; RBC can be useful in some cases if Hb < 70 g/L.
- Unstable: clinical judgment.*

**No hemorrhagic shock.**
- Post-operative care of a cardiac surgery:
  - Stable†: if Hb > 70 g/L, no RBC; RBC can be useful in some cases if Hb < 70 g/L.
  - Unstable: clinical judgment.*

**Hemorrhagic shock:**
- RBC transfusion must be given.

**Post-operative care of a cardiac surgery**
- Stable†, non-cyanotic:
  - a) < 28 days of age: clinical judgment.*
  - b) > 28: no RBC if Hb > 70 g/L?
- Unstable: clinical judgment.*

**Post-operative, cyanotic**: 
- Stable†, non-cyanotic:
  - a) < 28: clinical judgment.
  - b) > 28: no RBC if Hb > 90 g/L?
- Unstable: clinical judgment.*

* Hb level and other determinants may play a role, like acute blood loss, ScvO₂ (< 70%) and NIRS, but this remains to be determined.
Hemorrhagic shock: RBC transfusion must be given.

Critically ill cardiac children

Not a case of cardiac surgery

Stable $\dagger$: if Hb > 70 g/L, no RBC; RBC can be useful in some cases if Hb < 70 g/L.

Unstable: clinical judgment*.

Unstable: clinical judgment*.

Stable $\ddagger$, non-cyanotic:

a) < 28 days of age: clinical judgment*.
b) > 28: no RBC if Hb > 70 g/L?

Post-operative, cyanotic*:

a) < 28: clinical judgment.
b) > 28: no RBC if Hb > 90 g/L?

Post-operative care of a cardiac surgery

$\dagger$ Definition of stable derived from TRIPICU study (Lacroix et al, NEJM 2007): mean arterial pressure is not less than 2 SD below normal mean for age and cardiovascular support (vasopressors/inotropes and fluids) has not been increased in the last 2 hours.

* Hb level and other determinants may play a role, like acute blood loss, ScvO$_2$ (< 70%) and NIRS, but this remains to be determined.
Decision tree for red blood cell transfusion in PICU

**Critically ill cardiac children**

- Hemorrhagic shock: RBC transfusion must be given.
- No hemorrhagic shock.
- Not a case of cardiac surgery

**Post-operative care of a cardiac surgery**

- Stable*: if Hb > 70 g/L, no RBC; RBC can be useful in some cases if Hb < 70 g/L.
- Unstable: clinical judgment*.

**Unstable: clinical judgment***.

**Post-operative, cyanotic***:

- a) < 28 days of age: clinical judgment*.
- b) > 28: no RBC if Hb > 70 g/L?

**Stable†, non-cyanotic***:

- a) < 28 days of age: clinical judgment*.
- b) > 28: no RBC if Hb > 90 g/L?

*Hb level and other determinants may play a role, like acute blood loss, ScvO₂ (< 70%) and NIRS,, but this remains to be determined.
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