Transfusion for the sickest ICU patients: Are there unanswered questions?

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Professor of Critical Care
Edinburgh University
Conflict of Interest

• None
Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients.

BRITISH COMMITTEE FOR STANDARDS IN HAEMATOLOGY

Br J Haem. in press
Andrew Retter, Duncan Wyncoill, Rupert Pearse, Damien Carson, Stuart McKechnie, Simon Stanworth, Shubha Allard, Dafydd Thomas, Tim Walsh

<table>
<thead>
<tr>
<th>GRADE RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Determination of the quality of evidence</strong></td>
</tr>
<tr>
<td>A. Randomised control trial</td>
</tr>
<tr>
<td>B. A downgraded randomised control trial or high quality observational studies</td>
</tr>
<tr>
<td>C. Well-done observational studies</td>
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<tr>
<td>D. Case series or expert opinion</td>
</tr>
<tr>
<td><strong>Factors that may decrease the strength of evidence</strong></td>
</tr>
<tr>
<td>1. Poor quality of planning and implementation of available randomised control studies, increasing the risk of bias</td>
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<tr>
<td>2. Inconsistency of results</td>
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<td>3. Indirectness of evidence</td>
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<td>4. Imprecision of results</td>
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<tr>
<td>5. High likelihood of reporting bias</td>
</tr>
<tr>
<td><strong>Main factors that may increase the strength of the evidence</strong></td>
</tr>
<tr>
<td>1. Large magnitude of effect (direct evidence, relative risk &gt;2, with no plausible confounders)</td>
</tr>
<tr>
<td>2. Very large magnitude of effect with RR &gt;5 and no threats to validity</td>
</tr>
<tr>
<td>3. Dose respondent gradient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors determining strong vs. weak recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
</tr>
<tr>
<td>Relative importance of outcomes</td>
</tr>
<tr>
<td>Baseline risk of outcomes</td>
</tr>
<tr>
<td>Magnitude of relative risk</td>
</tr>
<tr>
<td>Precision of the estimates of effect</td>
</tr>
<tr>
<td>Cost</td>
</tr>
</tbody>
</table>
A transfusion threshold of 70 g/L or below, with a target Hb range of 70-90 g/L, should be the default for all critically ill patients, unless specific co-morbidities or acute illness-related factors modify clinical decision-making. **Grade 1B**

Transfusion triggers should not exceed 90 g/L *in most critically ill patients.*

**Grade 1B**

TRICC NEJM 1999

- Non-leucodepleted RBCs
- Storage age
- ICU practice >14 years ago
## Transfusion in Critical Care: Cohort studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Region</th>
<th>Participant Numbers</th>
<th>RBCT Prevalence</th>
<th>Hb level prompting transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rao et al., 2002)</td>
<td>UK</td>
<td>1500</td>
<td>53%</td>
<td>8.5g/dL</td>
</tr>
<tr>
<td>(Chohan et al., 2003)</td>
<td>UK</td>
<td>176</td>
<td>52%</td>
<td>-</td>
</tr>
<tr>
<td>(Walsh et al., 2004)</td>
<td>UK</td>
<td>1023</td>
<td>39.5%</td>
<td>7.8g/dL</td>
</tr>
<tr>
<td>(Vincent et al., 2002)</td>
<td>EU</td>
<td>3534</td>
<td>37%</td>
<td>8.4g/dL</td>
</tr>
<tr>
<td>(Sakr et al., 2010)</td>
<td>EU</td>
<td>5925</td>
<td>30.9%</td>
<td>8.2g/dL</td>
</tr>
<tr>
<td>(Corwin et al., 2004)</td>
<td>USA</td>
<td>4892</td>
<td>44%</td>
<td>8.6g/dL</td>
</tr>
<tr>
<td>(French et al., 2002)</td>
<td>AUS/NZ</td>
<td>1808</td>
<td>19.8%</td>
<td>8.2g/dL</td>
</tr>
<tr>
<td>(ANZICS CTG 2010)</td>
<td>AUS/NZ</td>
<td>5128</td>
<td>15%</td>
<td>7.7g/dL</td>
</tr>
<tr>
<td>(Cohen et al., 2010)</td>
<td>ISRAEL</td>
<td>238</td>
<td>50%</td>
<td>7.9g/dL</td>
</tr>
</tbody>
</table>
Variation in Transfusion practice in the UK
ISOC (2006-07) data (M Seretny unpublished)

29 General ICUs; 1900 sequential admissions

Mean Pre-transfusion Hb: 8.2g/dL (95%CI: 7.9 to 8.3).

Comparison across 29 participating centres  ANOVA  P =0.002
"weaning failure"

Scenario 1

Scenario 2

"weaning failure" stable ischaemic heart disease

Scenario 3

"weaning failure" with acute myocardial ischaemia

A clinical scenario-based survey of transfusion decisions for intensive care patients with delayed weaning from mechanical ventilation

Timothy S. Walsh and Caroline R. Maciver for the Scottish Critical Care Trials Group and Scottish National Blood Transfusion Service Clinical Effectiveness Group

ICU admission:
- Sepsis
- Elevated markers of cellular hypoxaemia
- Ischaemic heart disease

Worsening organ failure

Delayed weaning from mechanical ventilation

Post-extubation recovery
ICU admission:
- Sepsis
- Elevated markers of cellular hypoxaemia
- Ischaemic heart disease

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Post-extubation recovery

Admission

Discharge
Sepsis

In the early resuscitation of patients with severe sepsis, if there is clear evidence of inadequate DO$_2$, transfusion of RBCs to a target Hb of 90-100 g/L should be considered. **Grade 2C**

- Single centre RCT of complex intervention including transfusion
  “Rivers” NEJM 2001 345: 1368-1377

Await:
- ARISE (ANZICS); ProMISE (UK); PROCESS (USA)
- Transfusion Requirements in Septic Shock (TRISS; Scandinavian CCTG)

During the later stages of severe sepsis, a restrictive approach to transfusion should be followed with a target Hb of 70-90 g/L. **Grade 1B**

- TRICC NEJM 1999
Ischaemic Heart Disease

Patients suffering from *acute coronary syndromes* the Hb should be maintained at >80 g/L. **Grade 2C**

- Physiological rationale
- Cohort studies (conflicting results)
- Pilot RCT
  
  Am J Cardiol 2001 **108:**1108-1111

Anaemic critically ill patients with *stable angina* should have an Hb maintained >70 g/L, but transfusion to a Hb >100 g/L has uncertain benefit. **Grade 2B**

- Physiological rationale
- Sub-group analysis of TRICC trial
  
  Crit Care Med 2001 **29:** 227-234
- Trials in other patient groups (TRACS; FOCUS)
### Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al. NEJM 2001; 345:1230</td>
<td>Retrospective MI aged &gt;65</td>
<td>Anaemia associated with increased mortality. Transfusions associated with <strong>decreased</strong> risk</td>
</tr>
<tr>
<td>Rao et al. JAMA 2004; 292:1555</td>
<td>Retrospective Analysis of RCT data sets NSTEMI</td>
<td>Anaemia associated with increased mortality. Transfusions associated with <strong>increased</strong> mortality</td>
</tr>
<tr>
<td>Sabatine et al. Circulation 2005; 111:2042</td>
<td>Retrospective Analysis of RCT data sets STEMI and NSTEMI</td>
<td>Anaemia (&lt;14 g/dL) associated with increased mortality in STEMI. RBC transfusions <strong>decreased</strong> risk. Anaemia (&lt;11 g/dL) associated with increase in mortality for NSTEMI. RBC transfusions associated with <strong>increased</strong> risk</td>
</tr>
</tbody>
</table>

- Major clinical uncertainty
- PCA with widespread use of anti-platelet therapy increasing importance of issue
Is low transfusion threshold safe in critically ill patients with cardiovascular disease?
Hebert PC et al. Crit Care Med 2001; 29: 227

Subgroup of 357 patients with cardiovascular disease
30 day mortality
Difference 0.3% (-8.4% to 9.1%)

Subgroup of 257 patients with ischaemic heart disease
30 day mortality
Difference –4.9% (-15.3% to 5.6%)
• Similar rates of composite outcome (death, cardiogenic shock, dialysis, ARDS)
• Trend to higher death rates in liberal group
• Higher complication rates in liberal group
• Transfusion an independent risk factor for adverse outcomes in multivariable model
• Mean age 82 years; cardiovascular disease 63%
• Protocolised liberal versus “clinician judgement” restrictive
• No difference in death or physical ability
• No difference in cardiovascular complications
• No excess mortality among transfused patients (65% lower use of RBCs; 97% versus 41% transfusion exposure)
ICU admission:
- Sepsis
- Elevated markers of cellular hypoxaemia
- Ischaemic heart disease

Worsening organ failure

Delayed weaning from mechanical ventilation

Post-extubation recovery

Discharge
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Restrictive Transfusion Strategy (N=418)</th>
<th>Liberal Transfusion Strategy (N=420)</th>
<th>Absolute Difference Between Groups</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>78 (18.7)</td>
<td>98 (23.3)</td>
<td>4.7</td>
<td>−0.84 to 10.2</td>
<td>0.11</td>
</tr>
<tr>
<td>60-day†</td>
<td>95 (22.7)</td>
<td>111 (26.5)</td>
<td>3.7</td>
<td>−2.1 to 9.5</td>
<td>0.23</td>
</tr>
<tr>
<td>ICU</td>
<td>56 (13.4)</td>
<td>68 (16.2)</td>
<td>2.3</td>
<td>−2.0 to 7.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Hospital</td>
<td>93 (22.2)</td>
<td>118 (28.1)</td>
<td>5.8</td>
<td>−0.3 to 11.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Multiple-organ-dysfunction score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted score‡</td>
<td>8.3±4.6</td>
<td>8.8±4.4</td>
<td>0.5</td>
<td>0.1 to 1.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Adjusted score‡</td>
<td>10.7±7.5</td>
<td>11.8±7.7</td>
<td>1.1</td>
<td>0.8 to 2.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Change from base-line score§</td>
<td>3.2±7.0</td>
<td>4.2±7.4</td>
<td>1.0</td>
<td>0.1 to 2.0</td>
<td>0.04</td>
</tr>
<tr>
<td>No. of organs failing — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>100 (23.9)</td>
<td>82 (19.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>136 (32.5)</td>
<td>149 (35.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>109 (26.1)</td>
<td>108 (26.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>51 (12.2)</td>
<td>63 (15.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>22 (5.3)</td>
<td>18 (4.3)</td>
<td>1.8†</td>
<td>−3.4 to 7.1†</td>
<td>0.53†</td>
</tr>
<tr>
<td>Length of stay — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>11.0±10.7</td>
<td>11.5±11.3</td>
<td>0.5</td>
<td>−1.0 to 2.1</td>
<td>0.53</td>
</tr>
<tr>
<td>Hospital</td>
<td>34.8±19.5</td>
<td>35.5±19.4</td>
<td>0.7</td>
<td>−1.9 to 3.4</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Weaning failure

Recommendation:
Red cell transfusion should not be used as a strategy to assist weaning from mechanical ventilation when the Hb is >70 g/L. Grade 2D

- Sub-group analysis of TRICC trial
- Cohort studies
- Case reports
A feasibility randomized trial comparing restrictive and liberal blood transfusion strategies in patients requiring four or more days in intensive care

ISRCTN24842715; Clinicaltrials.gov NCT00944112
Inclusion Criteria

1. The patient remains in the ICU after 96 hours (4 days) or more following ICU admission
2. The patient has required mechanical ventilation via an endotracheal tube or tracheostomy tube for 96 hours or more
3. The patient is expected to require ≥24 hours of further mechanical ventilation at the time of assessment
4. The patient is aged >55 years of age
5. The patient has a Hb value of 90g/L or less at the time of assessment
Intervention

Restrictive Group:
• Single unit RBC transfusions with a transfusion trigger of ≤70 g/L
• Target Hb concentration of 71-90 g/L during the intervention period

Liberal Group:
• Single unit RBC transfusions with a transfusion trigger of ≤90 g/L
• Target of 91-110 g/L during intervention.
• All patients transfused within 24 hours of randomisation

Duration: 14 days or ICU discharge whichever longer
Total Admissions
N = 3394

Patients ≥55, ventilated >96 hours
N = 406

Failed to meet all inclusion criteria
N = 119

Not approached for consent
N = 40
No available relative (17)
No available research staff (2)
Clinician refusal (18)
Communication difficulties (3)

Eligible patients
N = 200

Exclusion criteria
N = 87
Bleeding (1)
Brain Injury (11)
Intracranial haemorrhage (25)
Survival expected <48 hours (18)
Transfusion objection (1)
Erythropoietin therapy (2)
Follow up not feasible (12)
Enrolled in another trial (17)

Approached for Consent
N = 160

Consent declined
N = 60

Randomised
N = 100

Restrictive group
N = 51

60 day follow up
Deaths 14
RMI complete 29
SF-12 complete 23

180 day follow up
Deaths 19
RMI complete 29
SF-12 complete 28
HE questionnaire 29

Liberal group
N = 49

60 day follow up
Deaths 22
RMI complete 26
SF-12 complete 23

180 day follow up
Deaths 27
RMI complete 21
SF-12 complete 21
HE questionnaire 20

6% of all ICU admissions eligible

Recruitment achieved
9% clinician refusal
63% consent rate from relatives/patients
50% of eligible patients entered trial

RELIEVE
## Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restrictive Transfusion Group (N = 51)</th>
<th>Liberal Transfusion Group (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male N (%)</td>
<td>36 (70.6)</td>
<td>24 (49.0)</td>
</tr>
<tr>
<td>Documented ischemic heart disease N (%)</td>
<td>17 (33.3)</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>APACHE II score Mean (SD)</td>
<td>20.2 (6.6)</td>
<td>21.5 (6.4)</td>
</tr>
<tr>
<td>Charlson comorbidity index Median (1\textsuperscript{st}, 3\textsuperscript{rd} quartile; range)</td>
<td>2 (1, 2; 0 – 9)</td>
<td>2 (1, 4; 0 – 9)</td>
</tr>
<tr>
<td>Proportion of patients with organ dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Coagulation</td>
<td>43.1</td>
<td>30.6</td>
</tr>
<tr>
<td>Hepatic</td>
<td>25.5</td>
<td>22.4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>76.5</td>
<td>59.2</td>
</tr>
<tr>
<td>Renal</td>
<td>56.9</td>
<td>57.1</td>
</tr>
</tbody>
</table>
Severity of anaemia (mean)
Liberal: Hb 95.7 (6.3) g/L  Restrictive: Hb 81.9 (5.1) g/L

Duration of intervention (median)
Liberal  16 days (15, 27; 1-61).
Restrictive  17 days (13, 32; 3-61)
Secondary outcomes

- **Mortality** (ICU; hospital; 30, 60, and 180 days after randomisation)
- **HRQoL** among survivors at 60 and 180 days after randomisation
- **Physical function** at 60 and 180 days after randomisation
- **ICU and hospital length** of stay following randomisation
- **Change in organ failures** occurring in the ICU post-randomisation
- **Ventilation free days** during 60 days after randomisation
- **Antibiotic-free days** during 60 days follow up
- **Incidence of adverse events:**
  - acute coronary syndromes
  - Thromboembolic (including stroke)
Difference in Mortality over 180 days follow up

Cohort mortality 46%

Unadjusted HR 0.60 (95% CI: 0.34 to 1.09; P = 0.093)
Adjusted HR 0.53 (95% CI: 0.28 to 1.03; P = 0.061)
(Gender; age; APACHE II; baseline SOFA; IHD)
Difference in physical function and quality of life among survivors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Restrictive Transfusion Group (N = 51)</th>
<th>Liberal Transfusion Group (N = 49)</th>
<th>Difference in medians (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivermead Mobility Index (0 to 15) 180 days</td>
<td>13 (7, 15; 0 – 15)</td>
<td>10 (5, 12; 0 – 15)</td>
<td>1.9 (-1.0 to 4.9)</td>
</tr>
<tr>
<td>SF-12 Physical Function Score (0 to 100) 180 days</td>
<td>30 (24, 40; 12 - 54)</td>
<td>31 (24, 39; 20 - 44)</td>
<td>-1.2 (-8.9 to 6.5)</td>
</tr>
<tr>
<td>SF-12 Mental Component Score (0 to 100) 180 days</td>
<td>51 (31, 57; 16 - 71)</td>
<td>39 (34, 48; 16 - 67)</td>
<td>12.1 (0.2 to 24.1)</td>
</tr>
</tbody>
</table>
### Pre-defined adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Restrictive Transfusion Group (N = 51)</th>
<th>Liberal Transfusion Group (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Coronary Syndrome N (%)</td>
<td>2 (3.9)</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Thrombotic events N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cerebral infarct</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other thrombotic event</td>
<td>5 (9.8)</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Any thrombotic event</td>
<td>6 (11.8)</td>
<td>3 (6.1)</td>
</tr>
</tbody>
</table>
ICU admission:
- Sepsis
- Elevated markers of cellular hypoxaemia
- Ischaemic heart disease

Worsening organ failure

Delayed weaning from mechanical ventilation

Post-extubation recovery
### Post-ICU anaemia: A consequence of evidence based transfusion practice

Walsh et al. Intensive Care Medicine 2006; 32: 1206

Prevalence of different degrees of anaemia at hospital discharge.

<table>
<thead>
<tr>
<th>Hb level</th>
<th>Males (n=161) N (%)</th>
<th>Females (n=122) N (%)</th>
<th>All patients (n=283) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &lt; 90 g/L</td>
<td>14 (8.7)</td>
<td>18 (14.8)</td>
<td>32 (11.3)</td>
</tr>
<tr>
<td>Hb &lt; 100g/L</td>
<td>48 (29.8)</td>
<td>44 (36.1)</td>
<td>92 (32.5)</td>
</tr>
<tr>
<td>Hb &lt; reference range.</td>
<td>137 (85.1)</td>
<td>82 (67.2)</td>
<td>219 (77.4)</td>
</tr>
</tbody>
</table>

85% normochromic normocytic

Bateman et al. CCM 2009; 37: 1906
- 32% Hb <11 g/dL at 3 months
- Associated with persisting inflammation and low QoL scores
Unanswered questions?

- Uncertainties about the product:
  - Leucodepletion; Storage age
- Variation in clinical practice
- Early sepsis
  - Answers coming?
- Comorbidities and illness severity
- Post-ICU recovery