Red Blood Cell Transfusion in the Intensive Care Unit

BY MARISA TUCCI, MD, LAURALYN McINTRYE, MD, MSC, DEAN FERGUSSON, PHD, ALAN TINMOUTH, MD, MSC, PAUL HEBERT, MD, MSC, AND JACQUES LACROIX, MD

With the high level of anemia in the intensive care unit (ICU), transfusion of red blood cells (RBCs) is a common practice in both adult and pediatric ICU patients. However, the risk-benefit ratio of such a procedure is less clear than once believed. This issue of Critical Care Rounds will discuss the physiological activity of RBCs, and address the concepts of goal-directed transfusion therapy and Hb concentrations that should trigger a RBC transfusion, as well as new concerns pertaining to RBC transfusion.

Red blood cells (RBCs) contain hemoglobin (Hb), which binds and carries oxygen to cells, thus allowing production of adenosine triphosphate (ATP) and cell survival. Because energy expenditure is high in intensive care unit (ICU) patients, it could appear useful to maintain high Hb levels in these individuals. Anemia is observed in up to 95% of adults¹,² and 74% of children³ during their ICU stay. RBC transfusion is the only effective way to rapidly increase the Hb level; at least one RBC transfusion is performed in 40% of adult ICU patients and 50% of children with ICU stay >2 days.¹¹

The risk-benefit ratio of RBC transfusion in critically ill patients is less obvious than it was a few decades ago. Bennett-Guerrero et al.¹ questioned the capacity of transfused RBC to deliver oxygen to peripheral cells. Moreover, new safety issues with respect to RBC transfusion have been raised. The most important concern in the 1980s was transfusion-transmitted infectious diseases (human immunodeficiency virus [HIV], hepatitis, etc.); preventive measures adopted in the 1990s decreased this risk substantially. However, it has been reported more recently that critically ill patients who received RBC transfusion contract more nosocomial infections and multiple organ dysfunction syndrome (MODS) than expected.⁶ In addition, transfusion-related immune modulation (TRIM),⁷ and transfusion reactions such as transfusion-related acute lung injury (TRALI) and transfusion-associated cardiac overload (TACO)⁸ have also become significant concerns. The risk:benefit and cost:benefit ratios of RBC transfusion in critically ill patients are not well characterized. New concepts and new knowledge must be taken into account when an intensivist is facing the decision to prescribe an RBC transfusion.

Physiological Functions of RBCs

Anemia is common in the ICU. There is evidence that profound anemia (Hb <50 g/L) is a risk factor for mortality in severely ill patients.⁹,¹¹ There is no doubt that an RBC transfusion increases systemic oxygen delivery (DO₂). Systemic DO₂ is calculated by multiplying the cardiac output (stroke volume x heart rate) by the arterial oxygen concentration (CaO₂). The latter is defined by the formula: CaO₂ (mL O₂/100 mL) = (Hb x SaO₂ x 1.39) + (0.0031 x PaO₂), in which the Hb level is expressed in g/dL (not g/L), arterial O₂ saturation (SaO₂) is expressed as a fraction rather than a percentage (0.93, not 93%), and PaO₂ is expressed in mm Hg or torr. Thus, increasing the Hb concentration should increase systemic DO₂ if nothing else changes (same cardiac output and SaO₂), but this does not necessarily imply that DO₂ in the microvasculature and oxygen delivered to cells (regional DO₂) increases, nor that cellular oxygen consumption increases. In fact, there are clinical data suggesting that this might not be
the case. Kiraly et al. have reported that tissue SO₂ (StO₂) declines from about 89% to 81% in critically ill patients who received a transfusion of RBC units stored more than 3 weeks, while this did not happen in controls. However, data on regional DO₂ are inconsistent, their clinical significance remains to be determined, and the mechanisms involved – which may include blood viscosity, microcirculatory flow and cellular respiration – are presently not well characterized.

RBC transfusion always increases blood viscosity, regardless of the pre-transfusion Hb concentration. A greater blood viscosity can lead to microcirculatory stasis and impaired DO₂ to tissues. However, no strong data indicate that blood viscosity is a clinically important problem unless the Hb is >200 g/L.

Activation of white blood cells (WBCs) in packed RBC units and cytokine generation in the supernatant of transfused RBC units may also have a microcirculatory effect: some cytokines can mediate vasoconstriction or thrombosis of small vessels and cause regional ischemia. However, all packed RBC units are now prestorage leukocyte-reduced in many countries, including Canada, which significantly decreases cytokine levels in the supernatant.

The clinical impact of cytokines in the supernatant of prestorage leukocyte-reduced packed RBC units remains to be determined.

There is evidence that RBC transfusion can cause vasoconstriction of small blood vessels via a mechanism involving an interaction between the Hb in RBCs and the nitric oxide (NO) released in the microvasculature. There is always some NO linked to Hb. With regional tissue hypoxia, intra-erythrocyte Hb in the microvasculature releases NO and triggers regional vasodilatation; conversely, if there is sufficient oxygen in the microvasculature, intra-erythrocyte Hb binds NO and causes vasoconstriction. There is disruption of this regulatory mechanism in stored RBCs, which occurs <3 hours after storage; reduced NO bioavailability results, which may cause vasoconstriction. Although the clinical significance of these observations is not yet clear, these findings nonetheless suggest that regional DO₂ can be disturbed by RBC transfusion.

Packed RBC units undergo several changes during storage, which are generally referred to as the “storage lesion.” The level of 2,3-diphosphoglycerate (2,3-DPG) in stored RBC units decreases over time and can induce a left shift in the oxy-Hb dissociation curve, which impedes oxygen release to tissues even if DO₂ is increased. In addition, RBC deformability decreases after 2–3 weeks of storage, which may alter their capacity to pass through the capillary bed. Furthermore, hemolysis in older packed RBC units releases substantial amounts of free Hb ranging from 5 mg/L in a 1-day-old RBC units to 2500 mg/L in a 25-day-old unit, free intravascular Hb can bind NO and therefore cause vasoconstriction.

Thus, while RBC transfusions certainly increase systemic DO₂, some available evidence suggests that they can impair microcirculatory flow and increase inflammation, and that they do not necessarily increase oxygen consumption by tissues.

Serious Hazards Associated With Transfusion

Serious infectious hazards

Transfusion-transmitted HIV and hepatitis were of primary concern during the 1980s. Over the past 30 years, several measures have been adopted (eg, better pathogen detection and reduction systems), and decreased the risk significantly. In 2006, the risk of contracting HIV was reported to be <1:4 million transfusions, and the risk for hepatitis C was 1:2.8 million. The incidence of bacterial contamination, which was also considered a significant health hazard, has decreased to 1:31189 platelet transfusions. However, new infectious disease agents are emerging as potential threats to transfusion safety, and a supplement of the journal Transfusion was recently dedicated to address this issue. Although a large number of pathogens were addressed, experts from the American Red Cross consider Babesia species, Dengue virus, and human variant of Creutzfeldt-Jakob disease (strong data support the possibility that vCJD can be transmitted by transfusion) to be the highest priorities to address. Epstein-Barr virus (EBV) is also a clinically significant threat in young children unexposed to the virus prior to transfusion.

Serious non-infectious hazards

Transfusion-related non-infectious adverse events can be severe, and more clinically significant in ICU patients than transfusion-transmitted infectious disease. Table 1 lists the non-infectious serious hazards of transfusion (NISHOTs) that occur within 6 hours after transfusion and their frequencies per transfusion of RBC, plasma, or platelets. Many other health problems can be categorized as NISHOTs, including TRIM, MODS, and transfusion-associated graft-versus-host disease (GVHD). Some of these NISHOTs deserve specific comment.

TRALI. Experts in hematology have defined TRALI as a new ALI that appears within 6 hours post-transfusion and for which no other risk factor can be found. While TRALI is a clinical syndrome with no pathognomonic laboratory test to permit diagnosis, the presence of human

<table>
<thead>
<tr>
<th>Table 1: Risk of Non-infectious Serious Hazards of Transfusion Within 6 Hours After Transfusion²⁴</th>
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<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Acute hemolytic reactions</td>
</tr>
<tr>
<td>ABO incompatibility</td>
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<tr>
<td>Anaphylaxis</td>
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</tbody>
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RBC = red blood cell; TRALI = transfusion-related acute lung injury; TACO = transfusion-associated cardiac overload.
leukocyte antigen and/or neutrophil antibodies in donor plasma is considered highly suggestive; however, the absence of such antibodies does not exclude the possibility of TRALI. The diagnostic criteria for TRALI, which were advocated by experts in 2004, exclude the possibility that TRALI can occur in a patient already afflicted by ALI or ARDS, a frequent occurrence in the ICU. Marik et al have suggested expanding the definition of TRALI in the ICU to ALI/ARDS observed within 72 hours after transfusion of a blood product and has reported that this “delayed TRALI syndrome” occurs in up to 25% of critically ill adults who receive a blood transfusion. Lefebvre et al have proposed the acronym TARD (transfusion-associated respiratory distress) to describe respiratory deterioration after RBC transfusion. Church et al also reported an association between transfusion of plasma and/or packed RBC units and ALI/ARDS. Bioactive substances present in packed RBC and plasma units can cause or add to the severity of cases of ALI/ARDS. Further investigation is required to better characterize the epidemiology, the mechanisms and the clinical impact of TRALI and TARD in the ICU.

TACO is an underreported complication in ICU patients. Rapid or massive transfusion, reduced cardiac reserve, chronic and severe anemia (Hb <50 g/L), and age (infants and elderly patients) are known risk factors. The main symptoms are respiratory distress, hypoxemia, tachycardia and hypertension. Slow transfusion (≤1 mL/kg/hour) in at-risk patients can prevent TACO.

Hypotension. Hypotensive reactions subsequent to transfusion are increasingly recognized, but their etiology remains uncertain. They are probably attributable to bradykinin generation. The risk of hypotensive reaction is increased if a blood product is exposed to negatively charged surfaces (eg, filters), and in patients receiving angiotensin-converting enzyme inhibitors or with diminished bradykinin metabolism. Hypotensive reactions are more frequently associated with platelets than with RBCs and plasma.

**Clinical Rationale for RBC Transfusion in the ICU**

Numerous reasons have been cited by intensivists, both adult and pediatric, to justify RBC transfusion. Intensivists working with critically ill adults have stated that their decision is based on type of disease (eg, trauma versus sepsis), severity of illness, preoperative status, hypoxemia, shock, lactic acidosis, coronary ischemia, and chronic anemia. Pediatric intensivists have stated in 2 surveys that their decision was based not only on justifications related to the disease involved (eg, trauma versus bronchiolitis) and severity of illness, but also on the presence of respiratory failure, low DO2, or oxygen consumption (VO2), cardiovascular insufficiency, or the use of certain technologies such as extracorporeal membrane oxygenation, hemodialysis, hemofiltration, plasmapheresis, or exchange transfusion. Nonetheless, when intensivists were asked at the bedside why they prescribe an RBC transfusion, the most frequent reason was reported to be a low Hb concentration. It therefore makes sense that the Hb concentration be the first parameter assessed when an RBC transfusion is considered.

**Threshold Hb levels in adults**

Surprisingly, despite millions of units transfused worldwide, there are very little data on what Hb concentration should be targeted in unstable critically ill adults. A randomized clinical trial (RCT) conducted by Rivers et al suggests that it is better during the first hours of treatment to maintain the hematocrit over 30% (about 100 g/L) in critically ill adults with sepsis, but RBC transfusion were given in this study only if other measures (eg, fluid bolus, vasoactive, and inotropic drugs) did not succeed to increase the central venous oxygen saturation (ScvO2) over 70%. Actually, the optimal best Hb concentration for unstable critically ill adults is unknown.

There are more data on what Hb concentration can be tolerated in euvoletic critically ill adults. Table 2 summarizes data extracted from the most important RCT in the field of RBC transfusion in critically ill adults: the Transfusion Requirements In Critical Care (TRICC) study which involved 838 adults, documented a nonsignificant decrease in 30-day mortality (17.8% in restrictive versus 23.3% in liberal group, P=0.11). This trial suggests that RBC transfusion is not required in euvoletic critically ill adults if their Hb concentration is >70 g/L. Subgroup analyses suggest that this holds true for adults with an Acute Physiology and Chronic Health Evaluation (APACHE) score above or below 20, as well as in patients with trauma.

A low preoperative Hb or a substantial operative blood loss is associated with an increased risk of postoperative mortality or serious morbidity. In a population who refused blood transfusion on religious grounds (Jehovah’s Witnesses), however, Carson et al demonstrated that the risk of postoperative mortality among subjects free of ischemic cardiac disease (ICD) increased significantly at presurgical Hb levels ≤40 g/L. A restrictive strategy with a threshold of 70 g/L is probably safe in the postoperative care of patients without ICD who are admitted to an ICU after elective surgery. Anemia is probably less well tolerated in patients with chronic disease. In an earlier study among Jehovah’s Witnesses, Carson et al reported that the odds ratio for postoperative mortality increased significantly in subjects with ICD whose presurgical Hb levels dropped below 90 g/L. In a retrospective study of 78,974 patients (age >65 years) hospitalized for an acute myocardial infarction (AMI), Wu et al determined that the mortality rate was lower in transfused patients who presented with a hematocrit level <33%, but it was higher in transfused patients with a hematocrit level >36%. In the TRICC study, a restrictive strategy seemed to be safe in the subgroup of patients with cardiovascular disease, although the data pertaining to patients with AMIs and unstable angina demonstrated benefit with a more liberal
transfusion threshold. An Hb concentration target of 70–100 g/L might be useful in patients with cardiac disease, but needs to be verified in clinical trials.

**Threshold Hb levels in children**

Many guidelines are published on RBC transfusion in critically ill children. Unfortunately, most recommendations are not evidence-based. Three large descriptive studies undertaken in anemic children requiring hospitalization have reported increased mortality with an Hb concentration <50 g/L, from these data has emanated the recommendation for transfusion below this Hb level in hospitalized children. The only available evidence to guide RBC transfusion therapy in critically ill children is the Transfusion Requirements In the Pediatric Intensive Care Unit (TRIPICU) study, which provides definitive evidence that RBC transfusion is not required in most stable critically ill children if their Hb concentration is above 70 g/L. Two subgroup analyses were subsequently undertaken and suggest that this seems to hold true in stable children with sepsis and in the postoperative care further to noncardiac surgery. The same threshold seems safe in stable severely burned children. However, determinants other than the Hb concentration must be considered, including age, severity of illness or evidence of organ dysfunction or oxygen dependence, such as high blood lactate level or low ScvO2. It would seem appropriate to consider a higher transfusion threshold and a more aggressive transfusion strategy in unstable patients, but the optimal and safe lower limit of the transfusion threshold has not been established for such patients. Moreover, any recommendations made must also consider certain specificities for disorders such as sickle cell disease, hemolytic uremic syndrome, and certain congenital heart malformations.

It is possible that children with uncorrected cyanotic heart disease require a higher Hb level; indeed, some experts advocate transfusion thresholds as high as 140–180 g/L in some cases. Experience with transfusion-free cardiac surgery for congenital heart disease in children whose families refuse transfusion for religious reasons seems to suggest that a lower Hb level may be well tolerated.

In this trial, patients were randomized to transfusion strategies that were restrictive (threshold Hb: 90 g/L) or liberal (threshold Hb: 120 g/L). No difference was found with respect to outcomes such as peak blood lactate level (3.0±1.5 mmol/L versus 3.1±1.3 mmol/L), duration of mechanical ventilation, duration of vasopressor therapy, ICU or hospital length of stay (LOS), or survival. More data are required before implementing a restrictive transfusion strategy in patients with cyanotic heart disease, but the available evidence suggests that threshold lower than that which is currently being recommended might be well tolerated.

On the other hand, an Hb threshold of 70 g/L may be safe in the postoperative care of stabilized children older than 28 days with non-cyanotic congenital heart disease. Willems et al analyzed a subgroup of 125 postoperative cardiac patients enrolled in TRIPICU after cardiac surgery. No significant difference was found between the restrictive and liberal groups in the incidence rate of new or progressive MODS (12.7% versus 6.5%; P=0.36), 28-day mortality (2 deaths in each group) or PICU LOS (7.0±5.0 versus 7.4±6.4 days). The British Society of Haematology and the Society of Thoracic Surgeons

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**Table 2: Outcomes in the TRICC and TRIPICU trials and in some subgroups**

<table>
<thead>
<tr>
<th>Original randomized clinical trials and subgroup analyses</th>
<th>MODS (n)*</th>
<th>30-day mortality (n)b</th>
<th>ICU mortality (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>P</td>
</tr>
<tr>
<td>TRICC12 (N=838)</td>
<td>182</td>
<td>189</td>
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</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>APACHE II ≥2018</td>
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<td>NA</td>
<td>0.36</td>
</tr>
<tr>
<td>Cardiac cases</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Trauma19</td>
<td>9</td>
<td>9</td>
<td>0.81</td>
</tr>
<tr>
<td>TRIPICU8 (N=637)</td>
<td>38</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>8</td>
<td>4</td>
<td>0.36</td>
</tr>
<tr>
<td>Other surgery</td>
<td>5</td>
<td>6</td>
<td>0.83</td>
</tr>
<tr>
<td>Sepsis8,9</td>
<td>13</td>
<td>13</td>
<td>0.97</td>
</tr>
</tbody>
</table>

TRICC = Transfusion Requirements In Critical Care; TRIPICU = Transfusion Requirements In the Pediatric Intensive Care Unit; MODS = multiple organ dysfunction syndrome; R = restrictive transfusion strategy (threshold Hb: 70 g/L in TRICC and TRIPICU); L = liberal transfusion strategy (threshold Hb: 100 g/L in TRICC, 95 g/L in TRIPICU); APACHE = Acute Physiology and Chronic Health Evaluation; NA = not available; NS = not significant

* Frequency in TRICC of MODS (≥2 organ dysfunctions), in TRIPICU of new/progressive MODS, which included ICU mortality. b 30-day mortality in TRICC, 28-day mortality in TRIPICU. Number of patients with APACHE II score ≥20: 207 R and 217 L; number of cardiac cases: 151 R and 175 L; number of trauma cases: 100 R and 100 L. All types of sepsis, including severe sepsis and septic shock.
support the acceptance of a postoperative Hb threshold of 70 g/L in children when there is good postoperative cardiac function unless there is a persistent cyanotic heart lesion.

Other Concerns

Length of storage of RBC units

In 1916, Rous and Turner\(^{58}\) discovered that blood could be stored, thus allowing better management of this resource. The first biological standards used to assess the adequacy of stored RBC units was low hemolysis and good survival of transfused RBCs. Presently, regulatory agencies and scientific societies like the Food and Drug Administration and the American Association of Blood Banks allow packed RBC units to be stored up to 42 days based upon the fact that at least 75% of transfused RBCs are alive 24 hours post-transfusion and hemolysis is <1%.\(^{59}\) This recommendation is not based on the functional assessment of other RBC parameters, nor does it consider the clinical impact of RBCs. It is now well recognized that “storage lesion” occurs over time in RBC units, which raises a number of concerns\(^{39}\) because changes are associated with potentially harmful RBC ATP depletion, accumulation of many immunomodulatory bio substances and disturbed RBC metabolism.

Timmouth et al\(^{60}\) described many of the known elements that define the storage lesions. Abnormalities are present both in the supernatant and within the RBCs themselves. Increasing amounts of various inflammatory mediators are generated in the supernatant over time, particularly in nonleukocyte-depleted units; these include cytokines, non Hb-bound iron and microparticles containing lipids that are shed by RBCs. TRIM may result,\(^{7}\) leading to multiple organ dysfunction syndrome and increasing the risk of nosocomial infections and death in critically ill patients. RBC dysfunction may disturb regulation of the microcirculation via disruption of NO homeostasis and its linkage or release from Hb.\(^{4}\) The latter problem can block regional oxygen delivery to cells, which may explain the effect of RBC transfusion reported by Kiraly et al\(^{14}\) on StO\(_2\) in critically ill trauma adults. A significant decline in StO\(_2\) was observed in 17 patients who received RBC units stored for more than 21 days in the post-transfusion period compared to baseline; this was not observed in 15 patients who received fresher blood, nor in 16 patients who were not transfused. Other well-documented time-dependent changes are described, including a progressive fall of 2,3-DPG content in stored RBC, and release in the supernatant of potassium, free Hb\(^{60}\) and free iron from lysed RBCs.\(^{40}\)

While laboratory data on the storage lesion in RBC units are compelling, it is less obvious to ascertain whether these lesions have a significant clinical impact. More than 20 observational studies have been published on the association between RBC unit length of storage and outcome in transfusion recipients. Positive associations between older RBC units and mortality, nosocomial infections and length of ICU stay were shown by some authors, while others did not find such associations.\(^{61-66}\) Edgren et al\(^{67}\) used the Scandinavian Donations and Transfusions (SCANDAT) database to study the effect of duration of RBC storage on survival of 404 959 transfused patients. The 7-day risk of death was similar in all exposure groups, but a tendency for a higher mortality risk emerged among recipients of blood stored for 30–42 days (hazard ratio [HR] 1.05; 95% confidence interval [CI] 0.97-1.12), compared to recipients of blood stored for 10–19 days. With a 2-year follow-up, this excess remained at the same level (HR 1.05; 95% CI 1.02-1.08). The authors concluded that “the risk pattern was more consistent with weak confounding than with an effect of the momentary exposure to stored RBCs.”

Few data are available in the PICU population on this issue. Two studies undertaken in critically ill children recruited prospectively suggest that outcome is less favourable with transfusion of packed RBC units stored for more than 2–3 weeks.\(^{65,66}\)

In all of the identified observational studies, “independent” associations are frequently reported, but such studies cannot prove a cause-effect relationship between older blood and worse outcome. Other “independent” associations were also frequently observed: patients who receive more RBC units stored for prolonged periods also receive more RBC transfusions and their severity of illness is greater. The observational studies suffer from 2 major flaws: confounding by indication and proper definition of exposure. Confounding by indication refers to the simple fact that patients with higher acuity receive more transfusions.\(^{62}\) The second flaw, proper definition of exposure, is related to defining old and fresh RBCs. As the majority of patients receive more than one transfusion, it is very difficult to identify the age of blood a particular patient has received. Some studies use average age while others use media or oldest unit received. Unfortunately all methods to define exposure are flawed. No amount of elaborate analysis can disentangle these serious flaws. Thus, it is presently unknown if the storage lesion translates to clinically significant morbidity and mortality.

There is some uncertainty regarding the safety of RBC units stored for short periods of time (ie, less than a few days): the risk of contracting infections caused by certain intracellular viruses such as cytomegalovirus and herpes\(^{68}\) and the risk of transfusion-associated GVHD\(^{69}\) may increase with “fresh” blood. A retrospective study conducted in 200 children <1 year of age undergoing cardiac surgery suggests that circuit priming with fresh whole blood (storage <48 hours) may be more detrimental than with reconstituted fresh whole blood.\(^{70}\) An RCT that enrolled 64 patients reported that the outcome of neonates undergoing cardiopulmonary bypass for cardiac surgery is better with reconstituted fresh whole blood compared to stored component blood therapy.\(^{71}\) The safety and clinical usefulness of “fresh” blood remain to be determined.

Prescribing “fresh” RBC units is not without societal and ethical consequences. RBC units are a limited resource.
If “fresh” blood is reserved for certain patients, this implies that other patients will receive older blood. If the upper limit of length of storage is decreased from 42 to 21 days, it is estimated that the wastage of RBC units will grow from 1% to 30%, resulting in a severe problem. There is presently no clear evidence supporting administering “fresh” blood to certain specific populations. Therefore, implementing a fresh RBC transfusion policy could be considered unethical given the lack of evidence and the impact of aging the residual and available blood supply. Clearly, obtaining reliable data on this question should be a priority. To this end, several RCTs are ongoing:

• The Age of BLOOD Evaluation (ABLE) study (ISRCTN44878718) has been enrolling 2510 critically ill adults since 2009.

• The Age of Red blood cells In Premature Infants (ARIPD) study (NCT00326924), which is recruiting 370 premature newborns allocated to receive either RBCs stored ≤7 days or transfusion therapy according to standard practice, is almost completed.22

• The Red Cell Storage Duration and Outcomes in Cardiac Surgery study (NCT00458783) is a single-center RCT comparing outcomes in 2800 patients who will be allocated to receive RBCs stored for <14 days or ≥20 days.

• The Red Cell Storage duration Study (RECESS; NCT00991341) will randomize 1434 cardiac surgery adults to receive either RBC units stored ≤10 days or ≥21 days.71

• The ABC-PICU study, with a targeted recruitment of more than 1500 critically ill children, is under preparation.

Until hard evidence is available, the use of “fresh” rather than “old” blood cannot be recommended for ICU patients.74

**Prestorage leukocyte reduction of RBC units**

Prestorage leukocyte reduction decreases the number of WBCs in packed RBC units from 1x10^6 per product; it also decreases the concentration of cytokines in the supernatant and induces some T cell-regulated immunomodulation. Henkelman et al recently reported that the rheologic properties of leukoreduced RBC units are well preserved during 7 weeks of routine blood bank storage.

A few studies have reported clinical benefit that can be attributed to prestorage leukoreduction. A before-and-after study in adult critical care reported a reduction in the incidence rate of mortality and febrile reaction after universal leukoreduction was adopted in Canada, while a retrospective before-and-after study in neonatal critical care showed that implementation of a universal leukoreduction policy in Canada was associated with a decreased risk of bronchopulmonary dysplasia and retinopathy of prematurity. In addition, 2 meta-analyses of clinical trials have suggested that the transfusion of leukoreduced RBC units may decrease postoperative infections. Unfortunately, many of the trials incorporated a premature point of randomization (eg, before surgery), which dilutes the ability of finding true effects, as many patients in both trial arms never received transfusions. On the other hand, a large pseudo-randomized clinical trial involving 2780 hospitalized adults – not only ICU patients – found no difference in the incidence of in-hospital mortality, hospital LOS after transfusion, total hospital costs, intensive-care LOS, postoperative LOS, antibiotic use, and readmission rate with prestorage leukoreduction.22 Thus, there is still debate regarding the effectiveness of universal pre-storage leukocyte reduction.83 It is now a standard procedure in many countries, including Canada, France, and the United Kingdom, to undertake prestorage leukoreduction. However, 88% of packed RBC units given in American PICUs were leukocyte-reduced at collection in 2005.3

**Conclusion**

Without question, RBC transfusions in the ICU can be life-saving, but it is not without hazards. The risk of death attributable to transfusion of a labile blood product is low: only 1 death over 2 845 459 blood component units was reported in the United Kingdom in 2008.84 However, transfusion-related serious hazards are not rare. In ICU patients, most are related to immune-mediated effects of blood products rather than to transfusion-transmitted infectious diseases.

A transfusion is a serious matter and it should be prescribed only when deemed necessary. All measures to prevent transfusion must be adopted, and the concept of “transfusion-free” or “bloodless” medicine must be considered when applicable.85 The decision to prescribe the transfusion of RBCs must be based on individualized indications and evidence-based practice, and must take into account specific health problems, such as cardiac disease. Common sense suggests administering RBC transfusions to critically ill patients with acute severe anemia (Hb concentration <50 g/L). On the other hand, there is no evidence that RBC transfusion is beneficial in euolemic and stable critically ill patients if their Hb concentration is >70 g/L. The optimal transfusion threshold for unstable critically ill patients is unknown, but is likely higher than 70 g/L. For patients with cardiac disease further evidence is required, but a trigger between 80–100 g/L seems reasonable.

**References**


