EDITORIAL

Age of Red Blood Cells for Transfusion in Critically Ill Pediatric Patients

Zoe K. McQuilten, MBBS, PhD; D. James Cooper, BMBS, MD

The use of modern additive solutions has allowed blood services to store red blood cells for transfusion for extended periods, commonly up to 42 days. To minimize red blood cell wastage, it is common practice for hospital blood services to issue the oldest compatible red cell unit available for transfusion as part of routine inventory management. During storage, red blood cells and their storage medium undergo numerous structural, biochemical, and metabolic changes, collectively referred to as the *storage lesion*. These are mostly evident after the second week of storage. Understanding of how red blood cells change during storage continues to evolve.[1,2]

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Observations of an association between transfusion of older red blood cells with greater morbidity and mortality in various patient populations, coupled with results of preclinical studies in animals and healthy volunteers, raised concerns about the implications of the red blood cell storage lesion on patient outcomes.[3-6] In response, some blood services internationally decreased red blood cell storage duration, for example from 42 to 35 days, and some clinicians and health services preferentially supplied fresher red blood cells for selected patient groups, including children.[7] However, the observational studies that suggested older red blood cells may have been associated with harm are inherently confounded by the number of units transfused because patients with more severe illness are more likely to receive greater numbers of red blood cells and therefore receive more red blood cells at the extremes of storage age.[8] Furthermore, some observational studies included transfusion of red blood cells that had not undergone leukocyte depletion, which may alter the changes that occur during storage.[3]

To address concerns about potential harm from transfusion of older red cells, large multicenter randomized trials involving adults have been conducted in patients undergoing cardiac surgery,[9] in critically ill adults,[10,11] and in diverse groups of other hospitalized patients.[12] In contrast to observational studies, all 4 of these randomized trials reported no differences in mortality or organ dysfunction between patients who received fresher compared with older red blood cells or standard care. Indeed, point estimates for mortality in 3 large adult trials unexpectedly favored older (standard care) red cells.[10-12]

Differences in physiology, underlying diagnoses, and transfusion practices in critically ill children compared with adults mean that findings from these randomized trials involving adult patients may not be generalizable to pediatric populations. For example, the practice of splitting single-donor units into multiple pediatric packs for transfusion for an individual patient to minimize donor exposure may result in some pediatric patients receiving relatively older red cells. Despite these differences, the effect of storage duration on patient outcomes has been studied mostly in preterm infants[13] and severely anemic children with malaria or sickle cell disease.[14] Until now, there have been no large trials evaluating age of transfused red blood cells on outcomes in critically ill pediatric patients.

In this issue of *JAMA*, Spinella and colleagues[15] report the results of the Age of Blood in Children in Pediatric Intensive Care Unit (ABC-PICU) trial, which randomized 1538 critically ill children (aged 3 days to 16 years; median age, 1.8 years) in 5 countries requiring a transfusion to receive either fresh (stored ≤7 days) or standard-care red blood cells, which involved issuing the oldest compatible unit available in the blood service on the day. The primary end point was a composite of new or progressive multiple organ dysfunction, plus death (called "organ dysfunction") up to 28 days, or until death or discharge. The investigators achieved treatment separation between the groups, with the median age of transfused red blood cells being 5 days in the fresh group compared with 18 days in the standard-issue group.

The authors hypothesized that if a red blood cell storage lesion were clinically relevant, children who received fresher red blood cells would have less organ dysfunction than those who received older standard-issue red blood cells. Concordant with the large trials involving critically ill adults, the ABC-PICU trial found no significant difference in the primary outcome of organ dysfunction (20.2% in fresh red cell group vs 18.2% in standard-care group), with the point estimate favoring standard care.

There are some caveats to the conclusions, including that the trial was powered to detect a 33% relative risk reduction in organ dysfunction, which leaves the possibility in this study with negative results that a real but smaller difference in organ dysfunction may have been missed. Moreover, the illness severity of this cohort of pediatric patients requiring transfusion was relatively low (median PRISM III score 5 in both groups), which may have limited the ability of the study to detect an effect. However, in a subgroup analysis, the authors found no difference in organ dysfunction between fresher and standard-care red blood cells in the quartile with the highest PRISM III score (11-40), again with the point estimate favoring standard-issue red blood cells. There was also no difference in the subgroup that received the highest volume of red blood cell transfusion, with the point estimate favoring standard-issue red blood cells. Although previous randomized trials involving adults have not found any mortality difference between fresher and standard units, there was a signal for higher infection risk with fresher red blood cells in one large trial (higher risk of bacteremia)[11] and also in meta-analyses of 6 trials.[16] Among children in the ABC-PICU trial, no between-group difference was observed in the rate of nosocomial infections.

Recent commentary has highlighted limitations in the design of the large trials that have investigated the effect of the storage lesion on patient outcomes conducted to date, and some of these limitations also apply to ABC-PICU.[16] These include use of standard-issue red blood cells, which makes it impossible to standardize red blood cell storage duration in a comparator group; overlap in age of red blood cells between treatment groups; heterogeneity in case mix; and multiple transfusions of different storage ages given to patients.[17] Given that transfusion is a common intervention used in many clinical settings, even a small effect on mortality or morbidity from the storage lesion has the potential to affect many patients worldwide. Therefore, relatively large trials are needed to detect small effects, which would not be practically possible to complete if red blood cell age duration was more strictly specified in future treatment groups. Importantly, the ABC-PICU trial, as with other clinical trials conducted to date, does not address the question of whether red blood cells at the extremes of storage age cause harm in critically ill pediatric patients.

The ABC-PICU investigators have addressed an important question about the clinical implications of red blood cell storage duration on outcomes in pediatric patients. They achieved this through a collaboration between 4 trial groups and networks across 5 countries, which enabled the trial to successfully enroll 1538 critically ill patients. There is unlikely ever to be a larger randomized trial involving pediatric patients comparing transfusion of red blood cells of varying storage duration. Prior to this trial, the most recent meta-analyses of randomized trials that examined the association between age of blood and patient outcomes included just 833 pediatric patients across 5 trials, resulting in considerable uncertainty about the effect of red blood cell age on outcomes (relative risk for mortality, 0.99; 95% CI, 0.69-1.42).[16] Therefore, the ABC-PICU trial provides important data to support the safety of current international transfusion practice in regard to allocation of red blood cells for transfusion in critically ill children. This trial also demonstrates the feasibility of large internationally collaborative randomized trials to address evidence gaps in transfusion medicine involving pediatric patients.

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REFERENCES

1. D'Alessandro A, Reisz JA, Zhang Y, et al. Effects of aged stored autologous red blood cells on human plasma metabolome. *Blood Adv*. 2019;3(6):884-896. doi:10.1182/bloodadvances.2018029629

2. D'Alessandro A, Kriebardis AG, Rinalducci S, et al. An update on red blood cell storage lesions, as gleaned through biochemistry and omics technologies. *Transfusion*. 2015;55(1):205-219. doi:10.1111/trf.12804

3. Wang D, Sun J, Solomon SB, Klein HG, Natanson C. Transfusion of older stored blood and risk of death: a meta-analysis. *Transfusion*. 2012;52(6):1184-1195. doi:10.1111/j.1537-2995.2011.03466.x

4. Solomon SB, Wang D, Sun J, et al. Mortality increases after massive exchange transfusion with older stored blood in canines with experimental pneumonia. *Blood*. 2013;121(9):1663-1672. doi:10.1182/blood-2012-10-462945

5. Hod EA, Zhang N, Sokol SA, et al. Transfusion of red blood cells after prolonged storage produces harmful effects that are mediated by iron and inflammation. *Blood*. 2010;115(21):4284-4292. doi:10.1182/blood-2009-10-245001

6. Hod EA, Brittenham GM, Billote GB, et al. Transfusion of human volunteers with older, stored red blood cells produces extravascular hemolysis and circulating non-transferrin-bound iron. *Blood*. 2011;118(25):6675-6682. doi:10.1182/blood-2011-08-371849

7. Spinella PC, Dressler A, Tucci M, et al; Pediatric Acute Lung Injury and Sepsis Investigators Network. Survey of transfusion policies at US and Canadian children's hospitals in 2008 and 2009. *Transfusion*. 2010;50(11):2328-2335. doi:10.1111/j.1537-2995.2010.02708.x

8. van de Watering L. Red cell storage and prognosis. *Vox Sang*. 2011;100(1):36-45. doi:10.1111/j.1423-0410.2010.01441.x

9. Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med*. 2015;372(15):1419-1429. doi:10.1056/NEJMoa1414219

10. Lacroix J, Hébert PC, Fergusson DA, et al; ABLE Investigators; Canadian Critical Care Trials Group. Age of transfused blood in critically ill adults. *N Engl J Med*. 2015;372(15):1410-1418. doi:10.1056/NEJMoa1500704

11. Cooper DJ, McQuilten ZK, Nichol A, et al; TRANSFUSE Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Age of red cells for transfusion and outcomes in critically ill adults. *N Engl J Med*. 2017;377(19):1858-1867. doi:10.1056/NEJMoa1707572

12. Heddle NM, Cook RJ, Arnold DM, et al. Effect of short-term vs long-term blood storage on mortality after transfusion. *N Engl J Med*. 2016;375(20):1937-1945. doi:10.1056/NEJMoa1609014

13. Fergusson DA, Hébert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA*. 2012;308(14):1443-1451. doi:10.1001/2012.jama.11953

14. Dhabangi A, Ainomugisha B, Cserti-Gazdewich C, et al. Effect of transfusion of red blood cells with longer vs shorter storage duration on elevated blood lactate levels in children with severe anemia: the TOTAL randomized clinical trial. *JAMA*. 2015;314(23):2514-2523. doi:10.1001/jama.2015.13977

15. Spinella PC, Tucci M, Fergusson DA, et al; ABC-PICU Investigators, the Canadian Critical Care Trials Group, the Pediatric Acute Lung Injury and Sepsis Investigators Network, the BloodNet Pediatric Critical Care Blood Research Network, and the Groupe Francophone de Réanimation et Urgences Pédiatriques. Effect of fresh vs standard-issue red blood cell transfusions on multiple organ dysfunction syndrome in critically ill pediatric patients: a randomized clinical trial. [published December 10, 2019]. *JAMA*. doi:10.1001/jama.2019.17478

16. McQuilten ZK, French CJ, Nichol A, Higgins A, Cooper DJ. Effect of age of red cells for transfusion on patient outcomes: a systematic review and meta-analysis. *Transfus Med Rev*. 2018;32(2):77-88. doi:10.1016/j.tmrv.2018.02.002

17. Trivella M, Stanworth SJ, Brunskill S, Dutton P, Altman DG. Can we be certain that storage duration of transfused red blood cells does not affect patient outcomes? *BMJ*. 2019;365:l2320. doi:10.1136/bmj.l2320

JAMA | Original Investigation

Effect of Fresh vs Standard-issue Red Blood Cell Transfusions on Multiple Organ Dysfunction Syndrome in Critically Ill Pediatric Patients
A Randomized Clinical Trial

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IMPORTANCE The clinical consequences of red blood cell storage age for critically ill pediatric patients have not been examined in a large, randomized clinical trial.

OBJECTIVE To determine if the transfusion of fresh red blood cells (stored ≤7 days) reduced new or progressive multiple organ dysfunction syndrome compared with the use of standard-issue red blood cells in critically ill children.

DESIGN, SETTING, AND PARTICIPANTS The Age of Transfused Blood in Critically-Ill Children trial was an international, multicenter, blinded, randomized clinical trial, performed between February 2014 and November 2018 in 50 tertiary care centers. Pediatric patients between the ages of 3 days and 16 years were eligible if the first red blood cell transfusion was administered within 7 days of intensive care unit admission. A total of 15 568 patients were screened, and 13 308 were excluded.

INTERVENTIONS Patients were randomized to receive either fresh or standard-issue red blood cells. A total of 1538 patients were randomized with 768 patients in the fresh red blood cell group and 770 in the standard-issue group.

MAIN OUTCOMES AND MEASURES The primary outcome measure was new or progressive multiple organ dysfunction syndrome, measured for 28 days or to discharge or death.

RESULTS Among 1538 patients who were randomized, 1461 patients (95%) were included in the primary analysis (median age, 1.8 years; 47.3% girls), in which there were 728 patients randomized to the fresh red blood cell group and 733 to the standard-issue group. The median storage duration was 5 days (interquartile range [IQR], 4-6 days) in the fresh group vs 18 days (IQR, 12-25 days) in the standard-issue group ($P < .001$). There were no significant differences in new or progressive multiple organ dysfunction syndrome between fresh (147 of 728 [20.2%]) and standard-issue red blood cell groups (133 of 732 [18.2%]), with an unadjusted absolute risk difference of 2.0% (95% CI, –2.0% to 6.1%; $P = .33$). The prevalence of sepsis was 25.8% (160 of 619) in the fresh group and 25.3% (154 of 608) in the standard-issue group. The prevalence of acute respiratory distress syndrome was 6.6% (41 of 619) in the fresh group and 4.8% (29 of 608) in the standard-issue group. Intensive care unit mortality was 4.5% (33 of 728) in the fresh group vs 3.5 % (26 of 732) in the standard-issue group ($P = .34$).

CONCLUSIONS AND RELEVANCE Among critically ill pediatric patients, the use of fresh red blood cells did not reduce the incidence of new or progressive multiple organ dysfunction syndrome (including mortality) compared with standard-issue red blood cells.

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Visual Abstract

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Supplemental content

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Transfusion is frequent in critically ill children, as reported in a 2009-2010 single-center study in which 10% to 20% of critically ill children received a red blood cell transfusion.[1] Red blood cell transfusion is associated with higher mortality, as reported in a cohort of children admitted to intensive care between 2009 and 2012 and who received a red blood cell transfusion, the reported 30-day mortality rate was 8%.[2] Transfusions in critically ill patients are primarily used to improve oxygen delivery and to prevent shock, organ failure, and death. Red blood cell units can be stored for up to 42 days. In vitro and ex vivo studies suggest that increased storage duration may impair red blood cell oxygen delivery as well as adversely affect immune, endothelial, and hemostatic function.[3] Through one or several of these mechanisms, transfusion of older red blood cells may increase the risk of organ failure or death in critically ill patients. Observational studies and exploratory analyses of randomized clinical trials also suggest that for patients who receive larger volumes of older red blood cells, there is an association with poor outcomes.[4-7]

Randomized clinical trials examining the effect of red blood cell storage age have been performed in critically ill premature neonates,[8] severely anemic children with malaria and thalassemia,[9] and hospitalized and critically ill adults.[10-13] None of these trials have demonstrated that fresh red blood cells improve clinical outcomes. However, these trials may not be generalizable to critically ill pediatric patients, for the physiology and etiologies of critical illness differ from that of neonates and adults. Furthermore, despite these trials, there is still wide variation in policies and practices on the use of fresh red blood cells (≤7 days of storage), particularly among neonates and those undergoing cardiac surgery, based on the expectation that they will improve outcomes.[14] We therefore performed a randomized clinical trial to determine the effect of red blood cell storage age on new or progressive organ failure in critically ill pediatric patients.

Key Points

Question What is the effect of fresh red blood cells on organ dysfunction in critically ill pediatric patients?

Findings In a randomized clinical trial involving 1538 critically ill pediatric patients, there were no significant differences in organ dysfunction between fresh (20.2%) and standard-issue red blood cell groups (18.2%).

Meaning This study did not demonstrate a benefit in the use of fresh red blood cell transfusions for critically ill children.

Methods

Study Design and Oversight

The Age of Blood in Children in Pediatric Intensive Care Unit (ABC-PICU) trial protocol was approved by institutional research boards at each clinical site. Written informed consent was obtained from a legal guardian for all study patients prior to study enrollment; trained research coordinators or medical practitioners at all study sites obtained consent. The trial was a multicenter, randomized, double-blind, superiority trial comparing red blood cells stored for no more than 7 days with standard-issue red blood cells (oldest in the inventory at time of the transfusion order). Blinding was accomplished by applying an opaque sticker over the expiration and collection dates in the blood bank prior to allocation to the patient care area or this information was deleted on the label of individual red blood cell units and associated documents to mask group allocation. Data management was shared between the Division of Biostatistics at Washington University in St Louis and the Methods Centre at the Ottawa Hospital Research Institute. The clinical trial protocol has been published.[15] The original trial protocol and its amendments are in Supplement 1, and the statistical analysis plan is provided in Supplement 2.

Study Population

Critically ill patients from pediatric intensive care units (PICUs) were enrolled at 50 centers (29 in the United States, 10 in Canada, 8 in France, 2 in Italy, and 1 in Israel; **Table 1**). Patients admitted to participating PICUs or in the process of being admitted from the operating room, aged 3 days to 16 years, were screened for eligibility. Patients were eligible if the first transfusion was administered within 7 days of PICU admission,[16] and if they were expected by the attending physician to stay in the PICU for at least 24 hours. Exclusion criteria are listed in **Figure 1**.

Randomization

Critically ill patients were randomly allocated by means of a centralized computer-generated assignment sequence using variable permuted block sizes of 2, 4, and 6 and were stratified according to patient age group (<29 days, 29-365 days, >365 days) and study site. The randomization process was initiated by study site blood bank personnel after the first transfusion was requested by treating clinicians or ordered to be on hold for a surgical procedure. Only the independent study statistician at the data coordinating center had knowledge of randomization codes.

Interventions

Fresh red blood cells (stored ≤7 days) were compared with standard-issue red blood cells (delivery of the oldest compatible units available). The intervention continued for 28 days after randomization or until hospital discharge or death, whichever occurred first. All red blood cells used in the trial were prestorage leukocyte-reduced. Although the transfusion guidelines were provided to all study sites (see Supplement 3), adherence to these guidelines was not monitored. All decisions about transfusions were at the discretion of the clinical team.

Outcomes

The primary outcome was the development of new or progressive multiple organ dysfunction (referred to as organ dysfunction herein). Organ dysfunction was measured as the proportion of patients who developed a new multiple organ dysfunction syndrome (new MODS) or among those whose multiple organ dysfunction worsened (progressive MODS) by

Table 1. Baseline Patient Characteristics

Characteristic	Red Blood Cell Group, No. (%) Fresh (n = 728)	Standard-issue (n = 733)[a]
Age, median (IQR), y	1.8 (0.5-6.9)	1.9 (0.5-7.0)
Weight at admission to ICU, median (IQR), kg	11.0 (6.8-21.9)	11.6 (6.5-24.0)
Sex		
Girl	352 (48.4)	339 (46.3)
Boy	376 (51.6)	394 (53.7)
Time between hospital admission and ICU admission, median (IQR), d	0.8 (0.6-1.6)	0.8 (0.6-1.5)
Recruitment per country, sites		
United States, 29	415 (57.0)	423 (57.7)
Canada, 10	196 (26.9)	194 (26.5)
France, 8	92 (12.6)	89 (12.1)
Italy, 2	19 (2.6)	18 (2.5)
Israel, 1	6 (0.8)	9 (1.2)
Type of ICU admission		
General medical	429 (58.9)	440 (60.0)
Medical, cardiac	20 (2.7)	24 (3.3)
Surgical, noncardiac	125 (17.2)	112 (15.3)
Surgical, cardiac	104 (14.3)	107 (14.6)
Trauma	50 (6.9)	50 (6.8)
Admission to randomization, median (IQR), h	23.0 (4.5-56.0)	33.0 (7.0-65.5)
Location of first transfusion		
No. of patients	726	733
Operating room	140 (19.3)	132 (18.0)
ICU	582 (80.2)	600 (81.9)
Other	4 (0.5)	1 (0.1)
Hemoglobin level before first transfusion, median (IQR), g/dL	7.20 (6.70-8.50)	7.30 (6.60-8.30)
PRISM III score at randomization, median (IQR)[b]	5.0 (2.0-9.0)	5.0 (1.0-9.0)
No. of patients	725	728
PELOD-2 score at randomization, median (IQR)[c]	5 (3-7)	5 (3-7)
No.	726	731
MODS at randomization[d]	257 (35.4)	265 (36.2)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MODS, multiple organ dysfunction syndrome; PELOD-2, Pediatric Logistic Organ Dysfunction 2 score; PRISM III, Pediatric Risk of Mortality III score.

[a] The total number of participants was 1461. One patient who was randomized to the standard-issue group died in the operating room during cardiac surgery and had no data available for the primary outcome and some secondary outcomes. This patient was not included in the primary outcome but was included in some baseline analyses and in mortality analyses.

[b] Score ranges from 0 to 71; with higher scores indicating higher risk of death.[22]

[c] The score ranges from 0 to 33; a higher score indicates greater severity of multiple organ dysfunction syndrome.[18] The score can be estimated over the entire stay in the ICU or over 1 day (daily PELOD-2).

[d] Defined by Proulx et al,[16] which is explained further in the Methods section.

experiencing another organ dysfunction as defined by Proulx et al.[16] We categorized patients with no organ dysfunction at randomization as having new MODS if they developed 2 or more concurrent organ dysfunctions; patients with 1 organ dysfunction that progressed to 1 or more, new MODS; patients with 2 or more organ dysfunctions that progressed to more, progressive MODS; and patients who died, progressive MODS.

We chose new or progressive MODS as the primary outcome because data indicating that it correlates with mortality and quality of life in critically ill pediatric patients was clinically relevant.[17] Organ dysfunction was monitored for up to 28 days or until death or discharge, whichever came first. Secondary outcomes included PICU and hospital mortality, 28- and 90-day all-cause mortality, highest number of organ dysfunctions, Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score,[18] nosocomial infections (pneumonia, blood stream infection, urinary tract infections, sepsis), acute lung injury, acute respiratory distress syndrome (ARDS), mechanical ventilation–free and PICU-free days, use of hemodynamic support (vasoactive drugs or extracorporeal support), renal support (renal replacement therapy), symptomatic deep vein thrombosis, reported transfusion reactions, and other adverse events.

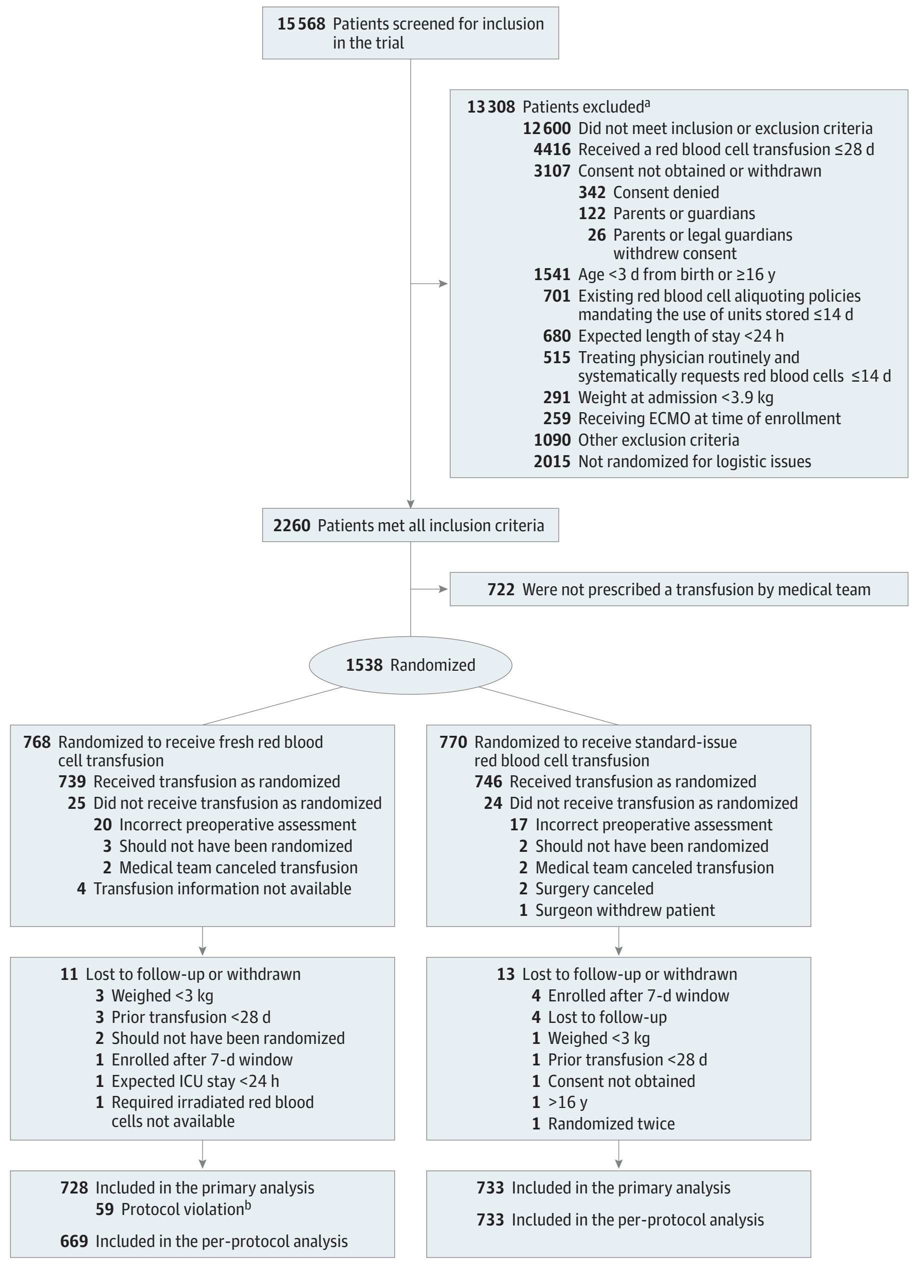
Power Analysis and Sample Size

The primary objective of the trial was to determine whether fresh red blood cells were superior to standard-issue red blood cells. Based on observational studies,[19,20] the incidence of organ dysfunction in the trial population was expected to be 18% in the standard-issue group and 12% in the fresh red blood cell group, representing an expected relative risk reduction of 33%. The sample size of 1538 (769 per group) was based on the formula for 2 independent proportions with an outcome incidence of 18% in the standard-issue and 12% in the fresh red blood cell groups, a 2-tailed α of .05, a power of 0.90, and an anticipated loss to follow-up rate of 1.7% based on results of the Transfusion Requirements in Pediatric ICU study.[21]

Statistical Analysis

Baseline characteristics in both study groups were assessed using frequency distributions and univariate descriptive

Figure 1. Screening, Randomization, and Follow-up in a Study of the Effect of Fresh vs Standard-issue Red Blood Cell Transfusions in Critically Ill Pediatric Patients



Patients were considered eligible for consent if they were admitted to pediatric intensive care unit (PICU) for an anticipated length of stay of more than 24 hours and if their first red blood cell transfusion was ordered during the first 7 days in PICU.

[a] Some patients met more than 1 exclusion criterion.

[b] Adherence to transfusion protocol was considered present if 80% or more of transfusions occurred with units stored for 7 days or less and if no units were stored for more than 14 days during the 28-day follow-up period. No crossover to the other study group occurred in either group.

ECMO indicates extracorporeal membrane oxygenation.

statistics including measures of central tendency and dispersion. Dichotomous data are presented as numbers and percentages; continuous data are expressed as mean (SDs) or medians (interquartile ranges [IQRs]), as appropriate. Any clinically relevant and statistically significant imbalances were considered for adjusted analyses of primary and secondary outcomes. Postrandomization characteristics of interventions and cointerventions are presented using frequency distributions with measures of central tendency and dispersion and analyzed using relative risks and 95% CIs for dichotomous data and either independent *t* tests or Wilcoxon rank-sum tests for continuous data as appropriate.

The prespecified primary analysis of the primary outcome included patients according to their randomization group and excluded patients who were lost to follow-up, patients whose parents or guardians withdrew consent, and patients who did not receive a transfusion if after randomization a transfusion was not performed. The primary analysis was performed using an unadjusted χ^2 comparing the proportion of patients who acquired organ dysfunction up to 28 days after randomization. The principal measure of effect was an unadjusted absolute risk reduction with 95% CIs. We also planned to report an unadjusted relative risk reduction as is reflected in Section 4.15.4 of the protocol (Supplement 1); however,

Table 2. Anemia and Red Blood Cell Transfusions: Intervention and Cointerventions[a]

	Red Blood Cell Group, No. (%)		
	Fresh (n = 728)	Standard-issue (n = 733)[b]	*P* Value
Transfusions after randomization			
No. of transfusions	1630	1533	
Duration of storage, median (IQR), d	5 (4-6)	18 (12-25)	<.001
Volume of units transfused per patient, median (IQR), mL/kg	17.5 (12.9-32.8)	16.6 (12.3-30.6)	.19
No. of patients	723	731	
Time from randomization to first transfusion, median (IQR), h	2.0 (1.0-3.0)	2.0 (1.0-3.0)	
No. of patients	726	733	
Donor exposure to red blood cell units in patients transfused, No. of exposures per patient, median (IQR)	1 (1-2)	1 (1-2)	.24
No. of patients	727	733	
Adherence, No./Total (%)			
Adherence to study protocol[c]	679/727 (93.4)	733/733 (100)	<.001
Adherence to transfusion protocol instructions[d]	1520/1630 (93.3)	1533/1533 (100)	<.001
Cointerventions after randomization			
Received other blood products	323 (44.4)	303 (41.3)	.24
Frozen or fresh frozen plasma	160 (22.0)	149 (20.3)	.44
Apheresis platelets	109 (15.0)	113 (15.4)	.81
Random donor platelets	63 (8.6)	53 (7.2)	.31
Cryoprecipitate	87 (11.9)	75 (10.2)	.30
Albumin 5%	116 (15.9)	95 (13.0)	.11
Albumin 25%	204 (28.0)	187 (25.5)	.28
Systemic corticosteroids	268 (36.8)	251 (34.2)	.30

Abbreviation: IQR, interquartile range.

[a] In all comparisons, the fresh group was used as the reference. Postrandomization characteristics of interventions and cointerventions are presented using frequency distributions with measures of central tendency and dispersion, and analyzed using relative risks and 95% CIs for dichotomous data and either independent *t* tests or Wilcoxon rank-sum tests for continuous data depending on their distribution.

[b] Total number of participants was 1461. One patient who was randomized to the standard-issue group died in the operating room during cardiac surgery and had no data available for the primary outcome, some secondary outcomes, and some cointerventions. This patient was not included in the primary outcome but was included in mortality analyses.

[c] For the purpose of this study, patients in the fresh group were considered adherent to protocol if 80% of the units were stored for for 7 days or less and if no units were stored for more than 14 days during the 28-day follow-up period.

[d] Adherence to transfusion protocol instructions was defined as (number of transfusions with units stored for ≤7 days)/(total number of transfusions) for fresh group and as (number of standard-issue transfusions)/(total number of transfusions) for the standard-issue group.

section 4.15.5 of the protocol omitted relative risk reduction as a measure of effect, which was an oversight. The decision to calculate and present both measures of effect (absolute risk and relative risk reduction) was made in advance of all analyses. All secondary outcomes were analyzed in the same manner as the primary outcome.

Secondary analyses of the primary outcome included a risk difference adjusted for center, age, sex, comorbid illnesses, and severity of illness scores. Post hoc, the adjusted measure of effect was the adjusted relative risk as the model, for the adjusted risk difference did not converge largely due to a number of centers with a small number of randomized patients. Thus, the primary outcome was analyzed using Poisson regression with robust standard errors, adjusting for age, sex, and PELOD-2 score at randomization and adjusting for all comorbidities at ICU admission. We performed mixed-effect modeling with each center treated as a random effect. Clustering by center was accounted for using an exchangeable correlation. The treatment effect was expressed as an adjusted relative risk with 95% CIs. Unadjusted and adjusted Cox proportional-hazards models were developed with the same variables used in the Poisson regression model. The treatment effects were expressed as a hazard ratio with 95% CIs. To assess proportionality, we added the time-dependent function of treatment by including the interaction of treatment and log function of time to the model. The interaction was not significant ($P = .32$); thus, the proportionality assumption was not violated. In addition to the primary analysis, the above analyses were repeated using per-protocol populations consisting of patients who exclusively received red blood cells within 7 days in the fresh group and consisting of all the patients in the standard-issue group. We also compared patients who exclusively received fresh red blood cells (≤7 days) in the fresh group with patients who only received red blood cells stored for more than 7 days.

Subgroup analyses of the primary outcome were also performed for the following: illness category, severity of illness evaluated by the Pediatric Risk of Mortality III (PRISM III) score, stable vs unstable patients[21] at the time of their first transfusion, ABO type, and volume of red blood cells transfused per kilogram. Interactions were assessed by adding the treatment, subgroup of interest, and interaction term in a multivariable logistic regression model. All analyses are presented without any adjustment for multiple comparisons. Missing data

Table 3. Clinical Trial Primary and Subset Outcomes[a]

Outcomes	Red Blood Cell Group, No./No. Evaluated (%)[b] Fresh	Standard-issue	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	*P* Value for Interaction Between Subgroups and Treatment
Primary					
Organ dysfunction development[c,d]	147/728 (20.2)	133/732 (18.2)	1.1 (0.9 to 1.4)	2.0 (−2.0 to 6.1)	
Subset Outcomes					
Organ function development					
Age, d					
≤28	9/30 (30.0)	6/24 (25.0)	1.2 (0.5 to 2.9)	5.0 (−18.8 to 28.8)	.98
29-365	50/245 (20.4)	48/261 (18.4)	1.1 (0.8 to 1.6)	2.0 (−4.9 to 8.9)	
>365	88/453 (19.4)	79/447 (17.7)	1.1 (0.8 to 1.5)	1.7 (−3.3 to 6.8)	
ICU admission type					
Surgical, cardiac	30/104 (28.5)	22/106 (20.7)	1.4 (0.9 to 2.2)	8.1 (−3.5 to 19.7)	.71
General, medical	94/429 (21.9)	86/440 (19.5)	1.1 (0.9 to 1.5)	2.4 (−3.0 to 7.8)	
Surgical, noncardiac	10/125 (8.0)	8/112 (7.1)	1.1 (0.5 to 2.7)	0.9 (−5.9 to 7.6)	
Trauma	8/50 (16.0)	8/50 (16.0)	1.0 (0.4 to 2.4)	0.0 (−14.4 to 14.4)	
Medical, cardiac	5/20 (25.0)	9/24 (37.5)	0.7 (0.3 to 1.7)	−12.5 (−39.6 to 14.6)	
PRISM III score at ICU admission, quartile[e]					
1 (0-1)	24/164 (14.6)	19/167 (11.4)	1.3 (0.7 to 2.3)	3.3 (−4.0 to 10.5)	.24
2 (2-5)	37/209 (17.7)	27/219 (12.3)	1.4 (0.9 to 2.3)	5.4 (−1.4 to 12.1)	
3 (6-10)	33/188 (17.5)	39/174 (22.4)	0.8 (0.5 to 1.2)	−4.9 (−13.1 to 3.4)	
4 (11-40)	53/167 (31.7)	48/172 (27.9)	1.1 (0.8 to 1.6)	3.8 (−5.9 to 13.6)	
Exploratory Subset					
Organ dysfunction by red blood cell volume, quartile, mL/kg[f]					
No. of patients	723	729			
1 (0.9-12.5)	26/175 (14.9)	24/188 (12.8)	1.2 (0.7 to 2.0)	2.1 (−5.0 to 9.2)	.71
2 (12.6-16.97)	22/177 (12.4)	28/187 (15.0)	0.8 (0.5 to 1.4)	−2.5 (−9.6 to 4.5)	
3 (17.0-31.8)	36/183 (19.7)	29/181 (16.0)	1.2 (0.8 to 1.9)	3.6 (−4.2 to 11.5)	
4 (31.9-920.0)	61/188 (32.4)	52/174 (29.9)	1.1 (0.8 to 1.5)	2.6 (−7.0 to 12.1)	

Abbreviations: ICU, intensive care unit; PRISM III, The Pediatric Risk of Mortality III score.

[a] In all comparisons, the fresh red blood cell group was used as the reference. Superiority was checked for the primary outcome and for all secondary outcomes analyzing patients according to their randomization groups. The principal analysis was performed using an unadjusted χ^2 comparing the proportion of patients who acquire new or progressive multiple organ dysfunction syndrome after randomization. The principal measure of effect is an unadjusted absolute risk reduction with a 95% CI. Dichotomous secondary outcomes were analyzed using risk differences and 95% CIs followed by logistic regression procedures. Continuous outcomes were analyzed using independent *t* tests or Wilcoxon rank-sum tests depending on distribution of data.

[b] No./No. evaluated (%) refers to No. with outcome/No. of patients evaluated (proportion). No. refers to number analyzed when it is less than the group total.

[c] Primary outcome are listed in the Methods section.

[d] Total number of participants was 1461. One patient who was randomized to the standard-issue group died in the operating room during cardiac surgery and had no data available for the primary outcome and some secondary outcomes. This patient was not included in the primary outcome but was included in mortality analyses.

[e] The score ranges from 0 to 71; higher scores indicate higher risk of death.[22]

[f] Development of primary outcome in patients who exclusively received red blood cells stored for 7 days or less in the fresh group and all the patients in the standard-issue group.

were treated as missing, and the number of patients missing for each variable is reported. No imputation was done for missing outcomes. In coding and analyzing variables with missing data, we did not generate a separate category for missing. Rather, we excluded patients with missing data for a variable from the respective analysis. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory. Data were analyzed with the SAS software version 9.1 (SAS Institute Inc). All statistical tests were 2-sided, and *P* values less than .05 were considered significant.

Results

Patients

From February 1, 2014, to August 15, 2018, a total of 15 568 patients were screened for inclusion. Of these, 13 308 met at least 1 exclusion criterion (Figure 1); the most frequent reasons for exclusion were having received a red blood cell transfusion within 28 days of eligibility, inability to obtain consent, and patient age being younger than 3 days or older than 16 years at time of the transfusion order. There were

2260 eligible patients who consented to participate; red blood cell transfusion was not administered to 722 patients. Therefore, a total of 1538 patients were randomized and received the intervention: 768 patients in the fresh red blood cell group and 770 in the standard-issue group. There were 40 patients in the fresh red blood cell group and 37 in the standard-issue group who were lost to follow up or withdrawn from the trial (Figure 1). The 2 study groups had similar characteristics at baseline (Table 1 and eTable 1 in Supplement 4).

Intervention

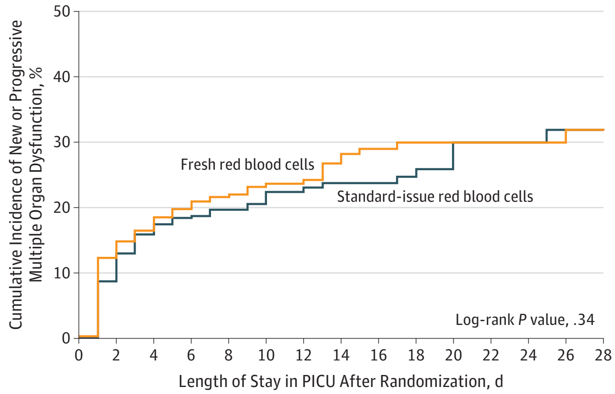
The median total volume of red blood cells transfused per patient in the fresh group was 17.5 mL/kg (IQR, 12.9-32.8 mL/kg) compared with 16.6 mL/kg (IQR, 12.3-30.6 mL/kg) in the standard-issue group (P = .19; **Table 2**). The median storage age in the fresh group was 5 days (IQR, 4-6 days) compared with a storage age of 18 days (IQR, 12-25 days) in the standard-issue group (P < .001). The median time from randomization to the first transfusion was 2.0 hours (IQR, 1.0-3.0 hours) in both study groups. In the fresh group, 679 of 727 patients (93.4%) exclusively received fresh red blood cells (Table 2; eFigure 1 in Supplement 4). Additional intervention data including adherence to the transfusion protocol instructions is provided in eTable 2 in Supplement 4.

Analysis of Primary Outcome

At 28 days after randomization, organ dysfunction occurred in 147 of 728 patients (20.2%) in the fresh red blood cell group and 133 of 732 (18.2%) in the standard-issue group (unadjusted absolute risk difference, 2.0%; 95% CI, −2.0% to 6.1%; P = .33; **Table 3**). The hazard ratio for the time to development of organ dysfunction in the fresh-blood group, compared with the standard-issue group, was 1.12 (95% CI, 0.88 to 1.41; P = .34; **Figure 2**).

The per-protocol analysis showed no significant differences in the primary outcome at 28 days between the patients in the fresh group who exclusively received red blood cells that had been stored for less than 7 days and the patients in the standard-issue group; organ dysfunction occurred in 129 of 699 patients (19.3%) in the fresh group and 133 of 732 (18.2%) in the standard-issue group, unadjusted absolute risk difference, 1.1 (95% CI, −3.0 to 5.2; P = .59; **Table 4**). Similarly, a sensitivity analysis showed no significant difference in the primary outcome between the patients in the fresh group who exclusively received red blood cells that had been stored for less than 7 days and patients in the standard-issue group who exclusively received red blood cells that had been stored for more than 7 days. Organ dysfunction occurred in 129 of 664 patients (19.3%) in the fresh group and in 114 of 671 patients (17%) in the standard issue group; with an unadjusted absolute risk difference of 2.3 (95% CI, −1.8 to 6.4; P = .28; Table 4). Multivariable analyses for the primary outcome also showed no significant differences for the fresh vs standard-issue groups with an unadjusted relative risk of 1.1 (95% CI, 0.9 to 1.4; P = .33) and adjusted relative risk of 1.2 (95% CI, 0.9 to 1.5; P = .19), respectively.

Figure 2. Kaplan-Meier Analysis of Time to Development of New or Progressive Multiple Organ Dysfunction Syndrome



The primary analysis set of patients included 1460 patients. The hazard ratio in the fresh-blood group compared with the standard-issue group, was 1.12 (95% CI, 0.88 to 1.44; P = .34). For a definition of new and progressive multiple organ dysfunction syndrome and how it is categorized for this study, see the Methods section. PICU indicates pediatric intensive care unit. The median observation time until new or progressive multiple organ dysfunction was 5.0 days (95% CI, 2.0-10.0 days) in each study group.

Analysis of Secondary and Subgroup Outcomes

No significant differences were observed in any of the secondary outcomes or subgroup analyses that were planned (Table 3, Table 4; eTable 3, and eFigures 2 and 3 in Supplement 3). Multiple exploratory analyses indicated that there was no statistically significant association between the red blood cell volume transfused and the primary outcome (Table 4, **Table 5**, and eTable 4 in Supplement 4). There were also no significant differences observed for individual organ failure after randomization (eTable 5 in Supplement 4). No significant differences were observed across countries (interaction effect between country and treatment: P = .21; eTable 3 in Supplement 4).

Discussion

In this trial involving critically ill children, the transfusion of fresh red blood cells did not affect the development of organ dysfunction or death compared with the use of standard issue red blood cells. Results in all subgroups and secondary outcomes analyses were consistent with the primary outcome. Current blood management policies that recommend fresh red blood cell units for certain populations of children, such as neonates and children requiring cardiac surgery,[14] are not supported by the outcomes of this trial.

There are several potential explanations for the results of this trial indicating that fresh red blood cells did not reduce organ dysfunction in critically ill children. The first possibility is that study patients may not have needed a red blood cell transfusion to improve oxygen delivery; if there was no potential benefit for transfusion then there would be no additional relative benefit to detect as a function of red-cell storage duration. Another explanation for the results could be that while there are well-described changes that occur over time

Table 4. Clinical Trial Secondary Outcomes[a]

Secondary Outcomes	Red Blood Cell Group, No./No. Evaluated (%)[b]				
	Fresh	Standard-issue	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	*P* Value
Per-protocol analysis[c]					
Development of organ dysfunction	129/669 (19.3)	133/732 (18.2)	1.1 (0.9 to 1.3)	1.1 (−3.0 to 5.2)	.59
Sensitivity analysis[d]					
Development of organ dysfunction	129/669 (19.3)	114/671 (17.0)	1.1 (0.9 to 1.4)	2.3 (−1.8 to 6.4)	.28
Mortality					
In ICU	33/728 (4.5)	26/732 (3.5)	1.3 (0.8 to 2.1)	1.0 (−1.04 to 3.0)	.34
In hospital	36/728 (4.9)	35/733 (4.8)	1.0 (0.7 to 1.6)	0.2 (−2.0 to 2.4)	.88
≤28 d	33/716 (4.6)	24/714 (3.4)	1.4 (0.8 to 2.3)	1.2 (−0.8 to 3.3)	.23
≤90 d	49/716 (6.8)	45/714 (6.3)	1.1 (0.7 to 1.6)	0.5 (−2.0 to 3.1)	.68
Morbidity outcomes[e]					
Sepsis	160/619 (25.8)	154/608 (25.3)	1.0 (0.8 to 1.2)	0.5 (−4.4 to 5.4)	.83
Severe sepsis	63/619 (10.2)	60/608 (9.9)	1.0 (0.7 to 1.4)	0.3 (−3.0 to 3.7)	.86
Septic shock	59/619 (9.5)	57/608 (9.4)	1.0 (0.7 to 1.4)	0.2 (−3.1 to 3.4)	.93
ARDS[f]	41/619 (6.6)	29/608 (4.8)	1.4 (0.9 to 2.2)	1.8 (−0.7 to 4.4)	.16
Nosocomial infections[g]	24/728 (3.3)	23/732 (3.1)	1.1 (0.6 to 1.8)	0.1 (−1.6 to 2.0)	.86

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

[a] See Table 3 footnotes for comparative explanations.

[b] No./No. evaluated (%) refers to No. with outcome/No. of patients evaluated (proportion). No. refers to number analyzed when it is less than the group total.

[c] Patients who exclusively received red blood cells 7 days or less in the fresh group and all patients in the standard-issue group.

[d] Patients who exclusively received red blood cells within 7 days in the fresh group and exclusively received old red blood cells 7 days or older in the standard-issue group.

[e] Sepsis, severe sepsis, and septic shock as defined by Goldstein et al.[23]

[f] Definition is drawn from Bernard et al and Thomas et al.[24,25]

[g] Nosocomial infection definitions by Lacroix et al,[26] Centers for Disease Control and Prevention,[27] and Calandra et al.[28]

Table 5. Patient Intensive Care Unit Secondary Outcomes

	Red Blood Cell Group[a]			
	Fresh	Standard-issue	Difference, Mean (95%CI)	*P* Value
28-d ICU-free days[b]				
Median (IQR)	21.9 (14.5-25.3)	22.0 (16.1-25.6)		.33
Mean (SD) [No.]	18.6 (8.8) [716]	19.1 (8.4) [712]	−0.6 (−1.5 to 0.3)	.21
28-d Mechanical ventilation-free days[c]				
Median (IQR)	25.4 (19.6-27.9)	25.8 (20.2-28.0)		.27
Mean (SD) [No.]	21.7 (8.6) [710]	22.3 (8.0) [707]	−0.5 (−1.4 to 0.3)	.21
Worst PELOD-2 score[d]				
Median (IQR)	5 (2-7)	5 (2-7)		.41
Mean (SD) [No.]	5.9 (6.4) [709]	5.5 (5.7) [713]	0.4 (−0.2 to 1.0)	.21
Δ PELOD-2 score, change from randomization to worst[e]				
Median (IQR)	0 (−2 to 1)	0 (−2 to 1)		.26
Mean (SD) [No.]	0.5 (5.8) [707]	−0.05 (4.7) [712]	0.5 (−0.003 to 1.1)	.051
Length of hospital stay, d				
Median (IQR)	12.7 (5.7 to 27.2)	13.1 (6.3 to 25.5)		.83
Mean (SD)	21.2 (23.5)	20.7 (23.4)	0.5 (−1.9 to 2.9)	.66

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PELOD-2, Pediatric Logistic Organ Dysfunction-2 score.

[a] Values in square brackets indicate number of patients analyzed among all participants.

[b] Calculated by subtracting the actual ICU length of stay in days from 28. If a patient died within 28 days or stayed in ICU for more than 28 days after randomization, 28-day ICU-free days were reported as 0.

[c] Calculated by subtracting from 28 the number of days spent receiving mechanical ventilation. If the patient died within 28 days or required mechanical ventilation for more than 28 days after randomization, 28-day mechanical ventilation-free days were reported as 0.

[d] The score ranges from 0 to 33; higher scores indicate greater severity of multiple organ dysfunction syndrome.[18] The score can be estimated over the entire stay in the ICU or over 1 day (daily PELOD-2).

[e] The change in the score is the difference between the daily PELOD-2 score at study entry and the worst daily PELOD-2 score thereafter. Patients whose score did not change or decreased after randomization were considered to have a change of 0.

in red blood cell units, these changes are not clinically relevant and there are no benefits of transfusing fresh red blood cells in a heterogenous group of critically ill children. It is possible that the current use of prestorage leukoreduction for red blood cell units has mitigated most of the storage lesion effects, which were predominantly described prior to its use.[29] Another theory is that any potential benefit from fresh red blood cells was mitigated by increased risk of adverse effects as a result of immune dysregulation or other mechanisms.[30,31] There is mounting evidence that the so called "chronological" age of a stored red blood cell unit does not equate to its "biological age." Metabolomic data indicate that there is wide variation in red blood cell unit quality upon donation and, moreover, that rate of change of red blood cell metabolic activity over time is also highly variable between donors.[32] This explanation may account for discordance between in vitro and animal data demonstrating adverse red blood cell storage lesion effects and the lack of effect of storage age on clinical outcomes in all large clinical trials performed.

The results of this trial were consistent with previously published randomized clinical trials examining the effect of fresh vs older red blood cells in critically ill neonates, severely anemic children, and adult patients. In these 6 trials there were no significant differences in clinical outcomes.[8-13] All point estimates, overall and in major subgroups, favored standard-issue red blood cells. These same observations were noted in 3 of 5 previously published randomized trials.[10-12] Therefore, it is highly improbable that fresh red blood cells were superior to standard-issue red blood cells in all the patient populations studied. This concept is supported in a recently published meta-analysis.[33]

This trial has several strengths. A wide spectrum of critically ill pediatric patients were included and the study population was representative of PICUs in developed countries, enhancing applicability of these findings. Adherence to the trial protocol was excellent. The trial also large enough to detect a reduction in organ dysfunction from 18% to 12%, a clinically important difference. Ascertainment bias was minimized by concealed randomization and blinded study group assignments.

Limitations

This study has several limitations. First, similar to prior randomized clinical trials addressing the question of red blood cell storage, it is possible that some subgroups of critically ill children more vulnerable to the adverse effects of prolonged red blood cell storage were underrepresented. Second, this trial, as well as all prior trials examining red blood cell storage age, have predominantly enrolled patients who did not require large volumes. The mean or median total volume transfused in adult trials was 2 to 4 units per participant.[10,12,13] In this trial, there was no effect of storage duration on outcomes even in the highest quartile of volume transfused (>30 mL/kg), which equates to approximately 2 to 3 transfusion events per patient over the study period. A dose effect with larger amounts of older red blood cells transfused over short periods of time adversely affecting outcomes is possible and has been reported in retrospective studies and secondary analyses of 2 randomized clinical trials.[4-7] Third, as a result of using standard delivery of red blood cells, the median storage age was low at 18 days. This did not allow for the examination of the effect of older red blood cells in the trial. This limitation also occurred in the majority of the other randomized clinical trials examining the clinical effects of red blood cell storage.[8,10-13] Thus this trial, as well as others, cannot address relative safety of transfusing red blood cells stored for 35 to 42 days.

Conclusions

In critically ill pediatric patients, the use of fresh red blood cells did not reduce the incidence of new or progressive multiple organ dysfunction syndrome (including mortality) compared with standard-issue red blood cells.

ARTICLE INFORMATION

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Data Sharing Statement: See Supplement 5

REFERENCES

1. Demaret P, Tucci M, Ducruet T, Trottier H, Lacroix J. Red blood cell transfusion in critically ill children (CME). *Transfusion*. 2014;54(2):365-375.

2. Rajasekaran S, Kort E, Hackbarth R, et al. Red cell transfusions as an independent risk for mortality in critically ill children. *J Intensive Care*. 2016;4:2. doi:10.1186/s40560-015-0122-3

3. Spinella PC, Doctor A. Role of transfused red blood cells for shock and coagulopathy within remote damage control resuscitation. *Shock*. 2014; 41(suppl 1):30-34. doi:10.1097/SHK.0000000000000089

4. Spinella PC, Carroll CL, Staff I, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. *Crit Care*. 2009;13(5):R151. doi:10.1186/cc8050

5. Jones AR, Patel RP, Marques MB, et al; PROPPR Study Group. Older blood is associated with increased mortality and adverse events in massively transfused trauma patients: secondary analysis of the PROPPR Trial. *Ann Emerg Med*. 2019;73(6): 650-661. doi:10.1016/j.annemergmed.2018.09.033

6. Mack J, Kahn SR, Tinmouth A, Fergusson D, Hebert P, Lacroix J. Dose-dependent effect of stored red blood: results of a sub-group analysis of the Age of Blood Evaluation (ABLE) Trial. Presented at: The 58th Annual American Society of Hematology Annual Meeting and Exposition; December 3-6, 2016; San Diego, CA.

7. Weinberg JA, McGwin G Jr, Vandromme MJ, et al. Duration of red cell storage influences mortality after trauma. *J Trauma*. 2010;69(6):1427-1431. doi:10.1097/TA.0b013e3181fa0019

8. Fergusson DA, Hébert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA*. 2012; 308(14):1443-1451. doi:10.1001/2012.jama.11953

9. Dhabangi A, Ainomugisha B, Cserti-Gazdewich C, et al. Effect of transfusion of red blood cells with longer vs shorter storage duration on elevated blood lactate levels in children with severe anemia: the TOTAL randomized clinical trial. *JAMA*. 2015;314(23): 2514-2523. doi:10.1001/jama.2015.13977

10. Lacroix J, Hébert PC, Fergusson DA, et al; ABLE Investigators; Canadian Critical Care Trials Group. Age of transfused blood in critically ill adults. *N Engl J Med*. 2015;372(15):1410-1418. doi:10.1056/NEJMoa1500704

11. Heddle NM, Cook RJ, Arnold DM, et al. Effect of short-term vs. long-term blood storage on mortality

after transfusion. *N Engl J Med*. 2016;375(20):1937-1945. doi:10.1056/NEJMoa1609014

12. Cooper DJ, McQuilten ZK, Nichol A, et al; TRANSFUSE Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Age of red cells for transfusion and outcomes in critically ill adults. *N Engl J Med*. 2017;377(19):1858-1867. doi:10.1056/NEJMoa1707572

13. Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med*. 2015;372(15):1419-1429. doi:10.1056/NEJMoa1414219

14. Spinella PC, Dressler A, Tucci M, et al; Pediatric Acute Lung Injury and Sepsis Investigators Network. Survey of transfusion policies at US and Canadian children's hospitals in 2008 and 2009. *Transfusion*. 2010;50(11):2328-2335. doi:10.1111/j.1537-2995.2010.02708.x

15. Tucci M, Lacroix J, Fergusson D, et al; Canadian Critical Care Trials Group; Pediatric Critical Care Blood Research Network (BloodNet); Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. The age of blood in pediatric intensive care units (ABC PICU): study protocol for a randomized controlled trial. *Trials*. 2018;19(1):404. doi:10.1186/s13063-018-2809-y

16. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest*. 1996;109(4):1033-1037. doi:10.1378/chest.109.4.1033

17. Morrison AL, Gillis J, O'Connell AJ, Schell DN, Dossetor DR, Mellis C. Quality of life of survivors of pediatric intensive care. *Pediatr Crit Care Med*. 2002;3(1):1-5. doi:10.1097/00130478-200201000-00001

18. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med*. 2013;41(7):1761-1773. doi:10.1097/CCM.0b013e31828a2bbd

19. Karam O, Tucci M, Bateman ST, et al. Association between length of storage of red blood cell units and outcome of critically ill children: a prospective observational study. *Crit Care*. 2010;14(2):R57. doi:10.1186/cc8953

20. Gauvin F, Spinella PC, Lacroix J, et al; Canadian Critical Care Trials Group and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Association between length of storage of transfused red blood cells and multiple organ dysfunction syndrome in pediatric intensive care patients. *Transfusion*. 2010;50(9):1902-1913. doi:10.1111/j.1537-2995.2010.02661.x

21. Lacroix J, Hébert PC, Hutchison JS, et al; TRIPICU Investigators; Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators Network. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med*. 2007;356(16):1609-1619. doi:10.1056/NEJMoa066240

22. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. *Crit Care Med*. 1996;24(5):743-752. doi:10.1097/00003246-199605000-00004

23. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8. doi:10.1097/01.PCC.0000149131.72248.E6

24. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-824. doi:10.1164/ajrccm.149.3.7509706

25. Thomas NJ, Shaffer ML, Willson DF, Shih MC, Curley MA. Defining acute lung disease in children with the oxygenation saturation index. *Pediatr Crit Care Med*. 2010;11(1):12-17. doi:10.1097/PCC.0b013e3181b0653d

26. Lacroix J, Gauvin F, Skippen P, Cox P, Langley JM, Matlow A. Nosocomial infections in the PICU: Epidemiology and control. In: Fuhrman BP, Zimmerman JJ, eds. *Pediatric Critical Care*. 2nd ed. St Louis, MO: Mosby Year Book; 2006:1394-1421. doi:10.1016/B978-032301808-1.50093-6

27. Center for Disease Control. CDC definitions for nosocomial infections, 1988. *Am Rev Respir Dis*. 1989;139(4):1058-1059. doi:10.1164/ajrccm/139.4.1058

28. Calandra T, Cohen J; International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med*. 2005;33(7):1538-1548. doi:10.1097/01.CCM.0000168253.91200.83

29. Zubair AC. Clinical impact of blood storage lesions. *Am J Hematol*. 2010;85(2):117-122.

30. Bakkour S, Acker JP, Chafets DM, et al. Manufacturing method affects mitochondrial DNA release and extracellular vesicle composition in stored red blood cells. *Vox Sang*. 2016;111(1):22-32. doi:10.1111/vox.12390

31. Chai-Adisaksopha C, Alexander PE, Guyatt G, et al. Mortality outcomes in patients transfused with fresher versus older red blood cells: a meta-analysis. *Vox Sang*. 2017;112(3):268-278. doi:10.1111/vox.12495

32. D'Alessandro A, Zimring JC, Busch M. Chronological storage age and metabolic age of stored red blood cells: are they the same? *Transfusion*. 2019;59(5):1620-1623. doi:10.1111/trf.15248

33. McQuilten ZK, French CJ, Nichol A, Higgins A, Cooper DJ. Effect of age of red cells for transfusion on patient outcomes: a systematic review and meta-analysis. *Transfus Med Rev*. 2018;32(2):77-88. doi:10.1016/j.tmrv.2018.02.002