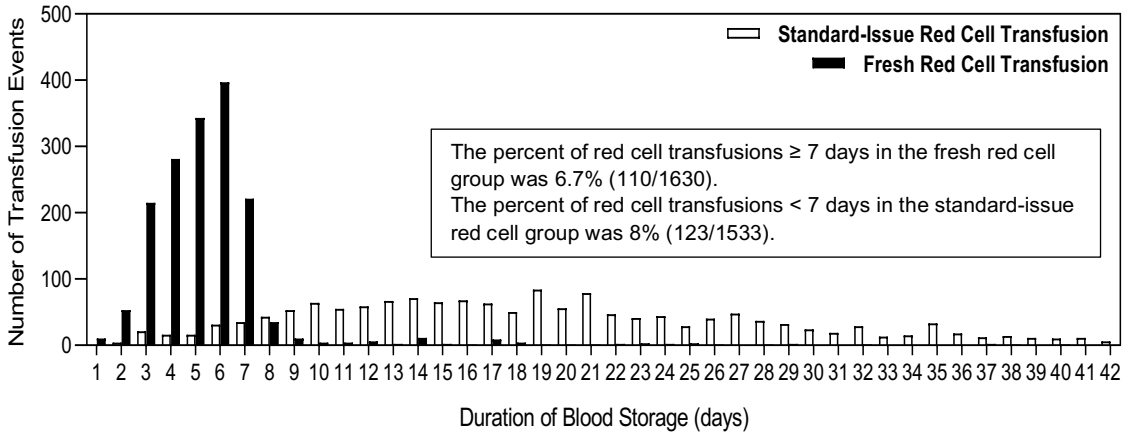
Supplementary Online Content

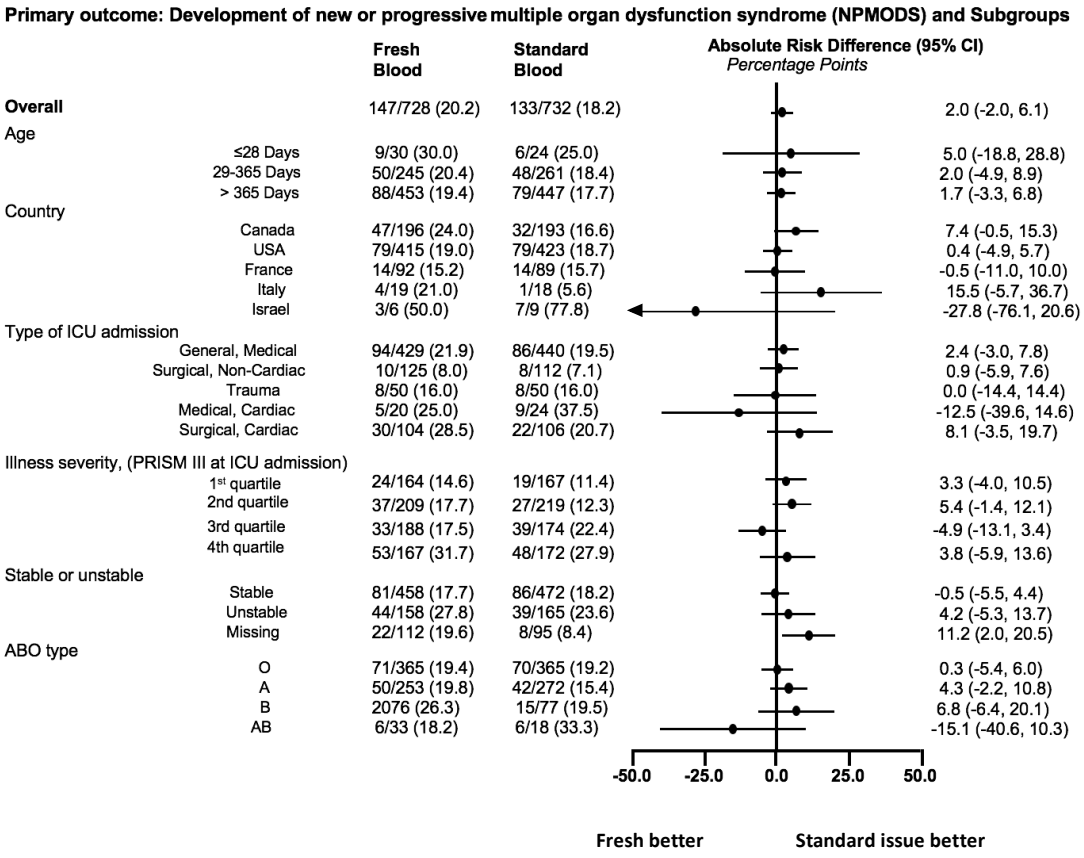
Spinella PC, Tucci M, Fergusson DA, et al. Effect of fresh vs standard-issue red blood cell transfusions on multiple organ dysfuntion syndrome in critically ill children: a randomized clinical trial; for the ABC-PICU Investigators, for the Canadian Critical Care Trials Group, for the Pediatric Acute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

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Distribution of red cell transfusions per length of storage in study arms.



Distribution of red cell transfusions per length of storage as transfused to patients allocated to the fresh red cell arm (black bars) and to the standard-issue arm (white bars).

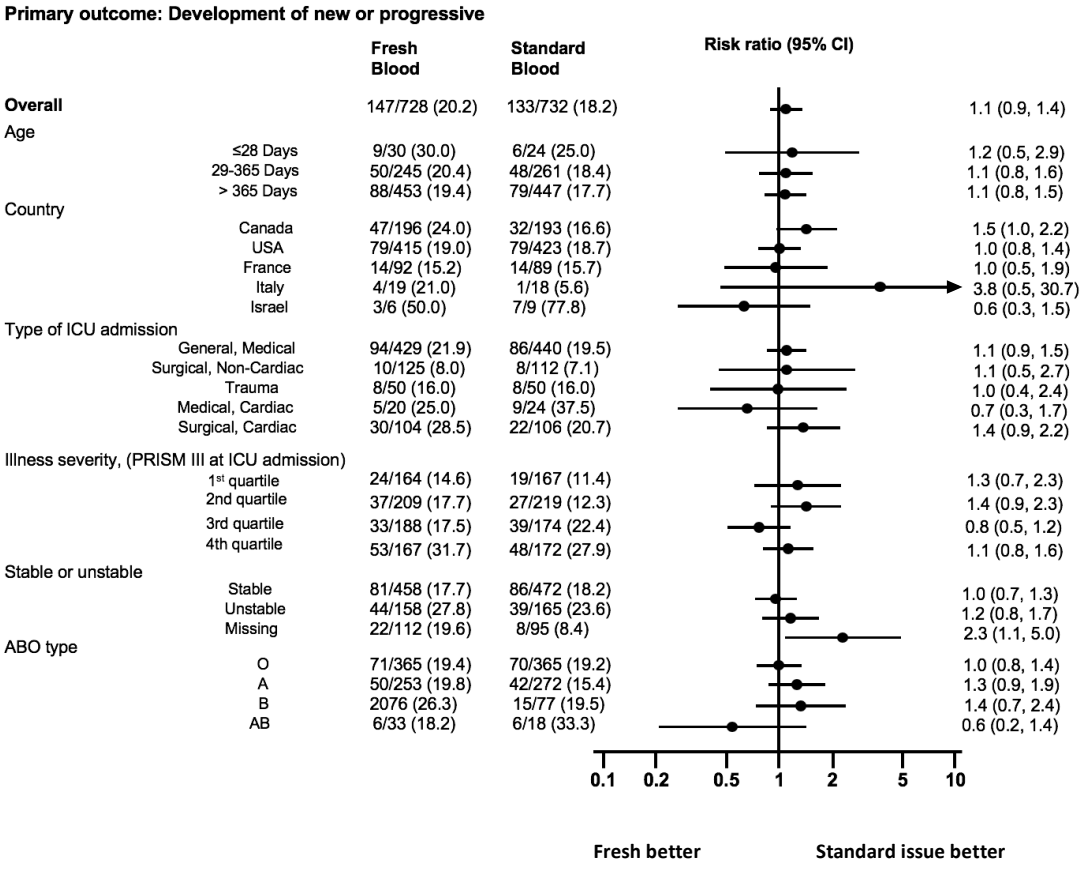


eFigure 2. Forest plot of Absolute Risk Differences for the Primary Outcome (development of New or Progressive Multiple Organ Dysfunction Syndrome) in all participants and in subgroups.

Majority fall on the "standard-issue blood better" side of the line. No significant differences were observed in any of the secondary outcomes, subgroup analyses or exploratory analyses.

ICU denotes intensive care unit. All estimates have 95% confidence intervals that include zero. In all comparisons, the fresh group was used as the reference.

PRISM III denotes the Pediatric Risk of Mortality III score (PRISM III) and can range from 0 to 71 with a higher PRISM score indicating higher risk of death.[2] Stable or unstable as defined in TRIPICU[7].



eFigure 3. Forest plot of Relative Risk Differences for the Primary Outcome (development of New or Progressive Multiple Organ Dysfunction Syndrome) in all participants and in subgroups

Majority fall on the "standard-issue blood better" side of the line. No significant differences were observed in any of the secondary outcomes, subgroup analyses or exploratory analyses.

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eTable 1. Additional baseline characteristics at admission and randomization

Characteristic[a]	Fresh red cells	Standard-issue red cells[b]
	N = 728	N = 733
On admission to ICU – no. (%)		
Patient ethnic group		
Hispanic or Latino	68 (9.3)	82 (11.2)
Not Hispanic or Latino	515 (70.7)	508 (69.3)
Unknown	145 (19.9)	143 (19.5)
Patient race – no. (%)		
Asian	37 (5.1)	29 (4.0)
North American Indian or Alaskan Native	22 (3.0)	11 (1.5)
White	399 (54.8)	415 (56.6)
Native Hawaiian or Other Pacific Islander	5 (0.7)	4 (0.5)
Black or African American in the US	86 (11.8)	103 (14.0)
Unknown	155 (21.3)	158 (21.6)
Other	24 (3.3)	13 (1.8)
PRISM III Score at ICU admission – median (IQR)[c]	5.0 (2.0, 10.0)	5.0 (2.0, 10.0)
PELOD-2 Score at ICU admission – median (IQR)[d]	5.0 (2.0, 6.0)	5.0 (2.0, 7.0)
MODS at ICU admission – median (IQR)[e]	1.0 (0.0, 2.0)	1.0 (1.0, 2.0)
Patients with MODS – no. (%)[e]	217 (29.8)	232 (31.7)
Comorbidities at ICU admission – no. (%)		
Chronic anemia[f]	41 (5.6)	44 (6.0)
Congenital heart disease	166 (22.8)	169 (23.1)
Cancer	41 (5.6)	35 (4.8)
Organ transplantation	24 (3.3)	18 (2.5)
Bone marrow/stem cell transplantation	10 (1.4)	6 (0.8)
Chronic respiratory disease[g]	82 (11.3)	95 (13.0)
Chronic renal failure[h]	34 (4.7)	21 (2.9)

Characteristic[a]	Fresh red cells	Standard-issue red cells[b]
	N = 728	**N = 733**
Chronic neurological disease	97 (13.3)	112 (15.3)
Sepsis or Severe sepsis[i]	123 (16.9)	139 (19.0)
Septic shock[i]	73 (10.0)	66 (9.0)
Acute respiratory distress syndrome[j]	64 (8.8)	71 (9.7)
Patient blood type – no. (%)	n=727	
A	253 (34.8)	272 (37.1)
B	76 (10.4)	77 (10.5)
AB	33 (4.5)	18 (2.5)
O	365 (50.2)	366 (49.9)
Rh+	630 (86.5)	640 (87.3)
Rh-	98 (13.5)	93 (12.7)
On Day 1 / Day of randomization		
Organ dysfunction on calendar day of randomization – no. (%)[e]	n=726	n=731
Neurologic	47 (6.5)	56 (7.7)
Cardiovascular	239 (32.9)	253 (34.6)
Respiratory	469 (64.6)	464 (63.5)
Renal	54 (7.4)	44 (6.0)
Hematologic	79 (10.9)	78 (10.7)
Hepatic	24 (3.3)	25 (3.4)
Gastrointestinal	6 (0.8)	7 (1.0)

[a]No. (%) denotes number and proportion (%). IQR refers to interquartile range. ICU denotes intensive care unit.

[b]Total number of participants was 1461; one patient 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.

[c]The Pediatric Risk of Mortality III score (PRISM III) can range from 0 to 71; higher PRISM score indicates higher risk of death.[2]

[d]The Pediatric Logistic Organ Dysfunction-2 Score (PELOD-2) can range from 0 to 33; higher PELOD-2 score indicates greater severity of multiple organ dysfunction syndrome.[3] The PELOD score can be estimated over the entire stay in the ICU or over 1 day (daily PELOD).

[e]MODS denotes multiple organ dysfunction syndrome. Multiple organ dysfunction syndrome and organ failures as defined by Proulx et al[1]

[f]Reduction in the hemoglobin level of circulating blood below the normal value for age. May be due to a nutritional cause (iron or folate deficiency), hemolytic (congenital such as sickle cell or thalassemia or acquired, such as autoimmune), aplastic condition (Fanconi or Diamond Blackfan Anemia), or malignancy (disease or treatment related). Refer to normal values in your laboratory to define anemia.

[g]Persistent inflammation, injury or scarring of lung tissue that occurs as a result of prolonged illness; in children this may include bronchopulmonary dysplasia, cystic fibrosis, interstitial pulmonary fibrosis, surfactant protein deficiency or any chronic lung disorder resulting in chronic oxygen dependency or any respiratory disease such as reactive airway disease (asthma) requiring maintenance therapy. Respiratory conditions that do not require maintenance therapy and only require as needed therapy such as mild reactive airway disease were not considered chronic respiratory disease.

[h]Any patient requiring chronic renal replacement therapy ie dialysis (peritoneal or hemodialysis).

[i]Sepsis, severe sepsis and septic shock as defined by Goldstein et al[4]

[j]Acute respiratory distress syndrome definition drawn from Bernard et al and Thomas et al.[5,6]

eTable 2. Additional intervention data including compliance to red cell transfusion protocol instructions in patients allocated to fresh red cell arm and red cell storage time in patients allocated to standard-issue arm[a]

	Fresh red cells	Standard-issue red cells	P-value
Hemoglobin level			
Number of patients evaluated	703	713	
Time between hemoglobin level measure and first transfusion, days; mean ± SD	0.7±5.3	0.6±5.3	0.63
Storage time of red cell transfusions			
Total number of transfusions	1630	1533	
Transfusions with units <= 7 days – no. (%)	1520(93.2)	123 (8.0)	<.001
Transfusions with units > 7 days – no. (%)	110 (6.75)	1410 (92.0)	
Transfusions with units 8 to 14 days – no. (%)	72 (4.4)	412 (26.9)	
Transfusions with units 15 to 21 days – no. (%)	19 (1.2)	465 (30.3)	
Transfusions with units 22 to 28 days – no. (%)	12 (0.7)	286 (18.7)	
Transfusions with units 29 to 35 days – no. (%)	3 (0.2)	165 (10.8)	
Transfusions with units 36 to 42 days – no. (%)	4 (0.2)	82 (5.3)	

[a]Number and proportion (%) or mean ±standard deviation or median and interquartile range. In all comparisons, the fresh red cell group was used as the reference.

eTable 3. Additional Analyses of Primary and Secondary Outcomes[a]

Primary outcome: New or Progressive Multiple Organ Dysfunction Syndrome[b]	Fresh red cells – No. / No. evaluated (%)	Standard-issue red cells – No. / No. evaluated (%)	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	P value for Absolute Risk Difference
All participants[c]	**728**	**733**			
USA	79/415 (19.0)	79/423 (18.7)	1.0 (0.8 to 1.4)	0.4 (-4.9 to 5.7)	0.89
Canada	47/196 (24.0)	32/193 (16.6)	1.5 (1.0 to 2.2)	7.4 (-0.5 to 15.3)	0.07
France	14/89 (15.2)	14/92 (15.7)	1.0 (0.5 to 1.9)	-0.5 (-11.0 to 10.0)	0.92
Italy	4/19 (21.0)	1/18 (5.6)	3.8 (0.5 to 30.7)	15.5 (-5.7 to 36.7)	0.17
Israel	3/6 (50.0)	8/9 (77.8)	0.6 (0.3 to 1.5)	-27.8 (-76.1 to 20.6)	0.33
Development of organ dysfunction in stable and unstable patients[d]					
Stable	81/458 (17.7)	86/472 (18.2)	1.0 (0.7, 1.3)	-0.5 (-5.5 to 4.4)	0.83
Unstable	44/158 (27.8)	39/165 (23.6)	1.2 (0.8, 1.7)	4.2 (-5.3 to 13.7)	0.39
Development of organ dysfunction according to transfusion ABO type					
O	71/365 (19.4)	70/365 (19.2)	1.0 (0.8, 1.4)	0.3 (-5.4 to 6.0)	0.93
A	50/253 (19.8)	42/272 (15.4)	1.3 (0.9, 1.9)	4.3 (-2.2 to 10.8)	0.19
B	20/76 (26.3)	15/77 (9.5)	1.4 (0.7, 2.4)	6.8 (-6.4 to 20.1)	0.31
AB	6/33 (18.2)	6/18 (33.3)	0.6 (0.2, 1.4)	-15.1 (-40.6 to 10.3)	0.30

	Fresh red cells – No. / No. evaluated (%)	Standard-issue red cells – No. / No. evaluated (%)	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	P value for Absolute Risk Difference
Other morbidities or adverse events					
Deep vein thrombosis[e]	20/728 (2.7)	14/733 (1.9)	1.4 (0.7, 2.8)	0.8 (-0.7 to 2.4)	0.29
Hyperkalemia[f]	30/728 (4.1)	36/733 (4.9)	0.8 (0.5, 1.3)	-0.8 (-2.9 to 1.3)	0.47
Hypocalcemia[g]	10/728 (1.4)	13/733 (1.8)	0.8 (0.3, 1.8)	-0.4 (-1.7 to 0.9)	0.54
Major allergic reaction[h]	2/728 (0.3)	2/733 (0.3)	1.0 (0.1, 7.1)	0.0 (-0.5 to 0.5)	>.99
Nosocomial pneumonia[i]	18/728 (2.5)	15/733 (2.0)	1.2 (0.6, 2.4)	0.4 (-1.1 to 1.9)	0.58
Hemolytic transfusion reaction[h]	0	1/733 (0.1)		-0.1 (-0.4 to 0.1)	>.99
Transfusion Associated Cardiac Overload (TACO)[h]	0	3/733 (0.4)		-0.4 (-0.9 to 0.1)	0.25
Transfusion Related Acute Lung Injury (TRALI)[h]	0	0			

No. / No. evaluated (%) refers to Number with outcome / number of patients evaluated (proportion). CI denotes 95% confidence interval. In all comparisons, the fresh red cell group was used as the reference. Superiority was checked for the primary outcome and for all secondary outcomes using an intention-to-treat analysis. The principal analysis was performed using an unadjusted Chi square 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 difference with a 95% confidence interval. Dichotomous secondary outcomes were analyzed using absolute risk differences and 95% confidence intervals.

[b]Primary outcome: Development of organ dysfunction refers to New or Progressive Multiple Organ Dysfunction Syndrome (NPMODS) and is the proportion of patients who die during the 28 days after randomization or who develop new or progressive MODS including

mortality (referred to as organ dysfunction). For patients with no organ dysfunction at randomization, New MODS is the development of ≥ 2 concurrent organ dysfunctions. For patients with 1 organ dysfunction at randomization, New MODS is the development of at least 1 other concurrent organ dysfunction. For patients with MODS (i.e. concurrent dysfunction of ≥ 2 organ systems) at randomization, Progressive MODS is defined as development of at least 1 additional concurrent organ dysfunction. All deaths are considered Progressive MODS. Multiple organ dysfunction syndrome and organ failures as defined by Proulx et al[1]

[c]Total number of participants was 1461; one patient 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.

[d]Stable vs unstable as defined in TRIPICU [7]

[e]Deep vein thrombosis as defined by Dubois et al [8]

[f]Hyperkalemia was defined as a potassium blood level > 5.5 mmol/L.

[g]Hypocalcemia was defined as an ionized calcium concentration < 0.8 mmol/L (<3.2 mg/dL).

[h]Diagnostic criteria for acute transfusion reactions attributed to red blood cell transfusion (hemolytic transfusion reaction, major allergic reaction, transfusion-associated cardiac overload, transfusion-related acute lung injury) were derived from Gauvin et al.[9] and/or were defined according to regional hemovigilance system or local blood bank.

[i]Nosocomial respiratory infections as defined by the CDC in Atlanta[10] and from the International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit[11]

eTable 4. – Exploratory analysis: effect of red-cell volume (mL/kg) on primary outcome

Primary outcome: Development of organ dysfunction	Fresh arm – No./ No. evaluated (%)	Standard-issue arm – No./ No. evaluated (%)	Absolute Risk Difference (95% CI)	Relative Risk (95% CI)	P-value
Red-cell volume (ml/kg): Discrete Categories					
<50	102/626 (16.3)	104/642 (16.2)	0.1 (-3.97, 4.2)	1.0 (0.8, 1.3)	0.96
50-100	20/54 (37.0)	17/60 (28.3)	8.7 (-8.5, 25.9)	1.3 (0.8, 2.2)	0.32
>100	23/43 (53.5)	12/28 (42.9)	10.6 (-13.0, 34.3)	1.2 (0.7, 2.1)	0.38

eTable 5. – Individual organ injury after randomization[a]

Organ injury[b]	Fresh red cells – No. (%)	Standard-issue red cells – No. (%)	Absolute Risk Difference (95% CI)	Relative Risk (95% CI)	P-value
	n=728	n=733			
Neurologic	31 (4.3)	38 (5.2)	-0.9 (-3.1 to 1.2)	0.8 (0.5, 1.3)	0,40
Cardiovascular	71 (9.7)	61 (8.3)	1.4 (-1.5 to 4.4)	1.2 (0.9, 1.6)	0,34
Respiratory	68 (9.3)	57 (7.8)	1.6 (-1.3 to 4.4)	1.2 (0.9, 1.7)	0,29
Renal	72 (9.9)	61 (8.3)	1.6 (-1.4 to 4.5)	1.2 (0.9, 1.7)	0,30
Hematologic	53 (7.3)	56 (7.6)	-0.4 (-3.0 to 2.3)	1.0 (0.7, 1.4)	0,79
Hepatic	22 (3.0)	17 (2.3)	0.7 (-0.9 to 2.4)	1.3 (0.7, 2.4)	0,40
Gastrointestinal	9 (1.2)	9 (1.2)	0.0 (-1.1 to 1.1)	1.0 (0.4, 2.5)	0,99

[a]Number and proportion (%) or mean ±standard deviation or median and interquartile range. CI denotes 95% confidence interval. In all comparisons, the fresh red cell group was used as the reference. Superiority was checked for all secondary outcomes using an intention-to-treat analysis. Unadjusted absolute risk differences with 95% confidence intervals were calculated for each individual organ injury.

[b]Individual organ injuries as defined by Proulx et al.[1]

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