Red blood cell transfusion thresholds in pediatric patients with sepsis*

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Objectives: **In children with severe sepsis or septic shock, the optimal red blood cell transfusion threshold is unknown. We analyzed the subgroup of patients with sepsis and transfusion requirements in a pediatric intensive care unit study to determine the impact of a restrictive vs. liberal transfusion strategy on clinical outcome.**

Design: **Subgroup analysis of a prospective, multicenter, randomized, controlled trial.**

Setting: **Multicenter pediatric critical care units.**

Patients: **Stabilized critically ill children (mean systemic arterial pressure >2 SD below normal mean for age and cardiovascular support not increased for at least 2 hrs before enrollment) with a hemoglobin ≤9.5 g/dL within 7 days after pediatric critical care unit admission.**

Interventions: **One hundred thirty-seven stabilized critically ill children with sepsis were randomized to receive red blood cell transfusion if their hemoglobin decreased to either <7.0 g/dL (restrictive group) or 9.5 g/dL (liberal group).**

Measurements and Main Results: **In the restrictive group (69 patients), 30 patients did not receive any red blood cell transfusion, whereas only one patient in the liberal group (68 patients) never underwent transfusion ($p < .01$). No clinically significant differences were found for the occurrence of new or progressive multiple organ dysfunction syndrome (18.8% vs. 19.1%; $p = .97$), for pediatric critical care unit length of stay ($p = .74$), or for pediatric critical care unit mortality ($p = .44$) in the restrictive vs. liberal group.**

Conclusions: **In this subgroup analysis of children with stable sepsis, we found no evidence that a restrictive red cell transfusion strategy, as compared to a liberal one, increased the rate of new or progressive multiple organ dysfunction syndromes. Furthermore, a restrictive transfusion threshold significantly reduced exposure to blood products. Our data suggest that a hemoglobin level of 7.0 g/dL may be safe stabilized for children with sepsis, but further studies are required to support this recommendation. (Pediatr Crit Care Med 2011; 12:512–518)**

KEY WORDS: child; critical illness; erythrocyte transfusion; infant; intensive care unit; mortality; multiple organ failure; pediatric; septic; shock

Severe sepsis and septic shock are major healthcare problems, both in adults and children (1–4). Because the pathophysiology of sepsis and septic shock involves decreased oxygen delivery, myocardial dysfunction, and mitochondrial depression, a therapeutic goal frequently advocated for these patients is to insure adequate oxygen delivery by optimizing their cardiac output and hemoglobin level (5).

It is frequently stated by intensivists that critically ill patients with sepsis require a higher hemoglobin level. In two surveys (6, 7) addressing this issue, pediatric intensivists replied that they prefer to maintain a high hemoglobin concentration in children with sepsis requiring intensive care and that sepsis would prompt them to administer red blood cell (RBC) transfusions at a higher hemoglobin threshold. In a landmark randomized clinical trial, Rivers et al (5) studied the efficacy of goal-directed therapy in adults with severe sepsis before they were stabilized and reported an improved outcome if the central venous oxygen saturation was maintained at >70% in the first 6 hrs after presentation; RBC transfusions were among the proposed means to reach a central venous oxygen saturation of 70%.

The 2008 guidelines from the Surviving Sepsis Campaign recommend that adults with sepsis with low venous oxygen saturation during the first 6 hrs of treatment should undergo transfusion to target a hematocrit >30%. Once tissue hypoperfusion is resolved, the guidelines propose that the hemoglobin level be maintained between 7.0 and 9.0 g/dL; RBC transfusion is recommended if the hemoglobin decreases to <7.0 g/dL (8, 9). The previous version of the Surviving Sepsis guidelines in 2004 (10) recommended that the hemoglobin concentration be kept within the normal range for age in children with severe sepsis and septic shock (≥10 g/dL); no specific recommendation was made for children in the more recently published guidelines (8). There is almost no evidence-based data on which to base recommendations regarding the optimal hemoglobin level for critically ill children with severe sepsis (10).

In 2007, Lacroix et al (11) published a large randomized controlled trial comparing a transfusion threshold of 7.0 g/dL and 9.5 g/dL in stabilized critically ill children and provided evidence that the lower threshold of 7.0 g/dL was safe in this patient population. In the present subgroup analysis, we compare the effect of restrictive and liberal transfusion strategies on multiple organ dysfunction and

*See also p. 592.

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Supported, in part, by the Canadian Institutes of Health Research (grants 84300 and 130770) and the Fonds de la Recherche en Santé du Québec (grant 13904).

Dr. Lacroix has disclosed that he has consulted for Novo Nordisk. The remaining authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e3181fe344b

adverse outcome in critically ill stabilized children with sepsis or septic shock.

MATERIALS AND METHODS

Protocol. A detailed description of the transfusion requirements in pediatric intensive care units (TRIPICU) results was previously reported (11). Briefly, the TRIPICU study enrolled stabilized critically ill children from 19 tertiary care pediatric intensive care units (PICUs) from four countries. Institutional review boards approved the study protocol, and parental consent was obtained. The condition of patients was considered stable if the mean systemic arterial pressure was not <2 SD below the normal mean for age and if cardiovascular support (fluid, vasoactive, and inotropic drugs) had not been increased for at least 2 hrs before enrollment. Once stabilized, children aged between 3 days and 14 yrs, with at least one hemoglobin concentration ≤9.5 g/dL within the first 7 days after PICU admission, were considered for inclusion. TRIPICU study exclusion criteria are listed in Figure 1.

Participants were randomly allocated to restrictive or liberal treatment arms. In the restrictive group, the transfusion threshold was hemoglobin of 7.0 g/dL, with a target range after transfusion between 8.5 and 9.5 g/dL; in the liberal group, the threshold was 9.5 g/dL, with a target range of 11.0 to 12.0 g/dL. Only pre-storage leukocyte-reduced allogeneic RBC units were used. Transfusion strategies were applied until intensive care unit discharge, 28 days after randomization, or until the time of death, whichever came first. Temporary suspensions from the protocol were allowed during active blood loss, emergency surgery, severe hypoxemia, or hemodynamic instability.

The primary outcome was the proportion of patients with development of or progression of multiple organ dysfunction syndromes (MODS) after randomization. MODS was defined by Proulx et al (1), and new or progressive MODS was defined by Lacroix et al (11). New MODS was considered if a patient with no organ dysfunction or one organ dysfunction at randomization developed two or more organs during the study. Progressive MODS was considered if a patient who already had MODS (dysfunction of at least two organs) at randomization had dysfunction of at least one other organ during the study. The secondary outcomes included nosocomial infections (12), mortality, duration of mechanical ventilation, and PICU length of stay.

Assignment. Randomization for the TRIPICU trial was centralized, with assignment data posted on the Internet. Patients were assigned to the study groups in blocks of two or four that were randomly distributed and stratified according to center and three age groups (28 days or younger, 29 to 364 days, and older than 364 days). Physicians, nurses, and research staff were unaware of the block randomization strategy.

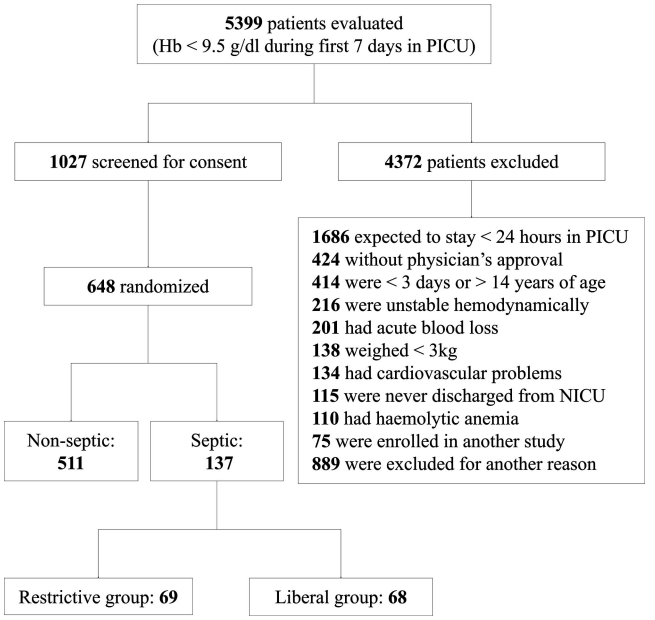

Figure 1. Enrollment and outcomes. Some patients had more than one exclusion criterion. In addition to the causes listed for exclusion, other causes were a postconception age of less than 40 wks (69 patients), severe thrombocytopenia (68), hypoxemia (65), a decision to withhold or withdraw critical care (59), predicted survival of <24 hrs (54), previous enrollment in the study (33), brain death (25), extracorporeal membrane oxygenation (22), hemofiltration (21), blood exchange transfusion (20), plasmapheresis (17), an inability to receive blood products (14), and pregnancy (1).

Blinding Procedures. The TRIPICU study was not blinded because this was not feasible. Clinical staff and parents were aware of the assignments to study groups (presence of blood bag at the bedside, increase in hemoglobin level after transfusion), but the statistician and members of the data and safety monitoring committee were unaware of the assignments.

Subgroup Study. The present study is a subgroup analysis of septic patients enrolled in the TRIPICU study. This subgroup analysis was planned before the TRIPICU study was started. Expected direction (noninferiority) of results was stated before this subgroup analysis began.

Systemic inflammatory response syndrome (SIRS) was defined by the presence of at least two of the following criteria: (1) temperature >38°C rectal or <36°C rectal; (2) heart rate >2 SD for age; (3) tachypnea with a respiratory rate >2 SD for age; and (4) white blood cell count >12 × 10^9/L (>12,000 cells/mm^3) or <4 × 10^9/L (<4,000 cells/mm^3) or >10% immature neutrophils. Sepsis was defined as a systemic inflammatory response syndrome caused by an infection (positive culture from any site or clinical evidence of infection or both). Severe sepsis was defined as sepsis with Glasgow score <15, serum lactate level above normal, or low urine output (<1 mL/kg/hr for >2 hrs). Septic shock was defined as severe sepsis with hypotension (blood pressure <2 SD for age) or need for inotropic or vasopressor agents (1, 13). Sepsis, severe sepsis, and septic shock are defined according to Bone et al (13); categories are mutually exclusive and the most severe was attributed to each patient.

Statistical Analysis. Continuous variables were compared using Student *t* test or Wilcoxon rank sum test; categorical variables were analyzed using chi-square testing. Baseline characteristics were compared using univariate descriptive statistics. Descriptive statistics are reported as mean ± SD or as numbers and proportions.

It was estimated that at least 626 patients would be required to complete the original TRIPICU study to test a noninferiority hypothesis ($p < .05$; power of 0.9; margin of safety, higher 95% CI of absolute risk reduction of 10%). The present subgroup analysis involved 137 septic patients and the statistical analyses tested noninferiority in a manner similar to that in the original study (11). Statistical analysis of the primary outcome measure was conducted using an intent-to-treat approach; for this analysis, we calculated 95% confidence intervals around the absolute risk reduction in the proportion of patients with new or progressive MODS.

All secondary analyses were conducted using an intent-to-treat approach. We compared daily pediatric logistic organ dysfunction scores, using the worst scores after baseline, and the total number of organ dysfunctions per patient. We also compared 28-day and hospital all-cause mortality, nosocomial infections, transfusion reactions, duration of mechanical ventilation, and PICU and hospital length of stay. To determine whether a restrictive transfusion strategy decreased exposure to RBCs, we compared the total number of trans-

fusions per patient and the proportion of patients who did not receive RBC transfusions in the two groups.

Differences were considered statistically significant when a two-sided α level was <0.05. No adjustments were made for multiple comparisons. Data were analyzed by a biostatistician (T.D.) with SAS software (version 9.1; SAS Institute, Cary, NC).

RESULTS

Patients at Admission and at Randomization. There were 137 septic patients enrolled from 19 sites and four countries in the septic patients subgroup, representing 21.5% of all TRIPICU patients: 69 were randomized to the restrictive group and 68 were randomized to the liberal group (Fig. 1). Table 1 describes patient characteristics on PICU admission. Both groups were similar with regard to demographic data, severity of (as measured by the Pediatric Risk of Mortality score) (14) and proportion requiring mechanical ventilation. There were fewer patients with septic shock in the restrictive compared to the liberal group (13 [19%] vs. 21 [31%]); this difference was not statistically significant ($p = .32$). Table 2 describes patient characteristics at randomization, which occurred 2.3 ± 1.7 days after entry into PICU. Severity of illness and need for mechanical ventilation were similar in both groups.

Intervention. The baseline hemoglobin concentration at randomization was 7.9 ± 1.0 in the restrictive group and 7.8 ± 0.9 g/dL in the liberal group. Time between randomization and first transfusion was 1.3 ± 2.1 days in the restrictive group vs. 0.2 ± 0.4 days in the liberal group ($p < .001$) (Table 3). As expected, the hemoglobin level before the first transfusion was significantly lower in the restrictive group (6.6 ± 0.5 vs. 7.9 ± 0.9 g/dL; $p < .01$), as well as the lowest hemoglobin level after randomization (8.3 ± 1.1 vs. 10.6 ± 1.7 g/dL; $p < .01$).

Overall, in the restrictive group, 30 patients (44%) did not receive any RBC transfusion, whereas only one patient (1%) in the liberal group did not undergo transfusion ($p < .01$). The median volume transfused was 7.6 vs. 15.7 mL/kg, respectively ($p < .01$).

Storage time of the transfused RBC units was similar in both the liberal and restrictive groups (14.3 ± 8.3 days vs. 15.6 ± 8.6 days, respectively). Eleven patients in the restrictive and six in the liberal group ($p = .96$) were temporarily suspended from the transfusion protocol.

Table 1. Patient characteristics at pediatric critical care unit admission and between admission and randomization

Characteristic	Transfusion Strategy	
	Restrictive (n = 69)	Liberal (n = 68)
Data at entry in pediatric intensive care unit		
Age (mos)	29.4 ± 39.6	32.9 ± 43.2
Gender (male)	41 (59%)	39 (57%)
Pediatric Risk of Mortality score	12.2 ± 7.4	11.3 ± 7.5
Mechanically ventilated	60 (87%)	58 (85%)
Severity of sepsis[a]		
Sepsis	37 (53%)	35 (51%)
Severe sepsis	19 (28%)	12 (18%)
Septic shock	13 (19%)	21 (31%)
Red blood cell transfusion between pediatric intensive care unit admission and randomization		
Number of transfused patients	11 (16%)	11 (16%)
Transfused volume (mL/kg) per patient	1.6 ± 4.0	2.1 ± 5.0
Red blood cell units (n) per transfused patient	1.5 ± 1.2	1.2 ± 0.4

Results are expressed as number of patients and proportions or means ± SD.

[a]Sepsis, severe sepsis, and septic shock are defined according to the study by Bone et al (13). Categories are mutually exclusive and the most severe was attributed to each patient.

Length of suspension in the restrictive group and liberal group was 6.7 ± 7.7 and 2.3 ± 2.0 days, respectively. Cointerventions, including requirement for vasoactive drugs (proportion of patients receiving at least one drug), and administration of fresh-frozen plasma, platelets, and albumin were similar in both groups.

Primary Outcome

Thirteen patients in the restrictive group and 13 in the liberal group had new or progressive MODS after randomization (18.8% vs. 19.1%; $p = .97$) (Table 4). In this subgroup analysis, the absolute risk reduction was 0.3%, whereas it was 0.4% in the original study; the 95% confidence interval (−12.8% to +13.4%) was outside the 10% margin of safety agreed on for the original study. There were no differences among the 17 patients who were temporarily suspended from the transfusion protocol, with the primary outcome being present in eight (72%) vs. five (67%) patients ($p = .56$).

Secondary Outcomes

There were no clinically significant differences in any of the measures of organ dysfunction analyzed (Table 4), including oxygenation markers and duration of mechanical ventilation. There were 12 cases (17%) of nosocomial infections in the restrictive group compared to 23 (34%) in the liberal group ($p = .02$).

There were no differences in the total PICU length of stay (13.2 ± 8.1 vs. 13.4 ± 8.4 days; $p = .74$) and in the PICU length of stay after randomization (7.5 ± 6.3 vs. 7.1 ± 6.2 days; $p = .74$). There were five deaths in the restrictive group and two in the liberal group in the PICU ($p = .44$). Two additional patients died in the restrictive group after PICU discharge but within 28 days after randomization ($p = .08$).

DISCUSSION

In this subgroup analysis of septic patients enrolled in the TRIPICU trial, an equal number of patients had new or progressive MODS in both transfusion strategy groups. Furthermore, there were no meaningful differences for any of the secondary outcomes analyzed. These results suggest that a restrictive transfusion threshold of 7.0 g/dL may be safe for hemodynamically stabilized septic patients admitted to the PICU, and that the outcome for this particular subgroup of patients was similar to that of other patients in the TRIPICU trial.

In the Surviving Sepsis campaign published in 2008, the recommended transfusion strategy for septic adult patients with low central venous oxygen saturation, who are considered to have tissue hypoperfusion and therefore are to be unstable, is to maintain a hematocrit level >30%; once stabilized, the recommended target hemoglobin level is 7.0–9.0 g/dL. The previous version of Surviv-

Table 2. Data at randomization

Characteristic	Restrictive (n = 69)	Liberal (n = 68)
Hemoglobin level (g/dL)	7.9 ± 1.0	7.8 ± 0.9
Days spent in pediatric intensive care unit before randomization	2.1 ± 1.5	2.5 ± 1.9
Age		
≤28 days	6 (9%)	1 (1%)
29–364 days	27 (39%)	29 (43%)
≥365 days	36 (52%)	38 (56%)
Sites		
Belgium (3 sites)	7 (10%)	5 (7%)
Canada (10 sites)	55 (80%)	49 (72%)
United Kingdom (2 sites)	5 (7%)	9 (13%)
United States (2 sites)	2 (3%)	5 (7%)
Pediatric Risk of Mortality score	7.4 ± 5.4	5.6 ± 4.2
Number of patients with at least one organ dysfunction	66 (96%)	65 (96%)
Organ dysfunctions[a]		
Respiratory dysfunction	63 (91%)	62 (91%)
Cardiovascular dysfunction	21 (30%)	22 (32%)
Hematological dysfunction	18 (26%)	16 (24%)
Neurological dysfunction	5 (7%)	3 (4%)
Gastrointestinal or hepatic dysfunction	3 (4%)	3 (4%)
Renal dysfunction	2 (3%)	4 (6%)
Number of patients requiring vasoactive drugs[b]	32 (46%)	37 (54%)

Results are expressed as number of patients and proportions or means ± SD.

[a]As defined by Proulx et al (1); [b]agents included dobutamine, dopamine (>5 μg/kg/min), epinephrine, milrinone, norepinephrine, phenylephrine, and vasopressin.

Table 3. Intervention (red blood cell transfusion), suspension, and cointerventions after randomization

Variable	Restrictive (n = 69)	Liberal (n = 68)	*p*
Lowest Hb level (g/dL) in pediatric intensive care unit after randomization	8.3 ± 1.1	10.6 ± 1.7	<.01
Number of patients undergoing transfusion at least once	39 (56%)	67 (99%)	<.01
Data of patients undergoing transfusion			
Patients with 1 RBC transfusion	20 (29%)	42 (62%)	<.01
Patients with 2 RBC transfusions	8 (12%)	15 (22%)	
Patients with >2 RBC transfusions	11 (16%)	10 (15%)	
Median volume transfused (mL/kg)	7.6	15.7	<.01
Data of first RBC transfusion			
Time between randomization and first transfusion (days)	1.3 ± 2.1	0.2 ± 0.4	<.001
Hb level before first transfusion (g/dL)	6.6 ± 0.5	7.9 ± 0.9	<.01
Hb level after first transfusion (g/dL)	9.2 ± 1.2	11.1 ± 1.1	<.01
Data of all RBC transfusions			
Mean length of storage (days)	14.3 ± 8.3	15.6 ± 8.6	.46
Longest length of storage (days)	17.5 ± 10.2	18.0 ± 10.5	.83
Patients temporarily suspended from study	11 (15%)	6 (9%)	.30
Cointerventions			
Fresh-frozen plasma	15 (21%)	16 (23%)	.80
Platelets	18 (26%)	11 (16%)	.14
Albumin	27 (39%)	22 (32%)	.37
Corticosteroids	30 (45%)	29 (43%)	.86
Vasoactive drugs (at least 1)	30 (44%)	31 (45%)	.80
Epinephrine	20 (29%)	14 (21%)	.25
Dobutamine	17 (24%)	13 (20%)	.49
Dopamine[a]	28 (41%)	20 (30%)	.17
Noradrenaline	15 (21%)	15 (22%)	.96

RBC, red blood cell; Hb, hemoglobin.

[a]To be considered on dopamine, the patient had to receive ≥5 μg/kg/min. Results are expressed as number of patients and proportions or means ± SD, except for the median transfused volume.

ing Sepsis published in 2004 stated that "the optimal hemoglobin for a critically ill child with severe sepsis is not known" and made no recommendations regarding the triggers (10). In the 2008 version of these guidelines, it is stated that "it is still unclear whether a lower transfusion trigger is safe or appropriate during the initial resuscitation of children with septic shock" and again made no recommendations for a hemoglobin threshold for RBC transfusion (8). In the present study, children with sepsis were evaluated once they were considered stabilized. The latter definition required that patients have a mean systemic arterial pressure not <2 SD below the normal mean for age and no increase in any cardiovascular treatment (fluids, vasoactive, and inotropic drugs) for at least 2 hrs before enrollment. Although this cohort of patients with sepsis did not include the most severely ill children with sepsis because TRIPICU exclusion criteria did not allow for their inclusion if unstable, it nonetheless suggests that a lower transfusion threshold may be safe for children with sepsis once stabilized (after the initial resuscitation phase). In addition, we found that a restrictive strategy resulted in a two-fold reduction in the number of septic patients who received a transfusion, as well as a two-fold reduction in the median volume and number of RBC transfusions, resulting in a significant reduction in exposure to blood products.

The treatment of septic patients requires optimization of oxygen delivery and utilization by tissues to minimize cellular dysfunction. RBC transfusion is administered to increase the oxygen content of arterial blood and oxygen delivery to tissues; however, increasing global oxygen delivery does not always improve oxygen consumption (15–17). In sepsis and septic shock, it is well established that microcirculatory dysfunction and mitochondrial depression occur despite adequate global oxygen delivery, resulting in regional hypoxia and oxygen extraction deficit. Microcirculatory dysfunction is characterized by heterogeneous abnormalities in blood flow, with some capillaries being underperfused, whereas others have normal to abnormally high blood flow. Sakr et al (18) have demonstrated that patients with septic shock had abnormal small vessel perfusion initially, which improved over time only in survivors. Similarly, Trzeciak et al (19) have shown that early microcirculatory perfusion indices in severe

Table 4. Outcome measures

Measure	Restrictive (n = 69)	Liberal (n = 68)	Mean Difference (95% confidence interval)	p
New or progressive multiple organ dysfunction syndrome	13 (18.8%)	13 (19.1%)	+0 (−0.128; 0.134)	.97
Specific organ dysfunctions				
Cardiovascular	5	3		
Hematological	4	5		
Renal	3	4		
Respiratory	0	0		
Neurological	3	1		
Hepatic	3	2		
Gastrointestinal	2	2		
Worst result within 24 hrs after randomization				
Pao_2/Fio_2 ratio	207 ± 102	192 ± 85	−15 (−49; −20)	.40
Blood lactate level (mmol/L)	1.7 ± 1.7	1.6 ± 2.1	−0.17 (−0.8; 0.6)	.81
Reactions to red blood cell transfusion	0 (0%)	1 (1%)		.50
Highest daily pediatric logistic organ dysfunction score after day 1	14.9 ± 16.4	12.6 ± 14.2	−2.6 (−7.7; 2.6)	.33
Patients with at least 1 adverse event	6 (9)	7 (10)		.74
Highest number of organ dysfunctions	2.13 ± 1.75	1.94 ± 1.31	−0.18 (−0.71; 0.31)	.47
Patients with at least 1 nosocomial infection	12 (17%)	23 (34%)		.02
Duration of mechanical ventilation after randomization	8.6 ± 7.2	7.3 ± 6.0	−1.2 (−3.7; 1.2)	.30
Pediatric intensive care unit length of stay after randomization	7.5 ± 6.3	7.1 ± 6.2	−0.4 (2.6; 1.9)	.74
Number of deaths in pediatric intensive care unit	5 (7%)	2 (3%)		.44
Number of deaths at 28 days	7 (10%)	2 (3%)		.08

Results are expressed as numbers and proportions or means ± SD.

sepsis and septic shock are more markedly impaired in nonsurvivors compared to survivors and are associated with increasing severity of global cardiovascular dysfunction. In addition, Brealey et al (20) showed that mitochondrial dysfunction is correlated with a less favorable outcome in sepsis. Both microcirculatory anomalies and mitochondrial dysfunction lead to the inability to increase oxygen consumption, which cannot be immediately improved with RBC transfusion because of the changes that occur during the storage process. Stored RBC units have decreased 2,3-diphosphoglycerate and S-nitrosohemoglobin levels, which cause abnormal vasodilatory responses to hypoxemia and mismatch between local oxygen delivery through small vessels and O_2 requirements in tissues (21, 22). Stored RBCs are less deformable (23), contain more extracellular ubiquitin (24) and advanced glycation end products (25), express more phosphatidylserine (26), and induce more cytokine production (27) and secretory phospholipase A_2 (28). All these changes are known to have immunologic or pro-coagulant properties, which may further contribute to the inability of RBC transfusion to rapidly increase tissue oxygen consumption in critically ill patients.

Besides uncertainty with regard to improvement of oxygen consumption, there are several other issues associated with transfusion of any blood product that require consideration. The risks associated with RBC transfusion are well established and include acute transfusion reactions (29, 30) and infectious disease transmission (31); some studies even suggesting an increased incidence rate of MODS, morbidity, and mortality (32–34). In this study, we found that a restrictive transfusion strategy resulted in a two-fold reduction in both the number of patients undergoing transfusion and the median volume transfused. Almost all patients (99%) in the liberal group received a transfusion compared to only 56% of those in the restrictive strategy group. Thus, a restrictive transfusion strategy allowed a significant reduction in RBC transfusion and its inherent risks without increasing the rate of new or progressive MODS, mortality, or any other MODS descriptor.

Interestingly, our data also showed that patients in the liberal group had significantly more nosocomial infections than those in the restrictive group (23 vs. 12 cases; $p = .02$). Whereas other studies have show that RBC transfusions are associated with increased nosocomial infections (33, 35, 36), there was only a trend in the initial TRIPICU study. This might be explained by a combined effect of transfusions and septic state, a hypothesis supported by data suggesting that preexisting infections and RBC transfusions are independently associated with nosocomial infections (37). One hypothesis could be that sepsis induces an immunomodulation that renders the patient more prone to contract transfusion-associated nosocomial infections.

Certain limitations in our study must be recognized. First, it could be argued that the patients included in TRIPICU were stabilized and therefore did not have the most severe cases of sepsis and septic shock, because patients had to have a mean systemic arterial pressure >2 SD below the normal mean for age and no increase in cardiovascular support (fluid, vasoactive, and inotropic drugs) for at least 2 hrs before enrollment. However, our cohort of septic patients was nonetheless quite ill, and half of them required inotropic or vasopressor support or both, and 90% had respiratory dysfunction. Second, because the TRIPICU trial protocol was written in 2000, the definitions of sepsis, severe sepsis, and septic shock used were based on the 1992 definitions of the American College of Chest Physicians (13), which were adapted for the pediatric population by Proulx et al (1), and not the more recent 2001 definitions (38). Nevertheless, the two sets of definitions are quite similar, because the 2001 definitions use the definition for organ dysfunctions in children cited by Proulx et al. Third, the deaths during PICU stay and at 28 days were not significantly different between both groups, but these results should be interpreted cautiously because the number of deaths was low. Nevertheless, no other secondary outcome measuring morbidity

was different between the two groups, and this further supports the findings with regard to mortality. Fourth, the investigators and members of the Canadian Critical Care Trials Group had *a priori* considered the following as a statistically significant result for the original TRIPICU noninferiority trial: a higher 95% confidence interval for the absolute risk reduction that is lower than a 10% margin of safety when comparing the proportion of patients with new or progressive MODS in the restrictive and liberal group. The 95% confidence interval of −12.8% does not confirm a noninferiority hypothesis, which is likely attributable to the fact that this subgroup analysis is underpowered to attain statistical significance. Finally, the most important limitations of our study are the pitfalls inherent to any subgroup analysis that preclude the possibility of generating definitive conclusions and, at best, allow for hypothesis generation only (39). Hence, no definitive recommendations regarding transfusion thresholds in stabilized children with sepsis can be made. It is nonetheless striking that the frequency of the primary outcome in the two transfusion groups was similar.

To our knowledge, there are no other studies that have prospectively evaluated the safety of a restrictive transfusion strategy in septic patients. Furthermore, it has been shown that there are significant variations in transfusion practice patterns among pediatric critical care practitioners with respect to the threshold hemoglobin concentration for RBC transfusion in critically ill septic patients (6, 33). Therefore, the results reported in this article are important, even though it is a subgroup analysis. Our results are certainly generalizable because the population is representative of North American and European centers. Furthermore, the trial was pragmatic, allowing for suspension from the study protocol for unstable patients and therefore reflecting real-life clinical situations of critically ill patients. The strength of these findings is enhanced by the excellent adherence to the research protocol (nearly 99% of patients in the TRIPICU study met the 80% adherence criterion), by the fact that no patient was lost to follow-up, and by the remarkable similarity of the results reported in the overall TRIPICU study and two other subgroup analyses of cardiac surgery (40) and general surgery patients (41).

CONCLUSIONS

In conclusion, in this subgroup analysis of children with stable sepsis, we found no evidence that a restrictive red cell transfusion strategy, as compared to a liberal one, increased the rate of new or progressive MODS. Furthermore, a restrictive transfusion threshold significantly reduced exposure to blood products. Our data suggest that a hemoglobin level of 7.0 g/dL may be safe for children with stabilized sepsis, but further studies are required to support this recommendation.

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