RBC Transfusion Practice in Pediatric Extracorporeal Membrane Oxygenation Support

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Objectives: To determine RBC transfusion practice and relationships between RBC transfusion volume and mortality in infants and children treated with extracorporeal membrane oxygenation.

Design: Secondary analysis of a multicenter prospective observational study.

Setting: Eight pediatric institutions within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's Collaborative Pediatric Critical Care Research Network.

Patients: Patients age less than 19 years old treated with extracorporeal membrane oxygenation at a participating center.

Interventions: None.

Measurements and Main Results: Clinical data and target hemoglobin or hematocrit values (if set) were recorded daily by trained bedside extracorporeal membrane oxygenation specialists and research coordinators. Laboratory values, including hemoglobin and hematocrit, were recorded daily using the value obtained closest to 8:00 AM. RBC transfusion was recorded as total daily volume in mL/kg. Multivariable logistic regression was used to determine the relationship between RBC transfusion volume and hospital mortality, accounting for potential confounders. Average goal hematocrits varied across the cohort with a range

of 27.5–41.3%. Overall, actual average daily hematocrit was 36.8%, and average RBC transfusion volume was 29.4 mL/kg/d (17.4–49.7 mL/kg/d) on extracorporeal membrane oxygenation. On multivariable analysis, each additional 10 mL/kg/d of RBC transfusion volume was independently associated with a 9% increase in odds of hospital mortality (adjusted odds ratio, 1.09 [1.02–1.16]; $p = 0.009$).

Conclusions: In this multicenter cohort of pediatric extracorporeal membrane oxygenation patients, daily hematocrit levels were maintained at normal or near-normal values and RBC transfusion burden was high. RBC transfusion volume was independently associated with odds of mortality. Future clinical studies to identify optimum RBC transfusion thresholds for pediatric extracorporeal membrane oxygenation are urgently needed. (*Crit Care Med* 2018; 46:e552–e559)

Key Words: blood transfusion; extracorporeal membrane oxygenation; pediatric

There are no prospective studies evaluating optimum RBC transfusion thresholds for infants and children on extracorporeal membrane oxygenation (ECMO) support, and it is believed that RBC transfusion is often guided by institutional policies targeting normal or near-normal hematocrit values (1). Consequently, RBC transfusion burden among neonatal and pediatric ECMO patients may be exceptionally high, with single-center reports suggesting up to 30–40 mL/kg/d (2–4). However, little is known about RBC transfusion practice across multiple centers.

The risk/benefit balance of RBC transfusion to treat mild anemia in infants and children on ECMO remains unclear. Certainly, maintaining normal or near-normal hematocrit values stands in stark contrast to current evidence-based RBC transfusion practice guidelines which recommend much lower transfusion thresholds for critically ill patients not on ECMO (5, 6). Likewise, multiple single-center reports suggest that RBC transfusion volume is independently associated with mortality (4, 7–9). However, relationships between RBC transfusion burden and clinical outcomes among neonatal and pediatric ECMO patients across multiple centers are unknown. These data are essential to inform future prospective trials to determine optimum RBC transfusion strategies for infants and children on ECMO.

The recently completed Bleeding and Thrombosis during ECMO (BATE) study which enrolled 514 consecutive pediatric ECMO patients at eight pediatric institutions within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's Collaborative Pediatric Critical Care Research Network (CPCCRN) offers a unique opportunity to evaluate multicenter RBC transfusion epidemiology in neonatal and pediatric ECMO patients (10). As such, we conducted a secondary analysis of the BATE dataset to determine RBC transfusion practice and relationships between RBC transfusion burden and mortality among infants and children receiving ECMO support.

METHODS

Setting and Subjects

This study is a secondary analysis of data collected for the BATE study. The details of the BATE study methodology are previously published (10). In brief, BATE was a prospective observational study which included all patients less than 19 years old treated with ECMO in a neonatal ICU (NICU), PICU, or cardiothoracic ICU (CICU) at one of eight participating centers within the CPCCRN between December 2012 and September 2014. The study was approved with a waiver of informed consent by the Institutional Review Boards at each of the participating hospitals and the Data Coordination Center at the University of Utah.

Clinical Data and Definitions

Data were recorded by trained bedside ECMO specialists and research coordinators. Baseline data included demographics, diagnoses, laboratory values, ventilator settings, Vasoactive Inotrope Scores (VIS), and ECMO indication. Laboratory values while on ECMO, including hemoglobin and hematocrit, were collected once daily using the value obtained closest to 8:00 AM. Transfusion data were collected as total daily volumes of RBCs or whole blood. Bleeding complication in the primary study was defined as either bleeding requiring RBC transfusion or intracranial hemorrhage (10). For the purposes of the current analysis, bleeding complication was defined as bleeding requiring RBC transfusion on any study day. Intended transfusion practice was defined by hemoglobin and/or hematocrit goals as recorded by the bedside ECMO specialist. Bedside ECMO specialists were asked to record whether a goal hemoglobin or hematocrit level was set at ECMO initiation and the value of that goal. For each subsequent ECMO day, the specialist was asked to record goal hemoglobin or hematocrit values only if they had changed from previous. Actual transfusion practice was defined by the surrogate marker of average daily hematocrit values across all days of ECMO support for each individual subject because pretransfusion hemoglobin/hematocrit values were not recorded. Transfusion practice was assessed by center and by ICU (NICU, PICU, CICU) rather than by patient diagnosis or ECMO indication because we were primarily interested in physician/ECMO team practice patterns. Acute and chronic diagnoses were identified by review of physician documentation. Multiple measures were used to assess baseline severity of illness, including pre-ECMO Pediatric Risk of Mortality III score (11), pre-ECMO arterial pH, pre-ECMO oxygenation index, and pre-ECMO VIS. VIS was categorized as none (no vasoactive medications), low (VIS < 20), or high (VIS ≥ 20). Baseline immunocompromised state was defined as acute or chronic diagnosis of cancer, hematologic disorder, transplant, HIV infection, immunodeficiency, or adrenal insufficiency.

Statistical Analysis

Interval variables were summarized using mean ± SD or median (interquartile range). Nominal variables were summarized

with counts and percentages and tested for associations using Fisher exact test. Monte Carlo approximations were used to estimate *p* values for Fisher exact test to make their computation more practical on large tables.

Univariable analyses were performed to identify factors associated with in-hospital mortality. Univariable analyses were stratified by PICU, CICU, and NICU locations and the overall cohort in order to assess for potential interactions based on ICU. A single multivariable logistic regression model was then created to assess the relationship between mean daily RBC transfusion volume and in-hospital mortality across the entire cohort. Variables were considered for inclusion in the multivariable model if they were 1) available for greater than 90% of the cohort and 2) associated with mortality ($p < 0.10$) on univariable analyses. The final model was selected using a bidirectional stepwise selection process with a criterion of *p* value of less than 0.05 to enter and stay in the multivariable model. Adjusted odds ratios and the associated 95% CIs are reported for all variables in the final model. Using the same methodology, a second multivariable logistic regression model was built to assess the relationship between mean daily hematocrit and in-hospital mortality. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

All 514 subjects in the BATE study were included in these analyses. Demographic information, ECMO indication, mode of ECMO, and subject outcomes are in **Table 1**. As expected, respiratory indications predominated in the NICU and PICU, whereas cardiac indications predominated in the CICU. Across all ICUs, the majority of subjects were supported with veno-arterial ECMO. Overall, average duration of ECMO support was 7.4 ± 8.3 days, with about a quarter of subjects treated with ECMO for greater than 9 days. Overall, in-hospital mortality was 45%, with the highest mortality rate among subjects treated in the CICU.

Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/D413) depicts how often a hemoglobin and/or a hematocrit goal was recorded by the bedside ECMO specialist on the first day of ECMO treatment. Across all centers and ICUs, an RBC transfusion threshold was set for 92% of subjects. However, the proportion of subjects with a specified threshold varied widely across units and centers, ranging from as high as 100% to as low as 23%. Hematocrit as opposed to hemoglobin values were used to define goals in the majority of cases. Goal hematocrit values varied across units and centers (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/D414). Within most centers/ICUs, goal hematocrit values were similar for veno-arterial versus veno-venous ECMO patients and were higher in NICU subjects compared with PICU and CICU subjects. Among PICU and CICU subjects, average goal hematocrit values ranged between 27.5% and 41.3%. These values approximate hemoglobin values of 9.2 g/dL to 13.3 g/dL, respectively. For the majority of subjects, there were no changes in goal

hematocrit across the study duration. In 21.5% of subjects, the goal hematocrit was decreased on at least 1 study day, and in 8.8%, the goal was increased.

Consistent with stated goals, average daily hematocrit values overall ranged from a median of 35.0% to 38.7% across ICUs (**Table 2**). Across study days, for subjects treated with ECMO in the PICU, daily mean hematocrit values remained fairly stable. The same was true for subjects treated in the CICU after ECMO day 2. Mean daily hematocrit values for NICU subjects, by contrast, tended to decrease over time (**Fig. 1**). Overall, average volume of whole blood or RBC transfusion was 29.4 mL/kg/d (17.4–49.7 mL/kg/d), with the highest transfusion burden among CICU subjects (Table 2). Whole blood transfusion was rare—representing only 0.3% of RBC-containing transfusions. Regarding potential causes of anemia, bleeding was very common. Details of bleeding events and anticoagulation management are previously published (10). Briefly, 65.8% of patients had bleeding requiring transfusion on any study day, and over 80% of subjects received greater than 40 mL/kg total blood products on at least 1 study day. Average daily blood loss from laboratory samples ranged from as low as 10% of average daily RBC transfusion volume in CICU patients to as high as 26% in NICU patients.

Variables associated with mortality on univariable analyses can be found in **Supplemental Table 3** (Supplemental Digital Content 3, http://links.lww.com/CCM/D415). By multivariable logistic regression, controlling for bleeding requiring transfusion on any study day, primary ECMO indication, baseline immune compromise, chronic neurologic condition, meconium aspiration syndrome, congenital diaphragmatic hernia, mean daily Pao_2, and presence of hepatic or renal organ failure, higher RBC transfusion volume remained independently associated with hospital mortality (**Table 3**). In a separate multivariable regression model, mean daily hematocrit was not independently associated with hospital mortality (adjusted odds ratio, 1.01 [0.94–1.07]; $p = 0.87$).

DISCUSSION

In the largest cohort to date to evaluate RBC transfusion practice in pediatric ECMO patients, RBC transfusion burden was high—roughly the equivalent of replacing the child's entire circulating blood volume for every 3 days on ECMO support. At the same time, the majority of subjects' hematocrit values were maintained at levels much higher than current standard of care for critically ill children not receiving ECMO support.

Our findings are consistent with previous single-center reports suggesting RBC transfusion burdens as high as 30–40 mL/kg/d among infants and children on ECMO (2–4). Some of the high RBC transfusion burden is likely due to bleeding, as evidenced by the majority of subjects having bleeding requiring transfusion on at least 1 study day. Blood loss due to laboratory sampling may also contribute to transfusion burden, particularly for neonates. However, some of the transfusion burden also likely stems from RBC transfusion to treat mild anemia. Although there was significant variation in RBC transfusion

TABLE 1. Description of Cohort

Characteristics	Location of ECMO Care			Overall (n = 514)
	PICU (n = 103)	Neonatal ICU (n = 156)	Cardiac ICU (n = 255)	
Age (mo), median (IQR)	25.0 (3.8–158.8)	0.1 (0.0–0.1)	2.4 (0.3–14.5)	0.7 (0.1–11.5)
Male, n (%)	48 (46.6)	96 (61.5)	158 (62.0)	302 (58.8)
Primary ECMO indication, n (%)				
Respiratory	66 (64.1)	143 (91.7)	28 (11.0)	237 (46.1)
Cardiac	28 (27.2)	13 (8.3)	166 (65.1)	207 (40.3)
Extracorporeal cardiopulmonary resuscitation	9 (8.7)	0 (0.0)	61 (23.9)	70 (13.6)
Veno-arterial ECMO, n (%)	62 (60.2)	119 (76.3)	250 (98)	431 (83.9)
Acute diagnoses, n (%)				
Airway abnormality	6 (5.8)	2 (1.3)	4 (1.6)	12 (2.3)
Cardiac arrest	10 (9.7)	4 (2.6)	35 (13.7)	49 (9.5)
Cardiovascular disease (acquired)	10 (9.7)	5 (3.2)	50 (19.6)	65 (12.6)
Cardiovascular disease (arrhythmia)	4 (3.9)	2 (1.3)	12 (4.7)	18 (3.5)
Cardiovascular disease (congenital)	20 (19.4)	5 (3.2)	168 (65.9)	193 (37.5)
Hypoxic/anoxic injury	2 (1.9)	14 (9.0)	1 (0.4)	17 (3.3)
Gastrointestinal disorder	4 (3.9)	2 (1.3)	17 (6.7)	23 (4.5)
Pertussis or sepsis	28 (27.2)	49 (31.4)	14 (5.5)	91 (17.7)
Pneumonia or bronchiolitis	15 (14.6)	3 (1.9)	6 (2.4)	24 (4.7)
Shock (nonseptic)	5 (4.9)	3 (1.9)	6 (2.4)	14 (2.7)
Respiratory distress/failure	75 (72.8)	20 (12.8)	75 (29.4)	170 (33.1)
Neurologic condition	5 (4.9)	10 (6.4)	2 (0.8)	17 (3.3)
Meconium aspiration syndrome	1 (1.0)	46 (29.5)	0 (0.0)	47 (9.1)
Congenital diaphragmatic hernia	3 (2.9)	53 (34.0)	0 (0.0)	56 (10.9)
Persistent pulmonary hypertension of the newborn	2 (1.9)	88 (56.4)	0 (0.0)	90 (17.5)
Chronic diagnoses, n (%)				
Chronic lung disease	8 (7.8)	2 (1.3)	7 (2.7)	17 (3.3)
Congenital anomaly or chromosomal defect	17 (16.5)	66 (42.3)	35 (13.7)	118 (23.0)
Neurologic condition	10 (9.7)	4 (2.6)	13 (5.1)	27 (5.3)
Cardiovascular disease (congenital)	15 (14.6)	34 (21.8)	48 (18.8)	97 (18.9)
Immunocompromised, n (%)	16 (15.5)	7 (4.5)	19 (7.5)	42 (8.2)
Duration of ECMO (d), n (%)				
< 2	13 (12.6)	12 (7.7)	63 (24.7)	88 (17.1)
2 to < 4	15 (14.6)	17 (10.9)	86 (33.7)	118 (23.0)
4 to < 9	36 (35.0)	61 (39.1)	76 (29.8)	173 (33.7)
≥ 9	39 (37.9)	66 (42.3)	30 (11.8)	135 (26.3)
Length of ICU stay (wk), median (IQR)	4.3 (2.0–8.2)	4.6 (2.3–8.4)	3.4 (1.9–6.2)	4.0 (2.0–7.3)
Length of hospital stay (wk), median (IQR)	5.5 (2.5–10.2)	4.9 (2.3–9.0)	5.0 (2.3–10.1)	5.2 (2.3–9.7)
New documented infection on at least 1 study day, n (%)	45 (43.7)	17 (10.9)	50 (19.6)	112 (21.8)
In-hospital mortality, n (%)	45 (43.7)	55 (35.3)	132 (51.8)	232 (45.1)

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

TABLE 2. Transfusion and Bleeding by ICU

| Characteristics | Location of Extracorporeal Membrane Oxygenation Care | | | |
	PICU (n = 103)	Neonatal ICU (n = 156)	Cardiac ICU (n = 255)	Overall (n = 514)
Mean daily hematocrit (%), median (IQR)	35.0 (33.1–37.5)	38.7 (36.4–40.1)	36.3 (34.0–38.8)	36.8 (34.6–39.3)
Average daily RBC transfusion volume (mL/kg), median (IQR)	15.8 (10.7–32.4)	29.3 (21.0–44.1)	35.0 (21.0–59.9)	29.4 (17.4–49.7)
Average daily platelet transfusion volume (mL/kg), median (IQR)	8.3 (4.4–14.9)	16.1 (11.6–21.8)	10.9 (5.4–19.7)	12.1 (6.8–20.4)
Average daily plasma transfusion volume (mL/kg), median (IQR)	3.4 (0.9–10.0)	7.1 (3.0–13.5)	8.2 (2.7–17.5)	7.0 (2.1–15.1)
Average daily cryoprecipitate volume (mL/kg), median (IQR)	0.0 (0.0–0.7)	0.5 (0.0–1.5)	0.6 (0.0–2.4)	0.4 (0.0–1.7)
Massive transfusion on any study day, n (%)[a]	69 (67.0)	143 (91.7)	211 (82.7)	423 (82.3)
Average daily blood loss from laboratory samples (mL/kg), median (IQR)	2.0 (0.6–3.8)	7.6 (5.1–10.4)	3.4 (1.2–6.1)	4.4 (1.5–7.7)
Bleeding requiring a transfusion on any study day, n (%)	70 (68.0)	83 (53.2)	185 (72.5)	338 (65.8)

IQR = interquartile range.

[a]Massive transfusion defined as receipt of > 40 mL/kg total blood products in 1 day.

practice across centers, most institutions transfused to maintain hematocrit values greater than 30% (roughly equivalent to a hemoglobin of 10 g/dL).

Current evidence-based guidelines recommend against routine RBC transfusion for hemoglobin levels greater than 7 g/dL (approximate hematocrit of 21%) in hospitalized patients, including hemodynamically stable critically ill patients (5). These recommendations stem from multiple randomized controlled trials of restrictive versus liberal transfusion strategies in critically ill adults and children which have failed to identify benefit to liberal RBC transfusion (5, 6, 12–16). These studies, however, excluded patients requiring ECMO support. In fact, no prior study has been conducted to establish optimum RBC transfusion thresholds for pediatric ECMO patients. Thus, it is not surprising that practice variability exists.

It is unclear whether the benefits of RBC transfusion to support near-normal hematocrit while on ECMO outweigh the risks. The primary goal of RBC transfusion in the ICU is to augment oxygen-carrying capacity in order to support adequate tissue oxygenation. ECMO patients may receive little benefit in this regard from RBC transfusion to treat mild anemia. In a prospective observational study of 45 children receiving ECMO support, Fiser et al (17) found that RBC
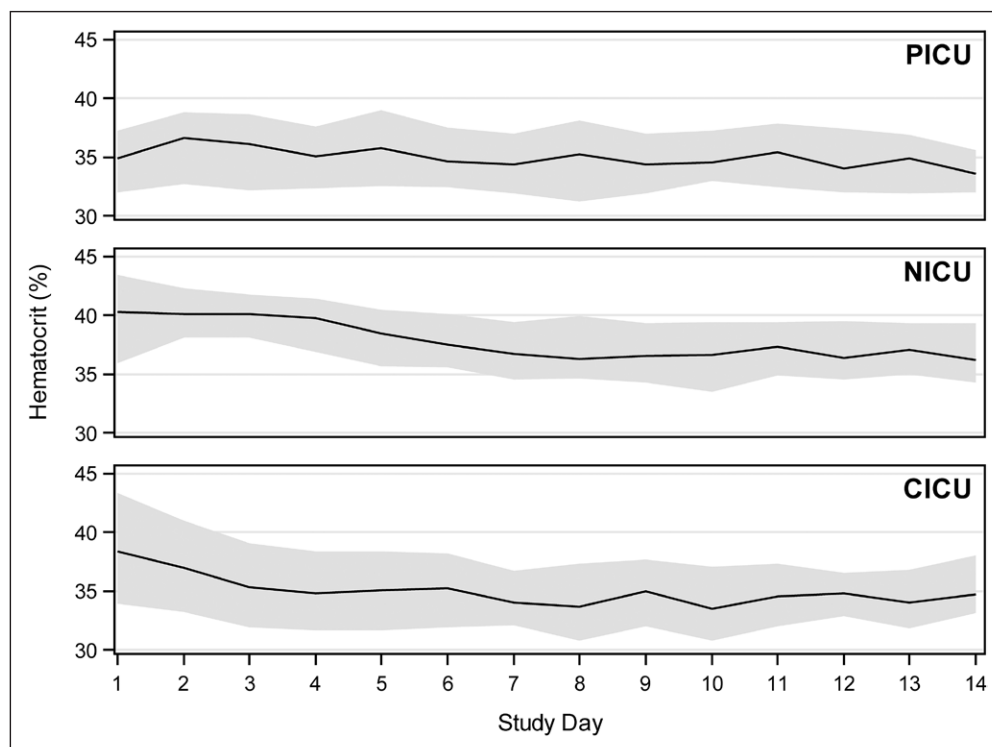
Figure 1. Median (*lines*) and 25–75th percentile ranges (*shaded areas*) of average daily hematocrit per patient are displayed across study days up to extracorporeal membrane oxygenation (ECMO) day 14 for subjects treated with ECMO in a PICU, neonatal ICU (NICU), or cardiothoracic ICU (CICU).

TABLE 3. Multivariable Model of Mortality

Characteristics	In-Hospital Mortality (n = 514)	
	Adjusted OR (95% CI)	p
Average daily RBC transfusion volume (10 mL/kg)	1.09 (1.02–1.16)	0.009
Bleeding requiring a transfusion on any study day	1.23 (0.79–1.92)	0.366
Primary extracorporeal membrane oxygenation indication		0.042
Respiratory	Reference	
Cardiac	1.48 (0.87–2.49)	
Extracorporeal cardiopulmonary resuscitation	2.40 (1.21–4.76)	
Mean daily Po_2 in arterial blood (10 mm Hg)	1.04 (1.02–1.07)	0.002
Hepatic organ failure on at least 1 study day	2.46 (1.60–3.78)	< 0.001
Renal organ failure on at least 1 study day	2.49 (1.61–3.85)	< 0.001
Immunocompromised	2.83 (1.29–6.20)	0.010
Chronic neurologic condition	0.20 (0.04–0.97)	0.046
Meconium aspiration syndrome	0.15 (0.04–0.55)	0.004
Congenital diaphragmatic hernia	2.82 (1.42–5.60)	0.003

OR = odds ratio.

Additional variables which were considered for inclusion in the multivariable model include weight, preextracorporeal membrane oxygenation (ECMO) Pediatric Risk of Mortality III score, baseline immunocompromised state, ICU location of ECMO care, mode of ECMO, hospital length of stay (LOS) prior to ECMO, ICU LOS prior to ECMO, massive transfusion on any study day, mean daily central venous oxygen saturation, mean daily Po_2 in arterial blood, duration of ECMO, mean daily ECMO flow rate, hepatic organ failure on at least 1 study day, renal organ failure on at least 1 study day, thrombotic event, and diagnoses of cardiac arrest, acquired cardiovascular disease, congenital cardiovascular disease, pertussis or sepsis, neurologic condition, meconium aspiration syndrome, congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn, and congenital anomaly or chromosomal defect.

transfusion failed to enhance tissue oxygenation, as measured by central venous oxygen saturation (Svo_2) and near-infrared spectroscopy, when used to treat mild anemia in children on ECMO. While the majority of transfusions were given to patients with an adequate Svo_2 of greater than 70%, even in those with a low pretransfusion Svo_2 of less than 70%, posttransfusion Svo_2 only increased in 16% of subjects. These data suggest that even with evidence of oxygen debt, RBC transfusion may not consistently improve tissue oxygenation. On the other hand, RBC transfusion may have benefits outside of oxygen-carrying capacity. For instance, preclinical and limited clinical evidence suggest that anemia may contribute to platelet dysfunction, although this has not been evaluated in the ECMO population (18, 19). If treating anemia helps preserve

platelet function on ECMO, RBC transfusion could help avoid bleeding complications, although relationships between anemia and bleeding on ECMO at this time are unknown. In the current analysis, lower daily hematocrit was not independently associated with mortality, supporting the hypothesis that at least mild permissive anemia is likely safe in pediatric ECMO. Likewise, limited adult data suggest that outcomes following the institution of restrictive RBC transfusion protocols for ECMO patients are similar to historical controls—again suggesting that permissive anemia may be safe (20, 21).

Regarding transfusion risks, given their severity of underlying organ dysfunction, ECMO patients may face particularly high risks of complications such as transfusion-related immunomodulation, transfusion-related respiratory dysfunction, and thrombotic complications (22–26). In the current analysis, each additional 10 mL/kg/d of RBC transfusion volume was independently associated with a 9% increase in odds of mortality. These findings are consistent with previous reports suggesting associations between RBC transfusion volume and mortality in ECMO patients (4, 7–9). A single-center retrospective study of 132 adults supported on ECMO for a variety of indications identified RBC transfusion volume as an independent predictor of mortality, accounting for important covariates including serious bleeding events (8). Among children, a previous single-center retrospective study reported a 24% increase in adjusted odds of death for each additional 10 mL/kg/d of RBC transfusion volume among 203 infants and children supported with ECMO for noncardiac indications (4). Relationships between RBC transfusion volume and mortality remained significant after accounting for potential confounders including patient weight, ECMO mode, diagnosis, and hemorrhagic complications. Unlike the current analysis, relationships between RBC transfusion volume and mortality were not significant in the combined cohort including cardiac and noncardiac indications. This may have been due to more significant bleeding complications in the cardiac cohort as evidenced by a very high RBC transfusion burden of 105 mL/kg/d on ECMO. Taken together, these data suggest that excess RBC transfusion may be harmful for ECMO patients. However, because of likely residual confounding in retrospective analyses, one cannot ascribe causality to these relationships. It is notable, therefore, that in a small pre-post analysis of neonates supported with ECMO for refractory hypoxemic respiratory failure, a protocol change from a target hematocrit of 40–35% was significantly associated with decreases in RBC transfusion volume and shorter ECMO durations (27). Although mortality differences were not observed, it is likely that the study was underpowered to detect such a difference. In adults, Cahill et al (28) recently published a single-center pre-post analysis of a comprehensive transfusion protocol in adult cardiac ECMO patients. The protocol included an RBC transfusion threshold of 8 g/dL and was associated with significantly reduced RBC transfusion burden and improved survival in the postprotocol era. Similarly, in a single-center report of 38 adults supported with ECMO for acute respiratory distress syndrome, a blood conservation protocol using an RBC transfusion threshold of

7 g/dL was associated with lower RBC transfusion burden and fewer bleeding events compared with historical controls (20). Taken together, these data suggest that more restrictive RBC transfusion thresholds may be beneficial for ECMO patients, although optimum thresholds for pediatric ECMO remain unknown. Given the exceptionally high RBC transfusion burden while on ECMO and the potential associated harm, additional prospective studies to determine and evaluate best RBC transfusion practice in neonatal and pediatric ECMO are urgently needed.

Our study has several limitations. First, because pretransfusion hematocrit values were not recorded, we are unable to determine what values prompted transfusion. However, daily hematocrit goals were recorded for most subjects such that intended practice could be assessed. Additional factors which may have prompted RBC transfusion outside of stated goals are unknown. However, overall mean daily hematocrit values were similar to stated goals suggesting that usual care likely guided RBC transfusion. Second, because bleeding was defined subjectively as bleeding requiring transfusion rather than a more objective measure, it is likely that at least some of the relationship between RBC transfusion volume and mortality may be due to differences in bleeding volume. Similarly, plasma hemoglobin values were not recorded for all centers, and therefore data on hemolysis as another potential cause for anemia were not available. Residual confounding due to bleeding or hemolysis may explain the observed increase in odds of mortality related to RBC transfusion burden without apparent benefit to lower hematocrit values. Given the limitations of the dataset, we are unable to definitively separate the effects of bleeding or other causes of anemia from those of RBC transfusion. Future prospective trials are necessary to answer this important question. Third, data about RBC product characteristics—including prestorage leukoreduction, storage duration, irradiation, or other special processing—were not recorded. This is important because the risk/benefit balance of RBC transfusion may differ based on the individual products used (29–32). We view this as a highly relevant topic for ongoing study. Additionally, pediatric ECMO represents a highly heterogeneous cohort, and it may be that relationships between RBC transfusion volume and mortality differ among ECMO subpopulations. While one of the largest multicenter prospective observational studies to date in pediatric ECMO, the sample size was still insufficient to allow robust multivariable analyses of subpopulations, while accounting for other center-related differences. Similarly, the sample size was inadequate to permit multilevel modeling to account for center-level, ICU-level, and patient-level factors. We view this as an important area for future study. Last, although mortality rates in pediatric ECMO remain high, additional outcome measures are also important and may differentially relate to RBC transfusion practice. Particularly, neurodevelopmental outcomes, ECMO duration, and duration of organ dysfunction among survivors are highly relevant outcome measures to consider in the design of subsequent studies evaluating RBC transfusion practice in pediatric ECMO.

In conclusion, in this multicenter cohort of pediatric and neonatal ECMO patients, RBC transfusion practice varied significantly across institutions, and overall RBC transfusion burden was high. Although RBC transfusion volume was independently associated with hospital mortality, these analyses are likely confounded by bleeding or other causes of anemia. A lower daily hematocrit was not associated with mortality, suggesting that more restrictive RBC transfusion strategies may be safe in pediatric ECMO. Optimum RBC transfusion strategies for pediatric ECMO remain unknown—representing a vitally important research priority.

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