Perioperative Pediatric Erythrocyte Transfusions: Incorporating Hemoglobin Thresholds and Physiologic Parameters in Decision-making

Laura A. Downey, M.D., Susan M. Goobie, M.D., F.R.C.P.C.

Erythrocyte transfusions in pediatric patients during the perioperative period are indicated for the treatment of severe anemia, bleeding, and/or decreased oxygen-carrying capacity resulting in end-organ dysfunction. However, erythrocyte transfusions can place pediatric patients at risk for transfusion-related adverse outcomes,[1] including infection,[2,3] respiratory complications,[2,4] increased transplant graft failure,[2,5,6] alloimmunization,[7,8] prolonged hospital stays,[9] multiorgan failure,[3,10] and death.[1,3] In addition to the risks, recent blood shortages and increased costs associated with allogeneic blood products have resulted in more healthcare entities focusing on minimizing transfusions without compromising patient safety as highlighted in a recent policy brief by the World Health Organization.[11,12]

In adult surgical patients, the adoption of patient blood conservation strategies, including the "tolerance of anemia," has reduced allogeneic erythrocyte transfusions, hospital costs, and adverse events.[13,14] However, physicians have been slow to adopt these strategies in pediatric patients despite multiple pediatric studies with matched controls showing that transfusions are associated with increased morbidity and mortality.[1–6,10] In a landmark trial in pediatric intensive care patients, TRansfusion strategies for patients In Pediatric Intensive Care Units (TRIPICU), Lacroix *et al.*[15] demonstrated that a restrictive strategy reduced erythrocyte transfusions by 44% with no increase in mortality. After a decade of research, Valentine *et al.*[16] summarized in the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) the current evidence and published guidelines regarding hemoglobin transfusion thresholds for critically ill children, which support a more restrictive approach to transfusion.

Although the recommendations by Valentine *et al.*,[16] as well as a few well designed randomized trials,[15,17,18] support lower hemoglobin thresholds for hemodynamically stable pediatric patients, multiple registry-based studies have demonstrated considerable variability in the incidence and indication for erythrocyte transfusion at tertiary care children's hospitals.[19–21] In fact, perioperative erythrocyte transfusions often result in higher hemoglobin levels than even "liberal" transfusion thresholds.[20–22] Therefore, the development of universal, specific, evidenced-based perioperative hemoglobin management and erythrocyte transfusion guidelines for the anemic and/or bleeding pediatric patient would standardize care, reduce practice variability, and potentially improve safety.

However, pediatric anesthesiologists may be hesitant to adopt restrictive transfusion strategies due to a lack of robust outcome data and few evidenced-based guidelines for optimal hemoglobin thresholds pertaining to the dynamic environment of the operating room. In this review, we will summarize the most up-to-date pediatric evidence addressing the equivalency or benefits of restrictive *versus* liberal transfusion strategies across various clinical scenarios. After presenting the evidence and, when evidence is lacking, expert consensus, we discuss a novel approach incorporating recommended restrictive hemoglobin transfusion thresholds with emerging data on physiologic parameters to define optimal decision-making strategies for perioperative erythrocyte transfusions.

Pediatric Patients with Massive Hemorrhage or Critical Bleeding

Perioperative erythrocyte transfusion management in the scenario of massive hemorrhage or critical bleeding involves a dynamic strategy focusing on the individualized child's resuscitation requirements. Massive hemorrhage is defined as blood loss and/or transfusion of more than 40 ml/kg without or without hemodynamic instability. However, evidence to guide erythrocyte transfusion management in the context of massive hemorrhage for pediatric patients is sparse.

For the actively bleeding, hemodynamically unstable pediatric patient, expert consensus recommends goal-directed massive hemorrhage guidelines, including

Submitted for publication March 9, 2022. Accepted for publication August 12, 2022.

Laura A. Downey, M.D.: Department of Anesthesiology, Emory University Medical School, Atlanta, Georgia; and Department of Pediatric Cardiac Anesthesiology, Children's Healthcare of Atlanta, Atlanta, Georgia.

Susan M. Goobie, M.D., F.R.C.P.C.: Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts.

 Anesthesiology 2022; 137:604–19. DOI: 10.1097/ALN.0000000000004357

transfusion of erythrocytes, plasma, and platelets in a 1:1:1 ratio (or a 2:1:1 ratio) until the bleeding is no longer life threatening.[16] This ratio-driven, balanced resuscitation strategy is extrapolated from adult trauma. While there is no clear consensus regarding the benefits of a balanced resuscitation strategy in pediatric trauma, recent retrospective studies demonstrate decreased 24-h mortality using a balanced ratio transfusion approach.[23,24] Prospective data from Spinella *et al.*[25] and the Massive Transfusion in Children (MATIC) investigators report that a balanced ratio transfusion strategy (plasma:erythrocyte ratio greater than 1:2) may improve early survival in children with life-threatening bleeding. In the actively bleeding, hemodynamically stable pediatric patient, international perioperative goal-directed massive hemorrhage guidelines and critical bleeding protocols derived from expert consensus suggest maintaining hemoglobin level in the range of 7.0 to 8.0 g/dL in children and 9.0 to 10.0 g/dL in neonates.[16,25–27] Despite expert consensus panel agreement of 95 to 100%, Valentine *et al.*[16] acknowledge that many of these international good practice recommendations are based on weak evidence due to lack of randomized controlled trials and due to studies influenced by survivorship bias. Thus, perioperative physicians must consider the challenges of dynamic fluctuations in the physiologic status of the bleeding child while weighing the risks and benefits of blood loss and blood product transfusion. While individualized goal-directed real time transfusion management of the bleeding child is the intent, with the hemodynamic instability of massive hemorrhage, resuscitation takes precedent. As a result, the decision to transfuse is often more empirically driven in the case of ongoing hemodynamically significant blood loss.

Pediatric Noncardiac Surgical Patients

Perioperative erythrocyte transfusions in the pediatric noncardiac surgical bleeding patient may be indicated for treatment of severe anemia, hypotension, and/or decreased oxygen-carrying capacity compromising end-organ function. Procedures such as liver transplantation, craniosynostosis repair, neurosurgery, major orthopedic surgery, and thoracic and abdominal surgery are historically associated with significant blood loss requiring erythrocyte transfusions in over 50% of pediatric cases.[19]

While there are many trials in adult patients supporting restrictive (7 or 8 g/dL) hemoglobin thresholds to be noninferior or superior compared with liberal thresholds (9 or 10 g/dL) across a wide variety of clinical scenarios, critical illness, and surgical procedures,[28–33] only a few prospective trials exist in the pediatric population.[15,17,18,34] Unfortunately, these trials are focused on nonsurgical critically ill children and do not specifically consider the perioperative period. These trials, together with a few observational reports in critically ill children with nonhemorrhagic shock, are presented in table 1.

Perhaps there is a lesson to be learned from the following example of a unique population requiring multiple transfusions throughout their hospitalization. Pediatric burn patients undergo frequent skin excision and grafting procedures. A single-center study implemented a restrictive transfusion strategy (hemoglobin level greater than 7.0 g/dL) and compared the outcomes to a historic cohort (hemoglobin level greater than 10.0 g/dL). The restrictive group had lower mortality rates and less erythrocyte transfusions with no difference in sepsis rates[42] (table 1). While this may represent a change in overall burn management, this study suggests that a restrictive transfusion strategy in pediatric burn patients may improve outcomes.

Restrictive erythrocyte transfusion strategies for management of the critically ill child recommended by expert group consensus guidelines are as follows (table 2)[16]: (1) consideration of erythrocyte transfusion in the hemodynamically stable critically ill pediatric patient based on clinical judgement for a hemoglobin level of 5.0 to 7.0 g/dL, (2) transfusion is not necessary for pediatric patients with hemoglobin level greater than 7.0 g/dL, and (3) transfusion is advised against for a hemoglobin greater than 9.0 g/dL. These recommendations pertain to the children with the following conditions: critical illness, postsurgery or postprocedural, respiratory failure, sepsis, non–life-threatening bleeding, or renal replacement therapy. These recommendations exclude children with the following conditions: acute brain injury, oncologic disease, stem cell transplantation, hemolytic anemia, sickle cell anemia, severe acute respiratory distress syndrome, mechanical support, or cardiac disease. Such high-risk patients may require higher transfusion targets (hemoglobin levels between 7.0 and 10.0 g/dL), guided by physiologic parameters and clinical judgement. According to Valentine *et al.*[16] in these patients, "transfusion should be based on evidence of inadequate cardiorespiratory support or decreased systemic and/or regional oxygen delivery." Based on the expert consensus recommendations of Lacroix *et al.*[15] and Valentine *et al.*,[16] the posttransfusion goal should be to relieve the indication for transfusion and not necessarily achieve a normal hemoglobin level for age, with a reasonable general posttransfusion hemoglobin target between 7.0 and 9.5 g/dL. Finally, it must be stated that these guidelines in hemodynamically stable noncardiac surgery are based on low-quality pediatric evidence (grade 1C or 2C) or expert consensus, except for the nonsurgical critically ill child (grade 1B evidence), and must be followed up by high-quality trials to determine safe transfusion strategies for specific pediatric surgical populations.[53] While these recommendations do not specifically cover the intraoperative period, they can be used as a good practice guide for anesthesiologists caring for a stable child undergoing noncardiac surgery.

Finally, perioperative management of the hemodynamically stable bleeding child for noncardiac surgery should consider the change from baseline hemoglobin level, the

Table 1. Overview of Hemoglobin Transfusion Threshold Trials in Pediatric Perioperative Patients

Subject	Authors	Trial Type	Population	Patients (N)	Inclusion Criteria	Transfusion Threshold	Outcome	Recommendations
Cardiac patients	Willems *et al.*[35]	Subanalysis of TRIPICU (randomized control trial)	Acyanotic	125	Age > 28 days to < 14 yr	7.0 *vs.* 9.5 g/dL (protocol could be suspended for surgery and/or hemodynamic instability)	No difference in new/progressive multiorgan dysfunction syndrome	Transfusion trigger 7 g/dL is safe in hemodynamically stable cardiac patients
	Cholette *et al.*[36]	Single-center randomized control trial	Cyanotic	60	Bidirectional Glenn or Fontan	9.0 *vs.* 13.0 g/dL	No difference in mean/peak lactate, arteriovenous oxygen, and arteriocerebral oxygen; erythrocyte transfusions and donor exposure lower in the restrictive group	Hemodynamically patients with single ventricle physiology safely tolerate hemoglobin 9.0 g/dL
	de Gast-Bakker *et al.*[37]	Single-center randomized control trial	Acyanotic	103	Age > 6 weeks to < 6 yr	8.0 *vs.* 10.8 g/dL	Hospital length of stay was lower in restrictive group; no difference in adverse events between groups	Hemodynamically stable patients with cardiac disease safely tolerate hemoglobin > 8.0 g/dL
	Cholette *et al.*[38]	Single-center randomized control trial	Cyanotic/acyanotic	162	Weight < 10 kg	9.0 *vs.* 12.0 g/dL (cyanotic)/7.0 *vs.* 9.5 g/dL (acyanotic)	Transfusion adherence was 100% in acyantoic patients and 79% in cyanotic patients; Patients in the restrictive group received less transfusion; no difference between hemoglobin level, lactate, and arteriovenous oxygen	The authors conclude that both cyanotic and acyanotic infants can tolerate a restrictive transfusion strategy
Nonhemorrhagic shock	LaCroix *et al.*[15] (TRIPICU trial)	Multicenter randomized control trial (noninferiority)	Patients in pediatric ICU	637	Stable ICU patients, age > 3 days and < 14 yr	7.0 *vs.* 9.5 g/dL	No difference in new or progressive multiorgan dysfunction syndrome or death between groups; restrictive transfusion reduced erythrocyte transfusions by 44%	Transfusion trigger of 7.0 g/dL is safe in stable critically ill pediatric patients
	de Oliveira *et al.*[39]	Single-center randomized control trial	Patients with nonhemorrhagic shock	102	Age > 1 yr and < 19 yr with severe sepsis	$ScvO_2$ < 70% and hemoglobin < 10 g/dL or "standard treatment"	Intervention group was more likely to receive a transfusion within the first 6 h	Goal-directed therapy with $ScvO_2$ monitoring
	Srouji *et al.*[40]	Single-center prospective observational trial	Patients with septic shock	94	Age < 18 yr with severe sepsis	Erythrocyte transfusion within first 48 h of sepsis onset	Early erythrocyte transfusion was independent predictor of organ dysfunction; early erythrocyte transfusion was associated with increased risk for patients with lowest shock severity	Consider alternative to transfusion in pediatric patients with less sever shock
	Muszynski *et al.*[41]	Multicenter cohort study	Patients with severe sepsis	401	Severe sepsis; > 44 weeks gestational age to < 18 yr of age; no ECMO	7.4 g/dL transfusion < 48 h 9.5 g/dL transfusion > 48 h	68% of children received erythrocyte transfusion in first 48 h; early erythrocyte transfusion associated with 2.9-fold higher odds of mortality	Erythrocyte transfusions are associated with increased mortality even when controlling for confounders indicating severity of illness.

(*Continued*)

Table 1. (Continued)

Subject	Authors	Trial Type	Population	Patients (N)	Inclusion Criteria	Transfusion Threshold	Outcome	Recommendations
Burn patients	Voigt *et al.*[42]	Single-center prospective cohort study	Patients with severe burns	1,460	Pediatric burn patients at a single center admitted between 1997 and 2003 and between 2008 and 2017	Preprotocol patients, transfusion < 10.0 g/dL (759 patients); postprotocol patients, transfusion < 7.0 g/dL (701)	Restrictive transfusion strategy had lower hemoglobin levels, low intraoperative transfusion rates, lower mortality, and decreased length of hospitalization; groups had similar rates of sepsis	Pediatric burn patients have improved outcomes using a restrictive transfusion strategy (hemoglobin < 7.0 g/dL)
Africa anemia studies	Lackritz *et al.*[43]	Prospective observational study	All children admitted to a Kenyan hospital 1989 to 1990	683	Age < 3 yr of age	Transfusion < 5.0 g/dL	Transfusion in patients with hemoglobin < 3.9 g/dL decreased mortality, whereas transfusion between 4 and 5.0 g/dL did not improve mortality	Transfusion is recommended in pediatric patients with hemoglobin < 5.0 g/dL with evidence of respiratory distress or hemodynamic instability
	Maitland *et al.*[44,45] (TRACT trial)	Open label randomized control trial	Children in Uganda and Rwanda with uncomplicated anemia	1,563	Pediatric patients with uncomplicated anemia (4 to 6 g/dL); age > 2 months and < 12 yr	Patients randomized to immediate transfusion or no immediate transfusion (control; triggered by new signs of clinical anemia or hemoglobin < 4.0 g/dL)	Delaying transfusion for clinical signs reduced overall transfusions by 50%; 28-day mortality was 0.9% in the immediate transfusion *versus* 1.7% in control group without increase risk of serious adverse events	Patients with chronic stable anemia (no clinical signs of anemia) tolerate hemoglobin 4.0 to 6.0 g/dL without increased mortality or serious adverse events
	Connon *et al.*[46]	Secondary analysis of TRACT trial	Children from Uganda and Malawi surviving anemia	3,894	682 pediatric patients readmitted of the 3,894 survivors of the TRACT trial	Patients randomized to immediate transfusion or no immediate transfusion (control; triggered by new signs of clinical anemia or hemoglobin < 4.0 g/dL) for first admission	Factors that increased risk of readmission included: severe anemia (hemoglobin < 3.6 g/dL), younger age, acute severe malaria, HIV infection, and sickle cell disease	Patients with uncomplicated severe anemia (4-6g/dL) who did not a have a transfusion during the initial admission had the lowest rates of readmission
Neonates	Kirpalani *et al.*[34] (PINT study)	Multicenter prospective randomized trial	Extremely low-birth-weight infants	451	< 1,000 g, gestational age of < 31 weeks, > 48 h since delivery	Hemoglobin (g/dL; central) threshold triggers erythrocyte transfusion based on age and respiratory support	The primary outcome was the combination of either death or survival with bronchopulmonary dysplasia, severe retinopathy of prematurity, or brain injury; fewer infants received one or more transfusions in the low threshold group; rates of the primary outcome were 74.0% in the low-threshold group and 69.7% in the high-threshold group	Restrictive transfusion strategy did not increase the likelihood of death, cognitive deficit, cerebral palsy, necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity at 24 months

(*Continued*)

Table 1. (Continued)

Subject	Authors	Trial Type	Population	Patients (N)	Inclusion Criteria	Transfusion Threshold	Outcome	Recommendations
	Whyte *et al.*[47] (PINTOS trial)	*Post hoc* analysis of PINT trial	Extremely low-birth-weight infants	430	Extremely low-birth-weight infants (from PINT trial)	From PINT trial High threshold (liberal): *1 to 7 days*: respiratory support (< 12.2); no respiratory support (< 10.9) *8 to 14 days*: respiratory support (< 10.9); no respiratory support (< 9.0) *> 15 days*: respiratory support (< 9.0); no respiratory support (< 7.7) Low threshold (restrictive): *1 to 7 days*: respiratory support (< 10.4); no respiratory support (< 9.0) *8 to 14 days*: respiratory support (< 90); no respiratory support (< 7.7) *> 15 days*: respiratory support (< 7.7); no respiratory support (< 6.8)	No differences between groups necrotizing enterocolitis, apnea, infections, need for postnatal steroids, oxygen requirements, time to extubation, or time to discharge	Suggested that a liberal transfusion threshold led to reductions in both cognitive delay and mortality
	Franz *et al.*[18] (ETTNO trial)	Multicenter randomized control trial	Extremely low-birth-weight infants (< 1,000 g) at 36 NICUs in Europe	1,013	Infants with birth weight > 400 g and < 1,000 g at less than 73 h after birth; gestational age < 30 weeks	Hematocrit threshold (%) sliding scale based on age and state of health Liberal: *< 7 days*: < 41 critical; < 35 noncritical *8 to 21 days*: < 37 critical; < 31 noncritical *> 21 days*: < 34 critical; < 28 noncritical Restrictive: *< 7 days*: < 34 critical; < 28 noncritical *8 to 21 days*: < 30 critical; < 24 noncritical *> 21 days*: < 27 critical, < 21 noncritical	Neurodevelopmental outcome was assessed in a *post hoc* analysis of PINT; significant difference in cognitive delay favoring liberal threshold group	Restrictive transfusion strategy is as safe as liberal transfusion in low-birth-weight infants with either critical or noncritical health state
	Kirpalani *et al.*[17] (TOP trial)	Multicenter randomized control trial	Extremely low-birth-weight infants at 41 NICUs in the NICHD	1,824	Birth weight < 1,000 g and gestational age of > 22 weeks and < 29 weeks	Sliding scale based on age Liberal: *< 7 days*: hemoglobin 12 g/dL *7 to 14 days*: 11.5 g/dL *> 14 days*: 10 g/dL Restrictive: *< 7 days*: hemoglobin 10 g/dL *7 to 14 days*: 9.5 g/dL *> 14 days*: 8 g/dL	Among infants with birth weights of < 1,000 g, no difference in death, cerebral palsy, cognitive delay, or severe hearing/visual impairment between restrictive and liberal transfusion strategies at 24 months of corrected age; at discharge, no difference in serious adverse events; at 24 months, no difference in death or developmental impairment	Restrictive transfusion strategy is as safe as liberal transfusion in very low-birth-weight infants

ECMO, extracorporeal membrane oxygenation; ETTNO, Effects of Transfusion Thresholds on Neurocognitive Outcomes; HIV, human immunodeficiency virus; ICU, intensive care unit; NICHD, Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; PINT, Premature Infants in Need of Transfusion; PINTOS, Premature Infants in Need of Transfusion Outcomes; $ScvO_2$, central venous oxygen saturation; TOP, Transfusion of Prematures; TRACT, Transfusion and Treatment of African Children; TRIPICU, Transfusion strategies for patients In Pediatric Intensive Care Units.

Table 2. Summary of Current International Expert Recommendations for Hemoglobin Transfusion Thresholds in Pediatric Patients

Organization	Recommendations for Children	Recommendations for Neonates
American Society of Anesthesiologists Task Force on Perioperative Blood Management[48] (currently being updated)	Excluded from the focus of these guidelines are neonates, infants, and children weighing less than 35 kg.	Excluded from the focus of these guidelines are neonates, infants, and children weighing less than 35 kg.
Guidelines from the European Society of Anesthesiology[49,50]	2013: We suggest that a critical hemoglobin threshold of 8 g/dL for erythrocyte transfusion may be safe in severe pediatric perioperative bleeding. Hemoglobin concentrations vary with age and sex, and erythrocyte transfusion should be tailored accordingly. The required transfusion volume can be calculated as: body weight (kg) × desired increment in hemoglobin concentration (g/dL). In massive bleeding, hemoglobin concentrations should be maintained at 8 g/day, while in stable, critically ill children, 7 g/dL may suffice. 2017: Except for premature babies and cyanotic newborns, hemoglobin targets in bleeding children are 7 to 9 g/dL	2013: Not applicable. 2017: Except for premature babies and cyanotic newborns, hemoglobin targets in bleeding children (includes term neonates) are 7 to 9 g/dL.
Patient Blood Management Guidelines: Module 6 Neonatal and Pediatrics, National Blood Authority Australia[51]	Hemoglobin concentration < 70 g/L: Erythrocyte transfusion is often appropriate. However, transfusion may not be required in wellcompensated patients or where other specific therapy is available. Hemoglobin concentration of 70 to 90 g/L: Erythrocyte transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anemia and the patients response to previous transfusions. Hemoglobin concentration > 90 g/L: Erythrocyte transfusion is often unnecessary and may be inappropriate.	Appendix F: In the absence of clear evidence from high-quality trials, there is wide variation in such thresholds in international practice, as demonstrated by a recent survey of 1,018 neonatologists in 22 countries. For infants of extremely low birth weight or < 28 weeks gestation, most neonatologists favored-hemoglobin thresholds for transfusion of 95 to 120 g/L for infants not receiving mechanical ventilation and then decreasingthresholds over subsequent weeks. Neonatologistsfavored higher thresholds for infants receiving increased respiratory support in the form of supplemental oxygen. New information is expected from large randomized controlled trials that are currently underway. The threshold for transfusion for premature infants within these ranges may be influenced by the presence of symptoms and other factors such as: • Anticipated blood loss (*e.g.*,hemolysis, phlebotomy, or surgery) • Quality of nutrition • Severity of illness • Site of sampling–hemoglobin measured on blood samples obtained from a large artery or from veins tendsto be lower than that from free-flowing capillary samples. In general, the decision to transfuse should be based on laboratory measurement of hemoglobin rather thanon estimates obtained from blood gas analyzers, except in cases of clinical urgency.
Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI)[16]	In children (not demonstrating the following: shock physiology, respiratory failure, acute brain injury, congenital heart disease, and hematological or oncological diagnosis and not on ECMO, VAD, or RRT) with hemoglobin < 5.0 g/dL,erythrocyte transfusion was recommended. If hemoglobinwas 5.0 to 7.0 g/dL, consideration of erythrocyte transfusion was recommended. In the majority of patients with hemoglobin > 9.0 g/dL, erythrocyte transfusion was advised against. Term infants and critically ill children up to 18 yr old were included.	Neonates are excluded.

(*Continued*)

Table 2. (Continued)

Organization	Recommendations for Children	Recommendations for Neonates
Society for the Advancement of Blood Management[27]	Transfusion guidelines for all blood components should be weight and age appropriate, based on both laboratory and physiologic clinical criteria, not based on a hemoglobin concentration alone, and should use restrictive transfusion thresholds for allogeneic erythrocyte transfusion when supported by published evidence and expert consensus.	Neonates are excluded.
Patient Blood Management for Neonates and Children Undergoing Cardiac Surgery: 2019 NATA Guidelines[52]	The authors suggest the addition of erythrocytes to maintain a hematocrit > 24% during CPB based on the estimation of the degree of hemodilution related to CPB prime and cardioplegia (grade 2C). The authors recommend a postoperative hemoglobin threshold or transfusion in stable, acyanotic cardiac children with hemoglobin 70 or 80 g/L in the presence of clinical signs suggestive of symptomatic anemia (grade 1B). The authors recommend a postoperative hemoglobin threshold for transfusion in stable, cyanotic cardiac children with clinical signs suggestive of symptomatic anemia as of 90 g/L (grade 1C).	No specific neonatal hemoglobin thresholds are recommended.

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; NATA, Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis; RRT, Renal Replacement Therapy; VAD, ventricular assist device.

calculated allowable estimated blood loss based on weight, the physiologic status of the child as determined by indicators of end organ perfusion, and comorbidities. High-quality outcomes research regarding restrictive transfusion strategies in pediatric perioperative patients is lacking, and while the focus on optimal hemoglobin transfusion parameters should be considered, it is equally important to consider the physiologic parameters that may influence short- and long-term patient outcomes (fig. 1). This concept of harnessing physiologic parameters to guide transfusion decisions will be explored in more detail in the latter part of this clinical focus review.

Pediatric Cardiac Surgical Patients

Pediatric patients undergoing cardiac surgery have additional factors increasing the likelihood of receiving allogeneic blood transfusions including complex surgeries, chronic cyanosis, hypothermia, and the effects of cardiopulmonary bypass (CPB). An analysis of the Society for Thoracic Surgery (Chicago, Illinois) database showed that all registry centers administered erythrocytes to 100% of patients less than 12 months of age undergoing cardiac surgery with CPB.[20] While transfusion rates decreased in older patients, variability across institutions increased (toddlers, 78.6% [54.6 to 91.7%]; children, 50.0% [25.5 to 63.7%]; adolescents, 25.8% [12.5 to 40%]).[20] Despite multiple studies associating bleeding and erythrocyte transfusions with worse postoperative outcomes,[4,9,10,54] the factors influencing transfusion thresholds in this population (age, cardiac physiology, cyanosis or intracardiac mixing, surgical complexity, and CPB effects) have made determining an optimal hemoglobin transfusion threshold elusive. With the increased focus on the risk–benefit profile of erythrocyte transfusions, it is worth revisiting the literature regarding the hemoglobin transfusion threshold trials in pediatric cardiac surgical patients (table 1).

Due to the high rate of bleeding and transfusion in cardiac surgery, the majority of pediatric perioperative transfusion trials supporting restrictive transfusion practices are in cardiac surgical patients. Many pediatric cardiac centers target hemoglobin level on-CPB of greater than 8 g/dL based on two randomized trials (and *post hoc* analyses) in infants undergoing biventricular repair with low-flow hypothermic CPB, which demonstrated improved outcomes and neurocognitive development.[55–58] However, a single pediatric center caring for Jehovah's Witness patients has provided some insight into the feasibility and safety of lower on-CPB hemoglobin triggers. Utilizing blood conservation techniques developed for their pediatric Jehovah's Witness patients, Naguib *et al.*[59] demonstrated that a target on-CPB goal of a hemoglobin level of greater than 7.0 g/dL allowed for bloodless surgery in 36% of children weighing between 6 and 18 kg and in 81% of those weighing more than 18 kg. While no major adverse events were reported, neurocognitive and developmental testing was not performed,

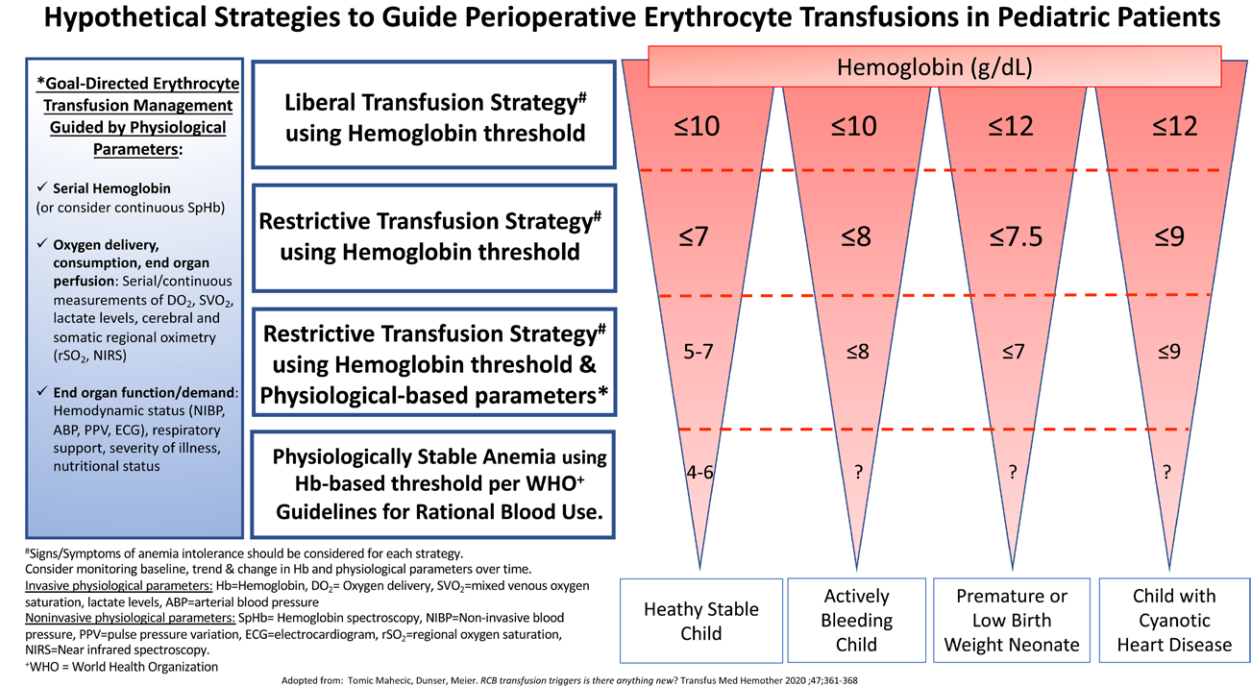

Fig. 1. Hypothetical physiologic strategies to guide erythrocyte transfusion decisions in pediatric patients perioperatively.

making it difficult to determine the long-term impact of this practice. A recent randomized trial in adult cardiac patients found that moderate hemodilution to a hematocrit of 21 to 25% on CPB was associated with increased risk of postoperative neurocognitive dysfunction and stroke compared to mild hemodilution (hematocrit greater than 25%), despite no differences in cerebral oximetry, hemodynamics, and pre- and post-CPB hematocrits.[60] While adult cardiac centers may tolerate on-CPB hemoglobin levels as low as 7.0 g/dL, with monitoring for evidence of tissue hypoxia through serial lactate levels, cerebral oximetry, and mixed venous oxygen saturation,[61] it is hard to extrapolate this data to pediatric patients due to differences in cyanotic and acyanotic heart disease, cerebral autoregulation, and preexisting cardiovascular and neurologic disease burden. Expert consensus recommends an on-CPB hemoglobin target of 8 g/dL or higher for acyanotic pediatric patients undergoing biventricular repair; however, there is currently not enough outcome data to make recommendations regarding on-CBP targets in cyanotic patients.

Relatively large CPB priming volumes result in hemodilution of erythrocytes, platelets, and coagulation factors, thus increasing the need for blood product transfusions. As clinicians consider ways to reduce transfusions, one method that has been shown to decrease CPB-related hemodilution and thus erythrocyte transfusions is to miniaturize CPB circuits. Allowing for a 50% reduction in the CPB prime volumes, these miniaturized circuits have permitted several institutions to perform complex neonatal surgeries without the need for erythrocyte or platelet transfusion in 30 to 50% of neonates.[62–65] In summary, despite the absence of prospective trials, minimizing CPB prime volumes can reduce the need for blood product transfusions in pediatric patients undergoing cardiac surgery.[52]

Three randomized trials have demonstrated that implementing a postoperative restrictive transfusion strategy resulted in fewer transfusions and lower hemoglobin levels but no difference in lactate levels or arteriovenous oxygen nor adverse clinical outcomes in children undergoing biventricular or palliative procedures[35–38] (table 1). These trials demonstrated that hemodynamically stable children who underwent biventricular repair tolerate hemoglobin levels greater than 7.0 g/dL without impaired clinical outcome, while children who underwent palliative procedures tolerate hemoglobin levels greater than 9.0 g/dL.[35–38] These trials focused on postoperative intensive care unit (ICU) transfusion practices, not intraoperative transfusion thresholds. Therefore, although individualized goal-directed transfusion is the aim, prospective studies focusing on intraoperative transfusion thresholds for complex cardiac surgical patients are lacking. A recent retrospective study demonstrated that each 5% increase in ICU arrival hematocrit greater than 38% for acyanotic and 42% for cyanotic children was associated with a significant increase in the odds of perioperative mortality and major complications.[22] While this retrospective study can only demonstrate an association

of worse outcomes with higher intraoperative hemoglobin level, it highlights the need for prospective studies with well defined perioperative transfusion guidelines reserving transfusions for patients with clinical evidence of poor oxygen delivery and avoiding overtransfusion in clinically stable patients.

Although a number of prospective studies demonstrate no benefit of higher hemoglobin thresholds[35–38] and a larger number of retrospective studies associate erythrocyte transfusions with worse outcomes,[4,10,66] clinicians remain skeptical in adopting restrictive transfusion strategies for pediatric cardiac surgical patients due to a lack of robust outcome data and the unique physiology requiring physicians to optimize oxygen delivery in patients with chronic hypoxemia and dynamic intracardiac shunts. A goal-directed erythrocyte transfusion strategy targeting specific physiologic parameters may be a more appropriate approach to transfusion than a specific hemoglobin target.[66] However, without high-quality outcome data on physiologic transfusion thresholds, expert consensus recommends a restrictive approach to transfusion in cardiac children. Current expert consensus recommends a postoperative hemoglobin transfusion threshold in stable, acyanotic cardiac patients with hemoglobin levels greater than 7.0 or 8.0 g/dL in the presence of signs of symptomatic anemia (grade IB evidence).[52,67] For stable, cyanotic cardiac children without signs of symptomatic anemia, the recommended postoperative transfusion threshold is a hemoglobin level greater than 9.0 g/dL (grade 1C).[52,67]

Term and Preterm Neonates

While there is a paucity of data on perioperative neonatal blood transfusions, neonates (age 0 to 30 days old) are one of the most frequently transfused groups, with up to 42 to 90% of premature and low-birth-weight neonates receiving at least one blood transfusion during their hospitalization.[18] Although most of the perioperative transfusion literature in neonates comes from the pediatric cardiac literature, a recent single-center study reported that 6% (25 of 420) of neonates undergoing index general surgery cases received perioperative transfusions. Risk factors for perioperative transfusion included surgery type, history of prematurity, prior transfusion, or structural heart disease.[68] High-quality outcomes data regarding transfusion triggers for neonates in the perioperative period are evolving. Herein is highlighted recent literature and expert consensus guidelines on transfusion thresholds in neonates, premature, and extremely low-birth-weight infants in an attempt provide guidance for perioperative transfusion decisions.

Neonates can be divided into two categories based on gestational age: term or preterm (preterm defined as gestational age less than 37 weeks); and/or based on weight: low birth weight (between 2,500 and 1,000 g) or extremely low birth weight (less than 1,000 g). There is no universally accepted definition of the "normal" hemoglobin level for neonates, as they have unique physiologic and developmental differences mandating a wide range of recommended hemoglobin thresholds (tables 1 and 2). Furthermore, the definition of liberal *versus* restrictive transfusion threshold varies widely across different weights, ages, and critical illnesses ranging from liberal (hemoglobin level of 7.5 to 12.0 g/dL) to restrictive (hemoglobin level of 6.5 to 10.0 g/dL) as detailed in tables 1 and 2. Due to the limited ability to tolerate physiologic stress, historical recommendations have favored more liberal transfusion strategies. Erythrocyte transfusions are independently associated with intraventricular hemorrhage,[69,70] necrotizing enterocolitis[69-72], bronchopulmonary dysplasia,[73] retinopathy of prematurity,[73–75] and death.[76] In fact, due to the lack of transfusion-related outcome data at the time, neonates were not included in the guidelines of Valentine *et al.*[16]

Although the trial of Lacroix *et al.*[15] suggests that restrictive transfusion strategies appear to be safe in the neonatal population, there has been a lack of consensus on the optimal hemoglobin levels for term and preterm neonates until recently. Previously, in the Premature Infants in Need of Transfusion Outcomes (PINTOS) trial, Kirpalani *et al.*[34] reported no difference in death, cerebral palsy, cognitive delay, or severe hearing/visual impairment between restrictive and liberal transfusion strategies at 18 to 21 months in extremely low-birth-weight neonates. However, a *post hoc* analysis of this study suggested that higher hemoglobin levels may be associated with better cognitive outcomes.[47] Consequently, multicenter randomized clinical trials by Kirpalani *et al.*[17] in the Transfusion of Prematures (TOP) study and Franz *et al.*[18] in the Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants (ETTNO) study were conducted comparing restrictive *versus* liberal transfusion thresholds in extremely low-birth-weight preterm infants on the risk of death or neurocognitive outcomes at 2 yr. Transfusion thresholds were determined by postconceptual age and state of health. Both trials found that a restrictive transfusion strategy did not increase the risk of death, cerebral palsy, cognitive deficit, necrotizing entercolitis, bronchopulmonary dysplasia, or retinopathy of prematurity.[17,18] While previous guidelines recommended higher hemoglobin thresholds for extremely low-birth-weight neonates, both studies demonstrated no difference in mortality or neurodevelopmental impairment at hospital discharge or at 22- to 26-month follow-up utilizing a restrictive transfusion strategy. As such, these studies recommend employing a restrictive transfusion strategy using a hemoglobin transfusion threshold ranging from 7.0 to 11.0 g/dL, based on postconceptual age, age-specific hemoglobin reference ranges, level of respiratory support, ongoing or anticipated red cell loss due to critical illness, and nutritional status (table 2).

In a recent review of evidence-based guidelines for neonatal transfusions, Zerra *et al.*[77] point out that the trials of Kirpalani

et al.[17] and Franz *et al.*[18] function to compare liberal *versus* restrictive transfusion strategies based on laboratory thresholds alone (hemoglobin or hematocrit). Zerra *et al.*[77] highlight the need to identify more all-inclusive markers of physiologically relevant outcomes such as tissue oxygen delivery and long-term effects of transfusions on neurodevelopment, immunity, and inflammation, especially in neonates with varying levels of illness, age, and gestational age. While these data are difficult to extrapolate to the intraoperative period, especially for neonates with ongoing bleeding, the current literature suggests that term and preterm, low-birth-weight and extremely low-birth-weight neonates appear to tolerate restrictive transfusion strategies without increased risk of neurocognitive deficits (tables 1 and 2) in a hemodynamically stable patient without evidence of end-organ tissue hypoxia.

Moving Away from a Hemoglobin Number: Incorporating Physiological Parameters to Guide Transfusion Management Decisions

The etiology of a low hemoglobin level in pediatric patients may stem from chronic anemia (nutritional deficiencies, disease state, and side effects of treatment) or acute blood loss from ongoing bleeding. Although the etiology of anemia is often not delineated, multiple studies have demonstrated that preoperative anemia is associated with increased blood transfusions[78] and overall mortality.[1,79] While an in-depth discussion of anemia as a risk factor for perioperative morbidity and mortality is beyond the scope of this review, these studies found that anemic children tend to be younger, required emergency surgery, and had a higher incidence of major comorbidities. Unfortunately, it is unclear whether the adverse outcomes from perioperative anemia are related to the etiology of anemia, the subsequent transfusions to treat the anemia, or both. Recent studies from Africa suggest that children with chronic anemia but without evidence of respiratory distress, hemodynamic instability, or altered consciousness may safely tolerate a hemoglobin level between 4.0 and 6.0 g/dL (table 1).[44–46] These data suggest that a child's ability to tolerate certain hemoglobin levels may differ depending on the cause and chronicity of the anemia, thus highlighting the importance of patient factors on anemia tolerance and the need for individualized goal-directed guidelines for transfusions.

In fact, patient blood management experts have called for goal-directed individualized guidelines for hemoglobin management including or withholding erythrocyte transfusion rather than focusing on a single hemoglobin threshold number. A 2021 Cochrane Review on transfusion thresholds for guiding erythrocyte transfusions[80] identified that the major limitation of most transfusion strategy trials is that these trials "compare only two separate thresholds for hemoglobin concentration, which may not identify the actual optimal threshold for transfusion in a particular patient. Hemoglobin concentration may not be the most informative marker of the need for transfusion in individual patients with different degrees of physiologic adaptation to anemia." This statement is reminiscent of an oft-repeated statement in pediatric medicine: *One size does not fit all.* Despite the increasing support for restrictive transfusion strategies in pediatric patients, international expert consensus guidelines on erythrocyte transfusions agree decisions to transfuse should not be dictated by hemoglobin concentration alone but should also consider the child's underlying physiologic condition and anemia-related signs and symptoms (table 2). Unfortunately, currently lacking is a decision-making algorithm that identifies specific individuals for whom permissive anemia is unsafe or, conversely, individuals that meet transfusion triggers for whom transfusion is actually unnecessary. However, emerging literature suggests that combining patient hemodynamics and serial measurements of biochemical markers indicative of sufficient perfusion (*e.g.*, lactate, base deficit, pH) with novel technologies, such as cerebral and somatic dynamic near infrared spectroscopy, may allow us to better quantify and monitor oxygen consumption and delivery and the decision to transfuse or to withhold transfusion.[81–86]

Recently, critics of the above neonatal transfusion trials, point out that erythrocyte transfusion strategies based on hemoglobin thresholds alone may not be an accurate predictor of physiologic relevant outcomes such as tissue oxygen delivery, especially in a neonate with varying levels of illness, age, and gestational age. Several studies, including two recent prospective trials, in extremely low-birth-weight preterm neonates demonstrated that cerebral and somatic oximetry may reflect tissue hypoxia better than the hemoglobin level alone.[81–83] In addition to increases in cerebral and somatic oxygenation and decreases in fractional oxygen extraction after blood transfusions, two recent studies found that oxygen extraction preferentially increases in the brain over the gut in more anemic and immature infants.[82,83] Another recent study compared the effect of erythrocyte transfusions on pulmonary vascular resistance by echocardiography and cerebral and splanchnic oxygen saturations in neonates with or without a patent ductus arteriosus.[84] The authors report a decrease in pulmonary vascular resistance (change in right ventricular pressure) and cerebral oxygen extraction after erythrocyte transfusion in all patients, but neonates with patent ductus arteriosus had significantly lower splanchnic oxygen saturation and higher fractional oxygen extraction, even after an erythrocyte transfusion.[84] This study highlights the complexity of the relationship between tissue oxygenation/extraction and transfusion decisions in patients with cardiac shunts. While the premature extremely low-birth-weight population has received significant attention due to large research networks, studies examining physiologic parameters for transfusion triggers in other pediatric populations are scarce. A single study in 92 pediatric scoliosis patients found associations between a 15% drop in cerebral oximetry with lower hematocrits and lower blood pressure.[85] Although the authors demonstrate that lower hematocrits are associated

with decreased cerebral oximetry, it is not clear whether a 15% drop in cerebral oximetry is clinically significant. Furthermore, this study does not differentiate the independent association of hypotension or anemia on decreases in cerebral oximetry. Highlighted is the need for future research to identify novel methods to monitor tissue oxygen delivery, as hemoglobin number alone may not be an accurate predictor of physiologic relevant outcomes in perioperative pediatric patients with different illness severities, comorbidities, ages, or surgical procedures.

Furthermore, although erythrocyte transfusion increases hemoglobin levels with a corresponding increase in blood oxygen content, a child's tolerance of anemia is based more on tissue oxygen delivery, end organ perfusion, oxygen extraction, and compensatory physiology than a single hemoglobin number. In a recent study of adult blunt-trauma patients, Özakın *et al.*[86] correlated multiple physiologic and laboratory parameters in patients who required erythrocyte transfusions with those who did not. Harnessing this data, the authors developed a score using lactate, base deficit, and systolic blood pressure to predict a need for blood transfusion. While this study does not specifically compare outcomes based on hemoglobin levels, it does emphasize the complexity of the decision to transfuse, as well as the need for developing more comprehensive tools utilizing multiple physiologic and laboratory parameters to guide transfusions in perioperative pediatric patients.

Therefore, prospective research harnessing restrictive hemoglobin strategies together with end organ monitoring, physiologic markers of tissue hypoxia, and long-term patient outcomes is needed to further guide goal-directed care of the anemic and/or bleeding child. We propose such a model in figure 1, which shows hypothetical physiologic strategies to guide erythrocyte transfusion decisions in pediatric patients perioperatively.

Conclusions

Pediatric erythrocyte transfusion practices have long been extrapolated from adult research and guidelines despite children being physiologically unique from adults. The development and acceptance of evidence-based pediatric restrictive hemoglobin transfusion thresholds has been challenging for numerous reasons. First, anemia tolerance, bleeding risk, and transfusion recommendations are dependent on weight, gestational age, physiologic parameters, surgical and medical complexity, and institutional practice. Second, prospective outcome studies focusing on pediatric erythrocyte transfusion thresholds are few and further complicated due to a smaller, heterogeneous patient population, varied institutional surgical volume, and limited resources directed at these studies.

Despite the lack of robust outcome data, several trials and expert consensus guidelines recommend utilizing a restrictive transfusion strategy in many pediatric populations. International expert consensus statements recommend against a single hemoglobin transfusion trigger, reinforcing that the decision to transfuse should be based on an assessment of the patient's underlying comorbidities and anemia symptoms.

The authors propose there is no ideal, one size fits all, hemoglobin threshold for the pediatric patient in the perioperative period. Instead, future research should focus on patient-centered outcomes that incorporate patient factors, surgical and medical complexity, and physiologic parameters to develop tools to guide the management of anemic and/or bleeding pediatric patients. Knowledge that the child is physiologically optimized would go a long way in promoting restrictive goal-directed transfusion decisions in the perioperative setting. In conclusion, anesthesiologists caring for pediatric surgical patients should turn our collective focus to the individualized patient and the physiologic status of the neonate, infant, child, or adolescent in deciding the optimal hemoglobin threshold, while avoiding erythrocyte transfusions whenever possible.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Goobie: Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115. susan.goobie@childrens.harvard.edu.

References

1. Goobie SM, DiNardo JA, Faraoni D: Relationship between transfusion volume and outcomes in children undergoing noncardiac surgery. Transfusion 2016; 56:2487–94
2. Benson AB, Burton JR, Austin GL, Biggins SW, Zimmerman MA, Kam I, Mandell S, Silliman CC, Rosen H, Moss M: Differential effects of plasma and red blood cell transfusions on acute lung injury and infection risk following liver transplantation. Liver Transpl 2011; 17:149–58
3. Manlhiot C, McCrindle BW, Menjak IB, Yoon H, Holtby HM, Brandão LR, Chan AK, Schwartz SM, Sivarajan VB, Crawford-Lean L, Foreman C, Caldarone CA, Van Arsdell GS, Gruenwald CE: Longer blood storage is associated with suboptimal outcomes in high-risk pediatric cardiac surgery. Ann Thorac Surg 2012; 93:1563–9
4. Kipps AK, Wypij D, Thiagarajan RR, Bacha EA, Newburger JW: Blood transfusion is associated with

prolonged duration of mechanical ventilation in infants undergoing reparative cardiac surgery. Pediatr Crit Care Med 2011; 12:52–6
5. Howard-Quijano K, Schwarzenberger JC, Scovotti JC, Alejos A, Ngo J, Gornbein J, Mahajan A: Increased red blood cell transfusions are associated with worsening outcomes in pediatric heart transplant patients. Anesth Analg 2013; 116:1295–308
6. Nacoti M, Cazzaniga S, Lorusso F, Naldi L, Brambillasca P, Benigni A, Corno V, Colledan M, Bonanomi E, Vedovati S, Buoro S, Falanga A, Lussana F, Barbui T, Sonzogni V: The impact of perioperative transfusion of blood products on survival after pediatric liver transplantation. Pediatr Transplant 2012; 16:357–66
7. Muszynski JA, Spinella PC, Cholette JM, Acker JP, Hall MW, Juffermans NP, Kelly DP, Blumberg N, Nicol K, Liedel J, Doctor A, Remy KE, Tucci M, Lacroix J, Norris PJ; Pediatric Critical Care Blood Research Network (Blood Net): Transfusion-related immunomodulation: Review of the literature and implications for pediatric critical illness. Transfusion 2017; 57:195–206
8. Linder GE, Chou ST: Red cell transfusion and alloimmunization in sickle cell disease. Haematologica 2021; 106:1805–15
9. Salvin JW, Scheurer MA, Laussen PC, Wypij D, Polito A, Bacha EA, Pigula FA, McGowan FX, Costello JM, Thiagarajan RR: Blood transfusion after pediatric cardiac surgery is associated with prolonged hospital stay. Ann Thorac Surg 2011; 91:204–10
10. Guzzetta NA, Allen NN, Wilson EC, Foster GS, Ehrlich AC, Miller BE: Excessive postoperative bleeding and outcomes in neonates undergoing cardiopulmonary bypass. Anesth Analg 2015; 120:405–10
11. Shander A, Goobie SM, Warner MA, Aapro M, Bisbe E, Perez-Calatayud AA, Callum J, Cushing MM, Dyer WB, Erhard J, Faraoni D, Farmer S, Fedorova T, Frank SM, Froessler B, Gombotz H, Gross I, Guinn NR, Haas T, Hamdorf J, Isbister JP, Javidroozi M, Ji H, Kim YW, Kor DJ, Kurz J, Lasocki S, Leahy MF, Lee CK, Lee JJ, Louw V, Meier J, Mezzacasa A, Munoz M, Ozawa S, Pavesi M, Shander N, Spahn DR, Spiess BD, Thomson J, Trentino K, Zenger C, Hofmann A; International Foundation of Patient Blood Management (IFPBM) and Society for the Advancement of Blood Management (SABM) Work Group: Essential role of patient blood management in a pandemic: A call for action. Anesth Analg 2020; 131:74–85
12. World Health Organization: The urgent need to implement patient blood management: Policy brief. 2021. Available at: https://apps.who.int/iris/handle/10665/346655. Accessed April 21, 2022.
13. Franchini M, Marano G, Veropalumbo E, Masiello F, Pati I, Candura F, Profili S, Catalano L, Piccinini V, Pupella S, Vaglio S, Liumbruno GM: Patient blood management: A revolutionary approach to transfusion medicine. Blood Transfus 2019; 17:191–5
14. Spahn DR, Muñoz M, Klein AA, Levy JH, Zacharowski K: Patient blood management: Effectiveness and future potential. Anesthesiology 2020; 133:212–22
15. Lacroix J, Hébert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano BJ, Robillard P, Joffe A, Biarent D, Meert K, Peters MJ; 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; 356:1609–19
16. Valentine SL, Bembea MM, Muszynski JA, Cholette JM, Doctor A, Spinella PC, Steiner ME, Tucci M, Hassan NE, Parker RI, Lacroix J, Argent A, Carson JL, Remy KE, Demaret P, Emeriaud G, Kneyber MCJ, Guzzetta N, Hall MW, Macrae D, Karam O, Russell RT, Stricker PA, Vogel AM, Tasker RC, Turgeon AF, Schwartz SM, Willems A, Josephson CD, Luban NLC, Lehmann LE, Stanworth SJ, Zantek ND, Bunchman TE, Cheifetz IM, Fortenberry JD, Delaney M, van de Watering L, Robinson KA, Malone S, Steffen KM, Bateman ST; Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI); Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Consensus recommendations for RBC transfusion practice in critically ill children from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med 2018; 19:884–98
17. Kirpalani H, Bell EF, Hintz SR, Tan S, Schmidt B, Chaudhary AS, Johnson KJ, Crawford MM, Newman JE, Vohr BR, Carlo WA, D'Angio CT, Kennedy KA, Ohls RK, Poindexter BB, Schibler K, Whyte RK, Widness JA, Zupancic JAF, Wyckoff MH, Truog WE, Walsh MC, Chock VY, Laptook AR, Sokol GM, Yoder BA, Patel RM, Cotten CM, Carmen MF, Devaskar U, Chawla S, Seabrook R, Higgins RD, Das A; Eunice Kennedy Shriver NICHD Neonatal Research Network: Higher or lower hemoglobin transfusion thresholds for preterm infants. N Engl J Med 2020; 383:2639–51
18. Franz AR, Engel C, Bassler D, Rüdiger M, Thome UH, Maier RF, Krägeloh-Mann I, Kron M, Essers J, Bührer C, Rellensmann G, Rossi R, Bittrich HJ, Roll C, Höhn T, Ehrhardt H, Avenarius S, Körner HT, Stein A, Buxmann H, Vochem M, Poets CF; ETTNO Investigators: Effects of liberal *vs.* restrictive transfusion thresholds on survival and neurocognitive outcomes in extremely low-birth-Weight infants: The ETTNO randomized clinical trial. JAMA 2020; 324:560–70
19. Keung CY, Smith KR, Savoia HF, Davidson AJ: An audit of transfusion of red blood cell units in pediatric anesthesia. Paediatr Anaesth 2009; 19:320–8
20. Kartha VM, Jacobs JP, Vener DF, Hill KD, Goldenberg NA, Pasquali SK, Meza JM, O'Brien SM, Feng L,

Chiswell K, Eghtesady P, Badhwar V, Rehman M, Jacobs ML: National benchmarks for proportions of patients receiving blood transfusions during pediatric and congenital heart surgery: An analysis of the STS Congenital Heart Surgery Database. Ann Thorac Surg 2018; 106:1197–203

21. Fernandez PG, Taicher BM, Goobie SM, Gangadharan M, Homi HM, Kugler JA, Skitt R, Cai L, Polansky M, Stricker PA; Pediatric Craniofacial Collaborative Group: Predictors of transfusion outcomes in pediatric complex cranial vault reconstruction: A multicentre observational study from the Pediatric Craniofacial Collaborative Group. Can J Anaesth 2019; 66:512–26
22. Long JB, Engorn BM, Hill KD, Feng L, Chiswell K, Jacobs ML, Jacobs JP, Goswami D: Postoperative hematocrit and adverse outcomes in pediatric cardiac surgery patients: A cross-sectional study from the Society of Thoracic Surgeons and Congenital Cardiac Anesthesia Society Database Collaboration. Anesth Analg 2021; 133:1077–88
23. Butler EK, Mills BM, Arbabi S, Bulger EM, Vavilala MS, Groner JI, Stansbury LG, Hess JR, Rivara FP: Association of blood component ratios with 24-hour mortality in injured children receiving massive transfusion. Crit Care Med 2019; 47:975–83
24. Noland DK, Apelt N, Greenwell C, Tweed J, Notrica DM, Garcia NM, Todd Maxson R, Eubanks JW 3rd, Alder AC: Massive transfusion in pediatric trauma: An ATOMAC perspective. J Pediatr Surg 2019; 54:345–9
25. Spinella PC, Leonard JC, Marshall C, Luther JF, Wisniewski SR, Josephson CD, Leeper CM; Massive Transfusion In Children (MATIC) Investigators and BloodNet: Transfusion ratios and deficits in injured children with life-threatening bleeding. Pediatr Crit Care Med 2022; 23:235–44
26. Leonard JC, Josephson CD, Luther JF, Wisniewski SR, Allen C, Chiusolo F, Davis AL, Finkelstein RA, Fitzgerald JC, Gaines BA, Goobie SM, Hanson SJ, Hewes HA, Johnson LH, McCollum MO, Muszynski JA, Nair AB, Rosenberg RB, Rouse TM, Sikavitsas A, Singleton MN, Steiner ME, Upperman JS, Vogel AM, Wills H, Winkler MK, Spinella PC: Life-threatening bleeding in children: A prospective observational study. Crit Care Med 2021; 49:1943–54
27. Goobie SM, Gallagher T, Gross I, Shander A: Society for the Advancement of Blood Management Administrative and clinical standards for patient blood management programs. 4th edition (pediatric version). Paediatr Anaesth 2019; 29:231–6
28. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E; Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999; 340:409–17
29. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C: Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013; 368:11–21
30. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, Nebrich L, Nibro HL, Rasmussen BS, Lauridsen JR, Nielsen JS, Oldner A, Pettilä V, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Møller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, Sjøbø B, Bundgaard H, Thyø MA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower *versus* higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014; 371:1381–91
31. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC; TITRe2 Investigators: Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015; 372:997–1008
32. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, McGuinness S, Royse A, Carrier FM, Young PJ, Villar JC, Grocott HP, Seeberger MD, Fremes S, Lellouche F, Syed S, Byrne K, Bagshaw SM, Hwang NC, Mehta C, Painter TW, Royse C, Verma S, Hare GMT, Cohen A, Thorpe KE, Jüni P, Shehata N; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group: Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 2017; 377:2133–44
33. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I, Arnaiz JA, Martínez-Sellés M, Silvain J, Ariza-Solé A, Ferrari E, Calvo G, Danchin N, Avendaño-Solá C, Frenkiel J, Rousseau A, Vicaut E, Simon T, Steg PG; REALITY Investigators: Effect of a restrictive *vs.* liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: The REALITY randomized clinical trial. JAMA 2021; 325:552–60
34. Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, Peliowski A, Rios A, LaCorte M, Connelly R, Barrington K, Roberts RS: The Premature Infants in Need of Transfusion (PINT) study: A randomized, controlled trial of a restrictive (low) *versus* liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006; 149:301–7

35. Willems A, Harrington K, Lacroix J, Biarent D, Joffe AR, Wensley D, Ducruet T, Hébert PC, Tucci M; TRIPICU investigators; Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: A subgroup analysis. Crit Care Med 2010; 38:649–56
36. Cholette JM, Rubenstein JS, Alfieris GM, Powers KS, Eaton M, Lerner NB: Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: Results of a prospective, randomized, controlled trial of a restrictive *versus* liberal red-cell transfusion strategy. Pediatr Crit Care Med 2011; 12:39–45
37. de Gast-Bakker DH, de Wilde RB, Hazekamp MG, Sojak V, Zwaginga JJ, Wolterbeek R, de Jonge E, Gesink-van der Veer BJ: Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: A randomized controlled trial. Intensive Care Med 2013; 39:2011–9
38. Cholette JM, Swartz MF, Rubenstein J, Henrichs KF, Wang H, Powers KS, Daugherty LE, Alfieris GM, Gensini F, Blumberg N: Outcomes using a conservative *versus* liberal red blood cell transfusion strategy in infants requiring cardiac operation. Ann Thorac Surg 2017; 103:206–14
39. de Oliveira CF, de Oliveira DS, Gottschald AF, Moura JD, Costa GA, Ventura AC, Fernandes JC, Vaz FA, Carcillo JA, Rivers EP, Troster EJ: ACCM/PALS haemodynamic support guidelines for paediatric septic shock: An outcomes comparison with and without monitoring central venous oxygen saturation. Intensive Care Med 2008; 34:1065–75
40. Srouji LS, Moore-Clingenpeel M, Hensley J, Steele L, Greathouse K, Anglim L, Hanson-Huber L, Nateri J, Nicol K, Hall MW, Ramilo O, Muszynski JA: Shock severity modifies associations between RBC transfusion in the first 48 hours of sepsis onset and the duration of organ dysfunction in critically ill septic children. Pediatr Crit Care Med 2020; 21:e475–84
41. Muszynski JA, Banks R, Reeder RW, Hall MW, Berg RA, Zuppa A, Shanley TP, Cornell TT, Newth CJL, Pollack MM, Wessel D, Doctor A, Lin JC, Harrison RE, Meert KL, Dean JM, Holubkov R, Carcillo JA; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN): Outcomes associated with early RBC transfusion in pediatric severe sepsis: A propensity-adjusted multicenter cohort study. Shock 2022; 57:88–94
42. Voigt CD, Hundeshagen G, Malagaris I, Watson K, Obiarinze RN, Hasanpour H, Woodson LC, Capek KD, Lee JO, Nunez Lopez O, Cambiaso-Daniel J, Branski LK, Norbury WB, Finnerty CC, Herndon DN: Effects of a restrictive blood transfusion protocol on acute pediatric burn care: Transfusion threshold in pediatric burns. J Trauma Acute Care Surg 2018; 85:1048–54
43. Lackritz EM, Campbell CC, Ruebush TK 2nd, Hightower AW, Wakube W, Steketee RW, Were JB: Effect of blood transfusion on survival among children in a Kenyan hospital. Lancet 1992; 340:524–8
44. Maitland K, Kiguli S, Olupot-Olupot P, Engoru C, Mallewa M, Saramago Goncalves P, Opoka RO, Mpoya A, Alaroker F, Nteziyaremye J, Chagaluka G, Kennedy N, Nabawanuka E, Nakuya M, Namayanja C, Uyoga S, Kyeyune Byabazaire D, M'baya B, Wabwire B, Frost G, Bates I, Evans JA, Williams TN, George EC, Gibb DM, Walker AS; TRACT Group: Immediate transfusion in African children with uncomplicated severe anemia. N Engl J Med 2019; 381:407–19
45. Maitland K, Olupot-Olupot P, Kiguli S, Chagaluka G, Alaroker F, Opoka RO, Mpoya A, Engoru C, Nteziyaremye J, Mallewa M, Kennedy N, Nakuya M, Namayanja C, Kayaga J, Uyoga S, Kyeyune Byabazaire D, M'baya B, Wabwire B, Frost G, Bates I, Evans JA, Williams TN, Saramago Goncalves P, George EC, Gibb DM, Walker AS; TRACT Group: Transfusion volume for children with severe anemia in Africa. N Engl J Med 2019; 381:420–31
46. Connon R, George EC, Olupot-Olupot P, Kiguli S, Chagaluka G, Alaroker F, Opoka RO, Mpoya A, Walsh K, Engoru C, Nteziyaremye J, Mallewa M, Kennedy N, Nakuya M, Namayanja C, Nabawanuka E, Sennyondo T, Amorut D, Williams Musika C, Bates I, Boele van Hensbroek M, Evans JA, Uyoga S, Williams TN, Frost G, Gibb DM, Maitland K, Walker AS; TRACT trial group: Incidence and predictors of hospital readmission in children presenting with severe anaemia in Uganda and Malawi: A secondary analysis of TRACT trial data. BMC Public Health 2021; 21:1480
47. Whyte RK, Kirpalani H, Asztalos EV, Andersen C, Blajchman M, Heddle N, LaCorte M, Robertson CM, Clarke MC, Vincer MJ, Doyle LW, Roberts RS; PINTOS Study Group: Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 2009; 123:207–13
48. Practice Guidelines for Perioperative Blood Management: An updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. Anesthesiology 2015; 122:241–75.
49. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, Fries D, Görlinger K, Haas T, Imberger G, Jacob M, Lancé M, Llau J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelsø AJ, Wouters P, Wyffels P: Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013; 30:270–382

50. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Haas T, Jacob M, Lancé MD, Pitarch JVL, Mallett S, Meier J, Molnar ZL, Rahe-Meyer N, Samama CM, Stensballe J, Van der Linden PJF, Wikkelsø AJ, Wouters P, Wyffels P, Zacharowski K: Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol 2017; 34:332–95
51. National Blood Authority Australia: Patient blood management guidelines: Module 6 neonatal and paediatrics. 2016. Available at: https://www.blood.gov.au/pbm-module-6. Accessed May 1, 2022
52. Faraoni D, Meier J, New HV, Van der Linden PJ, Hunt BJ: Patient blood management for neonates and children undergoing cardiac surgery: 2019 NATA guidelines. J Cardiothorac Vasc Anesth 2019; 33:3249–63
53. Cholette JM, Willems A, Valentine SL, Bateman ST, Schwartz SM; Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI); Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Recommendations on RBC transfusion in infants and children with acquired and congenital heart disease from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med 2018; 19:137–48
54. Iyengar A, Scipione CN, Sheth P, Ohye RG, Riegger L, Bove EL, Devaney EJ, Hirsch-Romano JC: Association of complications with blood transfusions in pediatric cardiac surgery patients. Ann Thorac Surg 2013; 96:910–6
55. Jonas RA, Wypij D, Roth SJ, Bellinger DC, Visconti KJ, du Plessis AJ, Goodkin H, Laussen PC, Farrell DM, Bartlett J, McGrath E, Rappaport LJ, Bacha EA, Forbess JM, del Nido PJ, Mayer JE Jr, Newburger JW: The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: Results of a randomized trial in infants. J Thorac Cardiovasc Surg 2003; 126:1765–74
56. Newburger JW, Jonas RA, Soul J, Kussman BD, Bellinger DC, Laussen PC, Robertson R, Mayer JE Jr, del Nido PJ, Bacha EA, Forbess JM, Pigula F, Roth SJ, Visconti KJ, du Plessis AJ, Farrell DM, McGrath E, Rappaport LA, Wypij D: Randomized trial of hematocrit 25% *versus* 35% during hypothermic cardiopulmonary bypass in infant heart surgery. J Thorac Cardiovasc Surg 2008; 135:347–54
57. Wypij D, Jonas RA, Bellinger DC, Del Nido PJ, Mayer JE Jr, Bacha EA, Forbess JM, Pigula F, Laussen PC, Newburger JW: The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: Results from the combined Boston hematocrit trials. J Thorac Cardiovasc Surg 2008; 135:355–60
58. Wypij D, Newburger JW, Rappaport LA, duPlessis AJ, Jonas RA, Wernovsky G, Lin M, Bellinger DC: The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: The Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003; 126:1397–403
59. Naguib AN, Winch PD, Tobias JD, Simsic J, Hersey D, Nicol K, Preston T, Gomez D, McConnell P, Galantowicz M: A single-center strategy to minimize blood transfusion in neonates and children undergoing cardiac surgery. Paediatr Anaesth 2015; 25:477–86
60. Soliman R, Saad D, Abukhudair W, Abdeldayem S: The neurocognitive outcomes of hemodilution in adult patients undergoing coronary artery bypass grafting using cardiopulmonary bypass. Ann Card Anaesth 2022; 25:133–40
61. Sevuk U, Altindag R, Baysal E, Yaylak B, Adiyaman MS, Akkaya S, Ay N, Alp V: The effects of hyperoxaemia on tissue oxygenation in patients with a nadir haematocrit lower than 20% during cardiopulmonary bypass. Perfusion 2016; 31:232–9
62. Boettcher W, Sinzobahamvya N, Miera O, Redlin M, Dehmel F, Cho MY, Murin P, Berger F, Photiadis J: Routine application of bloodless priming in neonatal cardiopulmonary bypass: A 3-year experience. Pediatr Cardiol 2017; 38:807–12
63. Koster A, Huebler M, Boettcher W, Redlin M, Berger F, Hetzer R: A new miniaturized cardiopulmonary bypass system reduces transfusion requirements during neonatal cardiac surgery: Initial experience in 13 consecutive patients. J Thorac Cardiovasc Surg 2009; 137:1565–8
64. Redlin M, Huebler M, Boettcher W, Kukucka M, Schoenfeld H, Hetzer R, Habazettl H: Minimizing intraoperative hemodilution by use of a very low priming volume cardiopulmonary bypass in neonates with transposition of the great arteries. J Thorac Cardiovasc Surg 2011; 142:875–81
65. Bojan M, Constanza Basto Duarte M, Lopez V, Tourneur L, Pouard P, Vouhé P: Use of a miniaturized cardiopulmonary bypass circuit in neonates and infants is associated with fewer blood product transfusions. ASAIO J 2011; 57:527–32
66. Faraoni D, DiNardo JA: Red blood cell transfusion and adverse outcomes in pediatric cardiac surgery patients: Where does the blame lie? Anesth Analg 2021; 133:1074–6
67. Cholette JM, Faraoni D, Goobie SM, Ferraris V, Hassan N: Patient blood management in pediatric cardiac surgery: A review. Anesth Analg 2018; 127:1002–16
68. Reppucci ML, Meier M, Stevens J, Shirek G, Kulungowski AM, Acker SN: Incidence of and risk factors for perioperative blood transfusion in infants undergoing index pediatric surgery procedures. J Pediatr Surg 2022; 57:1067–71

69. Baer VL, Lambert DK, Henry E, Snow GL, Butler A, Christensen RD: Among very-low-birth-weight neonates is red blood cell transfusion an independent risk factor for subsequently developing a severe intraventricular hemorrhage? Transfusion 2011; 51:1170–8
70. Christensen RD, Baer VL, Del Vecchio A, Henry E: Unique risks of red blood cell transfusions in very-low-birth-weight neonates: Associations between early transfusion and intraventricular hemorrhage and between late transfusion and necrotizing enterocolitis. J Matern Fetal Neonatal Med 2013; 26:60–3
71. Garg P, Pinotti R, Lal CV, Salas AA: Transfusion-associated necrotizing enterocolitis in preterm infants: An updated meta-analysis of observational data. J Perinat Med 2018; 46:677–85
72. Teišerskas J, Bartašienė R, Tamelienė R: Associations between red blood cell transfusions and necrotizing enterocolitis in very low birth weight infants: Ten-year data of a tertiary neonatal unit. Medicina (Kaunas) 2019; 55:16.
73. Ghirardello S, Dusi E, Cortinovis I, Villa S, Fumagalli M, Agosti M, Milani S, Mosca F: Effects of red blood cell transfusions on the risk of developing complications or death: An observational study of a cohort of very low birth weight infants. Am J Perinatol 2017; 34:88–95
74. Keir A, Pal S, Trivella M, Lieberman L, Callum J, Shehata N, Stanworth SJ: Adverse effects of red blood cell transfusions in neonates: A systematic review and meta-analysis. Transfusion 2016; 56:2773–80
75. Slidsborg C, Jensen A, Forman JL, Rasmussen S, Bangsgaard R, Fledelius HC, Greisen G, la Cour M: Neonatal risk factors for treatment-demanding retinopathy of prematurity: A Danish national study. Ophthalmology 2016; 123:796–803
76. dos Santos AM, Guinsburg R, de Almeida MF, Procianoy RS, Leone CR, Marba ST, Rugolo LM, Fiori HH, Lopes JM, Martinez FE; Brazilian Network on Neonatal Research: Red blood cell transfusions are independently associated with intra-hospital mortality in very low birth weight preterm infants. J Pediatr 2011; 159:371–6
77. Zerra PE, Josephson CD: Transfusion in neonatal patients: Review of evidence-based guidelines. Clin Lab Med 2021; 41:15–34
78. Fontanals M, O'Leary JD, Zaarour C, Skelton T, Faraoni D: Preoperative anemia increases the risk of red blood cell transfusion and prolonged hospital length of stay in children undergoing spine arthrodesis surgery. Transfusion 2019; 59:492–9
79. Faraoni D, DiNardo JA, Goobie SM: Relationship between preoperative anemia and in-Hospital Mortality in Children Undergoing Noncardiac Surgery. Anesth Analg 2016; 123:1582–7
80. Carson JL, Stanworth SJ, Dennis JA, Trivella M, Roubinian N, Fergusson DA, Triulzi D, Dorée C, Hébert PC: Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev 2021; 12:CD002042
81. Mintzer JP, Parvez B, Chelala M, Alpan G, LaGamma EF: Monitoring regional tissue oxygen extraction in neonates <1250 g helps identify transfusion thresholds independent of hematocrit. J Neonatal Perinatal Med 2014; 7:89–100
82. Balegar V KK, Low GK, Nanan RK: Regional tissue oxygenation and conventional indicators of red blood cell transfusion in anaemic preterm infants. EClinicalMedicine 2022; 46:101365
83. Chock VY, Smith E, Tan S, Ball MB, Das A, Hintz SR, Kirpalani H, Bell EF, Chalak LF, Carlo WA, Cotton CM, Widness JA, Kennedy KA, Ohls RK, Seabrook RB, Patel RM, Laptook AR, Mancini T, Sokol GM, Walsh MC, Higgins RD, Van Meurs KP: Early brain and abdominal oxygenation in extremely low birth weight infants. Pediatr Res 2022: 10.1038/s41390-022-02082-z
84. Smith A, Armstrong S, Dempsey E, El-Khuffash A: The impact of a PDA on tissue oxygenation and haemodynamics following a blood transfusion in preterm infants. Pediatr Res 2022: 10.1038/s41390-022-01967-3
85. Liu L, Qiang Z, Zhang J, Ren Y, Zhao X, Fu W, Xin Z, Xu Z, Wang F, Li L, Zou N, Zhang X, Feng L, Ma S: Effect of hemoglobin content on cerebral oxygen saturation during surgery for scoliosis in pediatric patients. BMC Anesthesiol 2021; 21:165
86. Özakın E, Özcan Yazlamaz N, Baloğlu Kaya F, Çanakçı ME, Bilgin M: Lactate and base deficit combination score for predicting blood transfusion need in blunt multi-trauma patients. Ulus Travma Acil Cerrahi Derg 2022; 28:599–606