

CME **Patient Blood Management in Pediatric Cardiac Surgery: A Review**

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Efforts to reduce blood product transfusions and adopt blood conservation strategies for infants and children undergoing cardiac surgical procedures are ongoing. Children typically receive red blood cell and coagulant blood products perioperatively for many reasons, including developmental alterations of their hemostatic system, and hemodilution and hypothermia with cardiopulmonary bypass that incites inflammation and coagulopathy and requires systemic anticoagulation. The complexity of their surgical procedures, complex cardiopulmonary interactions, and risk for inadequate oxygen delivery and postoperative bleeding further contribute to blood product utilization in this vulnerable population. Despite these challenges, safe conservative blood management practices spanning the pre-, intra-, and postoperative periods are being developed and are associated with reduced blood product transfusions. This review summarizes the available evidence regarding anemia management and blood transfusion practices in the perioperative care of these critically ill children. The evidence suggests that adoption of a comprehensive blood management approach decreases blood transfusions, but the impact on clinical outcomes is less well studied and represents an area that deserves further investigation. (Anesth Analg 2018;127:1002–16)

Pediatric cardiac surgery is associated with substantial bleeding and blood transfusion requirements. Anemia tolerance, bleeding risk, and transfusion therapy are influenced by various factors: (1) developmental: weight, corrected gestational age, immaturity of the hemostatic system; (2) physiologic: morphologic diagnosis, degree of cyanosis, and/or intracardiac mixing, balance of systemic and pulmonary vascular resistance; and (3) surgery and cardiopulmonary bypass (CPB): degree of hemodilution and the hemostatic alterations induced by CPB and duration and complexity of the surgical procedure (Table 1).^{1–7} Variations in morphologic diagnoses and physiology, surgical approaches, CPB techniques, and perioperative management strategies across institutions make generalization of various transfusion and blood conservation/patient blood management practices difficult. Pediatric literature is mainly observational and high-grade evidence is lacking (Table 2).

The association between transfusion and outcomes in children undergoing cardiac surgery has been extensively investigated. Indeed allogenic blood transfusion may be life saving in

circumstances such as massive hemorrhage or severe anemia⁴; however, blood product transfusion is also associated with an increased incidence of postoperative pulmonary complications, prolonged mechanical ventilation, hospital-acquired infections, and prolonged hospital length of stay.^{5–7} These findings suggest that minimizing blood product transfusion may be beneficial in the pediatric cardiac surgical patient population.

Efforts to improve hemostasis, reduce bleeding, correct coagulopathy, limit blood sampling, and incorporate blood sparing techniques (including restrictive transfusion practices) are a tenet of patient blood management, and should be applied to the pediatric cardiac surgical population as it is being considered across other disciplines.^{8,9} The objective of this review is to present the current literature regarding anemia management and blood transfusion practices in the perioperative care of these critically ill children, and highlight potential avenues where blood conservation is being applied.

PREOPERATIVE PATIENT BLOOD MANAGEMENT

Excellent preoperative planning assesses patient risk factors, plans surgical interventions, and ensures proper personnel and equipment preparation.¹⁰ Ideally each patient is discussed and evaluated by a multidisciplinary care team (cardiac surgery, anesthesiology, cardiology, and intensive care medicine), which includes anemia management and blood transfusion planning. Ideal team assembly and equipment availability require adequate communication and coordination of care across disciplines. Inclusion of perfusionists and transfusion medicine as team members in the care of these patients is essential for the successful adoption of blood conservation practices.

A detailed history, including relevant medical, surgical, and family history, as well as medications and supplements taken, should be performed to assess bleeding or clotting risk. Preoperative testing for anemia, iron deficiency, and coagulopathies should be performed, and corrected in the cases of elective surgery (Table 3). More elaborate testing for

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Table 1. Factors That Influence Pediatric Blood Management in Cardiac Operations (Bleeding Risk, Anemia Tolerance, and Transfusion Risk)

Factors Affecting Blood Management	Pathophysiology	Improvement Strategies
Hemostatic system alterations	Preoperative anemia, immature hemostatic system	<ul style="list-style-type: none"> Careful preoperative evaluations with assessment of coagulation, platelet function, and bone marrow reserve Abbreviated course of recombinant erythropoietin to improve hemoglobin levels
Morphologic diagnoses	Cyanosis, intracardiac shunt, balance of systemic/pulmonary flow	<ul style="list-style-type: none"> Preoperative optimization of preload/afterload and all hemodynamic parameters Recognition of all anatomic abnormalities and associated congenital anomalies
Surgery with CPB	Hemodilution, prolonged CPB	<ul style="list-style-type: none"> Intraoperative meticulous hemostasis CPB protocols appropriate for body size Prophylactic transfusion to keep Hct >20% on pump
Institutional management strategies	Wide variations among practitioners and institutions	<ul style="list-style-type: none"> Standardized protocols Multidisciplinary input PCICU protocols including limiting blood draws and well-defined decision tree for transfusion Critical care quality improvement efforts

Abbreviations: CPB, cardiopulmonary bypass; Hct, hematocrit; PCICU, pediatric cardiac intensive care unit.

Table 2. Consensus Recommendations for Blood Conservation Interventions in Children Having Cardiac Operations

Intervention	Type of Evidence	Expected Outcome
Preoperative interventions		
Treat preoperative anemia	Indirect evidence only	Anemic children undergoing noncardiac operations have increased in-hospital mortality
Treat iron deficiency	Indirect evidence from adults only	<ul style="list-style-type: none"> Intravenous iron preparations are preferred for quicker results rEPO for short preoperative course may be effective adjunct to increase red cell mass
Search for congenital bleeding disorders (von Willebrand's is most common undiagnosed congenital defect) Can have an acquired vWD in patients on LVAD	Anecdotal at best	May be important in ventricular assist patients
Intraoperative interventions		
Prophylactic transfusion to avoid excessive hemodilution while on CPB	Multivariate adjusted study comparing prophylactic transfusion for Hct <20%	Prophylactic transfusion to keep Hct >20% was associated with reduced composite morbidity and mortality compared to therapeutic transfusion after CPB
Intraoperative cell salvage	Observational data only	Benefit is not clear, but extrapolation from adults supports use in children
Miniaturized CPB circuits	Observation data only	Decreases intraoperative blood utilization
Topical hemostatic agents	Only observational data in adults	Low risk, effective therapy
Low-dose antifibrinolytic therapy especially with tranexamic acid	In vitro evidence coupled with observational study in children	Plasma concentration of TXA of ≤20 µg/mL provides effective antifibrinolytic effect
Point-of-care tests of clotting (TEG and ROTEM)	In children only observational studies	Reduced transfusion with use of point-of-care technology
Postoperative interventions		
Limit blood sampling and minimize blood wastage in the PCICU	Observational studies only, in children	Reduced blood loss, especially in neonates
Postoperative cell saver	Single randomized trial	<ul style="list-style-type: none"> Reduced transfusions Supported by single randomized trial³³
Restrictive transfusion practice	Three randomized trials and 1 subgroup analysis of a randomized trial	<ul style="list-style-type: none"> Trial data showed tolerance of restrictive transfusion Hb threshold in all trials Varied Hb thresholds Varied outcome measures Some key exclusions in certain trials (neonates, bleeding, hemodynamically unstable)

Abbreviations: CPB, cardiopulmonary bypass; Hb, hemoglobin; Hct, hematocrit; LVAD, left ventricular assist device; PCICU, pediatric cardiac intensive care; rEPO, recombinant erythropoietin alpha; TEG, thromboelastography; TXA, tranexamic acid; vWD, von Willebrand's disease.

bleeding or clotting disorders may be undertaken as necessary, with subsequent hematology consultation as required. Preoperative planning should also include a detailed plan for holding antiplatelet agents and/or anticoagulation. As

aspirin-mediated bleeding lasts for 5–7 days, traditional practice has been to stop aspirin 5–7 days before surgery to reduce bleeding risk.¹² Prospective randomized trials in adults comparing continuation versus discontinuation of

Table 3. Preoperative Anemia Evaluation 4 Weeks Before Surgery

- Screen for bleeding/clotting disorders and anemia by detailed history and physical examination, including family, perinatal, surgical, and menstrual history
- Routine laboratory testing (blood chemistry, urine analysis, ECG, ECHO, etc)
- CBC (MCV, MCHC, morphology, with reticulocyte count, reticulocyte hemoglobin)
- Serum iron saturation, ferritin, CRP if the CBC is abnormal
- PT, INR, PTT, platelets, fibrinogen
- Von Willebrand antigen and activity (suggested in high risk and lengthy procedures)
- Other tests only as indicated (other factors assay, platelets aggregation)
- Hematinics (iron and vitamin C) for hemoglobin <13 g%
- Procrit 600 U/kg weekly for hemoglobin <12 g%
- Contraceptives for menorrhagia (Depot Provera suppress menstruation for 2–3 cycles)
- Hematology consultation if indicated, team assembly and planning
- Proper family counseling and legal advice

Data were derived from Hassan and Rajasekaran.¹¹

Abbreviations: CBC, complete blood count; CRP, c-reactive protein; ECG, electrocardiogram; ECHO, echocardiography; INR, international normalized ratio; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time.

aspirin before coronary artery surgery and noncardiac surgery found that preoperative aspirin did not affect the incidence of bleeding or thrombotic events postoperatively.^{13,14} However 2015 meta-analysis of 2399 adults undergoing coronary artery bypass surgery demonstrated increased bleeding, red blood cell (RBC) transfusions, and surgical reexploration in patients who did not have their aspirin discontinued preoperatively.¹⁵ In the absence of pediatric data, most centers elect to hold aspirin before elective surgery based on the current adult literature.

Vitamin K antagonists (ie, warfarin) remain the most common oral anticoagulant utilized in children, and perioperative “bridging” to maintain anticoagulation during the period when there is a subtherapeutic international normalized ratio can be accomplished with either unfractionated (UFH) or low-molecular-weight heparin (LMWH). Little pediatric data are available, and bridging anticoagulation strategies is based on adult guidelines. Nguyen and Sharathkumar¹⁶ surveyed the perioperative anticoagulation practices for children with prosthetic mechanical heart valves and found nearly identical rates of UFH and LMWH use. Campbell et al¹⁷ describe their institution’s experience with oral anticoagulation interruption of which congenital heart disease (CHD) was the primary underlying disease. We refer the reader to their institutional protocol that stratifies patients according to their thrombotic risk and includes no bridging therapy for low-risk patients, LMWH for medium risk, and LMWH followed by UFH for high-risk patients.

Direct thrombin inhibitors are not currently recommended as first-line agents for thromboprophylaxis or anticoagulation in the infant or child with CHD.¹⁸ As the adult experience is broadened, it is likely that these agents will have increased use in children, but for now extrapolation from adult bridging guidelines is necessary.

Anemia is a logical target for preoperative assessment and optimization in children undergoing cardiac surgery as it is easily identifiable and potentially modifiable, and is a risk factor for postoperative adverse outcomes in adult cardiac surgery.¹⁹ In the adult cardiac population, as many as 30% of patients scheduled for cardiac surgery with CPB were anemic.²⁰ Anemia in this population often translates into an increased risk of acute kidney injury and increased

incidence of early and late mortality.^{21,22} As a consequence, preoperative identification and treatment of anemia are now integrated into different multidisciplinary patient blood management approaches.

The relationship between preoperative anemia and outcome in neonates and children undergoing cardiac surgery is not well characterized, and is more difficult to define, particularly in cyanotic children in whom iron deficiency anemia can exist even with increased hemoglobin levels. The incidence of preoperative anemia in children with CHD is not well described; 1 retrospective review of 195 children with ventricular septal defects and atrioventricular septal defects ≤12 months old found an incidence of preoperative anemia to be 23%.²³ Recent studies in neonates²⁴ and in children²⁵ undergoing noncardiac operations suggested that preoperative anemia is an independent predictor of in-hospital mortality. Further studies are needed to confirm the relationship between anemia and outcome in children undergoing cardiac surgery, and better define preoperative strategies to optimize hemoglobin concentrations before CPB and discern the effect of those strategies on postoperative outcomes.

When the diagnosis of iron deficiency anemia is made preoperatively, treatment with oral iron supplements may be inadequate to achieve timely correction. Newer intravenous iron preparations, like ferumoxytol and ferric iron gluconate, offer safer means for rapid iron replacement.²⁶ In conditions where surgery without blood products is scheduled, an abbreviated course of preoperative recombinant erythropoietin (rEPO) therapy has been found to allow for asanguinous case completion.²⁷ Administration of rEPO preoperatively is of limited use and has not been widely adopted; however, it may help minimize consequences of asanguinous CPB prime, increase hemoglobin reserves, and reduce transfusion requirements in select cases where avoidance of blood product transfusions is deemed essential. Whether rEPO has a meaningful role in patient blood management in pediatric cardiac surgical patients is uncertain at this time and deserves further study.

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, affecting 1%–2% of the general population, and carries a significant bleeding risk. Baseline screening for VWD should be considered when suggested

by patient and family history, with preoperative measurement of Von Willebrand activity undertaken to help quantify bleeding risk. However, it should be noted that even a borderline low level (<60% activity) has been associated with a higher risk of operative bleeding in pediatric patients with scoliosis.²⁸ Acquired VWD has been demonstrated with a higher frequency in children with CHD (12%), though a relationship with bleeding was not identified.²⁹ Additional work is needed to discern the clinical impact of acquired VWD in the pediatric cardiac surgical patient as qualitative abnormalities in Von Willebrand factor have been demonstrated in adults on continuous flow ventricular assist devices (VAD),³⁰ and their use in children is increasing.

INTRAOPERATIVE PATIENT BLOOD MANAGEMENT

Surgical Technique and Topical Hemostasis

Achievement of adequate surgical hemostasis is one of the main determinants of perioperative bleeding. Careful surgical techniques using conventional strategies such as manual compression, suture ligation, and cauterization are commonly used to control bleeding during surgery. However, in some situations, these conventional methods are impractical or ineffective and additional strategies are required. Topical hemostatic agents, such as Gelfoam, Floseal, Fibrin glue, and Surgicel, are other options for local control of bleeding during surgery although randomized trials to prove efficacy in this area are lacking.³¹

CPB Strategies

Hemodilution/Target Hemoglobin. Hemodilution to reduce RBC requirements and improve microcirculatory flow and therefore tissue perfusion was initially thought to be beneficial in adults undergoing surgery in the early days of CPB.³² The practice continued for decades as it appeared that hemodilution resulting in very low hematocrit (Hct) levels was well tolerated,³³ and Hct levels between 15% and 20% were targeted. However, when the increased incidence of postoperative cognitive impairment was recognized,³⁴ the potential adverse effects of hemodilution on cerebral blood flow from altered perfusion pressure and reduced oxygen delivery from decreased arterial oxygen content causing neurocognitive sequelae were postulated.³⁵

Certainly it is the youngest patients who incur the greatest degree of hemodilution on CPB as the ratio of prime volume to patient blood volume is greater in smaller patients. Profound hemodilution was documented in infants with early CPB strategies, 500 mL in infants <8 kg³⁶ and contributes to fluid shifts, excessive body water concentration, and aberrant coagulation mechanisms and led to the development of lower priming volume circuits of around 200 mL and hemoconcentration techniques.³⁷ In addition to hemodilution resulting in lower Hct levels, large priming volumes result in hemodilution of platelets and coagulation factors to a similar extent, resulting in increased risk for postoperative bleeding and platelet and coagulant product transfusions.³⁸

Jonas et al³⁹ performed a prospective randomized controlled trial (RCT) in infants <9 months of age undergoing biventricular repairs randomized to 2 hemodilution protocols during surgery with hypothermic CPB. Target Hct

levels were approximately 20% vs 30% stratified according to surgeon and diagnosis. The lower Hct group had significantly decreased cardiac index, higher 60 minutes post-CPB lactate levels, and greater percentage increase in total body water on postoperative day #1. Blood product transfusion and adverse events were similar between the 2 groups; however, at 1 year of age, the low Hct group had significantly worse psychomotor development scores on testing. The investigators performed a follow-up prospective randomized controlled trial with target Hct levels of 25% vs 35% in infants undergoing biventricular (but not aortic arch) repair. The 25% group demonstrated a more positive fluid balance but similar blood product transfusions, adverse events, and developmental outcomes.⁴⁰ Data from both trials were analyzed and the authors concluded that goal Hct on CPB >25% is necessary for optimal neurodevelopment.⁴¹

Desire to minimize RBC transfusions for Jehovah's Witnesses patients has allowed for examination of results where the goal Hct on CPB is >21% for biventricular repairs unless other clinical and laboratory parameters are not met. In concert with additional blood conservation techniques, allowance for these lower Hct levels on CPB allowed for bloodless surgery in 36% of patients between 6 and 18 kg and in 81% of those >18 kg.⁴² There were no major adverse events, but neurocognitive and neurodevelopmental testing was not performed, making the long-term impact of this practice unknown. Although not supported by additional high-grade evidence, and not without controversy, centers with blood conservation programs report targeting an "on-CPB" Hct of around 25%.^{43,44}

Furthermore the indication for RBC transfusion on CPB appears to predict the associated risk. RBCs may be therapeutically transfused in case of hemorrhage or low oxygen transport and/or may be added prophylactically to the CPB prime to maintain a predefined Hct to counter hemodilution.⁴⁵ In a retrospective study, Willems et al⁴⁶ compared outcomes in children based on the indication for transfusion. The authors compared children undergoing prophylactic transfusion (whose only RBC transfusion exposure was with CPB prime administered to maintain calculated Hct >20% after administration of cardioplegia) with children with asanguinous CPB prime (and therapeutic RBC transfusion only after separation from CPB or in the intensive care unit [ICU]). After multivariate adjustment for other risk factors, the authors found that children exposed to a therapeutic transfusion had significantly higher odds for the composite outcome of severe postoperative morbidity and mortality than children exposed to a prophylactic transfusion to avoid excessive hemodilution.

The greater the degree of priming- and CPB-related hemodilution, the greater the risk for RBC transfusions.⁴⁷ One method to reduce hemodilution from circuit prime volume and therefore maintain goal Hct and reduce RBC transfusions is "miniaturization" of modern CPB circuits with smaller prime volumes.⁴⁸ Miniaturization of the CPB circuit may also reduce inflammation and impaired coagulation that results from the blood-circuit interface (contact activation) which may help avoid platelet aggregation/activation and reduce plasma and platelet product transfusions.^{49,50}

In children weighing <5 kg undergoing ventricular septal defect repair, cardiac surgery with CPB could be performed without RBCs in the prime in >70% of the patients when using a miniaturized systems. In this study, 95% of patients were not transfused during the perioperative period.⁵¹ In 2007, Miyaji et al⁵² confirmed that it is possible to do complex transfusion-free procedures safely for patients weighing more than 4 kg by using the low priming volume circuit.

Hemoconcentration Techniques. Conventional ultrafiltration (CUF) techniques (continuous ultrafiltration and zero-balance ultrafiltration) have been developed to remove water from the patient's circulation and thereby reverse hemodilution and maintain an even fluid balance throughout CPB.^{43,53} CUF however is restricted by need to maintain a minimum CPB reservoir volume. For this reason, modified ultrafiltration (MUF), ultrafiltration immediately after discontinuation of CPB, was developed to allow for maximal hemoconcentration and create a concentrated product for return to the patient and limit early postoperative blood transfusion.³⁸

Thompson et al⁵⁴ performed a prospective RCT in children ≤15 kg undergoing biventricular repairs with CPB. Children were randomized to conventional or MUF for hemoconcentration. For both arms, the amount of fluid removal was standardized [(prime volume + volume added during CPB) – urine output] with the goal of 50% effective fluid removal for those <10 kg and 60% fluid removal for those 10–15 kg. Hct levels, cardiac indices, and outcomes were similar between groups and the authors concluded that when a standardized volume of fluid is removed, neither method of hemoconcentration appears superior.

However, there are additional differences between CUF and MUF that must be considered. The downside to MUF is that it typically requires 15–20 minutes after discontinuation of CPB (compared to CUF that does not extend the procedure time), adds a degree of complexity and potential for technical complications, and may affect the patient's hemodynamics.⁵⁵ Although MUF has been reported to be a more effective hemoconcentrator and more effective at inflammatory cytokines and mediator removal, it appears that both are safe and beneficial with no difference in clinical outcomes on meta-analysis.⁵⁶ Additional methods used commonly to improve hemoconcentration include administration of loop diuretics or mannitol.

Composition of CPB Prime. The decision to prime with RBC is dependent on patient weight and estimation of their blood volume, preoperative hemoglobin (Hb), prime volume, and the desired Hb on CPB.⁵⁷ Asanguinous prime is generally possible with weight >5.0–6.0 kg.^{58,59}

The decision to use fresh whole blood (whole blood <48 hours stored age) versus RBC and fresh frozen plasma (FFP) to prime the circuit has been surgeon and institution-dependent. Advocates for fresh whole blood prime believe that it reduces CPB-mediated inflammation and coagulopathy.⁶⁰ Fresh whole blood is also thought to provide improved coagulant factors and platelet function.⁶¹ However, fresh whole blood may not always be available and its use can be a logistical challenge for blood banks. Mou et al⁶² performed a prospective randomized controlled trial of children

<1 year randomized to receive either fresh whole blood or reconstituted blood for CPB priming. The authors found that those managed with fresh whole blood had increased ICU length of stay and more fluid overload compared to the group receiving RBCs and FFP.

Valleley et al⁶³ performed a retrospective analysis of 100 neonates and children up to 4 years old who received either fresh whole blood or RBC prime. They found patients receiving fresh whole blood had significantly fewer total blood product exposures but no clinical outcome differences. A prospective randomized controlled trial of 64 infants <1 month of age compared chest tube drainage and clinical outcomes between infants receiving either fresh whole blood or RBCs for pump prime and transfusions in the first 24 hours after CPB.⁶⁴ Significantly less chest tube drainage and shorter length of mechanical ventilation and ICU length of stay were found in the fresh whole blood arm. Jobses et al,⁶⁵ describe their institution's experience using fresh whole blood over a 15-year period for infants <2 years. They compared retrospectively collected data from their registry with published reports and concluded that their use of fresh whole blood reduced the number of donor exposures for their patients. Although limitations due to their study design limit the strength of their analysis, their experience does demonstrate that it is feasible to provide fresh whole blood at a large surgical center.

FFP is utilized in the CPB prime in many centers to prevent CPB-associated coagulation abnormalities and bleeding and to avoid dilutional coagulopathy⁶⁶; however, there is little high-grade evidence to support its use. A prospective randomized controlled trial of infants and children from 1 to 16 years with either 20% albumin (50–100 mL) or FFP (1–2 units) in the pump prime compared hematologic assays and clinical outcomes. Immediately after heparin reversal, improved hemostatic tests were found in the FFP group; however, these results were not sustained 24 hours after CPB and no clinical differences were seen between groups.⁶⁷ Some centers reserve FFP in their pump prime for children <1 month of age to increase fibrinogen levels and reduce blood loss.⁶⁸ A 2015 Cochrane review of FFP for cardiovascular surgery included 4 adult trials where FFP was used in pump prime and found no evidence to support the prophylactic administration of FFP.⁶⁹ Pump prime composition is currently institution-dependent. Additional pediatric-specific research to determine the optimal CPB prime composition is needed.

Hypothermia. Hypothermia is a fundamental component of CPB, utilized to reduce cerebral metabolic rate and thus metabolic demand. Hypothermia can be classified as “moderate” (26°C–31°C), “deep” (20°C–25°C), and profound (<20°C) and is typically used for aortic arch repairs.⁷⁰ Deep hypothermia with pH-stat acid–base management is utilized as a neuroprotective strategy to prevent neurologic injury during periods of circulatory arrest.⁷¹

Platelet function and enzyme activity along coagulation pathways are known to decrease with decreasing temperatures thought to increase bleeding risk associated with hypothermia.⁷² Use of hypothermia also prolongs CPB time and proponents for normothermic CPB argue that reducing CPB duration decreases CPB-related adverse events.

Xiong et al⁷³ performed a systematic review and meta-analysis of trials comparing normothermic and hypothermic CPB. Of the 7 studies (419 pediatric subjects) included, end points of serum lactate and creatinine were chosen and the authors concluded that normothermia is as safe as hypothermic CPB. However, the study had significant methodologic limitations that weaken its conclusions and it does not provide adequate evidence to support a move away from hypothermic CPB.⁷⁴

Intraoperative Cell Salvage

Intraoperative cell salvage reinfusion is another strategy utilized to reduce the need for allogeneic RBC transfusion. After separation from CPB, the residual blood in the circuit (cell salvage) is collected and commonly reinfused into the patient as needed for immediate, safe, and efficient volume and RBC replacement.^{57,75} Observational studies suggest that cell salvage can be safely used to decrease allogeneic transfusion in noncardiac surgeries performed in neonates, small infants, and children.^{76,77} There is growing literature to support the reinfusion of cell saver blood in pediatric cardiac surgery as a component of blood conservation programs.^{44,53,58,78} Additional cell salvage can be collected and processed in the operating room with cell saver devices that wash and hemoconcentrate the product to a Hct of 60% for postoperative use (see postoperative section).

Management of Coagulopathy and Systemic Hemostasis

Perioperative coagulopathy, bleeding, and platelet and coagulant product transfusions are common in the neonate and child undergoing cardiac surgery with CPB.^{79,80} Factors that predispose to coagulopathy (especially in pediatric patients) include hemodilution due to addition of crystalloid coupled with blood loss (eg, asanguinous CPB prime, cardioplegia, and administration of fluids to maintain optimal cardiac output) and contact activation from tissue injury and contact between blood and synthetic surfaces. There are at least 3 CPB-induced activation mechanisms that account for coagulopathy including: (1) activation of factor X leading to thrombin generation and platelet consumption, (2) tissue factor production, and activation of the coagulation and fibrinolytic pathways, and (3) consumption coagulopathy due to thrombin, plasmin, and inflammation-mediated processes that deplete clotting factors.^{79,80} There are synergistic events that amplify this coagulopathy and increase bleeding risk including heparin-related inhibition of clotting, homeostasis disturbances (hypothermia, acidemia, hypocalcemia, etc), and inadequate reversal of UFH and excess protamine.^{81,82}

Anticoagulation on CPB and UFH Reversal

Systemic anticoagulation is required during CPB to prevent circuit thrombosis and thromboembolic complications and ameliorate contact activation and inflammation. UFH is the primary anticoagulant utilized for its rapid onset, easy titration, and reversibility with protamine.⁸³ Adjustment of UFH dosing can be accomplished by following activated clotting times (ACT), heparin concentration (antiFactor Xa [aFXa] activity), or whole blood heparin concentrations.⁸⁴ ACT and

automated protamine titration devices that provide whole blood heparin concentration (Hepcon instrument; Hepcon Hemostasis Management System [HMS]; Medtronic, Inc, Minneapolis, MN) are generally preferred for rapid bedside assessment (point-of-care). Although commonly used to monitor anticoagulation, ACT does not correlate with circulating heparin concentration, particularly in the setting of hemodilution and hypothermia, and may be inadequate for heparin monitoring.⁸⁵ Hepcon HMS determines in vitro anticoagulation response of the patient's blood to a known concentration of heparin and calculates the dose of heparin necessary to reach a desired ACT.⁸⁶

A small study (N = 26) using the Hepcon HMS to guide heparin dosing, compared to standard weight-based heparin dosing, found higher doses of heparin but smaller doses of protamine, and decreased consumptive coagulopathy, blood loss, and blood product transfusions in those managed with Hepcon HMS.⁸⁷ Gruenwald et al⁸⁸ performed a prospective randomized controlled trial comparing standard weight-based ACT with the HMS system in 99 infants <1 year of age. The authors found more stable aFXa levels and decreased blood transfusions for the first 24 hours postoperatively in those with HMS management.

Guzzetta et al⁸⁴ evaluated different ACT and bedside whole blood measurements and laboratory measurement of aFXa activity in infants <6 months of age. Their results demonstrated poor correlation between ACT and plasma heparin concentration, but good agreement between aFXa activity and Hepcon values. The authors suggest caution with isolated dependence on ACT values for evidence of adequate heparin anticoagulation.

Age-related differences with heparin sensitivity and heparin-protamine interactions make heparin dosing and protamine reversal even more challenging in the pediatric patient.⁸⁹ There is little room for error as inadequate heparin reversal can lead to perioperative bleeding and increased blood transfusion postoperatively. Protamine sulfate binds to UFH, dissociating it from the heparin-antithrombin complex and thus reversing anticoagulation at case conclusion. Unfortunately protamine excess can actually promote coagulopathy and increase bleeding through platelet and serine protease inhibition.⁸² Protamine dosing is generally determined by ACT and heparin concentration and estimates of patient blood volume and based on institutional protocols.⁹⁰ Adding to the challenge is that ACT and bedside point-of-care testing with thromboelastography or rotational thromboelastometry (ROTEM) do not appear to correlate well and are not reliable predictors of bleeding risk.⁹¹

Antifibrinolytics

Activation of fibrinolysis plays a central role in bleeding during cardiac procedures,⁹² prompting the use of antifibrinolytic agents like tranexamic acid (TXA) or ε-aminocaproic acid.⁹³ These agents competitively inhibit plasminogen conversion to plasmin and reduce fibrin degradation. Although these agents significantly decrease blood loss and transfusion requirement,^{94,95} several concerns remain regarding pharmacokinetic mechanisms and optimal dosing strategies.⁹⁶

Published reports of intraoperative TXA dosing schemes vary considerably, with loading doses ranging from 10 to

100 mg/kg, either in association with a 10 mg/kg/h continuous infusion (CI) or with multiple boluses administered at the time of CPB initiation and termination.⁹⁷ Reports of dose-dependent side effects from TXA, including clinical seizures, make it crucial that the lowest effective dose possible be used to maximize efficacy while limiting adverse events.⁹⁸ Determination of the most effective TXA plasma concentration requires adequate and reproducible tests to assess the degree of fibrinolysis *in vivo*, as well as accurate pharmacokinetic data to define the optimal TXA infusion scheme. Optimal dosing results in the lowest TXA plasma concentration that adequately inhibits *in vivo* fibrinolytic activation. To date, these *in vivo* studies have not been undertaken.

Various *in vitro* reports focusing on inhibition of fibrinolysis, platelet activation inhibition, and enhanced thrombin generation have argued for target TXA plasma concentrations ranging from 10 to 150 µg/mL. A recent *in vitro* study in children undergoing cardiac procedures suggested that a TXA loading dose of 10 mg/kg followed by a CI of 10 mg/kg/h limited fibrinolysis even in the presence of extremely high tissue-type plasminogen activator concentrations.⁹⁹ Those results suggest that plasmatic concentrations ranging from 10 to 20 µg/mL are sufficient to inhibit fibrinolysis in children with CHD undergoing cardiac surgery with CPB.^{100,101}

Yee et al,¹⁰⁰ in an *ex vivo* study, reported that TXA inhibits fibrinolysis (when activated by high-dose tissue-type plasminogen activator) at a plasma concentration of 6.54 µg/mL in neonates and 17.5 µg/mL in pooled adult plasma, while Soslau et al¹⁰² found that, in an *in vitro* study, plasmin-induced platelet activation was reduced by 50% when platelet-rich plasma is incubated with 16 µg/mL of TXA.

Two recent pharmacokinetic studies^{103,104} suggest revised dosing schemes for TXA. By defining a TXA plasmatic target concentration of 20 µg/mL, Grassin-Delyle et al¹⁰³ calculated an optimal dosing regimen in children undergoing cardiac surgery (age 12 months to 12 years with weights between 10 and 30 kg). Loading doses of 6.4 mg/kg followed by a 2.0–3.1 mg/kg/h CI resulted in stable TXA concentrations with adequate drug levels <20 µg/mL.

However, concentrations as high as 100 µg/mL may be required to completely inhibit fibrinolysis.¹⁰⁵ To date, it is unclear what TXA plasma concentrations are required to optimally inhibit fibrinolysis *in vivo*, mostly because of the difficulty in accurately measuring drug effect. Indeed, Wesley et al,¹⁰⁴ in an innovative study, report 3 potential TXA plasma concentration targets, 20, 60, and 150 µg/mL which have been recommended for use in pediatric cardiac surgical patients. Higher *in vivo* plasma concentrations may be required to be clinically effective and indeed various studies substantiate the fact that higher doses have been shown to be more effective in decreasing bleeding.^{106,107} The Wesley paper recommends dosing regimens which are different depending on the age of the child (0–2, 2–12, and >12 months). These authors used an additional dose of 20 µg/mL of TXA in the CPB priming volume. If future prospective *in vivo* studies indeed confirm these promising *in vitro* findings and determine the ideal plasma concentration and the most efficacious TXA dosing regime, then prophylactic

TXA administration may prove to be a routine safe and effective option to decrease bleeding in all neonates and children undergoing cardiac operations.

Point-of-Care Hemostatic Assays

Activated partial thromboplastin time and prothrombin time/international normalized ratio, and fibrinogen remain widely used to assess coagulation status pre-, intra-, and postpediatric cardiac procedures. Unfortunately, these tests were neither not designed to monitor perioperative coagulopathy nor guide administration of hemostatic agents during active bleeding. Results from standard coagulation assays require 30–45 minutes, limiting their utility in the context of acute bleeding.¹⁰⁸ In addition, standard laboratory tests use platelet poor plasma and do not allow for a global assessment of coagulation, providing no information about clot firmness or clot lysis.

Over the past decade, thromboelastography and ROTEM proved useful to assess hemostasis and guide the administration of blood products in bleeding patients. These assays assess the intrinsic (INTEM) and extrinsic pathway (EXTEM), and fibrinogen function (FIBTEM). More recently, point-of-care platelet function assays allow near real-time assessment of platelet aggregation responses. Among the large number of parameters tested, viscoelastic assays measure clot initiation, firmness, and stability. This approach allows for a rapid assessment of coagulopathy, and a recent study suggested that early values of clot amplitudes could be used to predict maximum clot firmness in all ROTEM tests.¹⁰⁹

Transfusion algorithms now make use of viscoelastic assays, and guidelines support their use.^{110,111} In adults undergoing cardiac procedures, studies support the use of point-of-care hemostatic monitoring integrated into standardized transfusion algorithms. This addition results in a significant reduction in blood product transfusions.^{112,113} In children undergoing cardiac operations, viscoelastic tests can assess coagulopathy and guide the administration of blood products.^{114–117} In a recent study in pediatric cardiac surgical patients after CPB, Nakayama et al¹¹⁸ found reduced blood loss, decreased red cell transfusion requirements, and reduced critical care duration associated with ROTEM-guided early hemostatic intervention.

Of the different non-red cell blood products used to manage bleeding, platelet concentrates, FFP, and cryoprecipitate remain common. In adults, fibrinogen concentrate offers an alternative to plasma and cryoprecipitate.^{119–121} One small prospective study in children suggested that fibrinogen concentrate, as an alternative to plasma and cryoprecipitate, provided equivalent efficacy to cryoprecipitate in children undergoing cardiac operations.¹²² No evidence exists regarding use of prothrombin complex concentrates in children undergoing cardiac surgery. Recombinant activated factor VII (rFVIIa) is used in pediatric cardiac operations; however, a Congenital Cardiac Anesthesia Society Task Force acknowledged the paucity of quality data to make evidence-based recommendations regarding its administration.¹²³ In addition, there is an increased incidence of postoperative thrombotic complications in neonates and children undergoing cardiac operations who receive

rFVIIa.¹²⁴ Consensus suggests that use rFVIIa should be restricted to extreme clinical situations with uncontrolled bleeding despite use of standard blood products.¹²⁵

Many institutions have now adopted pediatric cardiac surgery blood conservation programs that include use of low priming volume circuits, ultrafiltration (both CUF and MUF), microsampling of blood, antifibrinolytics and point-of-care testing, and cell salvage blood reinfusion. With these techniques, many centers report not only decreased blood transfusions but improved clinical outcomes compared to their preconservation era.^{44,78}

POSTOPERATIVE PATIENT BLOOD MANAGEMENT

Antithrombotic Management

The need to control bleeding and correct coagulopathy, thrombocytopenia, and/or platelet dysfunction is complicated both intra- and postoperatively by the concomitant need to maintain patency of newly placed artificial valves, conduits, and/or shunts. A large retrospective study found similar prevalence of both postoperative bleeding (12%) and postoperative thrombosis (11%) in children after cardiac surgery (rising to >25% prevalence for both complications for children <1 year of age).¹²⁶ Thrombosis, particularly in patients undergoing stage 1 palliation procedures with Blalock-Taussig or central shunts, carries significant mortality from complete obstruction of pulmonary blood flow that occurs with an incidence of 10%–20%.¹²⁷ Thrombosis after stage 2 (Bidirectional Glenn) causing pulmonary embolism and increasing pulmonary vascular resistance that risks candidacy for stage 3 procedures accounted for 12% of total thrombosis in a large series of 3043 children undergoing cardiac surgery.¹²⁸ After stage 3 (Fontan or total cavopulmonary connection) procedures, incidence of thromboembolism ranges from 3% to 20%.¹²⁹ Retrospective analysis of venous thromboembolism in children after cardiac surgery has found a higher association of death in patients with venous thromboembolism although the retrospective study design prevents establishing causality.^{126,130}

Evidence-based shunt and venous thromboprophylaxis guidelines have been published and are beyond the scope of this review.^{131–133} However, it is important to note that several physiologic and maturational differences exist in children that further complicate their antiplatelet and anticoagulant management after cardiac surgery, namely aspirin resistance and low antithrombin levels. Aspirin resistance (or unresponsiveness) is well described in infants with CHD and has been associated with increased thrombotic risk.^{134,135} Low antithrombin levels (which are essential to bind heparin to suppress thrombin generation) are seen in neonates and small infants, and can reduce the ability to achieve target anticoagulation with UFH and therefore increase their risk of thrombosis.¹³⁶

Limiting Sampling and Blood Wastage

The goal of reducing blood sampling and blood wastage during “routine” ICU postoperative care is not unique to pediatric cardiac surgery. Critically ill patients have an increased number of blood draws and phlebotomy volume each day.¹³⁷ There is heightened awareness that the amount of blood “lost” in routine laboratory draws is

significant, and is associated with red cell transfusion.¹³⁸ Presence of indwelling arterial and central venous lines triggers increased frequency of blood sampling, blood volume drawn, and amount of discarded blood.¹³⁹ Blood conservation interventions including use of small-volume phlebotomy tubes, point-of-care devices, closed sampling systems, elimination of “standing daily” laboratory orders and nursing/provider education are proven interventions that decrease blood wastage and phlebotomy volume.¹⁴⁰ Adoption of closed sampling systems significantly decreases blood waste and phlebotomy losses.^{141,142} The critically ill neonate and infant is most vulnerable to phlebotomy loss and blood wastage, with those <10 kg subject to the greatest number of blood draws and blood volume loss through phlebotomy.¹⁴³ Further research on postoperative blood conservation strategies is necessary to help identify additional areas where patient blood volume can be conserved, iatrogenic anemia prevented, and number of postoperative transfusions reduced.

Cell Saver Utilization Postoperative

As described in the intraoperative section, cell saver devices to collect and reinfuse residual blood from the CPB circuit are being utilized as part of pediatric cardiac surgery blood conservation programs. Cell saver utilization in pediatric cardiac surgery was originally hampered by technical limitations due to the small volume of collection, but technical advances have allowed its use to become more widespread¹⁴⁴ and cost-effective.¹⁴⁵ Golab et al¹⁴⁶ performed a retrospective analysis of their blood conservation measures and found that the collection and reinfusion of cell saver blood for up to 12 hours after its collection significantly reduced the number of allogeneic RBCs transfused in the pediatric intensive care unit (PICU). The authors postulated that prolongation of the acceptable period for transfusion of cell saver blood would increase its benefit. Ye et al¹⁴⁷ performed a prospective study randomizing children weighing 2.4–3 kg to receive either cell saver blood or standard allogeneic transfusions after separation from CPB. They found that the subjects managed with cell saver blood had significantly higher Hct and significantly fewer postoperative allogeneic RBC transfusions. Furthermore, there was reduction of early postoperative renal dysfunction and no increase in chest tube drainage. This latter finding is of significance as the processing of cell saver blood, by removing the supernatant, reduces coagulation factors, platelets, and plasma proteins and increases risk for postoperative bleeding.¹⁴⁸

Cholette et al¹⁴⁹ published a prospective controlled trial examining the numbers of allogeneic RBC transfusions and donor exposures in 106 children ≤20 kg presenting for surgery with CPB. Half of the subjects were randomized to receive cell saver blood for volume replacement and/or RBC transfusion up to 24 hours after its collection. When compared with control subjects, children randomized to the cell saver group had significantly fewer RBC transfusions ($P < .01$), coagulant product transfusions ($P = .013$), donor exposures ($P < .002$), and no clinical outcome differences. No differences in mediastinal tube drainage or postoperative bleeding were found between groups.

Significant limitations of this study exist, as it is a single-center study that was not powered to assess clinical outcome measures. Increased subject numbers to allow for comparison of postoperative outcomes, restriction to smaller subjects (ie, infants <10 kg) and a more focused patient population (ie, limited to higher surgical severity) would be of more relevance. Obvious differences in packaging and labeling of blood products prevented blinding of the attending physician, and the study carries with it the potential bias of all nonblinded studies.

A review and meta-analysis of prospective controlled trials examining washed cell salvage in surgical patients. Unfortunately of the 47 included trials, only 2 were in children, 1 postcardiac surgery.¹⁵⁰ Although the vast majority of subjects were adults, no apparent increase in bleeding risk was seen in those receiving washed cell salvage as the number of reoperations, plasma, and/or platelet transfusions was similar between groups. Additional studies on transfusion of cell saver blood in pediatric cardiac surgery and its impact on clinical outcomes are warranted. Impact of cell saver administration on postoperative bleeding and coagulant product transfusion is of particular relevance, as is the timing of the reinfusion.

Restrictive Transfusion Practices

Mazine et al¹⁵¹ present the epidemiology of RBC transfusions across North America as a subset from their previous observational study of children >28 days and <18 years of age.¹⁵² Seventy-nine percent of patients studied received at least 1 RBC transfusion postoperatively. The distribution of pretransfusion hemoglobin levels is presented in the Figure. Despite the initial data from over a decade ago (from September 2004 to March 2005), and the exclusion of neonates who undergo the most complex surgeries, it is hard to dispute the authors' conclusion that clearer transfusion guidelines in this specific population are needed.

Although multiple studies demonstrate that RBC transfusions in children after cardiac surgery are associated with worse clinical outcomes,^{46,153–157} the optimal transfusion strategy for these critically ill children has not been established. Given that red cell transfusions in children track with worse outcomes, limiting red cell transfusions is justified and efforts to determine a safe lower Hb concentration are worth pursuing. It seems reasonable to reserve transfusion for those with supporting clinical indications.

The transfusion requirements in pediatric intensive care unit (TRIPICU) study is the landmark transfusion trial in critically ill children.¹⁵⁸ This multicenter, noninferiority prospective randomized trial compared a restrictive versus liberal transfusion strategy in critically ill but hemodynamically stable children with a primary outcome of new or progressive multiorgan failure. Children in the restrictive group were transfused for Hb <7.0 or 9.5 g/dL. As a noninferiority trial, neither group appeared better (or worse) than the other. Willems et al¹⁵⁹ performed a subgroup comparison of the TRIPICU trial examining children after cardiac surgery. They found that children maintained with significantly lower Hb levels demonstrated no significant difference in multiple organ dysfunction. Important limitations of the study include that patient enrollment could be within

the first 7 days of PICU admission and that exclusion criteria were acute blood loss and hemodynamic instability. Additional exclusions important to cardiac surgery were exclusion of those <28 days, cyanotic heart disease (with right to left shunt), and palliative procedures: all the stages of single ventricle palliations (Norwood, Glenn, Fontan) and systemic to pulmonary artery shunts. Despite that these exclusions preclude study of the most heavily transfused patients, the findings remain important as they "allow" the bedside clinician to not transfuse purely for a low Hb level.

The second randomized controlled transfusion trial in pediatric cardiac surgery was performed in the Netherlands and included 103 children noncyanotic children.¹⁶⁰ Inclusion criteria were "elective" surgery and an oxygen saturation >95%. Sixty-six percent of eligible children were randomized, and the Hb thresholds were 8.0 vs 10.8 g/dL for restrictive and liberal groups, respectively. In-hospital length of stay was the primary outcome and met significance in the restrictive (8 [7–11]) compared to liberal (9 [7–14]) group ($P = .047$); although duration of mechanical ventilation and PICU length of stay did not differ. Not surprisingly, there was significant cost savings in those managed with a restrictive transfusion strategy. Strength of this study was that study intervention was initiated at anesthesia induction, and therefore included the immediate postoperative period where potential for hemodynamic instability and bleeding/blood loss is most prevalent. Limitations include the study being performed at a single center, and exclusion of cyanotic children and neonates and small infants who undergo more complex surgical procedures.

The first prospective randomized trial to include children with cyanosis and single ventricle physiology¹⁶¹ compared restrictive and liberal transfusion strategies in children undergoing cavopulmonary connection (Bidirectional Glenn or Fontan). Study intervention included transfusion for Hb <9.0 with clinical indications (restrictive) or 13 g/dL regardless clinical indications (liberal group), from time of admission to PICU directly to 48 hours postoperatively. The sole exclusion was if consent could not be obtained; and 95% of eligible patients were studied. Higher Hb thresholds for transfusion were chosen reflective of the practice for cyanotic patients with single ventricle physiology. Primary outcome was mean and peak arterial lactate with secondary outcomes of arteriovenous and arterio-cerebral oxygen (as measured by regional somatic oxygen [rSO₂]) content differences. Mean Hb levels were significantly lower in the restrictively managed (11 ± 1.3 g/dL) compared to liberally managed (13.9 ± 0.5 g/dL) groups ($P < .01$). Correspondingly, significantly fewer transfusions (mean 0.43 ± 0.6 vs 2.1 ± 1.2; $P < .01$) and donor exposures (1.2 ± 0.7 vs 2.4 ± 1.1; $P < .01$) were seen in the restrictive group. Despite the lower Hb levels, no significant difference was seen in mean or peak arterial lactate or arteriovenous or arterio-cerebral oxygen content differences or clinical outcomes. Despite that surrogate measures of oxygenation were utilized to compare the 2 groups, the findings are important as they demonstrated no protocol violations and no obvious harm from maintenance of the lower Hb levels. The authors concluded that children after cavopulmonary connection despite their single ventricle physiology and immediate postoperative condition appeared able to accommodate for the lower Hb levels.

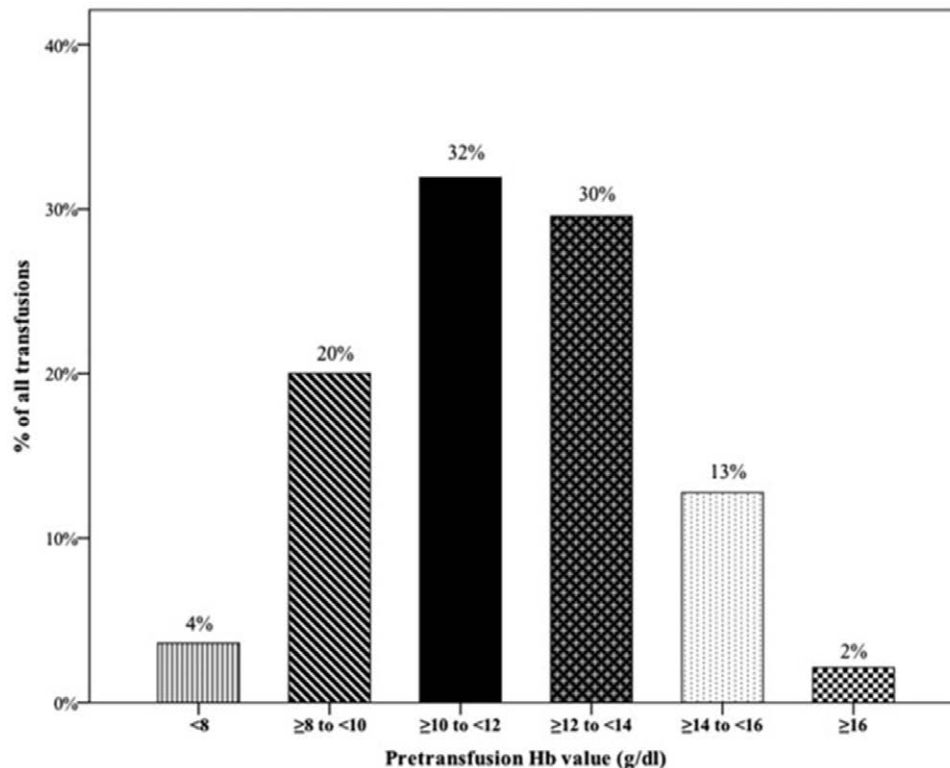


Figure. Distribution of pretransfusion hemoglobin levels in children after cardiac operations from Mazine et al.¹⁵¹

The same authors performed a follow-up study in children ≤ 10 kg with CHD.¹⁶² Patients were stratified according to biventricular repair versus palliative (nonseptated) procedure with correspondingly higher Hb thresholds in the palliated group. In restrictive managed subjects, Hb < 7.0 g/dL (biventricular) and < 9.0 g/dL (palliative) and clinical indications were required for RBC transfusion. For liberal managed subjects, transfusions were given for Hb < 9.5 g/dL (biventricular) and < 12 g/dL (palliative) regardless any clinical indication. Fifty-seven subjects underwent surgical palliations, including 12 modified Norwoods. There was 100% compliance with the restrictive group subjects undergoing biventricular repairs and 79.3% compliance in the restrictive palliative group. Restrictive group subjects had significantly lower Hb levels throughout admission and received significantly fewer RBC transfusions without differences in mean/peak or clearance of lactate, arteriovenous oxygen difference, or clinical outcomes.

Comparison of the 4 studies is presented in Table 4. Taken as a group, the evidence supports that children undergoing complete biventricular repairs appear to tolerate Hb levels down to 7 g/dL, even in the immediate postoperative period without clinical or surrogate markers of impaired oxygen delivery. Children undergoing second and third-stage cavopulmonary connection for single ventricle physiology appear to tolerate Hb levels down to 9 g/dL. In the Cholette 2017 study,¹⁶² the majority (80%) of neonates undergoing palliative procedures tolerated a restrictive transfusion strategy (Hb < 9 g/dL); however, the study group included only a small number of modified Norwood procedures (N = 12). Larger multi-center trials would be of great interest to confirm these results.

Use of Hb threshold to trigger a RBC transfusion is common place, and not altogether without merit, as certainly there is a lower level (currently unknown) that warrants transfusion regardless the clinical situation. However, best practice would include the clinical landscape (signs, symptoms, and situation) in addition to the Hb level in the decision to transfuse. The recent explosion of studies examining transfusion strategies (liberal versus restrictive) across a variety of clinical conditions and disciplines has prompted evaluation of postoperative transfusion practices even in this particularly vulnerable population. Whether the current body of literature applies across the variety of these unique and challenging children is uncertain and deserves further study.

Mechanical Circulatory Support

Mechanical circulatory support with either venous-arterial extracorporeal membrane oxygenation or VAD are used to support cardiac function when ventricular failure prevents adequate cardiac output to maintain normal end-organ function. Historically large numbers of RBC and coagulant product transfusions have been common in the management of extracorporeal membrane oxygenation (ECMO) patients due to the increased incidence of significant bleeding, coagulopathy, thrombocytopenia, and platelet dysfunction that occurs with ECMO.¹⁶³ However, practice variation exists across institutions and data on blood product use across centers are limited. The large national registry, Extracorporeal Life Support Organization tracks bleeding, but does not include transfusion data and pediatric patients on ECMO have been excluded from pediatric transfusion trials.

Table 4. Pediatric Postoperative Cardiac Surgery Restrictive Versus Liberal Red Blood Cell Transfusion Trials

First Author (Year)	Population	Patients (N)	Inclusion Criteria	Hb Thresholds	Outcome
Willems et al (2010) ¹⁵⁹	Noncyanotic	125	>28 d to <14 y Hemodynamic stable	7 vs 9.5 g/dL	New/progressive MODS
Cholette et al (2011) ¹⁶¹	Cyanotic	60	BDG or Fontan	9 vs 13 g/dL	Mean/peak lactate avDO ₂ and acDO ₂
De Gast-Bakker et al (2013) ¹⁶⁰	Noncyanotic	103	>6 wk to <6 y	8 vs 10.8 g/dL	Hospital LOS cost
Cholette et al (2017) ¹⁶²	Cyanotic and noncyanotic	162	≤10 kg	(C) 9 vs 12 g/dL + clinical (NC) 7 vs 9.5 g/dL	Protocol adherence No. transfusions Hb level Arterial lactate avDO ₂

Abbreviations: acDO₂, arterio-cerebral oxygen difference; avDO₂, arteriovenous oxygen difference; BDG, Bidirectional Glenn; C, cyanotic; Hb, hemoglobin; LOS, length of stay; MODS, multiorgan dysfunction syndrome; NC, noncyanotic.

Small observational studies have demonstrated worse clinical outcomes in ECMO patients who receive larger volumes of RBC transfusions.^{164,165} To our knowledge, there are neither no published studies that target blood conservation practices nor their association with clinical outcomes, in children on ECMO. Despite this, similar to advances in CPB strategies, ECMO strategies have evolved, including miniaturization of the circuit, and as clinical outcomes improve, efforts are being made to reduce blood product use on ECMO.

Current Extracorporeal Life Support Organization guidelines recommend maintaining a Hct >40% to maintain oxygen delivery with the lowest possible ECMO flow.¹⁶⁶ Despite these guidelines, ECMO medical directors report using lower transfusion thresholds in their practice, namely 35% median Hct (range, 25%–40%).¹⁶⁷ There is also no data to support Hb threshold for RBC transfusion in children supported with VADs. Future research examining transfusion thresholds in stable, nonbleeding ECMO and VAD patients is warranted, with the aim to determine optimal physiologic thresholds for transfusion and avoidance of reliance on a solely Hb-based strategy.

CONCLUSIONS

The complex relationship among anemia, transfusion, oxygen delivery, and oxygen utilization in children with cardiac disease is poorly understood. Traditionally children with CHD receive large-volume transfusions perioperatively due to bleeding and blood loss, altered hemostasis, hemodynamic instability, and impaired or threatened ventricular function and oxygenation. Furthermore those undergoing palliative procedures, or those with poor ventricular function, are uniquely susceptible to the impact of anemia as their ability to increase their oxygen saturation and cardiac output to maintain oxygen delivery is compromised.

Despite these challenges, it is becoming recognized that children with CHD, however vulnerable, can be managed safely with conservative blood management practices that span the pre-, intra-, and postoperative periods. The purpose of this narrative review is to present the current literature regarding anemia management and blood transfusion practices in the perioperative care of these critically ill children, and highlight potential avenues where blood conservation can be applied. Adoption of conservative transfusion strategies will decrease blood product transfusions and

potentially the associated risks, whether it will improve clinical outcomes is an area that deserves investigation. ■■

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Contribution: This author helped by writing the introduction, tables, initiating and organizing the work, creating the collaboration of authors, and reviewing and editing the entire text.

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