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Recommendations on Red Blood Cell Transfusion in Infants and Children with Acquired and Congenital Heart Disease from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

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Abstract

Objective—To present the recommendations and supporting literature for red blood cell (RBC) transfusions in critically ill children with acquired and congenital heart disease developed by the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI).

Design—Consensus conference series of 38 international, multidisciplinary experts in RBC transfusion management of critically ill children

Methods—Experts developed evidence-based and when evidence was lacking, expert-based clinical recommendations and research priorities for RBC transfusions in critically ill children. The cardiac disease subgroup included three experts. Electronic searches were conducted using PubMed, EMBASE, and Cochrane Library (CENTRAL) databases from 1980 to May 2017. Agreement was obtained using the Research And Development/University of California, Los Angeles (RAND UCLA) appropriateness method. Results were summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.

Results—21 recommendations were developed, and reached agreement. For children with myocardial dysfunction and/or pulmonary hypertension there is no evidence that transfusion > Hb of 10g/dL is beneficial. For children with uncorrected heart disease, we recommended maintaining Hb > 7–9.0 g/dL depending upon their cardiopulmonary reserve. For stable children undergoing biventricular repairs, we recommend not transfusing if the Hb is > 7.0 g/dL. For infants

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undergoing staged palliative procedures with stable hemodynamics, we recommend avoiding transfusions solely based upon Hb, if Hb is > 9.0 g/dL. We recommend intra- and postoperative blood conservation measures. There is insufficient data supporting shorter storage duration RBCs. The risks and benefits of RBC transfusions in children with cardiac disease requires further study.

Conclusions—We present RBC transfusion management recommendations for the critically ill child with cardiac disease. Clinical recommendations emphasize relevant Hb thresholds and research recommendations emphasize need for further understanding of physiological and Hb thresholds and alternatives to RBC transfusion in sub-populations lacking pediatric literature.

Keywords

blood; transfusion; red blood cell; consensus conference; critically ill child; heart disease

INTRODUCTION

Red blood cell (RBC) transfusion can be life-saving; certainly, in the setting of active bleeding, transfusions support hemodynamics and cardiac output, and increase arterial oxygen content with hope of improving oxygen delivery. As such, RBC transfusions are a critical element in the armamentarium required in the pediatric cardiac intensive care unit where perturbations in hemodynamics, volume status, cardiac function/output, oxygenation/ventilation, bleeding and altered hemostasis are common and often occur simultaneously. There are several rather unique characteristics of the child with acquired or congenital heart disease (CHD), as well as variations in the clinical setting (pre, intra or post-op), that influence the practitioner's decision to (or not to) transfuse.

There is little debate that the child being managed intra or post-operatively with active bleeding resulting in significant anemia and hemodynamic instability would likely benefit from RBC transfusion. Children with moderate to severe right or left ventricular dysfunction (systolic and/or diastolic), and/or abnormal heart rate or cardiac conduction, may be unable to augment their cardiac output in response to anemia or low intravascular volume, and likely would also benefit from RBC transfusion. Additionally, physiologic conditions that result in low arterial oxygen saturations (i.e., intra-cardiac or great-vessel level shunting, elevated pulmonary vascular resistance or pulmonary disease) are common in children with acquired or CHD and increase their risk for impaired oxygen delivery in the setting of anemia and/or poor cardiac output. For these reasons (either singularly or in combination) children with heart disease are heavily transfused (1, 2).

There is a growing body of literature illustrating a strong association between RBC transfusion and worse clinical outcomes, even after controlling for illness, in children with pediatric heart disease (3–5). These data increase the need for the bedside clinician to be judicious in his/her decision to transfuse, and to avoid reflexive (solely hemoglobin (Hb)-based) transfusions in patients with good hemostasis, stable hemodynamics, adequate oxygenation (for their cardiac lesion), and normal end-organ function. Unfortunately, there is a paucity of high-quality data exploring transfusion thresholds in many sub-populations of children with cardiac disease. There is generally a low level of evidence for most of the recommendations described in this article, and they are intended to initiate discussion and

identify research priorities regarding transfusion management in these very complex patients.

METHODS

The details of the methodology are described elsewhere in this supplement of *Pediatric Critical Care Medicine* (6). Briefly, we searched PubMed, EMBASE, and Cochrane Library from 1980 to December 2015, with an update in May 2017, using a combination of medical subject heading terms and text words to define concepts of RBC transfusion and acquired and CHD in children. We searched references from identified articles for additional publications. Two authors reviewed all citations independently. We used a standardized data extraction form to construct evidence tables and graded the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. A panel of 38 experts from 29 academic institutions in 8 countries met over the course of two years to develop evidence-based and, when evidence was lacking, expert-based recommendations for RBC transfusion in critically ill children. Three experts coordinated the cardiac disease subgroup. Recommendations developed and supporting literature were reviewed and scored by all panel members, using the Research And Development/University of California Appropriateness Method. All recommendations reached agreement (>80%). Final recommendations for RBC transfusion in critically ill children with acquired and CHD were divided into three categories: good practice statements, clinical recommendations, and research recommendations.

RESULTS

The final clinical and research recommendations and rationale for transfusion in critically ill children with acquired and CHD are presented below. Although transfusions in these children are not limited to the following, our recommendations focused on the topics of ventricular dysfunction, pulmonary hypertension, uncorrected CHD, intra-op, post-operative biventricular repairs, post-op palliation procedures and RBC storage duration. Included randomized controlled trials that formed the major evidence base for the recommendations are summarized in Supplemental Digital Data, Supplemental Table 1.

In addition, we emphasize five additional good practice statements that are particularly relevant for infants and children with acquired and CHD.

Good practice statements

6.1 In children with cardiac disease we recommend optimization of all the components contributing to oxygen delivery, including but not limited to achievement/maintenance of: normal sinus rhythm and/or heart rate control, optimal preload and contractility, optimal right ventricular and left ventricular afterload, adequate oxygenation and/or reduction of oxygen demand, as appropriate before initiation of RBC transfusion, except in the case of hemorrhagic shock. *Consensus panel expertise; 94% Agreement, (n=35), Median 8, IQR 8–9*

A common rationale for RBC transfusion is to increase oxygen delivery. Hemoglobin is a key element of oxygen delivery, and potentially the easiest to manipulate, but optimization of the other components is essential as manipulation of Hb concentration does not reliably impact oxygen delivery (DO_2) nor oxygen consumption (VO_2) (7). Global O_2-delivery (DO_2), the amount of O_2 delivered to the tissues, is the product of total blood flow or cardiac output (CO) and the O_2-content of arterial blood (CaO_2). Cardiac output is determined by heart rate and stroke volume (the volume ejected by the ventricle with each contraction). The CaO_2 is the sum of O_2 bound to Hb and O_2 dissolved in plasma. Therefore, the CaO_2 depends primarily on the Hb concentration and arterial O_2-saturation (SaO_2).

Robust homeostatic physiologic compensatory mechanisms counter decreasing Hb levels (8,9). In healthy hearts, increases in heart rate, contractility, preload and vascular tone (driven by adrenergic, autonomic and neuroendocrine systems) increase CO in response to decreased blood viscosity and lower CaO_2, to maintain DO_2. Blood flow is redistributed to organs with a high O_2-demand (brain and heart), at the expense of organs exhibiting a lower tissue O_2-demand (renal/splanchnic). At the cellular level, the O_2-Hb dissociation curve progressively adjusts during periods of anemia with an increase in 2, 3-diphosphoglycerate (DPG) that facilitates offloading to tissues by decreasing Hb affinity for O_2. Furthermore, VO_2 is maintained by the ability of peripheral tissues to increase proportional oxygen extraction (EO_2) in hypoxemic states by altering microvascular blood flow, resulting in lower venous oxygen content (CvO_2) and stable tissue pO_2.

There are different ways to maintain or increase DO_2 in addition to RBC transfusion. Cardiac output can be supported or augmented by inotropic/chronotropic and/or vasoactive agents that impact preload and afterload, and measures to maintain sinus rhythm (antiarrythmics, temporary pacing) and optimal cardiac filling (volume or diuretic administration). Optimization of ventilation and oxyenation to increase CaO_2 and/or decrease O_2-demand by treating fever, agitation, pain and septic states is also mandatory. Other determinants of DO_2 in addition to the Hb level should be considered and optimized (as able) in the management of acutely ill children with acquired or CHD before administration of RBC transfusion.

6.2 We recommend that for all children with congenital and acquired heart disease the benefits and risks of transfusion are considered before transfusion. Whenever possible, adoption of blood sparing and conservation procedures and guidelines should be implemented. ***Consensus panel expertise; 93% Agreement****, (n=30) Median 8, IQR 8–9*

Although RBC transfusion is the cornerstone treatment of anemia and blood loss in children with acquired or CHD, the decision to transfuse remains a true clinical dilemma. Both anemia and RBC transfusions are associated with risks and worse outcomes. Anemia decreases DO_2 and is unmistakably deleterious below a certain level. The critical Hb threshold below which tissue O_2-demand is in jeopardy is unknown and varies depending upon the underlying condition and clinical status of each patient. Patients with an alteration in their physiological compensatory mechanisms will present a reduced tolerance to anemia and require higher threshold Hb for transfusion (10, 11).

There are case reports of patients who have survived severe anemia without receiving blood transfusions (12). Nonetheless, case series of severe anemic adult patients refusing blood transfusions often provide evidence of the major consequences of acute severe anemia and critical Hb levels when DO_2 cannot sustain tissue O_2-demand. In these adult studies, the mean fatal Hb level was higher in patients with cardiovascular disease (13, 14). Conversely, studies show an association between RBC transfusions and worse outcomes and increased mortality risk (15). RBC transfusions are associated with potentially severe adverse events (i.e., infectious, non-infectious non-immune, and immune-mediated) (16). Patients with cardiac disease appear vulnerable to the adverse effects of transfusion (17). Several studies reported adverse clinical events associated with RBC transfusion in children undergoing cardiac surgery (18–22), including heart transplant (23). However, the indication for the transfusion must be taken into consideration as this is likely to impact outcome (24). The decision to transfuse should take into account the balance between the risk of transfusion and the risk of anemia (25).

Patient blood management (PBM) programs, including blood sparing and conservation procedures and transfusion guidelines, are designed to assist clinicians with appropriate transfusion decision making (26, 27). Those programs are associated with a decrease in blood product use without worsening outcomes (28–30). Monitoring blood utilization and assessing adherence to transfusion guidelines is the key to successful implementation of such programs. Data suggest that overall restrictive transfusion strategies should be used, but further research is needed to assess the best oxygenation requirements, hemoglobin threshold, and transfusion strategy for different patient situations. Perioperative blood management strategies include minimizing blood draws, restricting transfusions, intraoperative cell salvage, acute normovolemic hemodilution, antifibrinolytic agents, and using point-of-care tests to guide transfusion decisions. In the specific setting of cardiac surgery on cardiopulmonary bypass (CPB), minimizing CPB circuit size and ultrafiltration/hemoconcentration are other strategies to minimize RBC transfusion need (31–37).

The use of iron supplementation or erythropoiesis stimulating agents is another strategy to decrease RBC use; however, these treatments are only useful in an elective setting because of the time required for Hb to rise after their administration. The use of iron supplementation or the administration of erythropoiesis stimulating agents in the preoperative setting of children undergoing cardiac surgery is discussed following recommendation 6.4. Their use in the postoperative setting is not common and we lack data that demonstrate their safety, usefulness for reducing RBC transfusion and improving outcome.

6.3 In children undergoing cardiac surgery (repair or palliation) or heart transplants, when deciding to transfuse, we recommend considering not only the Hb concentration but the overall clinical context (e.g. symptoms, signs, physiological markers, laboratory results) and the risk, benefits, and alternatives to transfusion. ***Consensus panel expertise; 97% Agreement, (n=35),*** *Median 8, IQR 8–9*

Even if the Hb level is the major factor motivating the decision to transfusion cardiac children, we should not lose sight that the DO_2 is determined by variables other than the Hb level alone and that VO_2 and EO_2 vary by patient and context (1). Tolerance to anemia

depends on the ability of the child to mount physiological mechanisms that compensate for a low Hb level. These different mechanisms are summarized under recommendation 6.1. In children with acquired or CHD, those mechanisms may be impaired. A low O_2-saturation as seen in children suffering cyanotic heart disease will significantly decrease CaO_2, particularly if associated with a low Hb level. Furthermore, anemia may be poorly tolerated by patients with cardiac failure and/or coronary disease because of their limited ability to increase CO in compensate for anemia (11, 38, 39). When managing a child with a low Hb level and acquired or CHD, it important to evaluate clinical symptoms and signs, physiological markers and laboratory results for impaired anemia tolerance. As mentioned in recommendation 6.2, before transfusing these children, the benefits, risks and alternatives to RBC transfusions should be considered.

6.4 In infants and children with congenital heart disease we recommend investigating and treating pre-operative anemia in addition to implementing transfusion/blood management guidelines/blood conservation practices. ***Consensus panel expertise; 94% Agreement,*** *(n=35), Median 9, IQR 8–9*

In the adult cardiac population 22% to 30% of patients scheduled for cardiac surgery under CPB are anemic, and pre-op anemia is associated with post-op morbidity (40). The relationship between preoperative anemia and outcomes in children with CHD undergoing cardiac surgery is less well characterized and more difficult to define, particularly in cyanotic children where iron deficiency anemia can exist, even with increased Hb levels. The incidence of pre-operative anemia in children with CHD is not well described; a retrospective review of infants with ventricular septal and atrioventricular septal defects found the incidence of pre-op anemia to be 23% (41). Recent studies in neonates (42) and in children (43) undergoing non-cardiac operations suggest that preoperative anemia is an independent predictor of in-hospital mortality. Pre-operative anemia is also associated with increased RBC transfusions and worse clinical outcomes following pediatric cardiac surgery (44).

It is recommended that patients have a full assessment and subsequent optimization of their hematological function 30 days before any elective major surgery, to reduce the need for potentially avoidable intra-operative blood transfusions (45). In adults, preoperative anemia management is feasible using iron supplementation, with or without administration of recombinant human erythropoietin (rEPO) (46). Oral iron supplementation is preferred for treatment of iron deficiency anemia because of its effectiveness and low cost; however it is hampered by poor oral bioavailability, adverse gastrointestinal symptoms and the long duration of therapy required to treat anemia and replenish body iron stores. Intravenous iron is an alternative, and newer preparations have improved safety profiles (47) with clinical effectiveness if the infusion is administered at least 5 days preoperatively (though peak efficacy is 2–4 weeks after infusion) (45). In a meta-analysis, intravenous iron therapy effectively increased Hb concentration and reduced allogeneic RBC transfusion (48). However, there is potential for increased risk of infection as iron is a growth factor for bacteria and certain host defense mechanisms are iron-sensitive (49). Iron administration might therefore increase the host susceptibility for bacterial infection, although no data on critically ill patients are available to support such a hypothesis (50).

Administration of rEPO stimulates erythropoiesis in critically ill patients, even those with acute inflammation (51). Concurrent EPO and iron administration is thought to be safe, and decreases RBC transfusions in critically ill adults (52). However, the role and the safety of erythropoiesis-stimulating agents in the management of adults with preoperative anemia who are undergoing cardiovascular surgery remains unclear, as some studies demonstrate a substantial reduction in blood transfusions with no differences in mortality, thrombotic events, or serious adverse events (53), while another study showed late deaths in those receiving erythropoiesis-stimulating agents (54). Development of anti-EPO antibodies resulting in severe aplasia and transient alterations in RBC rheology have also been reported (55). Furthermore, some patients appear to have “EPO resistance”, possibly secondary to malnutrition and inflammation (56). For these reasons, its expense, and possible link to thromboembolic events and tumour growth via promotion of angiogenesis, the National Institute for Health and Care Excellence (NICE) guidelines warn against routine use of rEPO except in patients who decline blood transfusion or if transfusion is unavailable due to presence of alloantibodies (57). There is no clear support for routine rEPO therapy in children undergoing cardiac surgery.

Elective surgery should be delayed when untreated anemia is identified preoperatively so that effective treatment can be instituted, and risk of RBC transfusion can be reduced. Pre-operative blood transfusion is recommended for patients with persistent bleeding requiring urgent or emergency surgery (58). We recommend that preoperative identification and treatment of anemia should be integrated into a multidisciplinary patient blood management approach. Anemia itself compromises the outcome of surgical patients, results in more frequent RBC transfusions, and may potentially compromise patient outcome. In elective cardiac surgery use of a patient blood management program will minimize the exposure to blood products, lead to cost savings and likely improve patient outcomes.

6.5 In hemodynamically stable infants and children with CHD and adequate oxygenation (for their cardiac lesion) and normal end organ function who are awaiting cardiac surgery, we recommend that the risks, benefits, and alternatives of RBC transfusions must be carefully considered when deciding to give an RBC transfusion. ***Consensus panel expertise; 85% Agreement,*** *(n=35), Median 8, IQR 7.25–9*

We refer to the discussion of recommendation 6.1 to 6.3 to support this recommendation.

Clinical Recommendations

Myocardial Dysfunction—6.6 **In children with documented right or left ventricular myocardial dysfunction (acquired or congenital), there is insufficient evidence to support transfusion to target a specific Hb concentration. Furthermore, there is no evidence that transfusion for a Hb level > 10 g/dL is beneficial.** *Consensus panel expertise, 83% Agreement, (n=30), Median 8 IQR 7.25–8.75*

Rationale—No high grade pediatric evidence exists to support recommendations for transfusions to target a specific Hb concentration in patients with acquired or congenital myocardial dysfunction. Furthermore, myocardial dysfunction can result from a broad range of disease states (i.e., myocarditis, cardiomyopathy, sepsis) that can occur in the presence or

absence of CHD. Obvious differences between children and adults, and ischemic heart disease and CHD, and other causes of myocardial dysfunction prevent extrapolation of adult data to provide conclusions. That being said, in the absence of pediatric studies, the adult literature provides some data.

Adult cardiac surgery data is mixed; with some studies demonstrating worse (and dose-dependent) outcomes following RBC transfusions, even after controlling for severity of illness (59, 60). However, a prospective RCT found higher mortality rate in restrictive (transfused for Hb <7.5g/dL), compared to liberal group adults undergoing cardiac surgery (transfused for a Hb <9.0g/dL) (61). Systematic review and meta-analysis of adult transfusion trials in patients with cardiovascular disease concluded that there is no difference in outcomes for adults with chronic cardiovascular disease managed with restrictive v. liberal transfusion thresholds, but there was insufficient evidence to recommend a restrictive transfusion strategy in adults with acute coronary syndrome (62).

Septic shock is commonly associated with myocardial dysfunction (63). Data in this population is limited to adults as well; where no benefit from higher Hb levels has been demonstrated. Prospective RCT of adults with septic shock requiring intensive care demonstrated similar short and long-term outcomes in those managed with a lower (Hb <7.0g/dL) v. higher (Hb <9.0 g/dL) Hb transfusion threshold (64,65). Older adults (>65 years) with heart failure were followed and multivariate logistic regression analysis conducted to determine whether hematocrit (Hct) was an independent predictor of all-cause mortality and heart failure readmission at one year (66). The authors found no data to support an association between anemia and mortality, even at the lowest Hct levels (<24%). Anemia is common in heart failure, and its cause is multifactorial, e.g. renal disease (diminished Epo), fluid overload, iron (and other) nutritional deficiency and chronic inflammation. Goldberg and colleagues retrospectively reviewed data from children 4 months to 23 years admitted with heart failure and found anemia to be associated with increased risk of transplant, mechanical circulatory support and in hospital mortality (67). Mean Hb was 11.8g/dL on admission; RBC transfusion incidence in this population was not considered, confounding their results, which therefore do not provide sufficient evidence to recommend transfusion to maintain a particular Hb level.

The pivotal TRIPICU trial in critically ill children excluded patients who were not hemodynamically stable and the presence or degree of myocardial dysfunction was not assessed (68). Moreover, subgroup analysis of the TRIPICU study (69) of infants and children with CHD undergoing cardiac surgery did not provide detail on myocardial function. These studies were powered for multi-organ dysfunction and differences were not found between liberal or restrictively managed groups. Large subject numbers with adequate randomization in these studies would suggest that myocardial function as an independent variable would be similar between the two study arms. In the absence of a between-group difference, it can be postulated that, in a population with variable myocardial function, there is no evidence that higher Hb levels are beneficial.

Absence of high quality data does not negate the premise that patients with poor ventricular function may not tolerate “significant” (as yet to be defined) anemia. Severe ventricular

dysfunction may limit a patient's compensatory response to anemia, since they may not be able to augment cardiac output to maintain adequate end-organ oxygen delivery, in settings of low Hb levels. Transfusion in these children with tenuous ventricular function must be judicious, as increased blood viscosity and/or circulating blood volume may negatively impact cardiac output and therefore, diminish oxygen delivery to a greater degree than the potential increase afforded by improved oxygen content (via transfusion). Physiologic parameters (i.e., SaO2, SvO2, lactate, rSO2) must be followed closely, with transfusions prescribed as the individual patient's clinical condition demands. Although it is likely that "severe" anemia may not be tolerated, there is no evidence that transfusion to a "high" Hb level is of benefit.

Pulmonary Hypertension—6.7 **In children with structurally normal hearts and idiopathic or acquired pulmonary hypertension, (defined as a mean PA pressure > 25 mmHg with normal pulmonary capillary wedge pressure), there is insufficient evidence to support transfusion to target a specific Hb concentration. Furthermore, there is no evidence that transfusion for a Hb level > 10 g/dL is beneficial.** *Consensus panel expertise, 97% Agreement, (n=35), Median 9, IQR 8–9*

Rationale—Similar to myocardial dysfunction, pulmonary hypertension (pHTN) places the patient at increased risk for inadequate cardiac output, insufficient tissue oxygen delivery, multi-organ dysfunction and sudden death. Right ventricular (RV) dysfunction from systemic or supra-systemic RV pressures may accompany pHTN (as can left ventricular dysfunction) and chronic hypoxemia can develop (or be present in structural CHD) which further compromises adaptive responses to anemia and risks inadequate oxygen delivery. Moreover, in settings of chronic hypoxia, polycythemia is common, and therefore "lower" Hb levels may be all the more significant. Similar to those with LV dysfunction causing heart failure, anemia is also common with RV dysfunction from pHTN and has been associated with increased mortality on retrospective analysis (70). Additionally, anemia that accompanies pHTN has similar multifactorial etiologies and is also likely to be a marker of increased risk for poor outcomes.

Very little data exists on the impact of RBC transfusion in those with pHTN, but it is likely that transfusion of stored RBC impacts both the systemic (SVR) and the pulmonary vascular resistance (PVR). Stored allogeneic RBCs may alter nitric oxide signaling, causing vasoconstriction and impair vascular function, thereby exacerbating pHTN (71). A small physiologic study in infants with left to right shunts demonstrated an increase in SVR and PVR following isovolemic RBC transfusion (72). A finding that was also demonstrated in a small study of 14 obese adults with endothelial dysfunction where mean PA pressure rose significantly after transfusion of stored autologous blood (73). Beekman et al performed a study in 7 cyanotic children with CHD (6-Tetralogy of Fallot, 1- L-transposition with ventricular septal defect and pulmonary stenosis) who underwent partial exchange transfusion to raise their Hb from 13.7 to 16.4 g/dL. No pulmonary artery measurements were taken or PVR calculations performed. However, there was effective pulmonary blood flow improvement, presumably from relatively increased SVR (suggesting PVR < SVR) leading to decreased right to left shunting (74). Taken as a whole, these small studies do not

provide adequate evidence to support RBC transfusion to maintain any particular Hb threshold in children with acquired, idiopathic or congenital pHTN. Moreover, there is no high-quality evidence indicating that transfusion to maintain higher Hb levels in these children is of benefit. These high-risk patients have not been included in (adult or pediatric) transfusion trials, to our knowledge. As described above for children with myocardial dysfunction; the decision to transfuse must be guided by clinical metrics and physiologic parameters on a case-by-case basis.

Pre-operative/uncorrected congenital heart disease—6.8 **In hemodynamically stable critically ill infants and children with uncorrected CHD, we recommend RBC transfusion to maintain a Hb concentration of at least 7.0– 9.0 g/dL depending on the degree of cardiopulmonary reserve.** *Weak recommendation, Low quality pediatric evidence (2C). 81% Agreement, (n=35), Median 8, IQR 7–8*

Rationale—Recommendations for the child with uncorrected/unrepaired CHD are difficult to make due to the myriad of possible physiologic (and pathophysiologic) conditions in this complex group. Vast heterogeneity in cardiac morphology and physiology exist and will be affected by age and maturational factors, co-morbidities, and possible alterations in oxygen saturations and pulmonary vascular reactivity. The “well” child with an acyanotic cardiac lesion and good ventricular function, but without significant comorbidities awaiting elective cardiac surgery may tolerate significant anemia, and for these children transfusions can be “clinically based”, as for children without CHD. Alternatively, the premature infant maintained on prostaglandin awaiting sufficient maturation before cardiac surgery has threatened systemic oxygenation and/or tissue oxygen delivery, and these children may not tolerate anemia and require higher Hb levels to avoid symptoms.

Patients with unrepaired/uncorrected CHD have not been included in transfusion clinical trials; the data to support this recommendation comes from an extrapolation from a single high quality RCT (68) (TRIPICU study) for which the quality has been downgraded for imprecision and indirectness, making the evidence low. As described in the pHTN section, transfusion of stored allogeneic RBCs impacts the systemic and pulmonary vasculature, potentially impacting right and left ventricular function and the balance between systemic and pulmonary blood flow. Experience suggests that cyanosis may be reduced by increasing Hb level when other efforts to increase DO2 and/or reduce oxygen consumption are unsuccessful, and as such, maintenance of Hb levels of 7–9.0 g/dL appears prudent. However, there is no evidence that transfusion to raise the Hb > 9.0g/dL is beneficial, and may be of some risk. We recommend that the Hb level should not be used in isolation in the determination to transfuse, and should be considered along with a constellation of clinical indices, signs and symptoms. *GRADE 2C based on downgrading for risk of bias, imprecision, and indirectness*.

Intra-operative management of CHD—6.9 **In infants and children undergoing cardiac surgery, we recommend development and adoption of intra- and postoperative blood-sparing and blood conservation procedures and guidelines with the goal of reducing the number and volume of RBCs transfused (pump prime, on CPB, after separation from CPB, and post-op), and limiting donor exposures and other blood**

component transfusions. *Strong recommendation, Low quality pediatric evidence (1C); 100% Agreement, (n=35), Median 9, IQR 8*

Rationale—As mentioned in clinical practice guideline 6.2, patient blood management programs have been developed across institutions, with the goal of reducing the number and volume of RBC transfusions and donor exposures in children undergoing cardiac surgery. Advances in anesthesia management, CPB techniques, monitoring and point-of-care testing have allowed for significant reduction in blood product transfusions in those institutions adopting blood conservation practices (75, 76) and appear to demonstrate improved clinical outcomes (77). Miniaturization of the CPB circuit (31), smaller priming volumes (78) and hemoconcentration methods (35, 36) and re-infusion of cell saver blood (79, 80) has been proven to decrease intra and post-operative blood transfusions. Although the data supporting the adoption of blood conservation measures is low-grade, the results have been uniform and consistent and it is unlikely that clinical trials will be pursued. As strong associations exist between worse clinical outcomes and higher number of transfusions and donor exposures, additional effort to reduce intraoperative blood product transfusion is warranted. *GRADE 1C based on downgrading for risk of bias and imprecision*.

Post-operative management of CHD

Stage 1 palliations: 6.10 **In infants undergoing stage 1 palliation procedures (Norwood, Damus-Kaye-Stansel, Blallock-Taussig or central shunt, or pulmonary artery band) for single ventricle physiology, who have stable hemodynamics, adequate oxygenation (for their cardiac lesion) and normal end organ function we recommend avoiding reflexive ("solely Hb-based") RBC transfusions if the Hb concentration is >9.0 g/dL.** *Weak recommendation, Low quality pediatric evidence (2C); 96% Agreement, (n=29), Median 8, IQR 7–9*

Rationale—Historically, neonates and infants undergoing palliative procedures have received large numbers of blood product transfusions and have been maintained at higher Hb levels for the concern that they will not tolerate anemia and/or be able to maintain their oxygen delivery due to their single ventricle physiology and chronic hypoxia (1, 2, 44, 81). Despite this, observational studies do not indicate better outcomes for those infants maintained at higher Hb levels (82, 83) and in fact, in one study, a higher nadir Hb on POD#2-5 was associated with early mortality (84). Few data exist to guide the transfusion management of infants undergoing stage 1 palliations, as they have been nearly uniformly excluded from the few prospective randomized controlled transfusion trials of children with cardiac disease undergoing surgery.

Only one prospective controlled transfusion trial in 162 infants < 10 kg has been performed that included 57 infants undergoing palliative procedures randomized to a liberal or conservative RBC transfusion strategy immediately post-op to post-op day number 28 (85). Subjects were divided into those undergoing biventricular repairs or palliations, with different Hb thresholds for each subgroup. Palliated restrictive arm subjects were transfused for a Hb < 9.0 g/dL *with additional* clinical indications, compared to liberal arm subjects who were transfused for a Hb <12.0 g/dL *without requirement for additional* clinical

indications. Subgroup analysis of palliated subjects demonstrated a numerical, but not statistically significant, decrease in the median number of RBC transfusions per subject across the study period in restrictive compared to liberal subjects (1 (range 0–10) vs. 3 (range 1–10); p = 0.09). However, when the number of subjects that completed the study intervention without receiving a RBC transfusion was compared, the difference was significant (35% restrictive subjects never transfused vs. 0 liberal subjects never transfused) (p < 0.001). Six palliated group subjects (1 s/p BDG, 5 s/p stage 1 palliations) were transfused above their transfusion threshold for Hb values ranging from 9.3–12.5 g/dL. Compliance with the transfusion thresholds occurred, therefore, in 79.3% (23/29) of palliated subjects and the authors concluded that a restrictive transfusion strategy could be maintained, with transfusions reserved for clinical indications. The study goal was to determine feasibility of following a restrictive RBC transfusion strategy and it was not powered for clinical outcome differences in the palliated group.

Analysis of Society of Thoracic Surgery-European Association for Cardiac Surgery (STS-EACTS) categories 4 and 5 subjects from this work found similar clinical outcome differences between the two groups, except for infection which was higher in the restrictive group (p = 0.04). Seven (64%) deaths before hospital discharge were in subjects of STS-EACTS categories 4 and 5, three in restrictive and four in liberal group subjects. Additional analysis of the 12 subjects undergoing modified Norwood procedures (6 conservative, 6 liberal) demonstrated no significant differences in mortality or clinical outcomes.

As the data to support this recommendation comes from a single small RCT and multiple observational studies, this is a weak recommendation with low quality evidence. However, there are limited data indicating whether infants undergoing stage 1 palliations require higher Hb levels than infants with biventricular physiology, to preserve stable hemodynamics and maintain adequate oxygen delivery in the post-operative period. Interventions to increase Hb above 9.0 g/dL in the hemodynamically stable patient with adequate oxygen saturation (for their cardiac lesion), hemostasis and end-organ function may be of limited benefit and of potential risk as increased numbers of transfusions are associated with increased morbidity and mortality. We believe that, as in other patient populations, RBC transfusions should not be reflexive or “solely Hb based” but rather, based on a constellation of clinical indices (i.e., SaO2, SvO2, lactate) as well as clinical signs and symptoms. *GRADE 2C based on downgrading for risk of bias, imprecision, residual confounding*.

Stage 2 and 3 palliations: 6.11 **In hemodynamically stable infants and children with single ventricle physiology undergoing stage 2 and 3 procedures with adequate oxygen delivery we recommend not administering a RBC transfusion if the Hb concentration is > 9 g/dL.** *Weak recommendation, Low quality pediatric evidence (2C); 96% Agreement, (n=29), Median 8, IQR 8–9*

Rationale—Infants and children undergoing stage 2 (Bidirectional Glenn) and stage 3 (Fontan, or total cavopulmonary connection) procedures for single ventricle variations have unique physiology that depends upon venous pressures for pulmonary blood flow and requires low pulmonary vascular resistance. These patients have varying degrees of cyanosis

(those with total cavopulmonary connection are desaturated to a lesser degree), pulmonary vascular resistance, atrioventricular valve regurgitation, and/or ventricular dysfunction. Similar to those children having had stage 1 palliation, these children have historically received large numbers of blood transfusions to maintain higher Hb levels (1).

There are limited data whether infants and children undergoing stage 2 and 3 palliations require higher Hb levels than those with biventricular physiology to preserve their hemodynamics and maintain oxygen delivery in the post-operative period. A single prospective RCT of 60 infants and children undergoing stage 2 and 3 procedures, who were randomized to either a restrictive (transfusion for Hb < 9.0 g/dL *and* clinical indications) or liberal strategy (transfusion for Hb ≤ 13.0 g/dL) demonstrated significantly lower Hb levels in the restrictive group (11.1 ±1.3 vs. 13.9 ±0.5; $p < 0.01$) with significantly fewer mean number of RBC transfusions (0.43 ±0.6 vs. 2.1 ±1.2; $p < 0.01$) (86). There was 100% compliance with the transfusion protocols. No difference in arterial lactate or measurable end points of oxygenation and/or clinical outcomes were found between groups.

As the data for this recommendation comes from a single small RCT, this is a weak recommendation with low quality of evidence. With no obvious benefit, and with the known potential risks associated with increased numbers of RBC transfusions, there are no data to suggest benefit from maintenance of higher Hb levels in this population. As in the stage 1 palliations, decision to transfuse should be based on individual clinical indices, signs and symptoms, and not on the Hb level in isolation. *GRADE 2C based on downgrading for risk of bias, imprecision, residual confounding.*

Biventricular repairs: 6.12 **In infants and children with CHD undergoing biventricular repair who are hemodynamically stable and have adequate oxygenation and normal end organ function, we recommend not administering a RBC transfusion if the Hb concentration is ≥ 7.0 g/dL.** *Strong recommendation, Moderate quality pediatric evidence (1B); 100% Agreement, (n=29), Median 8.5, IQR 7–9*

Rationale—Moderate quality evidence exists to support recommendations for RBC transfusions in infants and children undergoing cardiac surgery for CHD. de Gast-Bakker (87) randomized children from 6 weeks to 6 years of age with acyanotic CHD to a restrictive or liberal transfusion strategy, from anesthesia induction to hospital discharge. Restrictive group subjects were transfused for Hb levels < 8.0 g/dL compared to liberal subjects whose transfusion threshold was 10.8 g/dL. Restrictive-group subjects received a significantly smaller mean volume of transfused RBCs ($p<0.001$) and had significantly lower hospital costs ($p = 0.002$) and shorter hospital length of stay ($p = 0.047$).

Willems et al, (2010) studied 125 acyanotic children ≥28 days randomized to a restrictive or liberal transfusion strategy from the TRIPICU trial (68). Mean Hb remained 2.1g/dL lower in the restrictive group following randomization (9.1 ±1.3 v. 11.2 ±1.4 g/dL) and was not associated with any significant difference in the primary outcome, which was new or progressive multiple organ dysfunction syndrome ($p = 0.36$) (69).

Cholette et al, in 105 children < 10 kg undergoing biventricular repairs, demonstrated 100% protocol compliance in the subgroup managed with a restrictive strategy (N = 53) with RBC transfusion reserved for Hb < 7.0 g/dL *and* clinical indications, compared to liberal strategy subjects (N = 52) transfused for Hb <9.5 g/dL *without requirement for* clinical indications (85). Restrictive group subjects were maintained at significantly lower Hb levels with fewer RBC transfusions and no significant differences in measures of oxygen utilization or clinical outcomes was found.

Taken as a whole, these 3 RCTs demonstrate that a restrictive transfusion strategy can be tolerated in infants and children undergoing biventricular repairs. Although the target Hb levels and age groups varied among studies, the adoption of a restrictive transfusion strategy decreased the number of RBC transfusions across the trials and did not adversely impact clinical outcomes. Use of a restrictive transfusion protocol from time of anesthesia induction (87), in the immediate post-op period (85, 86), and even in neonates (85) was well tolerated.

With no obvious benefit, and with the known risks associated with increased RBC transfusion frequency (88, 89), there are no data to support maintenance of higher Hb levels in children undergoing biventricular repairs who are hemodynamically stable with adequate oxygenation and normal end organ function. *GRADE 1B based on upgrading for three RCT's and downgraded for imprecision*.

Storage duration—6.13 **Standard issue RBC transfusions should be utilized in children with acquired or congenital heart disease as there are insufficient data supporting the transfusion of RBCs of shortened storage duration in this population.** *Weak recommendation, Low quality pediatric evidence (2C); 93% Agreement, (n=29), Median 8, IQR 8–9*

Rationale—There are limited observational data on the impact of RBC storage duration on clinical outcomes in children following cardiac surgery. It is difficult to control for confounding factors (i.e., volume of RBCs transfused, number of coagulant product transfusions, surgical complexity/severity, and differences in cardiac morphology), and no prospective randomized clinical trials have been performed in this population. Manlhiot and colleagues (2012) retrospectively studied children < 18yo with acquired or CHD undergoing cardiac surgery, with the goal of determining the relationship between clinical outcomes and RBC storage duration (90). They divided patients into high RBC use (>4 units or >150mL/kg) or low RBC use based on the 75th percentile as cut-off. Storage duration for low volume transfusions was not found to be associated with post-operative outcomes. Not surprisingly, the high RBC use group had statistically significantly higher surgical complexity and higher proportion of neonates and infants, and uniformly worse surgical outcomes. Despite lack of adjustment for these confounders, the authors concluded that blood of shortened storage duration should be utilized in pediatric cardiac surgery. It is however difficult to accept these conclusions given the rather immense volume of transfusions in the high RBC use group, and since these results have not been replicated by subsequent (albeit retrospective) studies.

Retrospective analysis of children receiving RBC transfusion of blood stored 5–7 days compared to 11–19 days demonstrated no difference in clinical outcomes, and when analyzed with storage duration as a continuous variable by multivariate regression analysis, still no outcome difference was found (91). Kawase studied 517 pediatric patients undergoing cardiac procedures with 22 (4.3%) having at least one serious adverse event. They found no association between maximum and mean storage duration of transfused RBCs and the likelihood of serious adverse events (92). Secondary analysis of a prospective RCT in pediatric cardiac surgery of subjects transfused only 1–2 units on the day of surgery (N = 74) demonstrated no association between storage duration and survival, but the post-op infection rate was significantly higher in children receiving blood of the longest storage duration (>25 days) compared to those receiving blood of shorter storage duration (< 15 days) (93). Generalizability of this work is limited to its secondary analysis, small subject numbers and low power, and RBC modifications (irradiation and washing) that were employed.

The data that support this recommendation come from sub-analysis of a single prospective RCT and multiple observational studies, making this a weak recommendation with low quality of evidence. As RBCs are a limited resource, without evidence that supports adoption of a “fresh” or short storage duration RBC transfusion blood bank protocol, standard issue RBC transfusions should be utilized in children with cardiac disease undergoing cardiac surgery. *GRADE 2C based on downgrading for risk of bias, imprecision, residual confounding*.

Research recommendations

Development of these evidence-based and expert-based recommendations has illustrated the paucity of high grade evidence to support RBC transfusion management for infants and children with acquired and CHD. The data to support our clinical recommendations is derived from observational studies or small single-center RCTs and a single sub-group analysis of the landmark TRIPICU multicenter trial. Below we list eight research recommendations (in no priority order) that we believe should be focus of future investigations.

R6.1 **We recommend further studies to determine the risks and benefits of RBC transfusion in critically ill children with documented right or left ventricular myocardial dysfunction (acquired or congenital).** *Consensus panel expertise; 97% Agreement, (n=35), Median 9, IQR 8–9*

R6.2 **We recommend further studies to determine the risks and benefits of transfusion in critically ill children with structurally normal hearts and idiopathic or acquired pulmonary hypertension (defined as a mean PA pressure > 25 mmHg with normal pulmonary capillary wedge pressure).** *Consensus panel expertise; 97% Agreement, (n=35), Median 9, IQR 8–9*

R6.3 **We recommend that further studies are needed in infants and children with CHD undergoing cardiac surgery to determine the impact of pre-operative anemia**

management on perioperative RBC transfusions and outcomes. *Consensus panel expertise; 97% Agreement, (n=35), Median 9, IQR 8–9*

R6.4 **In infants and children undergoing cardiac surgery with CPB, further research is needed to determine the benefits and risks associated with the administration of RBC to the CPB-prime, on-bypass and after separation of CPB.** *Consensus panel expertise; 97% Agreement, (n=35), Median 8, IQR 8–9*

R6.5 **In infants and children undergoing cardiac surgery further studies are needed to investigate the complex relationship between anemia, RBC transfusion, oxygen delivery and utilization and outcomes; with focus on which patient subgroups may benefit from, or be harmed by RBC transfusion.** *Consensus panel expertise; 100% Agreement, (n=35), Median 9, IQR 8–9*

R6.6 **We recommend that clinical trials on RBC transfusion in pediatric cardiac surgery should report the volume of RBC transfused and number of donor exposures.** *Consensus panel expertise; 94% Agreement, (n=35), Median 9, IQR 8–9*

R6.7 **Further studies are needed in infants undergoing stage 1 surgical palliations for single ventricle physiology on Hb concentration and physiologic indications for RBC transfusion.** *Consensus panel expertise; 100% Agreement, (n=35), Median 9, IQR 8–9*

R6.8 **In children with acquired heart disease or CHD, further studies are warranted to determine if RBC storage time impacts clinical outcomes.** *Weak recommendation, Low quality pediatric evidence (2C); 90% Agreement, (n=35), Median 8, IQR 8–9*

CONCLUSIONS

Red cell transfusions will continue to be a key component in the management of infants and children with acquired and CHD, for which there is no current substitute. Aberrations in cardiac function and oxygen saturations render these patients particularly vulnerable to anemia and blood loss. Wide variations in cardiac morphology and physiology both before and after surgery (even across specific cardiac lesions), and across the spectrum of pre, intra, and post-op, make extrapolation of anemia tolerance or transfusion thresholds from the literature exceedingly difficult. Furthermore, the complex interplay between anemia, transfusion, oxygen delivery, oxygen utilization, and clinical outcomes is poorly understood and in need of additional study.

Despite these challenges, in the face of risks for significant transfusion-associated complications, the bedside clinician must be judicious in transfusion decision making. Effort is warranted to avoid transfusion solely based upon Hb-level, and blood conservation practices should be undertaken whenever possible. Few data exist to guide transfusion in the sub-populations with cardiopulmonary disease (i.e., single ventricle, myocardial dysfunction, pulmonary hypertension) who are at greatest risk for both impaired oxygen delivery due to anemia and, potentially, increased risk from the RBC transfusion itself. Further research regarding transfusion management in infants and children with these subpopulations of heart disease is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1

Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) Members

(* for Executive Committee) Co-chairs: Stacey L. Valentine MD MPH* and Scot T. Bateman MD*, *University of Massachusetts, USA*, Content Experts: Section 1. General pediatric critical care patient based on physiologic and hemoglobin thresholds: Andrew Argent MD MBBBCh, *University of Cape Town, South Africa*, Jeffrey L. Carson MD, *Rutgers Robert Wood Johnson Medical School, USA*, Jill M. Cholette MD*, *University of Rochester, USA*, Allan Doctor MD*, *Washington University of St. Louis, USA*, Jacques Lacroix MD*, *Universite de Montréal, Canada*, Kenneth Remy MD, *Washington University of St. Louis, USA*, Section 2. Respiratory failure: Pierre Demaret MD MSc, *CHC Liege, Belgium*, Guillaume Emeriaud MD PhD, *Université de Montréal, Canada*, Nabil E. Hassan MD, *University of Illinois, USA,* Martin C.J. Kneyber MD PhD, *University of Groningen, Netherlands*, Marisa Tucci MD*, *Université de Montréal, Canada*, Section 3. Shock, excluding hemorrhagic shock: Nina Guzzetta MD, *Emory University, USA*, Mark W. Hall MD, *Ohio State University, USA*, Jennifer A. Muszynski MD MPH, *Ohio State University, USA*, Philip C. Spinella MD, *Washington University of St. Louis, USA*, Duncan Macrae MB ChB, *Imperial College London, UK,* Section 4. Hemorrhagic shock and non-life-threatening bleeding, Oliver Karam MD PhD, *Virginia Commonwealth University*, Robert T. Russell MD MPH, *University of Alabama, USA*, Philip C. Spinella MD*, *Washington University of St. Louis, USA*, Paul Stricker MD, *University of Pennsylvania, USA*, Adam M. Vogel MD, *Texas Children's Hospital, USA*, Section 5. Acute brain injury: Philip C. Spinella MD*, *Washington University of St. Louis, USA*, Robert C. Tasker MA MD MBBS, *Harvard University, USA*, Alexis F. Turgeon MD MSc, *Université Laval, Canada*, Section 6. Acquired or congenital heart disease, Jill M. Cholette MD*, *University of Rochester, USA*, Steven M. Schwartz MD, *University of Toronto, Canada*, Ariane Willems MD, *University of Brussels, Belgium*, Section 7. Sickle cell/ oncologic disease, Cassandra D. Josephson MD, *Emory University, USA*, Naomi LC Luban MD, *George Washington University, USA*, Leslie E. Lehmann MD, *Harvard University, USA*, Robert I. Parker MD*, *Stony Brook University, USA*, Simon J. Stanworth MD, *NHS Blood and Transplant, Oxford, UK*, Marie E. Steiner MD MS*, *University of Minnesota, USA*, Nicole D. Zantek MD PhD, *University of Minnesota, USA*, Section 8. Receiving support from extracorporeal, ventricular assist and renal replacement therapy devices: Melania M. Bembea MD PhD*, *Johns Hopkins University, USA*, Timothy Bunchman MD, *Virginia Commonwealth University, USA*, Ira M. Cheifetz MD, *Duke University, USA*, James Fortenberry MD, *Emory University, USA*, Marie E. Steiner MD MS*, *University of Minnesota, USA*, Section 9. Selection and processing of red blood cell components: Meghan Delaney DO, MPH, *Children's National Health System USA*, Cassandra D. Josephson MD, *Emory University, USA*, Robert I. Parker MD*, *Stony Brook University, USA*, Leo van de Watering MD, *Leiden University, Netherlands*, Nicole D. Zantek MD PhD, *University of Minnesota, USA*, Evidenced-Based Medicine: Karen A. Robinson PhD, *Johns Hopkins University, USA*, Melania M Bembea MD PhD*, *Johns Hopkins University, USA*, Implementation Science: Sara Small MS, *Washington University of St. Louis, USA*, Katherine Steffen MD, *Stanford University, USA*