Red blood cell transfusion in critically ill children: A narrative review*

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Objective: **To review the pathophysiology of anemia, as well as transfusion-related complications and indications for red blood cell (RBC) transfusion, in critically ill children. Although allogeneic blood has become increasingly safer from infectious agents, mounting evidence indicates that RBC transfusions are associated with complications and unfavorable outcomes. As a result, there has been growing interest and efforts to limit RBC transfusion, and indications are being revisited and revamped. Although a so-called restrictive RBC transfusion strategy has been shown to improve morbidity and mortality in critically ill adults, there have been relatively few studies on RBC transfusion performed in critically ill children.**

Data Sources: **Published literature on transfusion medicine and outcomes of RBC transfusion.**

Study Selection, Data Extraction, and Synthesis: **After a brief overview of physiology of oxygen transportation, anemia compensation, and current transfusion guidelines based on available literature, risks and outcomes of transfusion in general and in critically ill children are summarized in conjunction with studies investigating the safety of restrictive transfusion strategies in this patient population.**

Conclusions: **The available evidence does not support the extensive use of RBC transfusions in general or critically ill patients. Transfusions are still associated with risks, and although their benefits are established in limited situations, the associated negative outcomes in many more patients must be closely addressed. Given the frequency of anemia and its proven negative outcomes, transfusion decisions in the critically ill children should be based on individual patient's characteristics rather than generalized triggers, with consideration of potential risks and benefits, and available blood conservation strategies that can reduce transfusion needs. (Pediatr Crit Care Med 2011; 12:174–183)**

KEY WORDS: erythrocyte; red blood cell transfusion; blood conservation; critical illness; surgery; intensive care unit; pediatrics; children

The origin of transfusion medicine can be traced back to a 350-yr-old experiment performed by the English physician, Richard Lower, which marked the first recorded successful animal-to-animal blood transfusion. Since then, improvements in blood storage and banking have enabled remarkable advances in surgery and medicine. Allogeneic red blood cell (RBC) transfusion has been widely believed to be one of the greatest contributions to modern medicine. Nonetheless, issues surrounding the safety of the blood supply have emerged in the past and changed the concept of blood transfusion from being part of the solution to being part of the problem. As a result, avoidance of transfusions has gained popularity in the last two decades. In recent years, the risks of transmitting viral or bacterial diseases through transfused blood have been substantially reduced (1). Nonetheless, new concerns arise from a growing body of evidence, suggesting that the transfusion of blood products poses risks beyond infectious complications, especially in critically ill patients. These noninfectious risks include allergic reactions, immunomodulation, and hemolysis. These risks have been associated with prolonged length of stay in the intensive care unit (ICU) and hospital, and increased morbidity and mortality in several studies on adult patients (2, 3).

Despite the conviction among many caregivers that RBC transfusion can be lifesaving in a defined patient population, recent studies have demonstrated potential deleterious effects of liberal use of blood in critically ill adults (4) and children (5). Taken together with the possibility that RBC transfusion is currently overutilized to the point of rendering harm rather than benefit, a challenging question for every clinician is who should be transfused and when. Over 22 million units of blood products are transfused annually in the United States alone. The majority of transfusions are administered by anesthesiologists (1, 6) and intensivists (7, 8) in the perioperative and intensive care settings. The need to

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understand the ever-changing risk/benefit ratio of blood products cannot be overemphasized. The objective of this manuscript is to review current transfusion guidelines in light of the new evidence on risks in order to provide the reader with information that can be used to form the basis for informed decision making regarding RBC transfusion in critically ill children. As a prelude to discussing these recommendations, a thorough understanding of the physiology of blood transfusion, as well as the intended goals of blood transfusion, is necessary.

Literature Search Strategies

An electronic search of MEDLINE (OVID), EMBASE, Current Contents, and the Cochrane Library was performed. The search terms used included "blood products," "red blood cells," and "transfusion" in various combinations with "blood conservation," "critical illness," "perioperative," "resuscitation," "children," "infectious risks," "noninfectious risks," "side effects," and "outcome." In addition, we reviewed the authors' personal files for papers on the subject of blood transfusion and blood conservation in critically ill patients.

Physiologic Compensation in Anemia and Implications of Transfusion

The primary goal of RBC transfusion is to increase oxygen delivery ($\dot{D}o_2$) and, in turn, increase tissue oxygen utilization with preservation of organ function, which, in theory, would only be compromised if tissue oxygen utilization is restricted by $\dot{D}o_2$. Global $\dot{D}o_2$ is dependent primarily upon three factors: 1) hemoglobin (Hb) concentration; 2) cardiac output (CO); and 3) the relative proportion of oxyhemoglobin, i.e., percent oxygen saturation (Sao_2). Oxygen is transported in the blood combined with Hb, although a relatively small amount is freely dissolved in the plasma fraction of the blood. When fully saturated, each gram of Hb can carry approximately 1.34 mL of oxygen at normal body temperature. Conversely, plasma-dissolved oxygen is directly proportional to Pao_2. Thus, equation (Eq.) 1 determines the oxygen content of arterial blood,

$$\text{Arterial Oxygen Content } (Cao_2) = (Hb \times 1.34 \times Sao_2) + (0.0034 \times Pao_2) \quad [Eq.1]$$

where Cao_2 is expressed in mL oxygen/100 mL blood, Hb is expressed in g/dL, and Pao_2 is expressed in torr (kPa). Oxygen delivery ($\dot{D}o_2$) is then determined by Eq. 2,

$$\text{Oxygen Delivery } (\dot{D}o_2) = Cao_2 \times \text{Cardiac Output (CO)} \quad [Eq.2]$$

where $\dot{D}o_2$ is expressed in mL oxygen/min and CO is expressed in L/min. In theory, blood transfusion, by raising the Hb level, should increase the oxygen-carrying capacity of the blood, and provide an effective means to increasing global oxygen delivery in the clinical setting (9).

However, there are contradictory data, which suggest that simply increasing global $\dot{D}o_2$ by RBC transfusion does not necessarily translate into increased tissue oxygen utilization. Three mechanisms are implicated. The first is that 2,3-diphosphoglycerate is quickly depleted within days after blood storage and becomes virtually undetectable after 1 wk. It takes approximately 24 hrs to restore normal 2,3-diphosphoglycerate levels post transfusion (10). Depletion of 2,3-diphosphoglycerate results in a leftward shift of the oxyhemoglobin dissociation curve (11) and increases Hb affinity for oxygen at low oxygen tensions, thus decreasing oxygen release at the microcirculation level. Second, adenosine triphospate is also depleted during the storage process, leading to altered RBC membrane deformability and loss of membrane integrity, which could result in vesiculation and eventual untimely destruction of the RBCs (12). The end result of altered deformability is obstruction of flow at the level of the microcirculation (13–15). Finally, the small quantity of free Hb always present in banked RBC units quickly binds endogenously produced nitric oxide (16), resulting in vasoconstriction of small vessels and ultimately decreasing local $\dot{D}o_2$ at the tissue level. Furthermore, the Hb in RBCs can also interact with local nitric oxide with similar results (17). These factors, all contributing to reduction of local $\dot{D}o_2$ after transfusion, may in part account for data suggesting that RBC transfusion is associated with negative outcomes in critically ill patients despite an increase in the global Hb concentration and a theoretical increase in global $\dot{D}o_2$ (14).

Critical Hb Level and Tolerance of Anemia

The lower limits of Hb at which $\dot{D}o_2$ becomes critical (i.e., the critical Hb level) are not well defined in individual patients. In healthy adults undergoing experimental isovolemic anemia, the body's compensatory mechanisms, consisting of increased CO and oxygen extraction, are more than sufficient to meet the body's metabolic needs in very low Hb levels. However, in a bleeding patient, a point of "maximal compensation" may occur, at which compensatory mechanisms are no longer able to meet the body's metabolic requirements. Theoretically, this Hb level has been calculated to be approximately 2.5 g/dL (18). This threshold has been validated in anesthetized pigs (19), awake dogs (20), and baboons (21). In humans, Weiskopf and colleagues (22–25) examined healthy volunteers undergoing isovolemic hemodilution and found no evidence of impaired tissue oxygenation until the Hb concentration decreased to 4–5 g/dL. It should be emphasized that these findings have not been extensively validated and are likely to be dependent on clinical setting and physiopathologic status of the subjects. However, children seem at least as capable as adults in their ability to compensate for lower Hb concentration with increased oxygen extraction and CO (26).

Spence and colleagues (27) demonstrated that elective surgery could be safely performed in adults with a preoperative Hb as low as 6 g/dL, if estimated blood loss was kept at $<$500 mL. Investigation of a unique population of postsurgical Jehovah Witness's patients (who refused transfusion of blood or blood products based on religious preferences) has shown that, despite increasing morbidity and mortality as Hb decreases to extremely low levels, operative survival is still possible even with Hb as low as 3 g/dL. In a retrospective cohort study involving $>$300 adults by Carson and colleagues (28), there were no surgical deaths and only negligible morbidity (defined *a priori* as myocardial infarction, arrhythmia, congestive heart failure, or infection) associated with a postoperative Hb of $\geq$7 g/dL. However, both morbidity and mortality increased significantly if the postoperative Hb was allowed to drop $<$5 g/dL. After adjusting for age, cardiovascular disease, and Acute Physiology and Chronic Health Evaluation II score, the odds of death increased 2.5 times for every 1 g/dL decrease in Hb level of $<$8 g/dL. An earlier study by the same group (29) suggested that the presence of cardiovascular disease significantly in-

creased morbidity and mortality in patients refusing transfusion with a low preoperative Hb or substantial blood loss during surgery.

The experience in children is similar. Lackritz et al (30) retrospectively reviewed over 2,400 pediatric admissions to a hospital in Kenya and noted that 29% of all admitted children had an admission Hb of <5 g/dL. Most of these children had malaria. In children, severe anemia (Hb <5 g/dL) was associated with a significantly increased mortality (18% in the severe anemia vs. 8% in the control, $p = .0001$). On the other hand, Bojang et al (31) conducted a prospective study of 287 children also with malaria and severe anemia. Children presenting either with respiratory distress or a hematocrit of <12% (n = 173) were transfused, whereas the remaining 114 children were randomized to either blood transfusion or iron treatment for 28 days. Twenty-four children in the study died. Twenty-three of those children had an admission hematocrit of <12%. Fifteen (65%) of those children died before RBC transfusion. Of the children randomized to receive iron therapy, one child died and ten subsequently required RBC transfusion. After 28 days, hemoglobin levels improved significantly in children receiving the iron therapy compared with those treated by blood transfusion ($p = .02$). These results have been replicated in two additional studies (32, 33). Although the children in these studies are likely to be very different from pediatric patients commonly observed in more developed countries, these studies further underscore the imminent risk of extremely low Hb level as well as the resiliency of the physiologic mechanisms to maintain $\dot{D}o_2$ in the setting of severe anemia in the pediatric population.

Anemia and Blood Utilization in the ICU Setting

Critically ill children and adults are at significant risk for anemia (34). In a multicentered, observational, cohort study, Vincent et al (2) demonstrated that >60% of critically ill adults had an Hb concentration of <12 g/dL at the time of admission to the ICU. Hb decreased even further during the course of the ICU stay. The pathogenesis of this anemia of critical illness is multifactorial. Often cited causes include frequent blood draws (the so-called "medical vampire") (35), decreased erythropoietin production and responsiveness (36–38), nutritional deficits, alterations in iron metabolism (39, 40), increased RBC destruction, occult (e.g., gastrointestinal bleeding) or overt blood loss, and bone marrow suppression (34, 41). Although various blood conservation strategies are available in the critically ill populations (42, 43), nearly three fourths of all critically ill patients with an ICU stay of >7 days receive an RBC transfusion (2). Many of these transfusions may be inappropriate.

Between 15% to 50% of critically ill children admitted to the pediatric ICU (PICU) receive an RBC transfusion at some point during their stay (44, 45). Infants in the neonatal ICU (NICU) are among the most transfused patients, with transfusion rates usually inversely related to the infant's weight and/or maturity, in hope of maximizing the $\dot{D}o_2$ to critical organs. A retrospective analysis by Goodman et al (46) found that most critically ill children with an Hb of <6.5 g/dL will receive a transfusion. However, there is significant variation in transfusion practices among pediatric intensivists (47–50). Armano et al (44) analyzed factors that were associated with RBC transfusion in approximately 1,000 critically ill children over a 1-yr period. In this study, the mean transfused Hb was 8.8 ± 2.6 g/dL, which seems to be consistent with the current practice in many adult ICUs (2, 51). Factors that were independently associated with an increased rate of transfusion in PICU included admission Pediatric Risk of Mortality score of >10, presence of multiple organ dysfunction syndrome, an admission diagnosis of cardiac disease, and Hb of <9.5. The vast majority of these transfusions were administered during the first 3 days of hospitalization.

More recently, Bateman and colleagues (52) published the results of a multicentered, prospective, observational study that determined the frequency of anemia, blood draws, and RBC transfusions in critically ill children admitted >48 hrs to 30 North American PICUs. Anemia was present in nearly three fourths of these children, either during or immediately before PICU admission. Almost half of these children received at least 1 RBC transfusion during their PICU stay—most frequently during the first 2 days after admission. Notably, only 4% of children received RBC transfusion after 1 wk of hospitalization. Blood loss from frequent phlebotomy was a significant and independent risk factor for RBC transfusion.

Recommendations for RBC Transfusion in the Perioperative and ICU Settings

Historically, transfusion recommendations were based on expert opinion or consensus guidelines and circled around various Hb or hematocrit thresholds or triggers. The optimal Hb concentration for critically ill patients is still a matter of debate. For decades, anesthesiologists and intensivists advocated an Hb concentration of 10–13 g/dL. This concept was first introduced by Adams and Lundy (53) in 1942 based solely on their own clinical experience. Similarly, for years, the generally recommended transfusion threshold was a hematocrit of <30%. This number stems from an earlier study by Crowell and Smith (54) based on an *in vitro* model of the microcirculation. The investigators noted an increased viscosity and reduced blood flow through the glass capillaries of fixed diameter as the hematocrit increased. The hematocrit for optimal $\dot{D}o_2$ was calculated mathematically to be around 30%.

Experimental evidence (9) in animals has suggested that viscosity begins to compromise blood flow at hematocrit approaching 40% to 45%. However, the contribution of blood viscosity to flow resistance in the microcirculation is actually quite small due to the Fahraeus effect, which explains how a large diameter RBC may pass through a smaller diameter capillary. Each RBC must line-up in single file and deform before passing through the capillary. As a result of the Fahraeus effect, the hematocrit of the blood flowing through microvessels with diameters of <1000 μm is substantially smaller than the blood flowing freely in the large vessels, and it stays unchanged, despite large variations in blood hematocrit. This and several other direct and indirect lines of evidence question the validity of a hematocrit of 30% as the level for optimal $\dot{D}o_2$, and as the threshold of transfusion in majority of the patients.

Whether or not transfusing to achieve these high Hb levels improves outcome remains unproven. Studies have demonstrated that more limited transfusion strategies are at least as effective as liberal policies, if not better. Several studies (14, 55, 56) have suggested that transfusion can possibly have a negative effect on

clinical outcomes. These studies were based on a diverse group of critically ill adult patients, including patients with acute coronary syndrome, burns, trauma, sepsis, acute respiratory distress syndrome, and cardiovascular surgery.

Hébert et al (4) and the Canadian Critical Care Trials Group directly challenged the practice of transfusing RBC in adults to keep the Hb above 10 g/dL in the Transfusion Requirement in Critical Care trial. In this study, 838 euvolemic critically ill adults with initial Hb of ≤9 g/dL were randomized into either a restrictive or liberal transfusion strategy. In the restrictive transfusion strategy group, patients were transfused if Hb decreased <7 g/dL, whereas in the liberal transfusion strategy group, patients were transfused if the Hb decreased <10 g/dL. Overall, restricting transfusion in critically ill patients did not increase their mortality risk. Although there were no differences in 30-day mortality between the two groups (18.7% vs. 23.3%, $p = .11$), mortality was significantly lower in patients with an Acute Physiology and Chronic Health Evaluation II score of ≤20 who were randomized to the restrictive transfusion strategy group (8.7% in the restrictive strategy group and 16.1% in the liberal strategy group; $p = .03$). The in-hospital mortality rate was also significantly lower in the restrictive strategy group (22.3% vs. 28.1%, $p = .05$). Morbidity was reduced in patients randomized to the restrictive strategy group as well, with avoidance of one complication for every 20 patients following the restrictive transfusion strategy.

In a subsequent retrospective analysis of the Transfusion Requirement in Critical Care study, Hébert et al (57) investigated whether the restrictive strategy was safe in patients with acute myocardial infarction and unstable angina. The mortality and hospital and ICU stay were similar in both groups. The prevalence of multiple organ dysfunction syndrome was significantly less in the restrictive strategy group. These investigators concluded that the restrictive strategy was safe in critically ill patients with cardiovascular disease. However, there was a nonsignificant trend toward increased mortality in patients with severe ischemic heart disease, leading these authors to conclude that a restrictive strategy may not be safe in this particular patient population.

Although the Transfusion Requirement in Critical Care trial provides the best evidence regarding restrictive RBC transfusion strategy in critically ill patients published to date, the results should not be generalized to critically ill children who typically have different diseases and adaptive responses compared with adults (58) (Table 1). Furthermore, the study has been criticized for the following: 1) not using leukocyte reduced blood; 2) excluding about 87% of eligible patients; 3) not stratifying the included patients according to severity of disease; 4) using only two fixed Hb set points with an overly "liberal" method that may not necessarily reflect common practice; and 5) not including a third arm that is based on individual patient status (23).

Transfusion recommendations have been changed to reflect these observations. The College of American Pathologists recommends consideration of a patient's clinical status in addition to the amount of blood lost when making a decision about whether to transfuse, although the lowest absolute threshold for transfusion recommended is Hb of <6 g/dL. Most notably, these recommendations emphasize the importance of considering perceived tissue oxygenation obtained by continuous (e.g., heart rate, pulse oximetry, arterial blood pressure) and invasive monitoring (e.g., lactate, mixed venous oxygen saturation), rather than using any one single Hb value in clinical decision making (59). The American Society of Anesthesiologists recommends transfusion if the Hb is <6 g/dL, although they recommend against using a single transfusion trigger (60). The Canadian blood transfusion guidelines do not recommend a single value for transfusion but rather focus on transfusing to prevent or alleviate signs and symptoms of morbidity secondary to inadequate tissue $\dot{D}o_2$ (61). Unfortunately, most published guidelines for RBC transfusion in critically ill children are either based on expert opinion or derived from studies performed in critically ill adults (62, 63). Further studies in this population are warranted.

Risks of Blood Transfusion

Although the studies noted in the preceding paragraphs suggest that elective surgery when patients' religious prefer-

Table 1. Factors that may alter anemia adaptive mechanisms in critically ill children versus adults (61)

Factors	Comments
Disease process	Common in the Neonatal and Pediatric ICU Meconium aspiration, necrotizing enterocolitis, intraventricular hemorrhage, congenital heart disease, hemolytic uremic syndrome, meningitis, bronchiolitis Common in Adult ICU Atherosclerosis and coronary artery disease Emphysema and bronchitis
Increased fetal hemoglobin	Predominantly important in neonates, or older children with underlying conditions resulting in persistence of fetal hemoglobin A) Will cause an apparent left shift of the oxygen-hemoglobin dissociation curve, leading to increased affinity for oxygen (due primarily to altered interactions with 2,3-DPG) B) Less cell deformability leads to changes in viscosity
Increased energy requirement and nutrition needs	Up to 585.76 joule/kg per day for a child <1 yr old vs. <209.2 joule/kg for adults, resulting in higher tissue oxygen utilization in children
Increased baseline heart rate and limited myocardial compliance	Limited adaptive ability to increase cardiac output in response to anemia (particularly in neonates and infants)
Cyanotic heart disease may lead to significant polycythemia	Hb as high as 22 g/dL; increased viscosity will impede blood flow in smaller capillary network
Neonates release less erythropoietin	Physiologic anemia for the first few months of life

ICU, intensive care unit; 2,3-DPG, 2,3-diphosphoglycerate; Hb, hemoglobin.

Table 2. Commonly cited risks of blood transfusion

Infectious	Noninfectious
Viral	Febrile nonhemolytic transfusion reaction (10, 69, 85)
Cytomegalovirus (1, 73, 90, 94)	Hemolysis (6, 69)
Hepatitis B (1, 78) and C (66, 68, 78)	Volume overload (69, 85)
Human immunodeficiency virus (66, 70, 71, 83)	Metabolic abnormalities (67, 69, 74, 85)
Human herpes virus 8 (65)	Coagulation defects (75–77)
West Nile virus (84)	Transfusion-related acute lung injury (72, 81, 88, 92)
Bacterial	Transfusion-related immunomodulation (4, 82, 86, 91)
Commonly Gram-positive bacteria, but also Gram-negative bacteria (79)	Multiple organ dysfunction (4, 91)
Prions	Necrotizing enterocolitis in neonates (64)
Creutzfeldt-Jakob disease (80, 93)	Retrolenticular fibroplasia (only in neonates) (96)
Parasites	Transfusion-associated graft-versus-host disease (87)
Malaria (89)	
Babesiosis (95)	

ences preclude transfusion may be performed with a relative degree of safety in the presence of either a low preoperative Hb (27) or significant blood loss (28), it may not be unreasonable to speculate that transfusing blood to the patients with severe acute hemorrhagic anemia could result in improved outcome (survival). Nonetheless, it should be remembered that several factors impair the ability of stored blood to increase $\dot{D}o_2$ to local tissues. Furthermore, the majority of the transfused patients in practice are not hemorrhaging but rather only mildly or moderately anemic. These patients are usually well compensated and can be candidates for appropriate pharmacologic treatment for their anemia. For this patient population, transfusion may represent only risk without benefit (Table 2) (1, 4, 6, 9, 10, 64–96). When clinicians entertain the need for transfusion, the process must include not only consideration of indication and benefits but also immediate risks and possible negative clinical outcomes secondary to RBC transfusion.

Noninfectious Complications of Transfusion

Febrile Nonhemolytic Transfusion Reaction. The febrile nonhemolytic transfusion reaction is the most common reaction encountered and is usually self limited in nature. The febrile nonhemolytic transfusion reaction is believed to be due to the presence of pyrogenic cytokines and other intracellular contents released by the donor leukocytes or transfused within the blood component itself. This benign reaction occurs much more frequently with platelet transfusion (30.8%) compared with RBC transfusion (6.8%, $p < .0005$) (97). Leukocyte reduction significantly decreases the prevalence of this type of reaction (10, 69, 85).

Hemolysis. Acute hemolytic transfusion reactions due to ABO incompatibility are significantly more worrisome and are estimated to occur in 1 in 14,000 to 1 in 38,000 transfusions, although the reported frequency is probably a gross underrepresentation of the true incidence (69). The severity of the reaction is variable, and approximately half of all patients suffer no ill effects. However, these reactions account for the vast majority of transfusion-related deaths and are estimated to be responsible for one death in 100,000 transfused cases (6). Acute hemolytic transfusion reactions are less frequently caused by other minor blood group antigens. Unfortunately, these reactions can be difficult to detect, especially in patients under general anesthesia. In these cases, the ensuing hypotension, tachycardia, hemoglobinuria, and microvascular bleeding that occur from the transfusion reaction itself may be wrongfully attributed to other causes and potentially compounded even further by attempts to correct with additional blood products.

Volume Overload, Metabolic Abnormalities, and Coagulation Defects. Critically ill patients are particularly sensitive to the effects of volume overload, as may occur when either the total volume or rate of administration of blood products exceeds the capacity of a poorly functioning cardiovascular system. Acute volume overload manifests as hydrostatic pulmonary edema, and treatment is largely supportive. If a patient is at risk for acute volume overload, the rate of administration of blood products should be decreased, or alternatively, the component may be divided into several smaller aliquots (69, 85).

Electrolyte abnormalities can also occur post blood transfusion. Given the lower volume of distribution, these abnormalities are more likely to occur after massive blood transfusion or exchange in children with lower weight (e.g., more commonly in NICU than PICU) (67). The citrate anticoagulant in the transfused blood can chelate calcium and may produce a transient hypocalcemia (98). Patients with liver dysfunction are particularly at risk, as citrate metabolism and clearance are decreased. Hyperkalemia is also common and can even have fatal consequences in critically ill children, particularly in the NICU (67, 74). Both hyperglycemia and hypoglycemia have been reported post blood transfusion (69, 85). Finally, massive RBC transfusion without concomitant repletion of clotting factors may lead to a dilutional coagulopathy. A recent study (99) in the NICU has indicated that after transfusion of about 20 mL of RBC per kg on average, statistically significant changes in blood calcium and glucose occurred, but a very small number of the patients developed hyperkalemia or hypocalcemia, and these cases were not considered to be clinically relevant.

Transfusion-Related Acute Lung Injury. Transfusion-related acute lung injury (TRALI) is defined as the new onset of acute lung injury that is temporally related to the transfusion of blood products. By definition, TRALI must develop within 6 hrs of transfusion, but symptoms usually become manifest within the first 2 hrs after transfusion (88). The true prevalence of TRALI is not known, as many minor cases may be misdiagnosed as volume overload, although most experts estimate the incidence at 1 in every 5,000 transfusions (73). In a case-control study by Gajic et al (72), patients with TRALI were more likely to have had sepsis compared with controls (37% vs. 22%, $p = .016$). In addition, transfusion of plasma from multiparous female donors was also implicated as a significant risk factor. These observations are supportive of a "multiple-hit" model in which underlying patient's characteristics (e.g., sepsis) and specific transfusion factors (e.g.,

plasma) are associated with the development of TRALI. The importance of TRALI in the ICU is increasingly recognized, and several excellent reviews are available (69, 81, 85, 92).

Transfusion-Related Immunomodulation. It is not at all surprising that blood transfusions may lead to immunosuppression (73, 86). Before the cyclosporine era, kidney transplant recipients were transfused blood perioperatively for the sole reason of increasing the chance of graft survival (82). The exact mechanisms underlying transfusion-related immunomodulation are not completely understood; however, leukocytes and pro- and anti-inflammatory mediators that are found in blood products might be involved (86). Transfusion-related immunomodulation has been found to be associated with an increased risk of nosocomial infection (91) and multiple organ dysfunction syndrome (4) in critically ill patients.

Infectious Complications of Transfusion

Despite current stringent banking protocols rendering blood transfusions extremely safe, infection is still a potential threat (1, 73). It is possible that current transfusion practices are still exposing patients to viral, bacterial, protozoan, and fungal organisms (6). The overall risk of death from bacterial transmission is reported at 1 in 8 million units of packed red blood cells transfused. The culprit is most commonly Gram-positive-bacteria, but Gram-negative-bacteria also have been shown to be independently associated with an increased risk of death (79).

More than 40% of blood donors in the United States and worldwide were infected with cytomegalovirus (CMV) at some point and are now defined as being in the latent infection phase (90). CMV poses a great infectious threat, primarily to immunocompromised recipients who may become symptomatic after exposure to contaminated blood products. Although benign in immunocompetent recipients, CMV tainted blood may have devastating consequences in the immunocompromised child, such as the organ transplant patient (1, 73) and in neonates (94). Antibody testing on donated blood can be used to prevent transfusing CMV-infected blood to these patients, although leukocyte depletion can be equally effective in achieving this goal (100) Use of CMV-negative blood products should be considered for all transfusion needs of low birth weight infants of seronegative mothers as well as immunocompromised patients (101).

Although uncommon in today's clinical practice, transmission of viruses, such as hepatitis B (1), hepatitis C, and human immunodeficiency virus, remains a discrete threat. During the 2002 West Nile virus epidemic in the United States, despite rigorous screening, implementation of new strategies, and removal of 163 highly reactive units, blood transfusions were still implicated in 23 of the 4,000 known cases of West Nile viral encephalopathy (84). Transmission of parasites poses additional risks, especially in light of the fact that the technology to detect parasitic contamination of blood products is not widely available (89). There have been several isolated reports of transfusion-related parasitic infections (1, 7). Recently, there have been reports of the variant Creutzfeldt-Jakob disease acquired by a transfusion (80, 93).

RBC Transfusion and Outcomes in Critically Ill Pediatric Patients

RBC transfusion theoretically increases global $\dot{D}o_2$. However, regional $\dot{D}o_2$ may not follow the same trend. Counterintuitively, in many cases, transfusion has been associated with poor outcome. In a prospective observational study of 1,100 critically ill adults in 146 Western-European ICUs, Vincent et al (2) demonstrated a longer ICU stay and higher mortality in those patients who were transfused compared with nontransfused cases. The increase in mortality was independent of both the severity of illness and the level of anemia at the time of ICU admission.

Taylor et al (91) conducted a single-center, prospective, observational, cohort study and noted that RBC transfusion independently increased both the length of stay and mortality. The risk of nosocomial infection after transfusion increased by a factor of 1.5 for each transfused unit. These findings confirm an earlier study (46) performed in critically ill children and were again confirmed in a more recently published pediatric study (102).

Goodman et al (46) noted that blood transfusions were independently associated with increased days on mechanical ventilation (5.04 days ± 1.10 days), increased days on vasopressors (1.27 days ± 0.44 days), increased length of PICU stay (4.44 days ± 1.32 days), and mortality (although increased mortality could be partly explained by more critically ill cancer patients receiving transfusion therapy). Palmieri et al (103) reviewed their single-institution experience with a restrictive transfusion strategy (Hb of <7.0 g/dL) in critically ill children with burn injury. The restrictive transfusion strategy decreased the amount of blood transfused, resulting in significant cost savings to their institution with no adverse change in outcome. More recently, Lacroix et al (5) published the results of a multicenter, randomized, controlled, clinical trial comparing the use of a restrictive transfusion strategy (Hb of <7.0 g/dL) vs. a liberal transfusion strategy (Hb of <9.5 g/dL) in critically ill children—the Transfusion Requirements in Pediatric Intensive Care Units Study. The trial randomized 637 patients within 7 days of admission to the PICU. Excluding death as a reference outcome secondary to low mortality in children (104), no significant difference was found in any of the outcome variables examined, suggesting that a restrictive transfusion strategy decreases transfusion requirements without increasing adverse outcomes.

The observation that blood transfusions are associated with unfavorable outcomes has been replicated in extremely low birth weight infants in the NICU (105), although an earlier study (106) found that a restrictive transfusion strategy may increase the prevalence of neurologic complications in this population. Although mixed results have been reported on the effect of transfusions on cardiopulmonary function, apnea, and weight gain in premature infants (107–112), a recent study has indicated that, although blood transfusions in extremely low birth weight infants did not confer any benefits in terms of gaining weight, reducing ventilator support needs, or preventing apnea, they were associated with higher risk of bronchopulmonary dysplasia and necrotizing enterocolitis. Interestingly, although improving $\dot{D}o_2$ is among the common perceived reasons for giving blood, many infants required additional respiratory support after blood transfusion (113). As such, there is a growing recognition in the pediatric critical care community that blood transfusion may have untoward effects in critically ill children (62, 86, 114), similar to the experience in critically ill adults.

RBC Transfusion and Outcomes in Cyanotic Congenital Heart Disease

Critically ill children with cyanotic congenital heart disease, especially those with single-ventricle physiology, typically receive RBC transfusions to maintain Hb of >15 g/dL to sustain acceptable $\dot{D}o_2$ in the face of significantly desaturated arterial blood (Sao_2 70% to 75%) (115). Transfusion may have other beneficial effects in this population as well. For example, in children with large ventricular septal defects and significant shunting, increased viscosity of blood after transfusion can result in decreased pulmonary blood flow, which in turn can decrease shunting and thereby increase systemic blood flow, favorably improving the balance between systemic and pulmonary blood flow (116, 117). However, to date, no prospective study examining either transfusion practices or the efficacy of this aggressive transfusion strategy in children with cyanotic congenital heart disease has been performed. Szekely and colleagues (118) retrospectively reviewed 657 consecutive children undergoing open heart surgery for congenital heart disease and found that blood transfusions were independently associated with an increased risk of infection (odds ratio, 1.01; 95% confidence interval, 1.002–1.02, $p = .01$). In addition, Willems et al (119) conducted a retrospective subgroup analysis of 125 postoperative cardiac surgery patients enrolled in the Transfusion Requirements in Pediatric Intensive Care Units study. Importantly, neonates (aged <28 days) and patients who remained cyanotic after surgery were excluded from analysis. A restrictive transfusion strategy (Hb of ≤7.0) was not associated with any significant difference in new or progressive multiple organ dysfunction syndrome, PICU length of stay, or 28-day mortality compared with a liberal transfusion strategy, suggesting that a restrictive transfusion strategy is probably safe in this specific population. However, the exclusion of neonates or cyanotic patients precludes any recommendations regarding transfusion in children with complex cyanotic congenital heart disease. Regardless, the significant exposure of children with congenital heart disease to blood products, both during cardiopulmonary bypass (120) and in the perioperative period is not without concern and requires further study.

CONCLUSION

More than 22 million units of blood components are transfused annually in the United States alone (18), the majority of which are rendered by anesthesiologists (1, 6) and intensivists (7, 8). Unfortunately, the widespread and extensive use of blood products is not commensurate with the available evidence. Although blood transfusions are potentially lifesaving in limited scenarios, such as hemorrhagic shock, transfusion has been linked with significant risks and complications. These risks and complications likely outweigh the potential benefits in the majority of critically ill patients. Although further pediatric studies are necessary, especially in specific subgroups such as children with congenital heart disease, the available evidence would strongly suggest that withholding RBC transfusion in critically ill children with an Hb of ≥7.0 g/dL is appropriate and safe (5). Furthermore, until further evidence in unstable critically ill children is available, a conservative approach to RBC transfusion based on objective evidence of end-organ dysfunction, rather than on a single arbitrary trigger value would seem to be justified. The benefits and the risks involved with each RBC transfusion must be taken into consideration. Several blood conservation strategies are available in general as well as critically ill pediatric patients, which can reduce transfusion needs. Hopefully, by adopting new restrictive strategies and blood conservation techniques as well as transfusing when only clinically indicated, clinicians can decrease the load on the ever-limited blood supply, reduce cost, and most importantly save patients from a potential long and growing list of blood-related complications and unfavorable outcomes.

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