Published in final edited form as:

Pediatr Crit Care Med. 2018 September ; 19(9) : S163–S169. doi:10.1097/PCC.0000000000001625.

Recommendations on Selection and Processing of Red Blood Cell Components for Pediatric Patients from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

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Abstract

Objective—To present the recommendations and supporting literature for selection and processing of red blood cell (RBC) products in critically ill children developed by the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI).

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

Methods—The panel of 38 experts developed evidence-based and when evidence was lacking, expert-based clinical recommendations as well as research priorities for RBC transfusions in critically ill children. The RBC processing subgroup included 5 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

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Disclosures: NDZ – Octapharma, Terumo BCT, Bayer HealthCare (research funding), Endo International PLC, Boston Scientific (financial interest), North American Specialized Coagulation Laboratory Association (executive board). CDJ – Biomet Zimmer, Immucor, Octapharma (consultant). The other authors have no relevant disclosures.

Dr. Parker has disclosed that he does not have any potential conflicts of interest.

California, Los Angeles (RAND UCLA) appropriateness method. Results were summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.

Results—Five recommendations reached agreement (>80%). Irradiated cellular products are recommended for children at risk of transfusion associated graft versus host disease due to severe congenital or acquired causes of immune deficiency or when the blood donor is a blood relative. Washed cellular blood components and avoidance of other plasma containing products are recommended for critically ill children with history of severe allergic reactions or anaphylaxis to blood transfusions, although patient factors appear to be important in the pathogenesis of reactions. For children with history of severe allergic transfusion reactions, evaluation for allergic stigmata prior to transfusion is recommended. In children with severe IgA deficiency with evidence of anti-IgA antibodies and/or a history of a severe transfusion reaction, IgA deficient blood components obtained either from an IgA deficient donor and/or washed cellular components is recommended.

Conclusions—The TAXI consensus conference developed recommendations for selection and processing of RBC units for critically ill children. Recommendations in this area are largely based on pediatric and adult case report data.

Keywords

consensus development conference; critical illness; irradiation; IgA deficiency; allergic reaction; graft versus host disease

Introduction

Clinical studies demonstrating a reduced need for red blood cell (RBC) transfusions in critically-ill adults and children have resulted in a reduction in the number of blood transfusions administered in intensive care units (1–4). However, this decrease in RBC transfusions is not seen in all patient groups or in all institutions (5), and RBC transfusions are still frequently required for the optimal management of patients. The RBC product most often transfused is packed RBC unit rather than whole blood. Certain patient populations may require RBC units that have undergone additional or alternative processing steps in the laboratory before they are transfused. Most often, these procedures include irradiation of the RBC unit for those immune-incompetent children deemed to be at high risk for transfusion associated graft versus host disease (TA-GVHD), and the use of washed-resuspended RBC for children who have experienced, or are at risk for, severe allergic reactions from plasma proteins present in the residual plasma contained within the RBC unit. Identification of these “at risk” children is often difficult and key to deciding who requires the transfusion of RBCs subjected to these special processing steps. Outlined below are the recommendations developed by the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) on selection and processing of RBC units for children who are critically ill or at risk for critical illness.

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 RBC processing in children (supplemental digital data). 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. Five experts coordinated the RBC processing 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%).

Results

Prevention of transfusion associated graft versus host disease (TA-GVHD)

Severe congenital or acquired immune deficiency

Recommendation

9.1: We recommend the use of irradiated cellular blood components for all critically ill children at risk for transfusion associated graft versus host disease (TA-GVHD) due to severe congenital or acquired causes of immune deficiency. *Consensus panel expertise; Voting Data (n=35): 97% Agreement, Median 9, IQR 8-9*

Rationale: TA-GVHD is a rare transfusion complication with a high mortality (7–10). The central aspect of TA-GVHD is the presence of viable donor lymphocytes that react to recipient antigens (11). Host (immune-incompetence), donor T-lymphocyte, and environmental factors (e.g., inflammation) have been implicated in the development of this most often fatal complication of transfusion (12). While TA-GVHD is most commonly diagnosed in immune-incompetent recipients, it has been seen in rare patients with a presumed normal immune system (7). HLA mismatch alone is neither sufficient nor required for TA-GVHD to develop (7). Leukoreduction of blood components has been associated with a reduced rate of TA-GVHD on the population level (12), but this alone does not completely eliminate the risk of TA-GVHD (7, 13). Irradiation of cellular blood products (i.e. whole blood, RBC, platelets, and granulocytes) intercalates and cross-links the DNA of the residual donor T-lymphocytes in the blood product which negates their ability to proliferate, essentially eliminating the risk for TA-GVHD (14). Since TA-GVHD is nearly uniformly fatal, prospective randomized studies testing the efficacy of irradiation to prevent it in different at-risk populations would be unethical. The introduction of universal irradiation in Japan has dramatically reduced the incidence of TA-GVHD in that country (15). As newer immunosuppressive agents and therapies become available, each must be

individually assessed for its immunosuppressive potential and a recommendation for the need of irradiated blood products should be made for patients receiving these agents. Furthermore, as newer methods are made available for inactivating donor T-lymphocytes in cellular blood products, such as photochemical pathogen reduction technologies, the requirement for irradiation should be assessed in comparison to the new approaches using in vitro, animal model, and observational studies (16–18).

Blood relative donor

Recommendation

9.2: We recommend the use of irradiated cellular blood components for all critically ill children when the blood donor is a blood relative of the child. *Strong recommendation, Low quality pediatric evidence (1C); Voting Data (n=35): 100% Agreement, Median 9, IQR 8-9*

Rationale: Family donors increase the likelihood of human leukocyte antigen (HLA) matches between the donor and patient which decreases the patient's immune system from potentially identifying and destroying the transfused allogeneic donor cells (7, 19). Adult and pediatric studies demonstrate clear risk of blood relative blood donors and directed blood donors for the development of TA-GVHD (7, 19–27). The published data comes from observational studies and is therefore classified as evidence of low quality. However, as above, the risk of death when a patient acquires TA-GVHD is so high that a strong recommendation is made. As newer methods are made available for inactivating donor T-lymphocytes in cellular blood products, the requirement for irradiation should be assessed in comparison to the new approaches using in vitro, animal model, and observational studies. *GRADE 1C based on upgrading for large effect and downgrading for imprecision, indirectness and risk of bias.*

Allergic transfusion reactions

General Recommendations

Recommendations

9.3: We recommend the use of the washed cellular blood components and avoidance of other plasma containing products (e.g. plasma, cryoprecipitate, etc.) for critically ill children with history of severe allergic reactions or anaphylaxis to blood transfusions, although patient factors appear to be critically important in the pathogenesis. *Consensus panel expertise Voting Data (n=29): 100% Agreement, Median 9, IQR 8-9*

9.4: For critically ill children with a history of severe allergic transfusion reaction(s), we recommend considering evaluation of allergic stigmata (anti-IgA antibodies in IgA deficient individuals, anti-haptoglobin antibodies—using a pre-transfusion specimen) prior to RBC transfusion. *Consensus panel expertise Voting Data (n=29): 96% Agreement, Median 8, IQR 8-9*

Rationale: Allergic transfusion reactions commonly occur with blood transfusion (mild reactions ~1 in 100 transfusions, anaphylactic reactions ~ 1 in 30-50,000 transfusions) (28, 29), and have a 2.5 fold higher rate of occurrence in children compared to adults; 2.7/1000

vs. 1.1/1000, $p < 0.001$, respectively (30). Children in the pediatric intensive care unit were found to have transfusion reactions at a high rate, 1.6% (16/1000), with 24% being classified as minor allergic reactions or isolated hypotensive reactions (31). Platelets and RBCs had higher incidence of transfusion reactions in children than plasma and cryoprecipitate (30, 31). The pathophysiology of these transfusion-related allergic reactions is presumed to be type-1 hypersensitivity responses mediated by IgE. However, evidence is scant to confirm this mechanism. In this type of response IgE binds to mast cells and basophils via the IgE Fc receptors. When a plasma protein in a blood product, perceived by the patient's immune system as an allergen, binds the cell-associated IgE, mast cell activation and release of histamine, heparin, leukotrienes, platelet activating factor, cytokines and chemokines occurs simultaneously. Together they incite smooth muscle tone changes in addition to release of fluid into the tissues culminating in the allergic symptoms affecting the skin, pulmonary, cardiovascular, and gastrointestinal systems. Not only does IgE play a role in this reaction, but so does IgG via complement fixation resulting in C3a and C5a anaphylatoxins (32). Prevention of allergic transfusion reactions is preferable to treating the reaction once it has occurred. The use of premedication for all patients is neither warranted nor effective in all patients (33). Thus, the patient has to experience a reaction to reveal to the clinician the predisposition to this reaction before prevention strategies can be implemented.

One of the questions posed to the consensus panel was whether washing or volume reduction of cellular blood components should be employed for patients with mild to moderate allergic transfusion reactions in a critically ill context. Due to the lack of sufficient evidence addressing this issue, no consensus was reached among experts. Consequently, the recommendation was withdrawn; however, we provide here an explanation about this situation. In clinical practice, mild allergic reactions often only require temporary interruption of the transfusion and administration of diphenhydramine or another antihistamine to treat symptoms. If the symptoms resolve quickly, then transfusion of the product may be resumed. This is the only type of transfusion reaction where it is permissible under U.S. regulations to restart a transfusion after the reaction occurs. If the symptoms reappear or persist despite medication, then the transfusion should be discontinued (34). The second and more important reason causing a lack of support for this recommendation is that product manipulation by either volume reduction or washing may compromise the product (35, 36). Washing RBC units in an open system shortens the expiration date to 24 hours due to concern for bacterial contamination (37).

The application of laboratory techniques and avoidance of other plasma containing products (e.g. plasma, cryoprecipitate, etc.) for severe allergic/anaphylactic transfusion reactions with cellular blood components are based on evidence largely in adult patients and includes data from cellular components other than RBC and manipulations other than washing that lower plasma levels in the component (38–43). **It should be emphasized that an urgent/emergent RBC transfusion should not be withheld if washed RBC units are not available.**

For critically ill children with a history of severe allergic transfusion reaction(s), evaluation of allergic stigmata (anti-IgA antibodies in IgA deficient individuals, anti-haptoglobin antibodies) is recommended due to the possibility of identifying an association which might

explain the reactions and be avoided with future transfusions. A pre-transfusion specimen prior to RBC transfusion should be utilized for this investigation.

IgA deficiency

Recommendation

9.5: In critically ill children with suspected or documented severe IgA deficiency (undetectable), evidence of anti-IgA antibodies, and/or a history of a severe transfusion reaction, we recommend using IgA deficient blood components obtained either from an IgA deficient donor and/or washed cellular components. *Consensus panel expertise Voting Data (n=29): 100% Agreement, Median 8.5, IQR 8-9*

Rationale: Congenital IgA deficiency is the most common primary immunodeficiency (44). The incidence of IgA deficiency varies among populations based on ethnicity and based on the threshold IgA for diagnosis, ranging from 1 in 328 in a US population with a threshold of <50 mg/dL and 1 in 18,500 in Japan with a threshold of <5 mg/dL (45, 46). The clinical diagnosis of IgA deficiency is based on a threshold of <7 mg/dL (47), but for transfusion purposes, severe IgA deficiency is generally classified as <0.05 mg/dL. Individuals with severe deficiency are more likely to make antibodies against IgA. In one study, approximately 1 in 1,200 normal blood donors was found to have IgA deficiency with anti-IgA antibodies present in their serum (48). There have been many reports of transfusion reactions in IgA deficient individuals (49, 50). However, the association with IgA deficiency and allergic transfusion reactions is not entirely evidence-based (29). Non-IgA related patient and transfused unit factors likely contribute to the development of an allergic transfusion reaction. IgA deficiency or anti-IgA is not found in all patients with allergic reactions (29, 48). Not all patients with IgA deficiency and presence of anti-IgA will experience an allergic reaction with a transfusion (51). Follow-up studies of transfused units from IgA deficient donors with anti-IgA have not been associated with an increased rate of allergic reactions (52–54).

Based on the potential for a life threatening anaphylactic reaction and the desire to avoid a severe reaction when possible, the consensus of the TAXI experts is to recommend use of donor RBC units collected from IgA deficient donors (i.e., “IgA deficient” units) or washed/resuspended RBC units for patients with suspected or documented severe IgA deficiency (undetectable), evidence of anti-IgA antibodies, and/or a history of a severe transfusion reaction with the suspicion that anti-IgA antibodies are causal. It is often very difficult to obtain IgA deficient blood products, especially in the timeframe dictated by clinical care. Saline washing of RBC units has been shown to reduce the risk of transfusion reactions, including allergic reactions (40, 43) though not specifically in patients with IgA deficiency. RBC unit IgA levels are significantly lowered with saline washing (55) and reports of adult and pediatric patients in the literature describe the successful use of these RBC products [see for example (56–59)]. **It should be emphasized that an urgent/emergent RBC transfusion should not be withheld if washed or IgA deficient RBC units are not available.** In this situation, it may be prudent to monitor carefully for signs of allergic reaction, consider premedication, and be prepared to provide rapid treatment if an allergic reaction develops.

Additional considerations for blood production selection and processing—

This pediatric critical care blood management clinical guideline does not include a review and discussion of all potential blood product modifications that are available and offered by some laboratories. Choice of anticoagulant solution, processing, and storage procedures were excluded as they are not typically something that a clinician can order, and/or they may not have any evidence specifically related to pediatric critical care patients. Thus, these other modifications did not fit into the rigorous approach in which the guideline was constructed. However, we do feel it is important for an ordering provider to understand the indication and evidence about two in particular, leukocyte reduction and pathogen inactivation, although they were not specifically graded by the working group.

In modern day transfusion practice, leukocyte reduction (LR) is a nearly universal blood processing step employed with cellular blood products (RBCs and platelets) in industrialized nations. The process employs a filter to remove the bulk of the leukocytes from the blood product, leaving the product with a range of $<5 \times 10^6$ residual WBC per component (60). The step is typically carried out at the time donor whole blood is separated into components or during collection by automated methods, but may also be accomplished after storage prior to transfusion. LR has been proven to reduce the rate of HLA alloimmunization (61), reduce the rate of febrile transfusion reactions to platelets and RBC (39, 62), and reduce the rate of transfusion transmitted cytomegalovirus (CMV) infection (63, 64). On a population level, universal LR of the blood product inventory correlates with fewer reports of transfusion associated graft versus host disease (TA-GVHD), although the use of LR alone does not prevent TA-GVHD (13). Given the positive effect of LR on reducing the rate of transfusion related adverse events, many medical facilities have moved to universal pre-storage LR of their RBC and platelet components and providers may not be required to specifically order LR components. Because writing an order for a blood transfusion is a prescription that requires significant education, knowledge and credentialing, the ordering provider should be aware of the reasons that blood products are LR. Providers should also be able to explain this benefit of LR to patients and families as well as advocate for LR of blood products in situations where LR blood products are not routinely available.

Newer to the field of transfusion medicine is pathogen reduction technology. Pathogen reduction technology, in general, employs the addition of a detergent or other chemicals (with or without UV light exposure) that intercalates DNA to render any viral, parasite or bacterial contaminant unable to divide. Experts suggest that these technologies are an urgent need to keep the blood supply safe from emerging pathogens that will not be detected by the current FDA mandated testing for blood donations (65). In many countries outside of the USA, the pathogen reduction systems are integrated into the national blood systems and have been used for specific blood products for a number of years. The pathogen reduction system choices for RBC products are not as extensive as they are for platelet and plasma products. At this time, we suggest clinical providers stay abreast of the regulatory changes and costs associated with these technologies as they are destined to be part of the continued discussion to improve transfusion safety.

Summary

When deciding to transfuse RBC to a critically ill child, providers should be aware of the ways RBC units can undergo additional selection or processing prior to transfusion. To reduce the risk of specific transfusion related adverse events, providers should be aware of irradiated, washed, IgA deficient donors, leukocyte reduction, and pathogen inactivation. In addition, history and potential testing of the patient may be required to establish risk factors for allergic reactions.

Acknowledgments

We thank all members of the TAXI initiative for their support and their comments. The study was supported by grants from the Washington University Children's Discovery Institute (CDI-EI-2015-499), University of Massachusetts, CHU Sainte-Justine Foundation, National Institute of Child Health Development (1 R13 HD088086-01), National Heart, Lung and Blood Institute, and the Society for the Advancement of Blood Management. We also thank the World Federation of Pediatric Intensive and Critical Care Societies, Society for Critical Care Medicine and the AABB for their support of TAXI.

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Dr. Zantek's institution received research funding from Terumo BCT, Octapharma, and Bayer HealthCare; she received funding from Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)/National Heart, Lung, and Blood Institute (NHLBI) R13 (1 R13 HD088086-012); she disclosed she is on the College of American Pathologist Transfusion Medicine Resource Committee of the American Society for Apheresis Inbound Liaison and is an Executive Board Member for the North American Specialized Coagulation Laboratory Association, and her spouse is an employee of Boston Scientific and owns stock in ENDO International PLC. Dr. Zantek disclosed that TAXI was supported, in part, by funding from the National Institutes of Health (NIH) NICHD/NHLBI, Washington University at St Louis Children's Discovery Institute (CDI), the Society for the Advancement of Blood Management (SABM), the University of Massachusetts, and the CHU-Sainte Justine Foundation as well as support from the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Dr. Van de Watering received funding from the Sanquin Blood Supply Foundation. Dr. Josephson received funding from Immucor (consulting) and Octapharma, and she received support for article research from the NIH/NHLBI. Dr. Bateman's institution received funding from R13 conference grant from NICHD and NHLBI and SABM, and he received support for article research from the NIH. Dr. Valentine's institution received funding from NICHD and NHLBI under award number 1 R13 HD088086-01; the Society for the Advancement of Blood Management SABM-Haemonetics Research Starter Grant; and Washington University Children's Discovery Institute (DCI-EI-2015-499). She received other support from CHU-Sainte-Justine Foundation and the University of Massachusetts Medical School, and she received support for article research from the NIH, SABM SABM-Haemonetics Research Starter Grant, CHU-Sainte-Justine Foundation, Washington University CDI, and the University of Massachusetts Medical School. Dr. Delaney received unrelated funding from Sio Capital (consulting about blood bank instrument), Janssen (consulting about blood bank testing for cancer patients), and Grifols (teaching about blood bank molecular testing).

Appendix 1: Pediatric Critical Care Transfusion and Anemia eXpertise Initiative (TAXI) Members

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