Published in final edited form as:

Transfusion. 2017 June ; 57(6): 1568–1581. doi:10.1111/trf.14100.

2016 proceedings of the National Heart, Lung, and Blood Institute's scientific priorities in pediatric transfusion medicine

Pablo Cure¹, Melania Bembea², Stella Chou³, Allan Doctor⁴, Anne Eder⁵, Jeanne Hendrickson⁶, Cassandra D. Josephson⁷, Alan E. Mast⁸, William Savage⁹, Martha Sola-Visner¹⁰, Philip Spinella¹¹, Simon Stanworth¹², Marie Steiner¹³, Traci Mondoro¹⁴, Shimian Zou¹⁴, Catherine Levy¹⁴, Myron Waclawiw¹⁵, Nahed El Kassar¹⁴, Simone Glynn¹⁴, Naomi L.C. Luban¹⁶

¹Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, Bethesda, Maryland; ²Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, Maryland; ³Department of Hematology and the Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; ⁴Department of Pediatrics, St Louis Children's Hospital, St Louis, Missouri; ⁵National Institutes of Health, Bethesda, Maryland; ⁶Department of Laboratory Medicine, Yale University, New Haven, Connecticut; ⁷Department of Pathology and Laboratory Medicine, Emory University, Atlanta, Georgia; ⁸Blood Research Institute, Blood Center of Wisconsin, and the Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, Wisconsin; ⁹Department of Pathology, Brigham and Women's Hospital; ¹⁰Department of Newborn Medicine, Children's Hospital, Boston, Massachusetts; ¹¹Washington University in St Louis, St Louis, Missouri; ¹²NHS Blood and Transplant, John Radcliffe Hospital, and Oxford Clinical Research in Transfusion Medicine, Nuffield Division of Clinical Laboratory Sciences, University of Oxford, Oxford, UK; ¹³Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota; ¹⁴Division of Blood Diseases and Resources, NHLBI/NIH; ¹⁵National Heart, Lung, and Blood Institute, Bethesda, Maryland; ¹⁶Division of Laboratory Medicine, Children's National Health System, Washington, DC.

On April 5–6, 2016, the National Heart, Lung, and Blood Institute (NHLBI); the Department of Health and Human Services/Office of the Assistant Secretary of Health; and the Food and Drug Administration (FDA) sponsored a meeting on Scientific Priorities in Pediatric Transfusion Medicine at NHLBI in Bethesda, Maryland. The goal of this meeting was to identify important research questions that could be answered in the next 5 to 10 years and which would have the potential to transform the clinical practice of pediatric transfusion medicine. By applying basic, translational, and/or clinical research studies focused in six areas the science of/transfusion medicine would be advanced. The six areas were selected based on recognized gaps in knowledge and included neonatology and perinatology, oncology and transplant, chronic transfusion, devices and surgery, intensive care, and trauma and teenage blood donation. The meeting and premeeting teleconferences included 80 participants representing multiple stakeholders, academic medicine, the basic and clinical

research community, and the government. The participants had expertise in multiple relevant disciplines including transfusion medicine, pediatrics, neonatology, hematology, surgery, critical care, trauma, internal medicine, epidemiology, and study design. The speakers and participants identified research priorities based on unmet needs in the pediatric transfusion medicine arena and proposed strategies to overcome the knowledge gaps and address unanswered questions.

PRESENTATIONS AND DISCUSSIONS

The opening address by Drs Gary Gibbons, Keith Hoots, and Simone Glynn of the NHLBI and Dr Naomi Luban, of Children's National Health System, provided the context for the 2-day meeting. After the introductory presentations, three keynote lectures set the stage for the discussion. These included: 1) "Blood Elements" presented by Dr Steven Spitalnik of Columbia University; 2) "National Institute of Child Health and Human Development (NICHD) Resources and Networks" presented by Dr Rosemary Higgins including the Collaborative Pediatric Critical Care Research (CPCCRN), the Maternal Fetal Medicine Units (MFMU), and the Neonatal Research (NRN) Networks; and 3) "Regulatory Pathways in Neonatology and Pediatric Transfusion Medicine" by Pamela Clark of the FDA. After these presentations, sessions addressed the six key areas: neonatology and perinatology, oncology and transplant, chronic transfusion, devices and surgery, intensive care and trauma, and teenage blood donation (Fig. 1). The area leader and coleader had conducted fact finding through conference calls and e-mail exchanges in advance of the meeting. At the meeting the leader and coleader presented proposed priority research questions with background and supporting information. This was followed by an open discussion of the proposed questions, modification of and addition to the proposed research priorities, and a summary presentation of the final five priorities identified by consensus at the meeting. A postmeeting summary was provided to NHLBI by each group.

Priorities in each area are posted as questions. Below is a summary of the most important priorities and proposed research solutions extracted and edited from each group's postmeeting summary.

NEONATOLOGY AND PERINATOLOGY

How can primary red blood cell or platelet glycoprotein alloimmunization be prevented in the setting of pregnancy?¹⁻⁶

Prevention of pregnancy associated alloimmunization to paternally derived red blood cell (RBC) or platelet (PLT) antigens would decrease potentially devastating cases of hemolytic disease of the fetus and newborn and neonatal alloimmune thrombocytopenia. At present, prophylactic RhIG is the only therapy available for targeted alloimmunization and it is only effective against the D antigen. The ability to prevent alloimmunization to other paternally derived RBC antigens is desirable, as is the ability to prevent alloimmunization to paternally derived PLT glycoprotein antigens. A bench-to-bedside approach to understanding the mechanism of action of RhIG (and other immunoprophylaxis therapies shown to be effective in animal models) may permit the generation of novel immunoprophylaxis therapies. These therapies may include those recombinant proteins or may induce antigen-specific tolerance.

In addition to studies of hemolytic disease of the fetus and newborn prevention, mechanistic animal and human studies are needed to investigate strategies to prevent maternal alloimmunization to PLT glycoprotein alloantibodies.

Using targeted therapies that go beyond intrauterine transfusions, therapeutic plasma exchange, or intravenous immunoglobulin, can existing maternal RBC or PLT alloantibodies be minimized?^{7–11}

Although preventing primary RBC alloimmunization or PLT glycoprotein alloimmunization would be ideal, a number of women enter pregnancy already alloimmunized to RBC or PLT glycoprotein antigens through prior transfusion or pregnancy. At present, intrauterine transfusions, therapeutic plasma exchange, and IVIG are among the few effective therapies. These therapies are nonspecific and their use is not without risks and side effects. The ability to prevent the transplacental passage of specific alloantibodies in a targeted manner would decrease the necessity of utilizing these therapies, and would likely improve fetal outcomes. Recent advancements in bioengineering, glycobiology, metabolomics, and recombinant techniques may allow this issue to be approached in ways never previously feasible. Studies could be initiated in animal models, with parallel or subsequent studies completed in humans. Such studies may involve nonfunctional antibodies, antibody fragments, or other targeted therapies engineered to bind in a competitive manner to cognate antigenic sites on fetal RBCs or PLTs. Another approach may be the development of therapies that specifically target RBC or PLT antibodies in the maternal circulation, such that the circulatory half-lives of antigenpositive RBCs or PLTs in the fetal circulation are prolonged.

What are the best strategies to identify neonates who would benefit from transfusion (RBCs, PLTs, or fresh-frozen plasma), and what are the systemic effects of transfusions in this population?^{12–16}

Transfusion trials in neonates have been designed to compare liberal versus restrictive transfusion strategies based on hemoglobin (Hb), hematocrit, or PLT count thresholds. While these analytic assays are widely available and well suited for multicenter trials, it has become increasingly evident that cell counts alone are not good predictors of physiologically relevant outcomes, particularly in neonates of variable gestational and postnatal ages with different levels of illness. Thus, studies are needed to identify better markers of physiologically relevant outcomes (including tissue oxygen delivery and hemostatic function) suitable for neonates. With increasing awareness of the immunomodulatory effects of transfusions and the role of PLTs and RBCs in immune regulation and inflammation, studies to better understand the effects of transfusions on neonatal neurodevelopment, immunity, and inflammation are also needed. Longitudinal follow-up of infants who participated in neonatal transfusion trials is imperative to understand the long-term consequences of transfusion interventions. A combination of clinical and translational studies is needed to better understand the consequences of anemia, thrombocytopenia, and PLT and RBC transfusions on neonatal immune function, inflammation, and neurodevelopment.

What is the best way to gather national epidemiologic data on neonatal transfusions?^{17–20}

Isolated survey and retrospective studies have revealed extraordinary variability in neonatal transfusion practices. However, there is a lack of current epidemiologic data on neonatal transfusions that links comprehensive information on the characteristics of donors, recipients, and the attributes of the blood products transfused, the way it exists for adult patients through the Recipient Epidemiology and Donor Evaluation Study (REDS). Having access to this more global, multicenter epidemiologic data is essential to: “understand current neonatal transfusion practices,” identify gaps in knowledge to inform research questions, design clinical trials, and ultimately maximize transfusion benefits and reduce risks in this vulnerable and highly transfused patient population. With a projected life span of approximately 70 years after the neonatal intensive stay, interventions to increase the safety of transfusions in this population are of utmost importance from a public health perspective. Gathering comprehensive epidemiologic data on neonatal transfusions could be accomplished by adapting existing platforms developed for adult studies, such as REDS. Alternatively, epidemiologic transfusion data could be added to existing multicenter neonatal databases that already gather data from patients admitted to participating neonatal intensive care units (ICUs), such as the NICHD Neonatal Network or Vermont-Oxford. Efforts to this end should leverage existing infrastructure.

What are the best blood management strategies for neonates?^{21–24}

Current additives and pathogen reduction protocols have been tested almost exclusively in adult recipients. Thus, unanswered questions remain regarding the ideal blood management strategies for neonates (including collection, storage, and testing) and particularly regarding the safety of pathogen inactivated blood products on a developing neonate. Importantly, the potential risks associated with pathogen inactivation approaches will need to be balanced against the risks of transfusion-transmitted infections in neonates. These include infections that carry well-known risks, such as cytomegalovirus, as well as new infections with uncertain consequences in preterm neonates in the setting of transfusion transmission such as Zika. The safety and efficacy of different blood management strategies, such as pathogen reduction systems, should be adequately tested in neonates, with specific consideration given to potential developmental stagespecific effects associated with their use. This would be best accomplished using a combination of strategies: First, available neonatal data from countries that have already utilized pathogen inactivation methods should be analyzed and neonates should be specifically included in future and ongoing hemovigilance studies. Second, studies should be designed to address the efficacy and safety of pathogen-reduced products in neonates, particularly when administered to extremely preterm infants.

ONCOLOGY AND TRANSPLANT

Transfusion medicine and pediatric hematology-oncology physicians or transplant specialists share an interest in defining best transfusion practice, reducing risks associated with use of a biologic product, and minimizing costs. Strategies to address research gaps involves the application of a team science approach by 1) integrating transfusion into animal models of cancer treatment and hematopoietic stem cell transplant, 2) incorporating transfusion variables into cancer or transplant registries and observational studies, and 3)

undertaking clinical trials and correlative studies in this intensively transfused population. Overall, pediatric oncology or transplant patients are monitored closely and are often enrolled in therapeutic drug trials, which may include long-term follow-up and the collection and maintenance of a biologic sample collection or biobanks.

What are the mechanisms, biomarkers, and treatment adjuncts to prevent and/or manage hemorrhage in pediatric oncology and transplant patients?^{25,26}

Pediatric oncology and transplant patients may have a higher incidence of hemorrhage than adult oncology and transplant patients, but there is a dearth of prospective data. PLT count and PLT transfusion dose do not account for or modify this difference (see Question 2). There may be mechanistic differences in endothelial cell biology or treatment regimens that increase hemorrhagic risk, as well as the confounder of bacterial, viral, and fungal sepsis and treatment. A major research priority is to study adjunctive therapy such as antifibrinolytic agents to prevent hemorrhage in stable thrombocytopenic children. Other questions discussed by the group were: 1) What is the clinical impact of different grades of hemorrhage as evaluated by epidemiologic approaches? What are the incidence, severity, and associated outcomes of hemorrhage in the overall treatment course of these patients? 2) What are the causes of hemorrhage in thrombocytopenic pediatric oncology/transplant patients, including developmental, treatment, and disease-related factors? 3) Are there nonroutinely tested yet relevant biomarkers that predict hemorrhagic risk? 4) Can viscoelastography and PLT function testing assist in identifying the mechanisms responsible for hemorrhagic risk?

How can PLT transfusions be optimized including PLT refractoriness management?²⁷

Clinical studies increasingly suggest that PLT transfusion has limited efficacy in mitigating hemorrhage in oncology and transplant patients. The risk-benefit of prophylactic PLT transfusion should include an understanding of how repeated PLT transfusions contribute to immune-mediated refractoriness. Unanswered questions include: Are there certain children receiving cancer therapy who do not need PLT transfusions? What are the predisposing factors and diagnostic approaches to drug- and transplant-related thrombotic microangiopathy that increase PLT consumption? What is the epidemiology of humoral, cellular, and nonimmune causes of PLT refractoriness? The humoral and cellular activation mechanisms, antigenic targets, and clearance mechanisms have not been adequately studied in children. Anti-HLA and anti-HPA antigens do not account for all cases of PLT refractoriness. Although PLT refractoriness complicates only a minority of chronically transfused oncology and hematopoietic stem cell transplant (HSCT) patients, PLT management of these patients can place large burdens on PLT procurement activities in the blood bank, increase PLT transfusion, delay clinical procedures, and complicate treatment of hemorrhage. Approaches to identify immune versus nonimmune causes of PLT refractoriness would provide more rational PLT transfusion therapy.

What is the impact of PLT and RBC transfusions on transplant outcomes?^{28,29}

RBC and PLT transfusions expose recipients to RBC, PLT, and white blood cell antigens and to storage-related byproducts, such as free Hb, iron, pro- and antiinflammatory proteins, and microparticles. These exposures can promote alloimmunization and immune modulation.

Because immune responsiveness is critical for tumor control and transplant engraftment and transfusion may cause immune dysfunction, disease control and patient's outcomes may be modified by transfusion. Transfusion practice in pediatric oncology and transplant patients is prophylactic in nature; if transfusion were shown to negatively affect cancer or transplant outcomes, a shift to restrictive transfusion practices might ensue. Specific questions include: In the setting of HSCT, does the degree of Rh and minor antigen matching affect RBC engraftment? Can donor-recipient RBC antigen genotyping aid in HSCT donor selection? Can the risks of new anti-RBC antigen formation be estimated? Do reduced-intensity and haploidentical transplant protocols modulate the risk for alloimmunization to RBC antigens? For sickle cell disease transplant patients, what donor-recipient RBC antigen mismatches are favorable or unfavorable? Do HLA, HNA, and HPA antigen exposure from transfusion affect graft rejection, relapse, graft-versus-host disease (GVHD), or acute inflammatory transfusion reactions? Should prior HLA, RBC, or PLT alloimmunization influence the selection of transplant conditioning regimens? Does transfusion iron overload affect transplant outcome?

What are the physiologic responses, clinical consequences, and optimal use of RBC transfusions in children with anemia due to marrow failure?³⁰

The fate of transfused RBCs and free non-transferrin-bound iron in patients with primary or treatment-related marrow aplasia may differ from patients with "consumptive" causes including hemorrhage or inflammatory-driven anemia. Recent guidelines encourage measuring iron burden in chronically transfused oncology and transplant patients, but the effects and management of iron overload and its consequences are poorly understood in children with malignancies. Is posttransfusion RBC survival different in the setting of marrow aplasia and chemotherapy? Are the indications for transfusion different in hypoplastic anemia? Is transfused iron handled differently in the setting of marrow aplasia, and does this have implications for transfusion decisions? What happens to free iron in aplastic marrow? Does iron overload affect transplant and oncology outcomes? How are levels of iron overload classified as harmful, by what means, and over what period of time? Are the goals of RBC transfusion different in patients with marrow aplasia? Are there specific indicators of transfusion need in hypoproliferative anemia? Are restrictive thresholds for RBC transfusion appropriate in oncology and transplant patients? Is stroke risk increased in severe anemia in patients without sickle cell disease? What age-appropriate metrics should assess anemia-related quality of life? Does hypoplastic anemia intersect with PLT physiology or rheology to increase the risk of hemorrhage?

How does irradiation and pathogen reduction technology affect the safety and efficacy of products, and what studies are required in children?^{31,32}

Irradiation is commonly used in oncology and transplant settings to reduce the risk of transfusion associated GVHD. With the potential for pathogen reduction technology (PRT) to substitute for irradiation, the relative consequences on PLT and RBC quality and recovery are not known and poorly characterized in children. Additionally, PRT may be used in combination with irradiation. Both irradiation and PRT alter surrogate markers of quality and function of PLTs and RBCs. Do these measures have a meaningful clinical correlate? As clinical programs may be forced to choose between irradiation and PRT, the relative safety,

cost-effectiveness, and clinical efficacy of components treated with each process must be clear and to date have not been studied. Clinical studies for licensing new technologies (e.g., PRT) provide data on adults but often exclude children and rarely include neonates. What studies should be required in these populations, including children with cancer, who form the largest recipient group of PLT transfusions? Pre-post and parallel implementation studies, as well as crossover trials comparing irradiation to PRT and to PRT and irradiation need to be performed.

CHRONICALLY TRANSFUSED POPULATIONS

In children with sickle cell disease and thalassemia what are the host immunologic and donor RBC factors that determine alloimmunization risk?^{33–37}

The rate of RBC alloimmunization rates in patients with sickle cell disease (SCD) is significantly higher than transfused patient populations. There has been some decrease in overall alloimmunization rates with prophylactic matching for C, E, and K antigens which often requires RBC units from ethnically similar donors. Despite these strategies, Rh alloimmunization remains problematic since patients with SCD commonly inherit variant Rh alleles encoding partial D, C, and e antigens and form alloantibodies to the Rh epitopes they lack. These alloantibodies may be associated with delayed hemolytic transfusion reactions complicating transfusion management. Currently, RBC genotyping capabilities provide donor centers an efficient method to identify antigen-negative units and may potentially improve RBC antigen matching. Host immune factors also contribute to RBC alloimmunization. Patients with a concomitant inflammatory complication of SCD appear to be at increased risk for alloimmunization, but other host immune factors remain largely unknown. Both donor and host factors must be combined to identify new strategies to mitigate alloimmunization. Longitudinal studies of chronically transfused patients with SCD and thalassemia are needed to examine both host immunologic characteristics and donor exposures including antigen discrepancies to define alloimmunization risk. Longitudinal preand posttransfusion sample collections with a biobank of patient serum, DNA, and mononuclear cells as well as donor DNA would be needed. An observational birth or early childhood cohort study design is feasible since newborn screening for SCD occurs in every US state. Host immune status could be studied, including response to RBC antigenic exposures over time. The clinical context in which the children transfused as well as patient and donor RBC antigen genotypes would be examined. The REDS-III database developed for donor–recipient electronic, automatic data capture could be leveraged to facilitate this type of study.

Is chronic erythrocytapheresis a more effective RBC transfusion modality compared to chronic simple transfusion, to ensure adequate HbS suppression while avoiding or mitigating iron overload in patients with SCD?^{38–42}

Overt stroke affects 10% of children with HbSS disease before age 18 years, and silent cerebral infarcts occur in approximately 30% of children leading to neurocognitive impairment. Chronic transfusion remains the primary therapy to prevent stroke in children with SCD. However, transfusion therapy carries substantial risks, including alloimmunization and iron overload. It is unclear which transfusion modality, chronic

erythrocytapheresis or simple transfusion, is more effective in maintaining the goal of HbS reduction while mitigating iron overload and alloimmunization. A prospective study is feasible in the United States as multiple centers with large numbers of SCD patients use both strategies for chronic transfusion therapy. Outcomes would include pretransfusion HbS%, absolute reticulocyte count, volume, and RBC mass transfused; allo- and autoantibodies formed among others. Iron overload is evaluated by liver iron content quantification by R2 magnetic resonance imaging (MRI) techniques and serum ferritin trending combination. Compliance with prescribed dose of chelator (e.g., Deferoxamine or Deferasirox or no therapy) would need monitoring as well, but is more challenging.

What donor RBC characteristics in stored blood impact transfused RBC survival, function, and clearance (immunologic or nonimmunologic) in vivo in patients requiring chronic transfusion?^{43–45}

It is unknown whether storage conditions affect survival of some blood donors (i.e., being a poor storer or good storer of RBCs) leading to a rapid clearance and/or decreased survival of transfused RBCs and consequently to an increased number of RBC units transfused. In the United States, most transfusion services recommend RBCs that are less than 14 or 21 days old for patients requiring chronic RBC therapy. However, there is limited evidence to support this practice. It is also unknown whether the risk of RBC alloimmunization increases with storage time or if donor storage characteristics (i.e., being a poor storer or good storer of RBCs) influence immune modulation and the immunologic effect in recipients with SCD. The impact of transfusing shorter- versus longerstored RBCs on patient outcomes remains controversial. Two recently published trials evaluated the impact of the age of transfused RBCs in patients undergoing cardiac surgery or who were critically ill and admitted to ICU and found no difference in outcomes. However, no similar studies on the age of blood and outcomes in SCD or other patients with chronic transfusion dependent anemias have been conducted. A multicenter clinical study with standardized products (extent of RBC antigen matching, storage duration, and irradiation) would be required. Improved animal models and new tools such as RBC survival using biotinylated RBCs may facilitate mechanistic studies to understand donor RBC survival, function, and clearance in chronically transfused populations.

DEVICES AND SURGERY

What are optimal transfusion strategies to prevent and treat severe bleeding or reduce inappropriate blood exposure in children who require surgery or extracorporeal devices?

Evidence-based transfusion strategies for critically ill pediatric patients experiencing life-threatening bleeding during the perioperative period and/or extracorporeal support are essential as providers strive to improve outcomes in this challenging population. Preliminary data suggest that mortality in children with life-threatening hemorrhage due to traumatic injuries or medical etiologies is routinely greater than 50%. Common surgical and device-related complications of hemorrhage and thrombosis (e.g., 40 and 33%, respectively, in extracorporeal membrane oxygenation [ECMO] patients) continue to result in significant mortality, neurologic morbidity, and limb loss.⁴⁶ The Extracorporeal Life Support Organization estimates that more than 54,000 pediatric patients have received ECMO as of

December 2015.⁴⁷ All of these patients require complex decisions regarding utility of and indications for transfusions, types of products or hemostatic adjuncts to utilize and monitoring for and achieving effective anticoagulation while minimizing bleeding complications.⁴⁸ Transfusion strategies for life-threatening bleeding that should be evaluated include: 1) the study of whole blood as the primary resuscitative product for hemorrhagic shock; 2) the use of PLTs stored at 48C for bleeding; 3) the study of an empiric ratio of blood components versus a goal-directed transfusion strategy with functional measures of hemostasis and oxygen debt; 4) determining the appropriate indication for antifibrinolytics agents, fibrinogen concentrates, and other coagulation factor concentrates; 5) indications for transfusion by examining the effect of goal-directed transfusion algorithms, using functional measures of oxygen delivery and hemostasis; 6) development of blood management programs to evaluate the efficacy of novel technologies to reduce phlebotomy (e.g., nanotechnology, point-of-care, microfluidic devices) aiming at decreasing iatrogenic anemia; and 7) alternatives to transfusion comparing the efficacy and safety of salvaged blood with cell saver devices with banked RBCs.

What are optimal RBC transfusion strategies for anemia not related to acute hemorrhage in children who undergo surgery?^{49–51}

Data supporting RBC transfusion strategies for critically ill children undergoing surgical procedures (e.g., traumatic brain injury, congenital heart disease, liver transplant, spinal surgery) are limited, mainly retrospective, and single center. These surgical procedures are conducted in medically fragile patients whose complicated physiology, including altered vasomotor autonomic regulation, existing coagulopathy, myocardial depression, and/or varying degree of desaturation, may impair adaptive physiologic responses to shock (oxygen debt). Specific questions include: What are the epidemiologic characteristics, transfusion practice variations, and outcomes associated with RBC transfusions for children at risk of or with intra- and postoperative shock not related to acute hemorrhage? What are the optimal methods to determine indications for RBC transfusions in critically ill children undergoing surgical procedures and requiring postoperative intensive care? Do physiologic indices of oxygen delivery and consumption provide better indications for RBC transfusion compared to absolute Hb level triggers? What measures of oxygen delivery and consumption are suitable to guide RBC transfusion and are integrated measures (systems biology) required, rather than a single metric? How do RBC transfusions impact the endothelial function and permeability, vasomotor tone, sympathetic and parasympathetic nervous system activation, immune function, marrow response, and hemostasis? How do the various methods of collection, processing, storage, and compatibility determination of blood products, as well as donor characteristics, affect the efficacy and safety of RBC transfusions? Are there patient-specific variables that affect outcomes and safety for patients transfused RBCs who are undergoing major surgery and are at risk for or in shock?

What are optimal RBC transfusion strategies for anemia not related to acute hemorrhage in children on extracorporeal devices (e.g., ECMO, ventricular assist devices, cardiopulmonary bypass)?

The number of children supported on extracorporeal devices in hospitals across the United States has doubled in the past decade and includes sicker and more medically complex

patients. Children on extracorporeal life support receive volumes of RBCs as high as 40 to 105 mL/kg per ECMO day in some reports^{52,53} depending on institutional protocols.⁴⁸ No evidence-based guidelines on how to transfuse RBCs in patients on extracorporeal devices have been published, although growing experience suggests negative impact of transfusion on a variety of outcomes.⁴⁸ Specific research questions addressing the appropriate utilization of RBC transfusion in this population include: What are the epidemiologic characteristics, transfusion practice variations, and outcomes associated with RBC transfusions aimed at preventing or treating shock for children on extracorporeal devices? What is the optimal method to determine RBC transfusion indications? What are the appropriate indication(s) for RBC transfusion to prevent or reverse shock (oxygen debt) in nonbleeding children on venovenous ECMO, venoarterial ECMO, or ventricular assist device (VAD)? What are the effects of RBC processing methods on their efficacy and safety for children supported on extracorporeal devices (e.g., washing, irradiation)?

What are the mechanisms of hemostatic dysfunction for children with severe intra- or postoperative bleeding and children with severe bleeding while on venoarterial or venovenous ECMO or VAD support?

More than 18,000 children per year in the United States have critical coronary heart disease requiring surgery supported with cardiopulmonary bypass.^{54,55} More than half of postoperative coronary heart disease patients receive additional blood transfusions within 48 hours of surgery. ECMO- and VAD-induced coagulopathy is a complex and dynamic condition caused by a hypercoagulable state in the device and a mixed coagulopathic state in the patient. This topic is challenging to study for many reasons such as developmental hemostasis, limited pharmacokinetic and pharmacodynamic data for hemostatic agents, irregular coagulation therapy monitoring due to difficult vascular access, reliance on imprecise methods such as activated clotting times, inadequate validation of current diagnostic and treatment interventions, and lack of widespread experience and limited expertise with caregivers and physicians.^{56,57} Specific research questions include: What are the epidemiologic characteristics, transfusion practice variations, and outcomes associated with blood product transfusion? What are the mechanisms of hemostatic dysfunction? What is the contribution of developmental hemostasis and of circuit dilution to hemostatic dysfunction? What is the optimal anticoagulation monitoring practice that will reduce complications and improve outcomes?

What are optimal blood conservation and management methods to reduce inappropriate blood exposure for intra- and postoperative patients and patients on extracorporeal devices (ECMO, VAD, cardiopulmonary bypass)?

Critically ill children who have undergone surgery or are supported with extracorporeal devices are at risk for bleeding or can have active hemorrhage. Management of potentially catastrophic hemorrhage must be balanced against the risk of serious or life-threatening thrombosis or thromboembolic complications. RBC transfusions are frequently used to treat anemia due to all causes including ongoing bleeding, whereas plasma and PLT transfusions are frequently used to prevent or to stop bleeding. As blood product transfusions appear to be associated with worse clinical outcome even in patients with hemorrhage,^{58–60} it seems appropriate to evaluate strategies aiming at reducing blood transfusions in intra- and

postoperative patients and in those supported with extracorporeal devices. Studies addressing this priority may include: 1) indications for transfusion by examining the effect of goal-directed transfusion algorithms, using functional measures of oxygen delivery and hemostasis; 2) development of blood management programs to evaluate the efficacy of novel technologies to reduce phlebotomy (e.g., nanotechnology, point of care, microfluidic devices) to safely and effectively decrease iatrogenic anemia and the need to transfuse; 3) hemostatic management strategies to examine the effect of antifibrinolytics and factor concentrates on reduction of blood product exposure and improved outcomes; and 4) alternatives to transfusion comparing the efficacy and safety of salvaged blood with cell saver devices with banked RBCs.

INTENSIVE CARE AND TRAUMA

What are the optimum means to monitor and manage hemostatic dysfunction in trauma and critical illness?

Recent surveys indicate that hemostatic monitoring and resuscitation strategies for bleeding in children are, in fact, commonly based on adult trauma data.⁶¹ However, developmental differences in the proteins responsible for hemostasis and thrombosis require tailored approaches to both monitoring and therapy. Unfortunately, robust measures of functional in vivo hemostasis are not yet established and must be interpreted within the context of a systems approach that incorporates developmental evolution (e.g., major differences in hemostasis between infants and older children). Validated methods to investigate, monitor, and manage hemostatic dysfunction are lacking in children, yet are essential to guide use of blood products as well as to develop goal-directed therapies. Multicenter data indicate that the mortality associated with major threatening bleeding in children secondary to traumatic injury is 55% and for medical etiologies is 78%.⁶² Adult studies indicate that the death from hemorrhage is preventable in 20% to 25% of traumatic deaths.^{61–63} Additional research into the use of whole blood as the primary resuscitative product for hemorrhagic shock and/or the use of PLTs stored at 48C for bleeding, as well as the study of an empiric ratio of blood components versus a goal-directed transfusion strategy with functional measures of hemostasis and oxygen debt, should be considered. Other research priorities include determining the appropriate indication for antifibrinolytics agents, fibrinogen concentrates, and other coagulation factor concentrates. An incremental approach to address this opportunity to improve outcomes could integrate epidemiologic, clinical, and mechanistic studies to inform a systems biology model for subsequent validation in clinical trials.

What are the optimal means for RBC transfusion decision making in critical illness and trauma?

The goal for transfusion decision making in the pediatric ICU (PICU) is to maintain “adequate” [Hb] above thresholds that limit tissue O₂ delivery—balanced by consideration that: 1) processed and stored donor and native RBCs do not exhibit similar physiology and 2) transfusion may cause harm. As such, “restrictive” Hb thresholds for transfusion are now appreciated to be at least noninferior (and in many cases, superior) to “liberal” thresholds,^{64,65} even for bleeding patients.⁵⁸ Moreover, a paradigm shift is emerging, with reconsideration of the “Hb trigger” itself. Clearly, it is not feasible to individualize Hb

boundaries across the complex interaction of developmental-, condition-, and stress-specific situations in PICUs. Ideally, transfusion decision making should be based on “personalized” consideration of the degree to which anemia impairs O₂ delivery (and/or reserve).^{66–70} However, there are no data supporting use of a physiologic goal-directed strategy and no consensus on what goals or thresholds should be targeted. To resolve this knowledge gap, we need tools to better: 1) recognize the onset and severity of inadequate O₂ delivery, 2) identify anemia-attributable impairment of O₂ delivery, 3) quantify the likelihood that O₂ delivery lack will respond to transfusion, 4) assess the context-specific transfusion risk, and 5) determine means to titrate of transfusion to response.

What are the consequences of transfusion and the optimum approaches to identify and mitigate noninfectious serious hazards of transfusion, including transfusion-related acute lung injury, transfusion-associated circulatory overload, acute respiratory distress syndrome, and transfusion-related immunomodulation?

The full impact of noninfectious serious hazards of transfusion (NISHOT) in PICU patients remains unclear, as the few epidemiologic studies are hampered by inconsistent screening strategies (transfusion-related acute lung injury [TRALI], transfusion-associated circulatory overload), and/or standard definition (transfusion-related immunomodulation). Although data from hemovigilance programs have informed risk-reduction strategies,⁷¹ the true incidence of transfusion-associated circulatory overload and TRALI in infants and children is likely underestimated.⁷² Determining actual incidence rates, risk factors, and outcomes related to NISHOT are essential to designing clinical trials. Additional immunomodulation conferred by blood products should be relevant in critically ill children who already demonstrate dysregulated immunologic responses predictive of adverse outcomes.^{73,74} However, defining transfusion-related immunomodulation is challenged by confounding patient, blood product, and donor variability; immune response complexity; and transfusion timing. Prior plasma cytokine studies may not reflect the functional capacity of the immunologic response or the ability to respond appropriately to new challenges. Finally, no studies have addressed the likely developmental differences in infants and children from each other and from adults. Formal definitions for all NISHOT syndromes and common data elements for study will enable multicenter clinical trials to evaluate NISHOT in PICU populations using standardized, reproducible functional immune studies and other biomarkers demonstrated to be predictive of poor clinical outcomes.^{74,75}

What are the strategies to optimize blood product stewardship, including the best ways to identify, evaluate, and disseminate effective but safe blood management strategies?

Clinically significant anemia is observed in 75% of critically ill children.^{64,76} Nearly 50% of PICU patients admitted for more than 48 hours receive at least one RBC transfusion.⁷⁷ Data are lacking regarding effective and safe nonpharmacologic strategies to: 1) improve blood conservation, 2) minimize RBC transfusion-related complications, and 3) improve dissemination and implementation of these strategies. Approaches to blood conservation are numerous^{78,79} and a bundle of interventions applied with pharmacologic measures showed potential for reducing neonatal and pediatric transfusions and complications.⁸⁰ Novel blood products such as Octaplas along with innovative approaches to pathogen reduction and blood product preparation remain to be investigated in children as means to reduce transfusion-

related complications. In addition, availability and use of both traditional and novel blood products in remote locations and in disaster response are important but poorly studied in injured children. Reducing unnecessary transfusion is critical to limit product exposure and transfusion-associated complications.^{77,79} Restrictive Hb thresholds (7 g/dL) shown to be noninferior to liberal (9 gm/dL) strategies reduce transfusions and transfusion-related complications.⁶⁴ However, the threshold in practice remains higher,⁷⁹ underscoring the need for effective and timely approaches to dissemination of best available evidence to facilitate stable adoption of best practice.

TEENAGE BLOOD DONATION

What are the short-term effects of blood donation- induced iron deficiency in teenagers?

The group extensively discussed whether concerns about the safety of high school blood donors were research questions or policy issues. There was strong consensus that the risks to high school blood donors should be carefully reconsidered using the concept of “first do no harm.” FDA representatives said that they would discuss the concerns raised internally. There was consensus that this topic, in particular about teenage blood donor injuries and iron deficiency, should be brought to the attention of the American Academy of Pediatrics. One research area was the short- and long-term neurocognitive effects of blood donation–induced iron deficiency among teenagers. Donation-related iron depletion in high school blood donors could also provide the opportunity to identify and correct chronic iron deficiency in adolescents even when it is not related to blood donation. Blood donation removes approximately 525 mL of whole blood, which corresponds to 200 to 250 mg of iron. This represents approximately 25% of the average male iron stores and approximately 75% of the average female iron stores. Consequently, iron deficiency is common among repeat adult blood donors. The iron status of teenage blood donors and their susceptibility to blood donation–induced iron deficiency has not been well characterized. However, teenagers are likely to be more susceptible to iron deficiency than adults, because many are still growing, many have poor dietary habits, and girls suffer from menstrual blood loss. Nevertheless, teenage donors are allowed to donate every 56 days just like adults, using the same Hb cutoff values to qualify for donation. Iron deficiency is associated with several acute symptoms, including pica and restless leg syndrome. Perhaps most importantly, adequate iron has been repeatedly linked to better cognition and scholastic achievement in teenagers.^{80,81} The effect of blood donation–induced iron deficiency on cognitive function has not been assessed in teenagers. The study to examine the susceptibility of teenagers to donation-induced iron deficiency is straightforward, given the large number of teenage donors, multiple opportunities to donate at regularly scheduled high school drives, and the availability of serum or plasma samples from residual infectious disease testing that can be used to measure serum ferritin transferrin-bound and unbound iron and other measures indicators of iron status. A study of the effects of blood donation on cognitive function would entail having students perform a series of tests before and after blood donation over the course of a school year with concurrent assessment of iron status. These studies would require collaboration with neuropsychologists and with school districts. Parental consent and assent would be needed. There was an interest in the workshop regarding iron balance among high

school blood donors and in a study to examine the effects of blood donation–induced iron deficiency on cognition and/or athletic performance of high school students.

What are the long-term effects of blood donation–induced iron deficiency in teenagers?

Teenagers are still developing physically through adolescence and into early adulthood. Importantly, the brain is still actively forming and is vulnerable to insults during this time. Myelin production in the brain requires iron. Teenagers who donate blood have large amounts of iron removed from their bodies. Recovery of iron stores after whole blood donation takes 6 months or longer in adults, suggesting that a prolonged period of iron deficiency occurs in teenagers who donate blood. MRI “diffusion tensor images” map myelin connection strength and integrity in the brain. Otherwise, healthy young adults without current iron deficiency, but with iron deficiency as teenagers, have poorer fiber integrity in white matter than controls.^{82,83} Thus, the development of healthy adult brains depends on having adequate iron available for neurologic development during the adolescence. Young adults who were active blood donors in high school are a unique population for further study of the effects of iron deficiency on brain development. These studies could be performed in several different ways, one of which would be to examine young adult blood donors (23–25 years old) for myelin integrity using diffusion tensor MRI imaging compared to nondonors.

Can blood centers reduce the risk of syncope and injuries after blood donation on high school blood drives?

Encouraging teenage (16–18 years old) donation has been a focus for the past 10 years and now accounts for a significant proportion of the US blood supply, with approximately 14% of whole blood collections from teenagers. Although most adverse reactions after blood donation are mild, teenagers are more likely than older donors to experience syncope and related injury. There have been some controlled studies of interventions to decrease the rate of symptomatic reactions after blood donation, but none have effectively decreased syncope-related injuries. As blood donor centers increasingly recruit teenage donors, a more concerted effort to prevent reactions and injuries is warranted. To reduce such injuries, we must identify which individuals are most susceptible and then improve their ability to respond to the orthostatic changes that accompany donation.⁸⁴ Physiologists have successfully treated syncope in patients with dysautonomia using various physical maneuvers such as muscle tensing and water intake.⁸⁵ Fear of having blood drawn and orthostatic changes in blood pressure before blood donation have been shown to predict vasovagal reactions; whether these factors will translate into effective preventive strategies is unclear.^{86,87} Moreover, recent attempts to demonstrate the effectiveness of physical maneuvers or water intake after blood donation have not yielded definitive results in large operational studies or randomized trials.^{85–88} The group extensively debated whether there were research opportunities to further knowledge or whether this was a public health issue. Preventive measures typically have a relatively small effect (i.e., a 20% reduction) making a randomized intervention difficult. Another issue is that most injuries are idiosyncratic and may not be preventable.

Does the age at first blood donation correlate with the likelihood of future donation or long-term donation behavior into adulthood?

Blood centers depend on repeat blood donation and often encourage teenagers to become blood donors with a lifelong commitment to blood donation. Teenage donors are likely to return to donate while still in high school, which might simply reflect the convenience and frequency of high school drives.⁸⁹ However, there are no longitudinal studies evaluating the relationship between age at first donation and long-term commitment to blood donation, and this relationship remains undefined. Teenage donors are at greater risk for syncope and other reactions after donation than older donors. Reactions and other adverse experiences decrease the likelihood of return donation.^{90,91} Blood centers collect and manage large amounts of information on blood donors and their donation history. Moreover, large blood centers now have computer systems capable of tracking donors within their systems over long periods of time, even as they move between different states. A prospective study correlating donor retention with age at first donation, whether in high school, college, or in the community, is feasible within a blood center. Collaboration across blood systems will increase the capture of teenagers as they move through college and beyond, improving the generalizability of the results and conclusions.

Consensus and recommendations: overarching areas of need in pediatric transfusion medicine research

Gaps in knowledge were identified by each of the groups with common themes. These included the following.

Research Priority 1: establish a national data ecosystem to allow for the conduct of epidemiologic research and inform future clinical trials⁹²—All participants stressed the lack of accessible databases as a critical need. One recommendation was to establish a multisite vein-to-vein database similar to that developed through the NHLBI REDS-III program but which would provide access to not only data from large volumes of adult patients admitted to services where transfusion is common but also access to large numbers of pediatric patients (Fig. 2). In addition, the group agreed that, when possible, existing NICHD networks (CPCCRN, MFMU, PHN, NRN) as well as disease and disorders registries (Congenital Heart Surgery Database) and the expertise from clinician collaboratives such as the Pediatric Acute Lung Injury and Sepsis Investigators should be leveraged. In addition, participants agreed that existing subspecialty societies and organizations including the Children's Oncology Group and like organizations might yield a focused way to access data quickly by augmenting their hospital database with transfusion data and outcome variables.

Each of the groups stressed that data must be sharable and could provide valuable information to aid in successfully planning, implementing, and completing clinical studies in pediatric transfusion medicine. All participants agreed that this was a major area of need required to move the field forward and to ensure that future studies be tailored to the pediatric populations with attention to age and to disease state.

Research Priority 2: develop new in vivo tests and assays and validated in vitro systems and technologies to inform precise study of hemostasis and oxygen delivery in humans as well as in animal- and cellbased models—There is an absence of accurate age-specific assays and biomarkers of both hemostasis and oxygen delivery. Such assays are critical to the understanding of the effectiveness of transfusion therapy, including in situations of emergency, and to the delineation of key outcome variables. Ideally, such tests and assays would be designed as point-of-care and point-of-delivery systems requiring microscopic sample volumes with computerized download functions.

There is similarly a lack of in vitro hemostatic, immunologic, microfluidic, oxygen delivery and consumption, and rheologic models and devices to assist in understanding transfusion effectiveness and adverse consequences. Existing animal models including transgenic and knockout mice provide opportunity for mechanistic studies but are often not relevant to neonatal or pediatric populations. Involving systems biology and tissue engineering and regenerative medicine expertise will be required.

Research Priority 3: establish a clinical trials network—Well-designed, randomized controlled trials are needed to improve transfusion safety and efficacy and to develop evidence-based guidelines. A few diseases and disorders were identified where clinical trials could be done in a relatively short period of time; however, most would require baseline epidemiologic data, additional translational research, and in-depth evaluation of statistical power before a clinical trial could be successfully implemented. All participants agreed that every clinical trial should include mechanistic questions and translational science components when possible to maximize the efficacy and impact of the trial. All participants stressed that the dosing, half-life, survival, and adverse reaction profile of blood products are different from adults and vary with age among infants and children; these factors must be considered in the development of any trial or intervention with special attention to long-term adverse effects.

ACKNOWLEDGMENTS

We express our gratitude to the following preworkshop and workshop participants and NHLBI staff members for their contributions: Homa Ahmadzia, MD, MPH, Jennifer Andrews, MD, MSc, James Berger, MS, SBB, Scot Bateman, MD, Evan M. Bloch, MD, MS, Edward F. Bell, MD, Jeffrey Carson, MD, Robert Christensen, MD, Jill Cholette, MD, Della E. Claiborne, Naomi Clarke, Pamela Clark, MD, Angelo D'Alessandro, PhD, Meghan Delaney, DO, MPH, Nancy DiFronzo, Donna Di Michele, MD, Richard Francis, MD, PhD, Gary H. Gibbons, MD, Walter (Sunny) Dzik, MD, Richard Henry, ML, MPH, Rosemary D. Higgins, MD, Eldad Hod, MD, Shannon Kelly, MD, W. Keith Hoots, MD, Haresh Kirpalani, BM, MSc, Nobuyuki Ishibashi, MD, Harvey Klein, MD, Jacques Lacroix, MD, Bertram Lubin, MD, FAAP, Laura Loftis, MD, Catherine Manno, MD, Miriam Markowitz, John Luckey, MD, PhD, An Massaro, MD, Jennifer A. Muszynski, MD, Mohandas Narla, DSc, Chris Miller, Menachem Miodovnik, MD, Richard Phipps, PhD, Heike Rabe, MD, Beth Shaz, MD, John Roback, MD, PhD, Sujit Sheth, MD, Nareg Roubinian, MD, Steve Spitalnik, MD, Robert Tamburro, MD, MSc, Marisa Tucci, MD, Darrell Triulzi, MD, Lynne Uhl, MD, Sean Stowell, MD, PhD, Stacey Valentine, MD, MPH, Jack Widness, MD, Stephen Wagner, PhD, Alan Williams, PhD, and Connie Westhoff, SBB, PhD.

The meeting at the NIH/NHLBI was sponsored by NHLBI, the Food and Drug Administration, and the Department of Health and Human Services/Office of the Assistant Secretary of Health.

ABBREVIATIONS:

ECMO	extracorporeal membrane oxygenation
HSCT	hematopoietic stem cell transplant
ICU	intensive care unit
MRI	magnetic resonance imaging
NHLBI	National Heart, Lung, and Blood Institute
NICHD	National Institute of Child Health and Human Development
NISHOT	noninfectious serious hazards of transfusion
PICU	pediatric intensive care unit
PRT	pathogen reduction technology
REDS	Recipient Epidemiology and Donor Evaluation Study
SCD	sickle cell disease
VAD	ventricular assist device

REFERENCES

1. Brinc D, Denomme GA, Lazarus AH. Mechanisms of anti-D action in the prevention of hemolytic disease of the fetus and newborn: what can we learn from rodent models? *Curr Opin Hematol* 2009;16:488–96. [PubMed: 19730101]
2. Kapur R, Della Valle L, Verhagen OJ, et al. Prophylactic anti-D preparations display variable decreases in Fc-fucosylation of anti-D. *Transfusion* 2015;55:553–62. [PubMed: 25234110]
3. Bowman J Thirty-five years of Rh prophylaxis. *Transfusion* 2003;43:1661–6. [PubMed: 14641860]
4. Kumpel BM. Lessons learnt from many years of experience using anti-D in humans for prevention of RhD immunization and haemolytic disease of the fetus and newborn. *Clin Exp Immunol* 2008;154:1–5.
5. Li C, Piran S, Chen P, et al. The maternal immune response to fetal platelet GPIb causes frequent miscarriage in mice that can be prevented by intravenous IgG and anti-FcRn therapies. *J Clin Invest* 2011;121:4537–47. [PubMed: 22019589]
6. Stowell SR, Arthur CM, Girard-Pierce KR, et al. Anti-KEL sera prevents alloimmunization to transfused KEL RBCs in a murine model. *Haematologica* 2015;100:e394–7. [PubMed: 26185172]
7. Bakchoul T, Boylan B, Sachs UJ, et al. Blockade of maternal anti-HPA-1a-mediated platelet clearance by an HPA-1a epitope-specific F(ab')₂ in an in vivo mouse model of alloimmune thrombocytopenia. *Transfusion* 2009;49:265–70. [PubMed: 19000229]
8. Bakchoul T, Greinacher A, Sachs UJ, et al. Inhibition of HPA-1a alloantibody-mediated platelet destruction by a deglycosylated anti-HPA-1a monoclonal antibody in mice: toward targeted treatment of fetal-alloimmune thrombocytopenia. *Blood* 2013;122:321–7. [PubMed: 23645838]
9. Kapur R, Kustiawan I, Vestrheim A, et al. A prominent lack of IgG1-Fc fucosylation of platelet alloantibodies in pregnancy. *Blood* 2014;123:471–80. [PubMed: 24243971]
10. Moise KJ Jr, Argoti PS. Management and prevention of red cell alloimmunization in pregnancy: a systematic review. *Obstet Gynecol* 2012;120:1132–9. [PubMed: 23090532]
11. Zdravic D, Youghare I, Vadasz B, et al. Fetal and neonatal alloimmune thrombocytopenia. *Semin Fetal Neonatal Med* 2016;21:19–27. [PubMed: 26810319]

12. Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. *Cochrane Database Syst Rev* 2011;(11):CD000512. [PubMed: 22071798]
13. Mintzer JP, Parvez B, Chelala M, et al. Monitoring regional tissue oxygen extraction in neonates < 1250 g helps identify transfusion thresholds independent of hematocrit. *J Neonatal Perinatal Med* 2014;7:89–100. [PubMed: 25104129]
14. Muthukumar P, Venkatesh V, Curley A, et al. Severe thrombocytopenia and patterns of bleeding in neonates: results from a prospective observational study and implications for use of platelet transfusions. *Transfus Med* 2012;22:338–43. [PubMed: 22738179]
15. Ferrer-Marin F, Stanworth S, Josephson C, et al. Distinct differences in platelet production and function between neonates and adults: implications for platelet transfusion practice. *Transfusion* 2013;53:2814–21. [PubMed: 23889476]
16. Deschmann E, Sola-Visner M, Saxonhouse MA. Primary hemostasis in neonates with thrombocytopenia. *J Pediatr* 2014;164:167–72. [PubMed: 24094764]
17. Guillén U, Cummings JJ, Bell EF, et al. International survey of transfusion practices for extremely premature infants. *Semin Perinatol* 2012;36:244–7. [PubMed: 22818544]
18. Josephson CD, Su LL, Christensen RD, et al. Platelet transfusion practices among neonatologists in the United States and Canada: results of a survey. *Pediatrics* 2009;123: 278–85. [PubMed: 19117893]
19. Cremer M, Sola-Visner M, Roll S, et al. Platelet transfusions in neonates: practices in the United States vary significantly from those in Austria, Germany, and Switzerland. *Transfusion* 2011;51:2634–41. [PubMed: 21658049]
20. Kleinman S, Busch MP, Murphy EL, et al. The National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study (REDS-III): a research program striving to improve blood donor and transfusion recipient outcomes. *Transfusion* 2014;54:942–55. [PubMed: 24188564]
21. Knutson F A prospective, active haemovigilance study with combined cohort analysis of 19,175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. *Vox Sang* 2015;109:343–52. [PubMed: 25981525]
22. Josephson CD, Caliendo AM, Easley KA, et al. Blood transfusion and breast milk transmission of cytomegalovirus in very low-birth-weight infants: a prospective cohort study. *JAMA Pediatr* 2014;168:1054–62. [PubMed: 25243446]
23. Zubairi H, Visintainer P, Fleming J, et al. Lead exposure in preterm infants receiving red blood cell transfusions. *Pediatr Res* 2015;77:814–8. [PubMed: 25760547]
24. Blajchman MA, Carson JL, Eikelboom JW, et al. The role of comparative effectiveness research in transfusion medicine clinical trials: proceedings of a National Heart, Lung, and Blood Institute workshop. *Transfusion* 2012;52:1363–78. [PubMed: 22486525]
25. Josephson CD, Granger S, Assmann SF, et al. Bleeding risks are higher in children versus adults given prophylactic platelet transfusions for treatment-induced hypoproliferative thrombocytopenia. *Blood* 2012;120:748–60. [PubMed: 22538854]
26. Goerge T, Ho-Tin-Noe B, Carbo C, et al. Inflammation induces hemorrhage in thrombocytopenia. *Blood* 2008;111:4958–64. [PubMed: 18256319]
27. Waterman HR, Kapp LM, Munday A, et al. Transfusion-induced alloimmunization and platelet refractoriness in a mouse model: mechanisms and interventions. *Transfusion* 2016;56:91–100. [PubMed: 26400622]
28. Desmarests M, Cadwell CM, Peterson KR, et al. Minor histocompatibility antigens on transfused leukoreduced units of red blood cells induce bone marrow transplant rejection in a mouse model. *Blood* 2009;114:2315–22. [PubMed: 19525479]
29. Aslam R, Speck ER, Kim M, et al. Transfusion-related immunomodulation by platelets is dependent on their expression of MHC Class I molecules and is independent of white cells. *Transfusion* 2008;48:1778–86. [PubMed: 18522705]
30. Prescott LS, Taylor JS, Lopez-Olivo MA, et al. How low should we go: a systematic review and meta-analysis of the impact of restrictive red blood cell transfusion strategies in oncology. *Cancer Treat Rev* 2016;46:1–8. [PubMed: 27046422]

31. Osman A, Hitzler WE, Meyer CU, et al. Effects of pathogen reduction systems on platelet microRNAs, mRNAs, activation, and function. *Platelets* 2015;26:154–63. [PubMed: 24749844]
32. Marrocco C, D'Alessandro A, Girelli G, et al. Proteomic analysis of platelets treated with gamma irradiation versus a commercial photochemical pathogen reduction technology. *Transfusion* 2013;53:1808–20. [PubMed: 23305084]
33. Yazdanbakhsh K, Ware RE, Noizat-Pirenne F. Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. *Blood* 2012;120:528–37. [PubMed: 22563085]
34. Chou ST, Liem RI, Thompson AA. Challenges of alloimmunization in patients with haemoglobinopathies. *Br J Haematol* 2012;159:394–404. [PubMed: 23034087]
35. Svensson AM, Delaney M. Considerations of red blood cell molecular testing in transfusion medicine. *Expert Rev Mol Diagn* 2015;15:1455–64. [PubMed: 26367503]
36. Casas J, Friedman DF, Jackson T, et al. Changing practice: red blood cell typing by molecular methods for patients with sickle cell disease. *Transfusion* 2015;55(6Pt2):1388–93. [PubMed: 25573464]
37. Fasano RM, Booth GS, Miles M, et al. Red blood cell alloimmunization is influenced by recipient inflammatory state at time of transfusion in patients with sickle cell disease. *Br J Haematol* 2015;168:291–300. [PubMed: 25256676]
38. Adams RJ, McKie VC, Hsu L. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5–11. [PubMed: 9647873]
39. Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med* 2005;353:2769–78. [PubMed: 16382063]
40. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med* 2014;371:699–710. [PubMed: 25140956]
41. Singer ST, Quirolo K, Nishi K, et al. Erythrocytapheresis for chronically transfused children with sickle cell disease: an effective method for maintaining a low hemoglobin S level and reducing iron overload. *J Clin Apher* 1999;14:122–5. [PubMed: 10540366]
42. Porter J, Garbowski M. Consequences and management of iron overload in sickle cell disease. *Hematology Am Soc Hematol Educ Program* 2013;2013:447–56. [PubMed: 24319218]
43. Alexander PE, Barty R, Fei Y, et al. Transfusion of fresher vs older red blood cells in hospitalized patients: a systematic review and meta-analysis. *Blood* 2016;127:400–10. [PubMed: 26626995]
44. Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med* 2015;372:1419–29. [PubMed: 25853746]
45. Lacroix J, Hébert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. *N Engl J Med* 2015;372:1410–8. [PubMed: 25853745]
46. Dalton HJ, Garcia-Filion P, Holubkov R, et al. Association of bleeding and thrombosis with outcome in extracorporeal life support. *Pediatr Crit Care Med* 2015;16:167–74. [PubMed: 25647124]
47. Extracorporeal Life Support Organization. ECLS Registry Report, International Summary. Ann Arbor (MI): ELSO Office; 2016.
48. Bembea MM, Annich G, Rycus P, et al. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation. *Pediatr Critical Care Med* 2013;14:e77–84. [PubMed: 23287906]
49. Figaji AA, Zwane E, Kogels M. The effect of blood transfusion on oxygenation in children with severe traumatic brain injury. *Pediatr Crit Care Med* 2010;11:325–31. [PubMed: 19794323]
50. Wilkinson KL, Brunskill SJ, Doree C, et al. Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease. *Cochrane Database Syst Rev* 2014; (2):CD009752. [PubMed: 24510598]
51. Huang CJ, Cheng KW, Chen CL, et al. Predictive factors for pediatric patients requiring massive blood transfusion during living donor liver transplant. *Ann Transplant* 2013;18: 443–7. [PubMed: 23999839]

52. Henríquez-Henríquez M, Kattan J, Chang M, et al. Blood component usage during extracorporeal membrane oxygenation: experience in 98 patients at a Latin-American tertiary hospital. *Int J Artif Organs* 2014;37:233–40. [PubMed: 24744168]
53. Smith A, Hardison D, Bridges B, et al. Red blood cell transfusion volume and mortality among patients receiving extracorporeal membrane oxygenation. *Perfusion* 2013;28: 54–60. [PubMed: 22892295]
54. Faraoni D, Nasr VG, DiNardo JA, et al. Hospital costs for neonates and children supported with extracorporeal membrane oxygenation. *J Pediatr* 2016;169:69–75.e1. [PubMed: 26547402]
55. Razzaghi H, Oster M, Reefhuis J. Long-term outcomes in children with congenital heart disease: National Health Interview Survey. *J Pediatr* 2015;166:119–24. [PubMed: 25304924]
56. Saini A, Spinella PC. Management of anticoagulation and hemostasis for pediatric extracorporeal membrane oxygenation. *Clin Lab Med* 2014;34:655–73. [PubMed: 25168949]
57. Monagle P, Newall F, Campbell J. Anticoagulation in neonates and children: pitfalls and dilemmas. *Blood Rev* 2010; 24:151–62. [PubMed: 20663595]
58. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368:11–21. [PubMed: 23281973]
59. Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma* 2009;67:221–7. [PubMed: 19667872]
60. Karam O, Lacroix J, Robitaille N, et al. Association between plasma transfusions and clinical outcome in critically ill children: a prospective observational study. *Vox Sang* 2013; 104:342–9. [PubMed: 23294337]
61. Kwon A Pooled preventable death rates in trauma patients. *Eur J Trauma Emerg Surg* 2014;40:279–85. [PubMed: 26816061]
62. Spinella PC. Presentation, Pediatric Acute Lung Injury and Sepsis Investigators, San Diego, CA, 3, 2016
63. Eastridge B Death on the battlefield (2001–2011). *J Trauma Acute Care Surg* 2012;73:S431–7. [PubMed: 23192066]
64. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med* 2007;356:1609–19. [PubMed: 17442904]
65. Holst LB, Petersen MW, Haase N, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *BMJ* 2015;350:h1354. [PubMed: 25805204]
66. Sisak K, Manolis M, Hardy BM, et al. Acute transfusion practice during trauma resuscitation: who, when, where and why? *Injury* 2013;44:581–6. [PubMed: 22939180]
67. Lacroix J, Demaret P, Tucci M. Red blood cell transfusion: decision making in pediatric intensive care units. *Semin Perinatol* 2012;36:225–31. [PubMed: 22818542]
68. Hébert PC, Tinmouth A. Clinical consequences of anemia and red cell transfusion in the critically ill. *Crit Care Clin* 2004;20:225–35. [PubMed: 15135462]
69. Vincent JL. Indications for blood transfusions: too complex to base on a single number? *Ann Intern Med* 2012;157:71–2. [PubMed: 22751765]
70. Vallet B, Adamczyk S, Barreau O, et al. Physiologic transfusion triggers. *Best Pract Res Clin Anaesthesiol* 2007;21: 173–81. [PubMed: 17650770]
71. Marshall JC. Transfusion trigger: when to transfuse? *Crit Care* 2004;8:S31–3. [PubMed: 15196320]
72. Bolton-Maggs PH. Transfusion and hemovigilance in pediatrics. *Pediatr Clin North Am* 2013;60:1527–40. [PubMed: 24237986]
73. Mulder HD, Augustijn QJ, van Woensel JB, et al. Incidence, risk factors, and outcome of transfusion-related acute lung injury in critically ill children: a retrospective study. *J Crit Care* 2015;30:55–9. [PubMed: 25457117]
74. Hall MW, Geyer SM, Guo CY, et al. Innate immune function and mortality in critically ill children with influenza: a multicenter study. *Crit Care Med* 2013;41:224–36. [PubMed: 23222256]

75. Muszynski JA, Frazier E, Nofziger R, et al. Red blood cell transfusion and immune function in critically ill children: a prospective observational study. *Transfusion* 2015;55: 766–74. [PubMed: 25355535]
76. Bateman ST, Lacroix J, Boven K, et al. Anemia, blood loss, and blood transfusions in North American children in the intensive care unit. *Am J Respir Crit Care Med* 2008;178:26–33. [PubMed: 18420962]
77. Carroll PD, Widness JA. Nonpharmacological, blood conservation techniques for preventing neonatal anemia—effective and promising strategies for reducing transfusion. *Semin Perinatol* 2012;36:232–43. [PubMed: 22818543]
78. Valentine SL, Bateman ST. Identifying factors to minimize phlebotomy-induced blood loss in the pediatric intensive care unit. *Pediatr Crit Care Med* 2012;13:22–7. [PubMed: 21499175]
79. Demaret P, Tucci M, Ducruet T, et al. Red blood cell transfusion in critically-ill children (CME). *Transfusion* 2014;54: 365–75. [PubMed: 24517132]
80. Bruner AB, Joffe A, Duggan AK, et al. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet* 1996;348:992–6. [PubMed: 8855856]
81. Halterman JS, Kaczorowski JM, Aligne A, et al. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. *Pediatrics* 2001;107: 1381. [PubMed: 11389261]
82. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 2004;101:8174–9. [PubMed: 15148381]
83. Jahanshad N, Kohannim O, Hibar DP, et al. Brain structure in health adults is related to serum transferrin and the H63D polymorphism in the HFE gene. *Proc Natl Acad Sci U S A* 2012;109:E851–9. [PubMed: 22232660]
84. Eder AF, Hillyer CD, Dy BA, et al. Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. *JAMA* 2008;299:2279–86. [PubMed: 18492969]
85. Eder AF. Current efforts to reduce the risk of syncope among young blood donors. *Curr Opin Hematol* 2012;19:480–4. [PubMed: 22954724]
86. Wieling W, France C, Van Dijk N, et al. Physiologic strategies to prevent fainting responses during or after whole blood donation. *Transfusion* 2011;51:2727–38. [PubMed: 21645008]
87. Ando S, Kawamura N, Matsumoto M, et al. Simple standing test predicts and water ingestion prevents vasovagal reaction in the high-risk blood donors. *Transfusion* 2009;49:1630–6. [PubMed: 19413739]
88. France CR, France JL, Carlson BW, et al. Fear of blood draws, vasovagal reactions, and retention among high school donors. *Transfusion* 2014;54:918–24. [PubMed: 23915025]
89. Van den Berg K, Lam J, Bruhn R, et al. Water administration and the risk of syncope and presyncope during blood donation: a randomized clinical trial. *Transfusion* 2012;52: 2577–84. [PubMed: 22486209]
90. Notari EP, Zou S, Fang CT, et al. Age-related donor return patterns among first-time blood donors in the United States. *Transfusion* 2009;49:229–36.
91. Custer B, Rios JA, Schlumpf K, et al. Adverse reactions and other factors that impact subsequent donation visits. *Transfusion* 2011;52:118–26. [PubMed: 21682732]
92. Kleinman S, Glynn SA. Database research in transfusion medicine: the power of large numbers. *Transfusion* 2015;55: 1591–5. [PubMed: 26172144]
93. Zangrillo A, Landoni G, Biondi-Zoccai G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Crit Care Resusc* 2013;15:172–8. [PubMed: 23944202]
94. Wong HR, Cvijanovich N, Wheeler DS, et al. Interleukin-8 as a stratification tool for interventional trials involving pediatric septic shock. *Am J Respir Crit Care Med* 2008;178:276–82. [PubMed: 18511707]
95. Rader AW, France CR, Carlson B. Donor retention as a function of donor reactions to whole blood and automated double red cell collections. *Transfusion* 2007;47:995–1001. [PubMed: 17524088]

Fig. 1.

Six clinical focus areas in pediatric transfusion medicine were identified by the workshop participants. Five of the areas (dark circles) focused on the transfusion recipients and one (light circle) focused on the donors.

Fig. 2.

Developing a vein-to-vein database in transfusion medicine is an area of need in pediatric transfusion medicine from fetal and neonatal stages to adolescence and transition to adulthood.