Commentary

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The role of policy in red blood cell storage and transfusion in children

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Red blood cell transfusion represents a critical therapy to reducing morbidity and mortality among vulnerable populations of children. Specific pediatric subgroups benefitting from red blood cell (RBC) transfusion include premature infants, children with sickle cell disease, the critically ill, and those with chronic transfusion need (1). Blood storage serves a vital role in ensuring safe and adequate blood supply in order to meet routine and emergent demands for children as well as adults (2). The Food and Drug Administration (FDA) mandates that RBCs be stored for a maximum of 42 days. The mean age of RBC units at the time of transfusion has been reported to be 21 days (3). Refrigerated storage of RBCs leads to a well-documented cascade of biochemical changes that may adversely alter the function of RBCs over time (4). Consequently, the storage age of transfused RBCs has been at the center of an evolving debate in transfusion medicine as to whether the differences between fresh blood and old blood matter clinically (1,5–8). In this issue, Kalhan *et al.* (9) report on whether the storage duration affects markers of hemolysis in transfused very-low birth weight (VLBW) infants. In this single center, prospective, observational study, the authors found that the storage age of transfused RBCs positively correlated with increases of non-transferrin-bound iron (NTBI) following transfusion ($P<0.001$, $R^2=0.44$). This finding is notable, as NTBI may cause oxidative damage and increase the risk of infection. More broadly, the findings from this study highlight some of the central controversies in the debate on RBC storage age at the time of transfusion and subsequent clinical outcomes. In this commentary, we summarize the basic science and clinical research of RBC storage and the role of existing transfusion policies on receipt of RBC units in children.

Much of the debate regarding RBC storage has been propelled by a disconnect between findings in basic science and clinical research. During storage, the RBCs undergo a distinct series of biological changes collectively referred to as "storage lesions" (4). These changes impact RBC survival, function, and deformability. Adverse biological changes exacerbated by longer storage times include decrease in key mediators of RBC function, release of harmful by-products of lysed RBCs, increase in vascular tone, induction of cytokine release, advanced glycation end products, and increase in ferrophilic bacteria. Although basic science research of RBC storage has demonstrated numerous harmful effects of longer storage on RBC function, clinical research has shown mixed findings as to whether these biological changes have clinical consequences (e.g., mortality, organ dysfunction, and infection) (5,10–13). Although some retrospective studies have reported that transfusion with older RBC units results in significantly worse clinical outcomes compared with transfusion of fresher RBCs, other studies have indicated no difference between fresh and old blood. Individual retrospective studies have been so variable in their approach and limited by confounders that formal meta-analysis may not be feasible (14).

Randomized controlled trials (RCTs) offer a more scientifically rigorous approach to assess the impact of RBC storage on clinical outcomes. The Age of Red Blood Cells in Premature Infants (ARIPI) trial showed no difference in morbidity between groups receiving "fresh" and "standard" RBCs (15). The conclusion was that a fresh RBC transfusion policy did not improve outcomes in premature, VLBW infants. However, the mean ages of RBCs in the "fresh" and "standard" groups were 5.1 and 14.6 days, respectively. Therefore, it is unclear whether ARIPI had a group with old enough RBCs to test its hypothesis. Recent adult-focused RCTs of transfusion among critically ill and those undergoing cardiac surgery have shown no difference in multiple organ dysfunction or mortality according to the duration of RBC storage (11,12). Despite the equivocal findings from RCTs, concerns remain that recent results may not apply to all patient cohorts, given confounders such as heterogeneity of recipient pathology and donor-to-donor variation in how well RBCs store (5).

With an evolving research base and questions of applicability of findings regarding RBC storage, transfusion policies at numerous levels affect the storage age of RBCs received by children. The FDA sets the policy on RBC storage enacted by a network of community-based blood collection centers, hospital-based collection centers, and transfusing facilities. The FDA criteria by which storage solutions are approved include the following: hemolysis of $<1\%$ and average 24 h post-transfusion recoveries of 75% or greater (16). These current metrics by which we assess RBC storage quality focus

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on circulation as a proxy for function rather than the actual function (e.g., ability to deliver oxygen or regulate vascular tone). Current metrics have value as RBCs that do not survive storage or cannot circulate after transfusion will not practically be able to deliver oxygen, collect carbon dioxide, or carry out other RBC functions (5). However, the FDA approval criteria create a disconnect between what is evaluated as metrics of RBC quality and the *in vivo* function intended with transfusion.

In addition to the FDA, transfusion facilities and blood collection centers generate and maintain policies that also impact the age of RBCs received by children. The standard of care transfusion policy in many hospitals is "first in, first out" where the oldest available ABO identical RBC unit is transfused first (1). The rationale behind this policy is to minimize the number of outdated RBC units. The transfusion volume is high enough in academic hospitals to ensure that the outdates will be minimized (10). The median storage age of RBCs is 22–27 days at academic centers (11). Although the "first in, first out" policy may define how hospitals provide transfusions in general, different policies may exist based on specific pediatric subgroups. For infants, many hospitals have a policy of using dedicated blood donors to reduce exposure to multiple donors and decrease transmission of viral pathogens. This policy leads to infants receiving older RBCs with each subsequent transfusion. In some hospitals, children with sickle cell disease may receive transfusion with fresher RBC units under the premise that the physiology promoted by RBC storage lesion shares features with sickle cell disease and, therefore, fresher RBCs will mitigate these effects (10). The National Heart, Lung, and Blood Institute's guidelines for sickle cell disease management do not currently address the age of blood for transfusion (17).

With the goal of maintaining a safe, effective, and sufficient reserve of RBCs for children, researchers, clinicians, and policy makers must outline an agenda that considers the research findings to date on RBC storage and transfusion, their limitations, and variable institutional policies that define the age of RBCs children receive in transfusion. Some might advocate implementing a transfusion policy with fresher RBCs for all patients with the rationale that it could only be of benefit. However, a study using a simulation approach demonstrated that a more restrictive maximum shelf life policy would result in an increase in RBC outdate rate with a shortfall in RBC availability for transfusion (2). Compounding these issues, blood collection centers would experience significant financial losses with a higher RBC outdate rate. As the adverse public health and financial consequences of a more restrictive maximum shelf life policy would be too great, other policy strategies must be developed in order to advance knowledge on the use of fresher RBC units in children. A core component of any strategy should include targeted investment in RCTs focused on well-defined, particularly vulnerable pediatric subgroups (e.g., premature infants, newborns, children with sickle cell disease, and transfusion-dependent children). These trials must be designed with large enough cohorts and sufficient distinction between study arms to discriminate what may constitute clinically relevant and important differences in outcome (1,5). In addition to more research, more systematic monitoring should be recommended for hospitals that maintain different policies for various subgroups of children. Such monitoring should focus on outdate rates and clinical outcomes. Lastly, more guidance is needed from federal agencies so that hospital policies are informed by more than the local expert opinion.

The question of whether transfusion with fresher RBCs confers clinical benefit is often grossly oversimplified as the answer depends on a complex array of factors and considerations including recipient pathophysiology, donor-to-donor variation in how well RBCs store, availability of cost-effective assays to measure the RBC function prior to transfusion, maintenance of an adequate blood supply, and minimization of outdate rates. Even with well-designed retrospective studies and RCTs, some confounders are still unavoidable such that the negative findings have not ended the ongoing debate. Public policy can guide future efforts by emphasizing the need for focus on targeted subgroups of children and standardization in hospital policies. Such efforts will ensure that forthcoming research, medical practice, and storage technology improve the outcomes for children requiring transfusion.

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