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Red Blood Cell Alloimmunization Mitigation Strategies

Jeanne E. Hendrickson [a], Christopher A. Tormey [a,b], Beth H. Shaz [c,d,*]

[a] Yale University School of Medicine, New Haven, CT
[b] VA Connecticut Healthcare System, West Haven, CT
[c] New York Blood Center, New York, NY
[d] Emory University School of Medicine, Atlanta, GA

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ABSTRACT

Hemolytic transfusion reactions due to red blood cell (RBC) alloantibodies are a leading cause of transfusion-associated death. In addition to reported deaths, RBC alloantibodies also cause significant morbidity in the form of delayed hemolytic transfusion reactions. These alloantibodies may also cause morbidity in the form of anemia, with compatible RBC units at times being unable to be located for highly alloimmunized patients, or in the form of hemolytic disease of the newborn. Thus, preventing RBC alloantibodies from developing in the first place, or mitigating the dangers of existing RBC alloantibodies, would decrease transfusion-associated morbidity and mortality. A number of human studies have evaluated the impact on RBC alloimmunization rates of providing partially phenotypically or genotypically matched RBCs for transfusion, and a number of animal studies have evaluated the impact of single variables on RBC alloimmunization. The goal of this review is to take a comprehensive look at existing human and animal data on RBC alloimmunization, focusing on strategies that may mitigate this serious hazard of transfusion. Potential factors that impact initial RBC alloimmunization, on both the donor and recipient sides, will be discussed. These factors include, but are not limited to, exposure to the antigen and an ability of the recipient's immune system to present that antigen. Beyond these basic factors, coexisting "danger signals," which may come from the donor unit itself or which may be present in the recipient, also likely play a role in determining which transfusion recipients may become alloimmunized after RBC antigen exposure. In addition, to better understanding factors that influence the development of RBC alloantibodies, this review will also briefly discuss strategies to decrease the dangers of existing RBC alloantibodies.

Contents

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* Corresponding author. Beth Shaz, MD, Chief Medical Officer, New York Blood Center, 310 E 67th St, New York, NY 10065.
E-mail address: bshaz@nybloodcenter.org (B.H. Shaz).

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Red blood cell (RBC) alloimmunization can result in delayed or acute hemolytic transfusion reactions (HTRs), resulting in significant morbidity and mortality. Fifteen percent of transfusion-related fatalities in the United States are due to non–ABO-related HTRs, and the risk of delayed HTRs (DHTRs) being 1:20 569 and the risk of non-ABO acute HTRs being 1:124 525 components transfused [1,2]. In addition to being detrimental in transfusion settings, transfusion-acquired RBC alloantibodies may also be detrimental in pregnancy settings, potentially putting a developing fetus at risk for hemolytic disease of the fetus and newborn.

Recipients with multiple alloantibodies impair the ability of blood banks to provide antigen-negative, compatible RBCs for transfusion because of the need to phenotype many times the number of units necessary to find an appropriate product [3]. The numbers of products screened multiplies depending on the RBC antigen prevalence and the number of negative antigens necessary, placing a burden on the hospitals and donor centers needing to identify such products. Donor centers currently screen and stock RBC products to keep a pool of frequently needed antigen-negative products. However, batch serologic screening is time intensive, typing reagents are expensive, and appropriate controls are required. As a result, donor centers may perform automated high-throughput serologic screening using Food and Drug Administration–approved reagents to type for E, e, C, c, and K as well as ABO and D. Many blood centers are now also performing mass-scale genotyping, which enables the expansion of phenotyped/genotyped products [4].

Regardless of the work involved, it cannot be disputed that preventing primary alloimmunization is instrumental in reducing the risk of HTRs and improving transfusion safety. Furthermore, regardless of the logistics involved in identifying or recording antibodies, it cannot be disputed that avoiding repeat exposures to the cognate antigen against which a patient is alloimmunized is critical in preventing acute and DHTRs. However, optimal strategies to (1) decrease primary RBC alloimmunization and to (2) mitigate the dangers of existing RBC alloantibodies are not clearly defined. The goal of this review is to take a comprehensive look at existing human and animal data on RBC alloimmunization, exploring factors that contribute to this serious hazard of transfusion and discussing potential mitigation strategies.

Mechanisms of Alloimmunization

In order to develop strategies to mitigate RBC alloimmunization, factors influencing the development of RBC alloantibodies must be considered. Some potential factors to consider include the differences between donor and recipient RBC antigens, recipient genetic factors, and recipient inflammatory state at the time of initial antigen exposure. Table 1 lists potential factors influencing RBC alloimmunization, separated by donor and recipient.

The best-described factor associated with alloimmunization risk is donor and recipient RBC antigen disparity. If a transfusion recipient is never exposed to a particular foreign RBC antigen, then they are not at risk for making an alloantibody. Studies have reported alloimmunization rates of patients with sickle cell disease (SCD) in the range of 19% to 43% in the absence of phenotypic matching [5]. One study reported alloimmunization rates of 29% in pediatric and 47% in adult SCD patients, with more females than males being alloimmunized [6]. In contrast, multiply-transfused non-SCD patients had alloimmunization rates of approximately 5%. The most common antibodies found were against K, E, C, and Jk(b), which are related to the antigenic frequencies in donors vs SCD patients (K: 9% vs 2%, E: 35% vs 24%, C: 68% vs 28%, and Jk(b): 72% vs 39% are positive, respectively) [7].

Genetic factors may also result in some patients being more likely to be responders than nonresponders to RBC antigens. Using mathematical models based on both adult and pediatric patients, it was determined that 13% of patients were responders, with a 30% chance of making additional alloantibodies with each transfusion event [8]. A recent study evaluated 27 single nucleotide polymorphisms in the *CD81*, *CHRNA10*, and *ARHG* genes of SCD patients who had formed or not formed alloantibodies; 2 single nucleotide polymorphisms in the *CD81* genes were found to be strongly associated with alloimmunization [9]. Other than genetic polymorphisms that may predispose a transfusion recipient to be a responder, it must also be considered that certain RBC antigens are likely HLA restricted [10–13]. Transfusion recipients would only be predicted to be capable of responding to RBC antigens that their individual HLA antigens could present.

Another consideration in the development of RBC alloantibodies is the inflammatory status of the transfusion recipient at the time of antigen exposure, with data from murine as well as human studies supporting a correlation between inflammation and RBC alloimmunization. In multiple murine models, recipient inflammation with polyinosinic polycytidylic acid has been shown to enhance the magnitude of the RBC alloimmune response [14–16], or to turn nonresponders into responders [17]. In a retrospective review of transfused humans, a febrile reaction within 10 days of RBC transfusion was associated with higher RBC alloimmunization rates [18]. In a different retrospective review, patients with inflammatory bowel disease had higher alloimmunization rate than did controls, and in the multivariate analysis, immunomodulatory therapy was associated with a decreased risk ($P = .01$) and number of transfusions increased risk ($P = .04$) of alloimmunization [19]. Another study demonstrated reduced Treg activity or increased Th2 responses in SCD or thalassemia patients in alloantibody responders vs nonresponders [20], with similar results being reported in a murine model [21]. Lastly, data were recently presented in abstract form, suggesting that children with SCD transfused in a state of inflammation (eg, during an episode of acute chest syndrome) had higher RBC alloimmunization rates than did patients transfused in noninflamed states (eg, during routine chronic transfusion) [22].

Table 1
Factors that may[a] influence the development of RBC alloantibodies

Recipient factors	Antigen exposure and disparity between donor and recipient
	Ability of the recipient's HLA to present the foreign antigen(s)
	Genetic predisposition to "respond"
	Health status at the time of antigen exposure
	Prior exposures, including non-RBC exposures
	Method of exposure (eg, transfusion vs pregnancy)
Donor factors	Genetic factors that may inherently impact RBC storage characteristics
	Length of RBC storage
	Presence of contaminating white cells and/or platelets
	Damage to RBCs resulting from processing and/or storage
	Antigen dose

[a] Some factors listed have been shown in animal studies to impact RBC alloimmunization; others have been shown in human studies to impact RBC alloimmunization. Future studies are needed to investigate the clinical impact in humans of factors shown to influence RBC alloimmunization in animals.

Mitigation Methods

Methods to reduce RBC alloimmunization are derived from factors that increase risk. In order to decrease alloimmunization rates due to donor and recipient antigen disparities, patients may be transfused with RBCs that are phenotypically matched, that is, RBC products that are negative for the most immunogenic antigens the recipient lacks. Genotyping may also be used to predict phenotypes of patients and donors. Methods to decrease RBC alloimmunization associated with the inflammatory state may include modification of the transfused product itself or recipient immunomodulation (Table 2 briefly outlines potential mitigation strategies based on murine data, to be discussed in more detail below). Selection of products in part based on recipient HLA type or other genetic attributes may also be useful in the future to decrease rates of RBC alloimmunization and to conserve resources. Lastly, in instances in which RBC alloantibodies are already present, a number of potential strategies can be used to minimize reexposure to these antigens and other dangers of these existing alloantibodies.