Transfusion Medicine Reviews 30 (2016) 209–212

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Gaps in Research on Adverse Events to Transfusion in Pediatrics

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ARTICLE INFO

Available online 18 June 2016

Keywords:
Pediatric
Transfusion
Transfusion reaction
Transfusion complications

ABSTRACT

Adverse consequences of blood transfusion in children are not completely understood. Much remains to be learned about defining their mechanisms, learning how they can be avoided, and improving our understanding how to minimize the morbidity of their consequences. All types of transfusion reactions can occur in children. This article focuses on four adverse consequences that have particular relevance for pediatric populations: cytomegalovirus transmission, red blood cell alloimmunization, immune altering consequences of transfusion, and necrotizing enterocolitis.

Contents

Cytomegalovirus

Cytomegalovirus (CMV) is a member of the DNA herpesvirus family that may be transmitted through respiratory secretions, breast milk, and blood transfusion. Although CMV infection is asymptomatic in most individuals, certain patient populations are at higher risk of life-threatening disseminated infection. Among pediatric patients, these high-risk populations include low-birthweight neonates and recipients of hematopoietic stem cell transplants (HSCT).

The incidence of transfusion-transmitted CMV (TT-CMV) infection has gradually decreased due to improved donor screening and technological advances in blood product safety, such as pre-storage leukoreduction [1,2]. A recent prospective birth-cohort study identified zero cases of TT-CMV in 310 very-low-birthweight neonates who received 2061 transfusions of CMV-seronegative, leukoreduced blood [3]; interestingly, almost all cases of postnatal CMV infection identified were attributed to transmission through breast milk from CMV-seropositive mothers. Other recent studies have similarly demonstrated zero incidence of TT-CMV in adult HSCT patients following transfusion with CMV-untested, leukoreduced blood [4,5], though these studies have not been reproduced in pediatric populations. No fatality due to TT-CMV has been reported to the FDA in at least a decade [6].

Given this success, the focus of current clinical research is not on whether TT-CMV can be prevented, but on the most effective method to do so. The two most common strategies to provide "CMV-safe" blood components, i.e. pre-storage leukoreduction and the use of blood from CMV-seronegative donors, as well as the combination of the two, have been compared in multiple meta-analyses, with inconclusive results [1,2]. Furthermore, no comparative studies have been performed recently in any high-risk pediatric population. Because of these limitations, a recent AABB committee report concluded that it could not develop evidence-based clinical practice guidelines for the provision of CMV-safe blood components [7].

As a result of this uncertainty, perceptions of the safety of each CMV-safe strategy, as well as the actual practice of each strategy, vary widely among healthcare institutions. In a 2007 survey of 183 institutions,

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http://dx.doi.org/10.1016/j.tmrv.2016.06.001
0887-7963/

almost 40% provided only CMV-seronegative blood products to premature/low-birthweight neonates, over 20% provided only pre-storage leukoreduced products, while the remainder used hybrid strategies; similar proportions were seen in pediatric HSCT patients [8]. Because a majority of institutions in the United States now employ universal leukoreduction (73% in 2011 [9]), a more valid question to ask is in which populations it is necessary to add a CMV-seronegative donor requirement on top of leukoreduction.

Given how uncommon TT-CMV is with current strategies, as well as the observation that CMV-seronegative, leukoreduced blood virtually eliminates TT-CMV in very-low-birthweight neonates, it is unlikely that an appropriately powered, randomized, controlled trial comparing these strategies will ever be performed in a pediatric population. Future studies in this area will likely take two forms: 1) newer, more effective strategies in addition to, or instead of, the current CMV-safe strategies; and 2) approaches to balance the impact of rare disseminated CMV infection with other clinical and societal objectives [7]. These studies will need to take into account the unique characteristics of pediatric populations, given the disproportionate effect of CMV infection on them.

Pathogen reduction technology promises to replace the need for CMV screening of donors by reducing the load of infectious particles by several logs [10]. However, as only one method has been recently approved in the United States by the FDA, studies of its effectiveness and possible adverse reactions in pediatric populations are needed. The additional cost of this strategy currently outstrips the cost of screening for CMV-seronegative donors, though a recent analysis suggests that pathogen reduction is cost-effective when all possible benefits (e.g., costs of other screening tests and potential for reduced blood component wastage) are accounted for [11].

While the potential benefits of preventing TT-CMV in children are well-documented, the costs are not. These costs are not only financial (e.g., charges associated with CMV testing of donors), but also evident in the inventory management of a scarce product, management of the donors themselves, and in the ethical considerations of appropriate distribution to specific at-risk populations of children. These costs, when evaluated on a per-unit basis, may seem small compared to the risk of disseminated CMV infection in a child, but when aggregated over thousands or millions of blood components, may impact clinical decision making. Studies in this area may be quantitative or qualitative, including cost-effectiveness analyses, surveys of clinical practice, or focus groups of provider or family attitudes.

While TT-CMV is a rare event, its clinical impact in certain pediatric populations remains a significant concern for transfusion specialists. Compounding these concerns are the uncertainties surrounding the best strategy to prevent TT-CMV and the costs for maintaining these strategies.

Red Blood Cell Alloimmunization

Red blood cell (RBC) alloimmunization, though a fairly uncommon risk of transfusion in children, requires an outsize dedication of resources from blood banks and transfusion services, including labor-intensive compatibility testing and provision of antigen-negative blood. Hemolytic transfusion reactions caused by undetected alloantibodies, though rare, may require clinical intervention, and are implicated in 14% of transfusion-related fatalities reported to the FDA [6].

RBC alloimmunization occurs in <5% of pediatric patients, a rate that does not appear to be significantly different from adults [12], with the exception of neonates, in which alloimmunization is extremely rare. In contrast, alloimmunization is much more common in young patients with sickle cell disease [13]. For this reason, and because the transfusion rate is much higher than in the general population, sickle cell disease often serves as a model for studying the mechanisms and management of RBC alloimmunization.

Management currently consists of prospective antigen-matching for high-risk populations, such as those with sickle cell disease, as well as mandatory antigen-matching for patients who have formed alloantibodies. Other management strategies have been implemented or proposed, but not all have been widely adopted [14]. These strategies have varying promise and potentially high costs. Even the well-accepted practice of limited prospective matching (for the C, E, and K antigens) in sickle cell disease may not be optimally cost-effective [15], and is still associated with significant breakthrough alloimmunization [16]. The effectiveness of prospective matching may be improved using genetic testing, as discussed in another review in this issue.

Much of the resources used to prevent alloimmunization are potentially wasted on patients with little to no risk of developing alloantibodies. Stochastic modeling has revealed that only a minority (~13% in one study) of transfused patients are at significant risk of alloimmunization ("responders") [12]. If these patients could be identified prospectively, mitigation strategies could be targeted to them, thereby improving effectiveness and minimizing waste. However, there are many factors associated with an increased risk of alloimmunization, including patient-specific, antigen-specific, and situation-specific factors, which may make accurate identification of responders difficult [17].

Multiple studies have demonstrated increased or decreased RBC alloimmunization risk associated with certain class II HLA alleles, suggesting a genetic predisposition [18]. Unfortunately, most of these associations are weak and specific only to certain RBC antigens [17]. In addition, different RBC antigens are known to induce alloimmunization at different rates [19]. Alloimmunization risk also appears to be increased during clinical events associated with a heightened inflammatory state, such as acute chest syndrome in children with sickle cell disease [20].

With so many factors individually contributing a small increased risk of alloimmunization, future studies should focus on aggregating these factors into a single, unified formula to predict when to employ escalated strategies to prevent alloimmunization. Such a task seems daunting, but has become more feasible with the advent of deep machine learning models [21]. In this case, the inputs to such a model could include the patient's demographics, RBC and HLA antigen profile, previous transfusion and antibody history, and relevant clinical diagnoses; and the outputs could include an estimate of alloimmunization risk and a priority list of which RBC antigens are most important to avoid. The model could then be fine-tuned as new studies emerge that identify new risks.

In addition to in silico modeling, another innovative "virtual" path to study the properties of alloimmunization follows the basic science route. A murine model system has recently demonstrated that alloimmunization to human antigens can be reproduced [22]. Such a model may be used not only to identify the factors that cause alloimmunization, but to identify new strategies to prevent alloimmunization and to treat patients with alloantibodies.

The effectiveness and value of mitigation strategies for RBC alloimmunization depend heavily on the identification of individuals at high-risk of developing alloantibodies. Efforts at improving such identification, including the characterization of the biological mechanisms of alloimmunization, should improve the clinical outlook for all children who receive transfusions.

Immune Altering Consequences of Transfusion

Transfusion of red blood cells includes an obligatory transfusion of leukocytes and hemolytic byproducts. Even with short storage duration and leukoreduction, hemoglobin, non-transferrin bound iron (NTBI), and leukocyte transfusion are unavoidable. These elements of transfused blood may affect recipient immune function. However, they may influence recipients in ways that are not immediately apparent after transfusion, e.g., by increasing infectious risk or promoting immune tolerance. Sequelae of the immune consequences of transfusion are