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In reply:

We thank Dr Magalon and colleagues for their insightful comments related to our recent article entitled "Optimizing donor selection for public cord blood banking: influence of maternal, infant, and collection characteristics on cord blood unit quality." We agree with all of the points made by Dr Magalon and colleagues in their letter. To really answer the question of whether it is important to target strategies that increase ethnic and racial diversity of the inventory of public cord blood units, the banking and transplantation communities need to further investigate the impact of race/ethnicity matching on patient outcomes after umbilical cord blood transplantation. These results can then be used to guide cord blood banks in creating algorithms for their operations. Furthermore, we never meant to imply that increasing diversity of public cord blood banking inventory should not be prioritized. Rather, we agree that this is highly important and that it has many implications. The fact that we observed that cord blood units collected from African American infants had lower cellular content compared to Caucasian infants

means that additional resources will need to be applied to bank sufficient numbers of units from African American donors. We look forward to ongoing interchanges on this topic as we optimize approaches to cord blood banking.

CONFLICT OF INTEREST

The authors report no conflicts of interest or funding sources.

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Desensitization in allergic transfusion reactions: evidence from the Trial to Reduce Alloimmunization to Platelets

Allergic transfusion reactions (ATRs) occur in up to 3% of platelet (PLT) transfusions,¹ are underreported, and range in severity from mild itching and hives to fatal anaphylaxis. Clinical data have broadly defined factors that may be involved, such as a pathogenic role for plasma. Retrospective data of plasma reduction maneuvers to prevent ATRs to blood products are confounded by selection bias: patients always receive unmanipulated PLTs before being switched to volume-reduced or washed PLTs after ATRs. An individual's risk of ATRs might decrease with increasing numbers of PLT transfusions, independent of PLT product manipulation. Thus, plasma reduction may temporally coincide with, but not cause, a reduction in ATR risk.²

To address the question of whether ATR risk varies with increasing PLT transfusion number, we analyzed severe urticarial reaction data from the Trial to Reduce Alloimmunization to Platelets (TRAP).³ There were 31 severe urticarial reactions reported in 24 subjects in the TRAP study (n = 8770 transfusions). Details about minor allergic reactions or the criteria for defining a severe urticarial reaction were not recorded in the study. Anaphylaxis was an evaluable outcome, but anaphylaxis was not reported after any PLT transfusion. However, three severe urticarial reactions were accompanied by dyspnea or bronchospasm. These reactions meet current criteria for likely anaphylaxis.⁴

Figure 1 shows the frequency of severe urticarial reactions by transfusion number. The risk for a severe urticarial reaction is not constant and is highest among the first five transfusions: 18 severe urticarial reactions

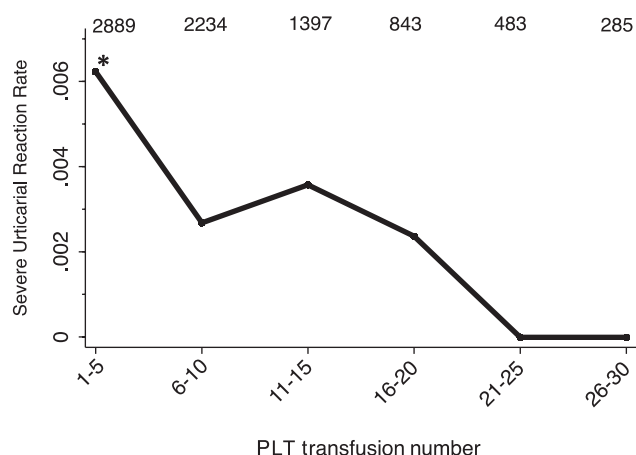


Fig. 1. The rate of severe urticarial reactions to PLTs in the TRAP decreases over time. PLT transfusion exposure was grouped into bins of five transfusions. The number of PLT transfusions in each bin is indicated above the graph. *Indicates when the three likely anaphylactic reactions occurred: two occurred at Transfusion 3 and one at Transfusion 4.

in Transfusions 1 through 5 ($n = 2889$) versus 13 severe urticarial reactions in the remaining transfusions ($n = 5881$; $p = 0.006$, Fisher's exact test). We conducted a logistic regression analysis using a clustered sandwich estimator to account for subjects receiving different total numbers of transfusions. The odds ratio (OR) for a severe urticarial reaction for every additional PLT transfusion is 0.91 (95% confidence interval [CI], 0.85-0.98; $p = 0.007$). Five percent of PLTs in TRAP were volume reduced. When these transfusions are excluded from the analysis, the findings do not materially change (OR, 0.92; 95% CI, 0.86-0.98).

It is possible that subjects with an increased ATR predisposition received fewer PLT transfusions than subjects with no predisposition to ATRs, and this would bias the results. Indeed, the 24 subjects who experienced a severe urticarial reaction had a median (range) of 7 (1-32) PLT transfusions during the study period versus 9 (1-92) for the subjects who did not have a severe reaction ($p < 0.001$). Nevertheless, even if the analysis is restricted to the 24 subjects who had a severe urticarial reaction, the risk still decreases with each transfusion (OR, 0.94; 95% CI, 0.88-0.99; $p = 0.03$). Additionally, the three likely anaphylactic reactions occurred in the first four transfusions, while the majority of PLT transfusions in this susceptible group occurred after PLT Transfusion 4.

A second possible confounder might be that subjects suffering from ATRs benefited from pretransfusion medication in subsequent transfusions. We consider this unlikely because multiple observational studies and trials have failed to show a reduction in ATRs with pretransfusion medication.⁵ The TRAP study did not record pretransfusion medications for transfusion, so

an analysis of pretransfusion medications cannot be performed.

The observation that severe urticarial and anaphylactic reactions may occur earlier during serial PLT transfusion has several implications. First, it provides some reassurance that the risk of severe allergic reactions diminishes over time, regardless of intervention. Second, any study evaluating ATRs should account for the risk of ATRs varying with PLT transfusion number. Third, it supports the hypothesis that recipient susceptibility is critical for the risk for ATRs. If PLT product and donor factors were primarily responsible, one would expect a relatively constant rate of ATRs and anaphylaxis over the course of TRAP. Finally, it leads to a hypothesis that serial exposure to PLTs may desensitize susceptible PLT recipients, at least to severe reactions, similar to widely used allergy desensitization methods that initiate desensitization with allergen immunotherapy ("allergy shots") one to three times per week. Patients who have ATRs have been shown to be more atopic than those who do not,⁶ consistent with this hypothesis. An alternative hypothesis is that ongoing immunosuppression in leukemia patients blunts allergic responses. Understanding of the pathophysiology of ATRs is critical for developing strategies to reduce the clinical burden of these reactions.

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