Published in final edited form as:

J Allergy Clin Immunol. 2014 June ; 133(6): 1772–1775.e9. doi:10.1016/j.jaci.2014.03.030.

Defining risk factors and presentations of allergic reactions to platelet transfusion

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Keywords

transfusion; platelet; immediate hypersensitivity; anaphylaxis; hay fever; blood donor; tryptase; eicosanoid; IgE

To the Editor

Allergic transfusion reactions (ATRs) are a frequent complication of blood transfusion, occurring in at least 2% of platelet transfusions^{1, 2}. The mechanisms of most ATRs are not understood. Antibodies to plasma proteins such as IgA^{3, 4}, haptoglobin⁵, and C4⁶ in blood transfusion recipients are reported but rarely identified. Furthermore, individuals react sporadically to transfusions, which is inconsistent with a recipient having hypersensitivity to a ubiquitous plasma protein.

We hypothesized that understanding the epidemiology and clinical presentation of ATRs will elucidate the underlying mechanism and guide strategies to prevent ATRs. We developed a cohort of platelet donors and the platelet transfusion recipients who received their donated products. The goals of this study are 1) to identify risk factors for ATRs, using platelet transfusion as a paradigm, and 2) to define the clinical and biochemical presentation of ATRs.

We conducted a longitudinal cohort study of patients receiving single donor apheresis platelet transfusions and their platelet donors. We defined an ATR as an acute transfusion

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reaction that included pruritus, urticaria, or angioedema. We took an allergy history, measured allergic sensitization and tryptase on the ImmunoCAP platform, and measured urine eicosanoid metabolites by mass spectrometry. Additional details of the study design, laboratory measures, and analysis are provided in the online supplement.

Recipients who did (n=124) and did not (n=44) experience ATRs were similar in terms of transfusion history (Table E1). A primary oncology diagnosis was present in 92.9% of platelet recipients. Including transfusions prior to enrollment, 36 subjects had 2 ATRs to platelet transfusion. ATRs manifested during or within 1 hour after platelet transfusion in 95% of ATRs. Diphenhydramine premedication was given in 27.9% of control transfusions and 42.3% of transfusions that resulted in an ATR. For two transfusions in the ATR group (1.4%), ACE inhibitor medication was given in the 24 hours prior to transfusion.

Urticaria and pruritus were the most common symptoms (Table E2). Criteria for anaphylaxis were met in 26 ATRs (18.2%). Diphenhydramine was used to treat 77 ATRs (53.9%), an H2 receptor antagonist in 22 ATRs (15.4%), and glucocorticoids in 19 ATRs (13.3%). Epinephrine was given in one case (0.7%). A typical cutaneous reaction is shown in Figure E1.

A history of hay fever and food allergy were more frequent in platelet recipients experiencing an ATR (Table I). Reported grass sensitivity was more prevalent among ATR recipients than never ATR recipients (37% vs. 18%, $P=0.02$, Table E3). When we defined hay fever and food allergy as reporting symptoms plus a positive Phadiatop or fx5, respectively, the association of atopy with ATRs persisted for hay fever, but not for food allergy. In contrast, there was no association between Phadiatop concentrations and ATRs in donors.

Among recipients, total and aeroallergen-specific IgE was higher in those with ATRs than those without (Figure 1). IgE concentrations in platelet donors are not associated with ATRs. For platelet recipients, each quartile increase of Phadiatop concentrations was associated with a 43.5% increase in ATR incidence (95% CI: 27.2%–62.0% increase; $P<0.001$), controlling for the number of transfusions. Similarly, there was a 44.9% increase in ATR incidence for each quartile increase of total IgE (95% CI: 21.7%–72.5% increase; $P<0.001$). No ethylene oxide specific IgE was detected in 25 platelet recipients with a high incidence of ATRs (data not shown). To validate the IgE results, we studied archived samples from the Trial to Reduce Alloimmunization to Platelets⁷ (Figure E2). As in the present cohort, there was a direct relationship between incident ATRs and concentrations aeroallergen-specific and total IgE.

Older subjects tended to have milder ATRs. For the risk of anaphylaxis vs. mucocutaneous reaction, the OR is 0.75 for each 10-year increase in age (95% CI: 0.61–0.91; $P=0.004$). The association of ATR severity with age remained statistically significant after controlling for the number of platelet transfusions an individual received (OR 0.73, 95% CI: 0.59–0.90). The risk for an ATR of any severity decreases with increasing number of platelet transfusions (Figure E3). No donor characteristic was statistically significantly associated with ATR severity.

We evaluated recipient and donor co-dependent risk factors. There was no ATR in which a donor reported food allergy matched a platelet recipient's food ingestion. There was no case of a platelet recipient with an active food allergy who received a platelet from a donor who had ingested the cognate food. In two ATR cases, donors reported remote histories of possible penicillin allergy (rash, rash/vomiting) and the patient was receiving a penicillin (ampicillin, amoxicillin). Neither donor had detectable penicilloyl G, penicilloyl V, or amoxicilloyl IgE antibodies.

To establish the involvement of mast cells in ATRs, plasma total tryptase was measured prior to and 25–90 minutes following an ATR in a convenience sample of 11 subjects. Plasma tryptase was elevated in 2 of 2 anaphylactic ATRs and 1 of 9 mucocutaneous ATRs (Figure E4). Among urine eicosanoids measured, PGD-M and LTE₄ correlated best with ATR severity (Figure E5).

In summary, we examined the atopic history and allergic mediators in platelet donors and recipients to determine the natural history of and identify risk factors for ATRs. We demonstrate that 1) ATRs to platelet transfusion resemble Type I, IgE mediated hypersensitivity reactions both clinically and biochemically; 2) recipient atopy, particularly hay fever, is a risk factor for ATRs to platelets; 3) ATR rates decrease with increasing transfusion exposure, raising the possibility that desensitization to platelet transfusion may occur; and 4) atopy in blood donors is not associated with ATRs. Complementary combinations of food/drug allergy and food/drug exposures in blood donors and recipients are not a common source of ATRs, although they have been reported elsewhere^{8, 9}. Given the involvement of mast cell degranulation and leukotriene pathway activation in ATRs, compounds that block these pathways may have utility for preventing ATRs in highly susceptible transfusion recipients, i.e. those with hay fever and recurrent ATRs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of funding:

Supported by an American Society of Hematology Scholar Award

This manuscript was prepared using TRAP Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the TRAP or the NHLBI.

Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R21HL107828.

A.A.R.T. was supported by the NIH 1K23AI093152-01A1 and Doris Duke Charitable Foundation Clinician Scientist Development Award (#22006.02). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supported by a Brigham and Women's Hospital Biomedical Research Institute Microgrant

We are thankful for the efforts and collegiality of Katherine Condon, Rosemary Case, Alice Fuller, Erica Arnold, Gabriel Verzino, and the technologists and supervisors at Johns Hopkins and Brigham and Women's Hospital blood

banks and immunology labs. We are especially appreciative of the time and efforts of patients, blood donors, and their families who participated in this study.

Abbreviations

ATR	allergic transfusion reaction
TRAP	Trial to Reduce Alloimmunization to Platelets
SBP	systolic blood pressure
LT	leukotriene
PG	prostaglandin

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Figure 1. Plasma concentrations of IgE are higher in platelet recipients who have ATRs, not donors

Phadiatop (A,B) and fx5 (C,D) was tested in platelet recipients who did and did not have a history of ATRs and platelet donors whose products did or did not cause an ATR. The reference line at 0.35 kUa/L indicates a likely clinically significant result. (E) Platelet recipient total IgE levels. (F) The relationship between quartiles of Phadiatop concentration and the frequency of ATRs among platelet recipients (minimum 10 transfusions). Bars represent median values.

Table 1

Atopic phenotype of platelet recipients and donors

	Platelet Recipient		Platelet Donor		P	ATR (n=87)	P
	Never ATR (n=44)	ATR (n=124)	No ATR (n=46)	ATR (n=87)			
Reported Atopic History [*]							
Hay fever	23 (53.5%)	86 (71.7%)	36 (78.3%)	60 (69%)	0.04		0.31
Asthma/albuterol use	17 (38.6%)	38 (31.7%)	10 (21.7%)	15 (17.2%)	0.46		0.64
Eczema	7 (15.9%)	16 (13.1%)	13 (28.3%)	10 (11.5%)	0.62		0.03
Food allergy	1 (2.3%)	18 (14.6%)	3 (6.5%)	8 (9.2%)	0.03		0.75
Symptoms in last week	2 (4.8%)	10 (8.9%)	6 (13%)	7 (8.0%)	0.52		0.37
Specific IgE Screen ^{**}							
Phadiatop positive	10 (28.6%)	62 (55.9%)	9 (40.9%)	23 (41.8%)	0.006		1
fx5 positive	2 (10.5%)	4 (5.8%)	3 (15%)	7 (14.6%)	0.61		1
Confirmed hay fever [†]	7 (18.9%)	51 (47.7%)	8 (29.6%)	22 (34.4%)	0.002		0.81
Confirmed food allergy [†]	0 (0%)	2 (2.9%)	0 (0%)	1 (1.5%)	1		1

^{*} Responses have <5% missing data

^{**} Phadiatop and fx5 tests were performed on subsets of platelet recipients (Phadiatop n=144, fx5 n=88) and platelet donors (Phadiatop n=78, fx5 n=69)

[†] Confirmed = positive history + positive specific IgE screen