

Allergic Transfusion Reactions

An Evaluation of 273 Consecutive Reactions

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• **Context.**—Allergic reaction to transfusion is common. However, the review of a large series of allergic transfusion reactions has not been performed.

Objective.—To review a large series of allergic transfusion reactions.

Design.—A retrospective review of all reported and evaluated transfusion reactions during a 9-year period at 1 institution was performed. Associated clinical signs and symptoms were evaluated.

Setting.—Large, tertiary-care teaching hospital.

Results.—A total of 1613 adverse reactions to transfusion were evaluated. Allergic transfusion reactions accounted for 17% (273 of 1613) of the transfusion reactions. Severe allergic reactions (anaphylaxis, anaphylactoid signs and symptoms, and/or hypotension) were observed in 21 patients (7.7% of allergic reactions, or 1.3% of all transfusion reactions). Serum tryptase, a marker for anaphylaxis, was measured in 1 patient and determined to be

borderline elevated. Five patients experienced allergic transfusion reactions to autologous red cell transfusions. One patient experienced hives during the transfusion of a major ABO mismatched red blood cell. A wide variety of skin manifestations were observed, but 26 (9.5%) patients did not have skin manifestations. Allergic transfusion reactions were estimated to occur in approximately 1 in 4124 blood components transfused, or 1 in 2338 transfusion episodes. Severe allergic reactions occurred in approximately 1 in 30 281 transfusions. No deaths directly attributable to transfusion were observed in this patient group.

Conclusions.—The clinical presentation of allergic transfusion reactions was quite variable, and the pathophysiology remains unclear. Recommendations for clinical evaluation and therapy remain problematic and often empirical. (*Arch Pathol Lab Med.* 2003;127:316–320)

Allergic (urticarial) transfusion reactions are reported to complicate approximately 1% to 3% of all blood transfusions.¹ Most reactions are mild and are usually associated with cutaneous manifestations such as urticaria, rash, pruritis, and flushing. Severe allergic reactions, such as anaphylactic shock, are rare, with an estimated incidence of 1 per 20 000 to 47 000 units of blood and components.¹ Immunoglobulin (Ig) E or anti-IgA antibodies are often implicated in severe reactions, although the cause and effect are not always evident.^{1–4} The cause of less severe allergic reactions is often unclear, but several different mechanisms have been implicated, including pre-existing antibodies to serum proteins (eg, albumin, complement components, IgG, and IgA), human leukocyte antigen antibodies, transfusion of allergens, and passive transfer of IgE antibodies.^{1,2}

In 1932, Polayes and Lederer⁵ presented one of the earliest papers examining a series of transfusion reactions and a review of the literature. They noted that “allergic reactions to blood transfusion are not uncommon.”⁵ Weiner et al⁶ subsequently studied more than 3000 blood transfusions and reported that allergic reactions were found in approximately 1% of transfusions. In 1941, Hox-

worth and Skinner⁷ also studied more than 3000 blood transfusions and found the overall incidence of urticarial reactions to be 1.82% of all transfusions and 30.6% of all transfusion reactions. Another study found the incidence of allergic reactions to be 33.3% of all adverse reactions to transfusion.⁸ In 1968, a 6-year study found the incidence of allergic reactions to be 13.6% of all transfusion reactions.⁹ Also, in 1968, the first report of an anaphylactic transfusion reaction related to anti-IgA was published.²

Despite these reports examining adverse reactions to blood transfusion and a sense that allergic transfusion reactions are relatively common, a study devoted to the examination of a large series of allergic transfusion reactions has not, to our knowledge, been performed. The purpose of this study was to evaluate 1 large institution's experience with allergic transfusion reactions over almost a decade.

MATERIALS AND METHODS

A 9-year retrospective review of all transfusion reactions reported to the hospital's transfusion service was performed for 1993 through 2001. All reactions reported to the transfusion service were clinically evaluated or reviewed by a physician expert in blood banking and transfusion medicine. Reactions associated with skin manifestations were generally classified as allergic. Reactions without skin manifestations but with associated laryngeal or pulmonary manifestations were classified as allergic if clinical evaluation supported an allergic etiology (ie, if fluid overload, transfusion-related acute lung injury [TRALI], or other etiologies were ruled out). The implicated blood component, the patient's

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Table 1. Allergic Reactions Associated With 5 Cases of Autologous Red Blood Cell Transfusion

Patient	Reported Clinical Signs and Symptoms
1	Skin rash (salvaged red cell unit from the operating room)
2	Hives on back and arms and chest tightness
3	Chills, chest pain, wheezing, and hypotension that responded to diphenhydramine and acetaminophen (first of autologous blood was transfused without difficulty)
4	Urticaria on arms and back (first unit of autologous blood was transfused in operating room 4 d earlier without apparent difficulty)
5	Chills and possible hives over shoulders (patient was a bone marrow donor)

clinical signs and symptoms, and the associated clinical condition of the patient were routinely evaluated.

An attempt was made to calculate the incidence of allergic transfusion reactions per component transfused. Complete data for transfused units were available for 6 of the 9 years of the study period (1993–2001). Total red blood cells transfused during those 6 representative years were averaged and extrapolated to a per-year average number. A similar extrapolation was performed for non-red blood cell components transfused. The total number of individual platelet pools or apheresis platelets transfused was not known, but since approximately 70% of our non-red blood cell transfusions were platelets and the average number of platelet concentrates per pool was known, the number of individual platelet transfusions was estimated. Similar calculations were performed for fresh frozen plasma (FFP), which comprised approximately 20% of non-red blood cell components transfused.

Serum tryptase was determined in one patient suspected of having an anaphylactic/anaphylactoid transfusion reaction (performed by Dr Lawrence B. Schwartz, Medical College of Virginia, Richmond, Va).

RESULTS

During the 9-year study period, a total of 1613 adverse reactions to transfusion were reported to the transfusion service. Of these, 273 (17%) reactions were identified as allergic. These allergic reactions occurred in 151 male and 122 female patients.

Red blood cells were implicated in 123 (45.1%) of the allergic reactions; FFP in 66 (24.2%) reactions; platelets in 81 (29.7%) reactions (51 pooled and 30 apheresis platelets); FFP and pooled platelets in 2 (0.7%) reactions; and pooled cryoprecipitate in 1 (0.3%) reaction.

One reaction associated only with hives involved a unit of red blood cells that was found, during the posttransfusion clerical and laboratory checks, to be a major ABO mismatch (a B, Rh[D]-positive unit was transfused to an A, Rh[D]-negative patient).

Five reactions were associated with autologous units of red blood cells. Four of these allergic reactions involving autologous blood were previously reported.¹⁰ These reactions are detailed in Table 1.

Severe allergic reactions were observed in 21 patients (7.7%). These reactions were associated with anaphylaxis or anaphylactoid signs and symptoms and/or hypotension or a documented decrease in oxygen saturation. Seven of these 21 reactions (33.3%) involved red blood cell transfusions, and 14 (66.7%) involved platelet or FFP transfusions. Nine (42.9%) had associated hypotension. The severe reactions were observed in 14 males and 7 females and are detailed in Table 2. The overall incidence

of anaphylactic or anaphylactoid, or severe allergic, reactions during the 9-year study period was 1.3% (21 of 1613) of all reported transfusion reactions.

Fourteen (5.1%) allergic reactions were associated with a temperature increase of 1°C or greater. Two of these febrile, allergic reactions were associated with hypotension and are detailed in Table 2. One allergic reaction was associated with fever, rigors, a perioral maculopapular rash, and an increase in blood pressure.

The clinical manifestations of the allergic reactions were quite variable, and various types of skin manifestations were observed. Hives or urticaria, maculopapular rash, periorbital edema, erythema, flushing, and pruritis were commonly noted. Skin rashes were often localized to various parts of the body and were sometimes generalized. No consistent skin presentation was identified.

Twenty-six (9.5%) patients did not have skin manifestations but were thought to have allergic transfusion reactions on the basis of additional clinical evaluations and/or response to therapy. These patients often demonstrated primarily pulmonary signs and symptoms such as wheezing and shortness of breath.

Approximately 1 125 846 blood components were transfused during the study period, or 125 094 components per year. Red blood cells averaged approximately 45 009 per year (a total of 405 083 for the 9-year study period). Platelet doses transfused were estimated to average 9630 per year (a total of 86 670 transfusions for the 9-year study period), and FFP units transfused averaged approximately 16 017 per year (a total of 144 153 for the study period). Using these numbers, the overall incidence of allergic transfusion reactions is estimated to be 1 in 4124 blood component transfusions (273 of 1 125 846); 1 in 1070 platelet transfusions (81 of 86 670); 1 in 2184 FFP transfusions (66 of 144 153); and 1 in 3293 red blood cell transfusions (123 of 405 083). Severe allergic transfusion reactions (Table 2) were estimated to occur in 1 in 9630 platelet transfusions (9 of 86 670); 1 in 28 831 FFP transfusions (5 of 144 153); 1 in 57 869 red blood cell transfusions (7 of 405 083); and 1 in 53 612 blood component transfusions (21 of 1 125 846). Considering only red blood cells, platelets (doses), and FFP transfusions (405 083 + 86 670 + 144 153 = 635 906 total), the overall incidence of allergic reactions for these components was 1 in 2338 transfusions (272 of 635 906); severe reactions were observed in 1 in 30 281 transfusions (21 of 635 906).

COMMENT

Several possible mechanisms exist to explain allergic reactions to blood component transfusion (Table 3).¹ One of the earliest descriptions of a probable allergic reaction following blood transfusion was reported in 1919.¹¹ A patient with no underlying history of allergy received a blood transfusion and suffered an attack of bronchial asthma when exposed to horses 2 weeks later. The donor, who suffered “persistent and long-standing asthma and bronchitis,” underwent skin testing and was found to react to horse dandruff (1:50 000 dilution).¹¹ Similar allergic reactions have been reported in patients exposed to food and animal allergens presumably present in the donated blood.^{12,13} As a result, some authors have raised the question of screening blood donors for allergies to prevent the passive transfer of IgE or other allergens.¹⁴ Until more detailed cause-and-effect analysis can be performed, it is dif-

Table 2. Severe Allergic Transfusion Reactions*		
Patient	Reported Clinical Signs and Symptoms	Blood Component
1	Acute shortness of breath, wheezing, tachypnea, tachycardia, increased blood pressure; intubated for hypoxia and respiratory distress	Pooled platelet
2	Cyanosis, hypotension, tachypnea, bronchospasm; responded to treatment with diphenhydramine, hydrocortisone, and epinephrine (serum tryptase measured at 1.0 ng/mL)	Pooled platelet (leukoreduced and irradiated)
3	Severe hypotension, anaphylaxis (14-d-old male infant)	Platelet concentrate
4	Hives, chest pain, wheezing, decreased oxygen saturation	Pooled platelet (leukoreduced and irradiated)
5	Acute hypotension, anaphylaxis	Pooled platelet
6	Skin erythema, chills, dizziness, shortness of breath, and decreased oxygen saturation necessitating emergent intubation	Pooled platelet
7	Pruritis and numerous wheals and oxygen saturation 88% (room air); treated with diphenhydramine, albuterol, and oxygen; cutaneous manifestations and oxygen saturation improved (95% on room air)	Pooled platelet (leukoreduced and irradiated)
8	Acute shortness of breath and chills; symptomatic relief with diphenhydramine and oxygen administration	Pooled platelet
9	Shortness of breath, wheezing, and stridor; treated with diphenhydramine, prednisone, and epinephrine	Apheresis platelet (irradiated)
10	Severe bronchospasm, increased blood pressure; responded to treatment with epinephrine and bronchodilators	FFP
11	Acute shortness of breath, tachypnea, hypoxia, stridor, and increased blood pressure; responded to treatment with epinephrine, Solu-Cortef, and albuterol nebulizer	FFP
12	Wheezing and lung crackles, difficulty ventilating immediately postoperation for liver transplant, hypotension; oxygen saturation decreased from 100% to ca 70%; responded to treatment with epinephrine	FFP
13	Acute respiratory distress during fourth unit of FFP, dyspnea, wheezing, tachycardia; treated with epinephrine and methylprednisolone	FFP
14	Chest/throat pain and tightness, cough and wheezing at the level of the neck; treated with intravenous diphenhydramine with resolution of symptoms	FFP
15	Acute, severe hypotension	Red blood cell
16	Nausea, respiratory distress, hypertension, and tachycardia after 40 mL of red cells transfused in a patient with COPD and GI bleeding; treated with diphenhydramine and prochlorperazine	Red blood cell (leukoreduced)
17	Acute dyspnea with expiratory wheezing and decreased oxygen saturation; treated with intravenous diphenhydramine, hydrocortisone, lasix, and albuterol treatment (3 times)	Red blood cell
18	Hives on arms, back, and legs, pruritis, fever, hypotension (70/40); responded to acetaminophen and diphenhydramine	Red blood cell
19	Facial flushing and hypotension (140/70 to 100/50 that normalized when transfusion stopped)	Red blood cell
20	Maculopapular rash and hypotension (100/70 to 78/40); responded to treatment with fluid replacement, epinephrine, diphenhydramine, and hydrocortisone	Red blood cell
21	Hives and hypotension	Red blood cell

* Severe reactions included anaphylaxis/anaphylactoid signs and symptoms and/or hypotension or a documented decrease in oxygen saturation. COPD indicates chronic obstructive pulmonary disease; FFP, fresh frozen plasma; and GI, gastrointestinal.

Table 3. Possible Mechanisms Producing Allergic Transfusion Reactions* ^{1,4,12,13,20}
1. Preexisting IgE or IgG antibody in the recipient reacts with allergens or proteins in the transfused blood (eg, drugs or chemicals [ethylene oxide, plastics]). 2. Class- or subclass-specific anti-IgA antibody in the recipient reacts against IgA in the transfused blood. 3. Preexisting IgG or IgE in the recipient that reacts against allotypic serum protein forms in the transfused blood (eg, albumin, haptoglobin, and complement component). 4. Passive transfer of IgE antibodies from the donor to the recipient. 5. Transfusion of complement-derived anaphylatoxins (C3a and C5a) produced during blood storage. 6. Transfusion of cytokines, bradykinin, histamine, or other biological mediators produced during blood storage. 7. Other.

* Ig indicates immunoglobulin.

difficult to justify donor deferral for atopic-type manifestations.

Almost half (45.1%) of the allergic transfusion reactions were thought to be related to red blood cell transfusions. However, two thirds of the most severe reactions (Table 2) were associated with FFP or platelet components. Although not confirmed, this observation suggests that those blood components containing larger amounts of plasma may be associated with more severe allergic reactions. Volume could be important if the reaction is related to the infusion of an inflammatory substance (eg, cytokines or bradykinin). Additional study of this observation is warranted.

Since our study is a retrospective review, we did not routinely perform any specific studies, such as IgA antibody levels, to investigate these cases further. Nine (42.9%) of the 21 severe allergic transfusion reactions (Table 2) were associated with hypotension that was sometimes severe (5 with red blood cell transfusion, 3 with platelet transfusion, and 1 with FFP). A previous study

reported on hypotensive reactions with platelet transfusion.¹⁵ Our study adds to this observation and further reports that hypotension can also be observed with red blood cell or FFP transfusion. Cytokines, bradykinin, histamine, or other biologic mediators may be present in stored blood components, but their role in these reactions remains speculative. Prospective studies will need to be performed. Bacterial contamination was not suspected or documented in any of these cases, but cultures of blood components were obtained only if clinical suspicion warranted further investigation. Four cases demonstrated an increase in blood pressure. It is possible that some of these severe reactions, particularly those with more prominent pulmonary symptoms, were unrecognized cases of TRALI. The increasing recognition of milder cases of TRALI makes diagnostic separation of these cases of greater importance since therapeutic approaches are different.¹⁶

Specific diagnostic tests to differentiate TRALI from anaphylaxis do not currently exist, and clinical recognition remains paramount for the diagnosis. Although characteristic findings on chest x-ray films are usually observed in TRALI, the differential diagnosis may not be clear in the critically ill patient. Serum tryptase has been advocated by some researchers as a marker of anaphylaxis.¹⁷⁻¹⁹ Tryptase is a mast cell enzyme and is released into the serum during mast cell activation and degranulation.¹⁷⁻¹⁹ Thus, increased serum tryptase may be observed in allergic and anaphylactic reactions. Serum tryptase peaks in 1 to 2 hours and may return to normal in 3 to 4 hours, but it can remain elevated for up to 48 hours.^{17,18} A serum tryptase level was obtained in one of our suspected anaphylactoid cases (patient 2, Table 2). The level was determined to be 1.0 ng/mL (normal, <1.0 ng/mL) and is suggestive of mast cell activation in our patient. To our knowledge, only one other study has examined serum tryptase in allergic transfusion reactions, primarily manifested by pulmonary symptoms, and did not report any positive association.⁴ Serum tryptase has never been studied as a potential diagnostic marker for anaphylactic or anaphylactoid transfusion reactions or to differentiate anaphylaxis secondary to transfusion from TRALI. Serum tryptase deserves further study as a potential marker for severe allergic transfusion reactions, with or without anaphylaxis.

Five cases of allergic transfusion reaction were associated with autologous red cell transfusions. Four of these cases were previously reported.¹⁰ The mechanism (or mechanisms) causing allergic reactions in these cases is (are) unclear but may be related to a storage lesion (eg, plastic leaching from the bag, ethylene oxide, white cell degradation and release of enzymes).^{4,20} Again, these data suggest that patients can have adverse reactions to their own blood, and it should not be automatically assumed that such an observed adverse effect is due to something other than the transfusion.

One of our cases involved a major ABO mismatch that was first manifested by hives in the recipient. The post-transfusion clerical and serologic evaluations revealed that the unit of red blood cells was type B and that the patient was type A. The patient was observed closely, and although there was a short period of oliguria and hematuria, these were thought to be related to underlying clinical problems and not to the transfusion. The direct antiglobulin test remained negative, and she subsequently received a transfusion with 2 units of type A red cells with-

out complications. Although the development of hives in this patient may have been purely coincidental, this unusual case nevertheless suggests that the initial clinical manifestation(s) in potentially serious (eg, hemolytic) transfusion reactions may appear to be relatively "benign." A complete evaluation is warranted in every adverse reaction to transfusion.

Unfortunately, the retrospective nature of our study leaves many questions unanswered. However, several important points are evident. First, most allergic transfusion reactions are relatively benign and require no, or minimal, therapy other than stopping the infusion and perhaps administering an antihistamine drug.²¹ Since some type of skin manifestation typically defines an allergic transfusion reaction, we were not surprised to observe that 90.5% of our reactions had a dermatologic (cutaneous) component. However, we observed that the cutaneous presentation was quite variable, and no specific manifestation or presentation could be delineated. Second, we identified 1 ABO mismatched red blood cell transfusion that was first manifested by hives in the recipient. Because the transfusion was stopped at that point, it is unclear if more serious sequelae were averted, but it underscores the importance of thoroughly investigating each transfusion reaction.²¹ Third, severe allergic reactions were observed in 21 patients, and most were related to platelet or FFP transfusions, although red cell transfusions were associated with one third of the episodes. Nine of these 21 reactions had associated hypotension. Additionally, no deaths directly attributable to the transfusion were noted in our study. The importance of the separation of these reactions from unrecognized or milder cases of TRALI is underscored. Fourth, the incidence of allergic transfusion reactions is approximately 17% of all adverse reactions at our institution. The overall incidence of allergic transfusion reactions was estimated to be 1 in 4124 blood component transfusions, 1 in 1070 platelet dose transfusions, 1 in 2184 FFP unit transfusions, and 1 in 3293 red blood cell transfusions. Our observed incidence of allergic transfusion reactions is lower than the typically reported rate of 1% to 3%.¹ The explanation for this is unclear. The rate of 1% to 3% may relate to older data and may not be applicable to today's component preparation and usage.^{1,22} More recent data are not readily available, but a 1994 College of American Pathologists survey suggests an overall transfusion reaction rate of <0.5% for 81.1% of survey respondents.²³ Additional surveillance data are needed to clarify the true or expected incidence. Severe allergic reactions were observed in our study in approximately 1 in 30281 transfusions, which is similar to the commonly reported rate of 1 in 20000 to 47000 units for severe and anaphylactic reactions.^{1,24}

This is the first large series of allergic transfusion reactions. A better understanding of the pathophysiology underlying these reactions will require prospective studies.

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