

Mild Allergic Transfusion Reactions

Impact of Associated Clinical Symptoms?

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ABSTRACT

Objectives: Transfusions are often needlessly aborted after occurrence of a mild allergic transfusion reaction (ATR), leading to wastage and reexposure of recipients to additional blood products (with potential alloimmunization). We aimed to determine the symptoms associated with such reactions (along with other parameters) as a possible reason of concern for transfusionists aborting such transfusions.

Methods: We reviewed the symptomology of all mild ATRs (as well as the associated wastage and costs of aborted transfusions) at an academic medical center that occurred over a period of 1 year.

Results: Of the patients, 52.3% had nonatopic-associated symptoms. The most common associated symptom was tachycardia (37.8%), followed by dyspnea (28.9%), hypotension (17.8%), and hypertension (13.3%). More than half of patients (54.7%) required retransfusion. The estimated cost of product wastage was \$12,507.

Conclusions: Understanding symptoms associated with mild ATRs may lead to improved management of patients, with fewer unnecessary transfusions and less wastage.

Allergic transfusion reactions (ATRs) occur in up to 3% of transfusions, with rates being highest in platelet and plasma products.¹ Most of these reactions are mild and do not progress in severity.² Severe ATRs occur at a lower rate, 7.7% of ATRs or 1 in 20,000 to 47,000 products transfused, but represent 4% of transfusion-related mortalities.^{1,3} As such, great care must be taken in evaluating these patients, although symptoms encountered during severe ATRs typically have more rapid onset compared with symptoms of mild ATRs that rarely evolve to anaphylaxis.^{1,2} It is therefore allowable for the transfusion associated with mild ATRs to be restarted after pausing and administering treatment with an antihistamine medication, usually diphenhydramine, if the patient's symptoms resolve.²

Resuming and completing transfusions in mild ATRs prevents unnecessary blood product wastage and expense. With the increasing cost of health care, blood products account for approximately 1% of hospital expenses.⁴ Most discarded blood products are due to expiration or improper storage/transport. Rates of disposal of in-date blood products are estimated at up to 6.7% and are mostly attributed to products being dispensed but not administered or unacceptable temperature variation during intrainstitutional transport.⁵ The number and volume of products wasted due to transfusion reactions are less well characterized.⁶

There have been significant advances both nationally and internationally pertaining to the stewardship of blood products in the form of blood utilization and hemovigilance.^{7,8} In keeping with this culture of quality, it is paramount that patients receive transfusion only when

clinically indicated and do not receive excess products. Discontinuing a transfusion due to a mild allergic reaction responsive to treatment not only prevents completion of the transfusion but often necessitates additional transfusions and donor exposures for the patient.

Identifying patients at risk for ATRs may be important and could aid in appropriate utilization of potential preventative measures and enhanced patient monitoring. An association between recipient characteristics such as atopy and previous ATRs has been described and investigated in recent years.⁹ Increased immunoglobulin E levels appear more common in patients who develop ATRs, but among atopic conditions, only a history of hay fever was found to be a risk factor.¹⁰ Premedication has been shown in numerous studies not to decrease rates of ATR.

At issue is the finding in mild ATRs that transfusions are frequently aborted instead of being resumed (following appropriate treatment), leading to wastage and increased potential for recipient alloimmunization. The reasons for aborting transfusions following mild ATRs are not clear but may be related to other clinical symptoms associated with the mild ATR that transfusionists find concerning. A goal of this study was to determine the prevalence and kinds of such clinical symptoms associated with mild ATRs.

Materials and Methods

This study was approved by the institutional review board at Vanderbilt University Medical Center (VUMC). We reviewed all mild ATRs reported over a period of 12 months (November 2013 to November 2014). Transfusion reactions are identified by clinical staff and then reviewed and categorized by technologists, pathology residents, and transfusion medicine attending physicians as part of practice and teaching rounds at our institution. A review of our transfusion reaction reports was performed to identify reactions previously categorized as mild ATRs. Reactions were reviewed and confirmed by two members of the research team (B.D.A. and M.J.).

We assessed each reaction for eight symptoms of atopy and 10 symptoms less classically associated with ATRs. This was done to qualify reactions as mild ATRs and to identify associated symptoms in these reactions. The type of product, amount transfused, and amount returned to the blood bank were noted. This information was used to calculate the total volumes and costs of product wastage. The starting platelet count, hematocrit level, and hemoglobin level were noted for assessing the appropriateness of transfusion. The number of subsequent transfusions after the reaction was also noted.

We also compiled the patients’ transfusion histories and noted any prior transfusion reactions.

In addition, a review of the electronic medical record (StarPanel; at VUMC, HealthIT, Nashville, TN) was performed to assess history of atopy in patients with ATRs. The patients’ listed conditions were reviewed as well as any drug allergies. A full-text search of StarPanel was conducted for specific words associated with atopic conditions (allergy, allergic, atopic, atopy, rhinitis, asthma, eczema, dermatitis). Each patient’s history of food allergy, drug allergy, allergic rhinitis, asthma, or atopic dermatitis was assessed. All drug allergies were reviewed, and reactions consistent with drug side effects were excluded.

Results

We evaluated allergic and nonallergic symptoms in 86 ATRs reported over the period of 1 year from 78 individual patients at VUMC **Table 1**. We assessed predefined allergic symptoms as set out by the Centers for Disease Control and Prevention (CDC) in the National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol.¹¹ Symptoms deemed associated with mild ATRs were rash (general), isolated urticaria, diffuse urticaria, flushing, mild bronchospasm, mild laryngospasm, and pruritus. Skin manifestations were the most common finding in mild ATRs (92%) and included rash (general), urticaria, flushing, and pruritus. In patients without skin manifestations, mild respiratory symptoms were present. Of those

Table 1
Rates of Reported Symptoms Associated With Mild Allergic Transfusion Reactions

Symptom	No. (%)
Atopic symptomatology	
Rash	13 (15.1)
Isolated urticaria	3 (3.5)
Generalized urticaria	47 (54.7)
Flushing	41 (47.7)
Mild wheezing	6 (7)
Mild throat tightness	3 (3.5)
Itching	9 (10.5)
Nonspecific symptomatology	
Fever	3 (6.7)
Chills and/or rigors	5 (11.1)
Hypertension	6 (13.3)
Hypotension	8 (17.8)
Tachycardia	17 (37.8)
Nausea/vomiting	7 (15.6)
Dyspnea/shortness of breath	13 (28.9)
Headache	0 (0)
Abdominal pain/diarrhea	0 (0)
Other	20 (44.4)

Table 2
Rates of Atopic Disease in Patients With Mild ATRs vs the General Population^a

Rate	Food Allergy, %	Drug Allergy, %	Allergic Rhinitis, %	Asthma, %	Atopic Dermatitis/Contact Dermatitis, %
Rate among patients with ATR	1	41	23	8	12
Prevalence in general population	6.70 ¹²	26.6-36 ¹³	9-42 ¹⁴	8.20 ¹⁵	11 ^{16,17}

ATR, allergic transfusion reaction.

^aRates in general population are based on epidemiologic data.¹²⁻¹⁷

experiencing mild ATRs, 33% had only skin manifestations. We found that in addition to atopic symptomatology, 52.3% of patients had symptoms not classically associated with allergic reactions. The most common of these was tachycardia (37.8%). Upon review, all patients who experienced tachycardia during transfusion had been previously tachycardic at some stage during the admission prior to transfusion (100%), and 65% were tachycardic at the initiation of transfusion. Among patients who experienced tachycardia during transfusion, 82% had low hemoglobin (Hb)/hematocrit (HCT) with a mean Hb of 9.4 g/dL and HCT of 28.6% (reference intervals of Hb/Hct at our institution: male, 14-18.1 g/dL and 41%-49%; female, 11.8-16 g/dL and 36%-43%).

We identified characteristics associated with patients who developed ATRs. Of patients developing ATRs, 17% had a history of ATR. A history of an allergic condition was present in 59% (46/78) of patients who developed ATRs, the most common being drug allergy in 41%. Individually, the rates of each allergic condition were compared with rates among the general population, and we did not observe a significantly increased rate among patients who experienced an ATR **Table 2**.¹²⁻¹⁷ In patients with a history of allergic conditions, 31% had two or more allergic conditions concurrently in their history. In addition, 43% of patients received pretransfusion medications (75.7% diphenhydramine and acetaminophen, 13.5% only diphenhydramine, and 5.4% only acetaminophen or diphenhydramine, acetaminophen, and steroids).

We evaluated the number, volume, and kinds of products that were transfused. Platelets were most frequently associated with ATR (57/86, 66.3%) followed by plasma (17/86, 19.8%) and RBCs (12/86, 14%). Of patients developing reactions, 63.9% (55/86) had incomplete transfusions and the remaining products returned to the blood bank for evaluation. In total, 6,892.3 mL of blood products was returned to the blood bank with an estimated cost of \$12,646 **Table 3**, based on historic negotiated prices of blood products at our institution that were used to determine a cost per milliliter for each component. Of these patients, 54.7% received further transfusion, with 34% requiring only one additional transfusion. Of patients

Table 3
Blood Product Wastage Associated With Mild Allergic Transfusion Reactions^a

Product	Volume, mL	Cost, US\$
Plasma	1,292	196.38
Platelets	4,992.3	11,981.52
RBCs	608	330.06
Total products	6,892.3	12,507.96

^aEstimates are based on historic institutional prices for blood products.

receiving RBC transfusions, the average Hb and HCT were 8.28 g/dL and 23.4%, respectively. Those receiving platelets had an average platelet count of $44.3 \times 10^3/\mu\text{L}$ (reference interval for platelets at our institution: $135-371 \times 10^3/\mu\text{L}$).

We evaluated discontinuation and management in the perireaction period. Symptoms resolved in 85% (73/86) of reactions, and there was symptom improvement in 100% (86/86) reactions. The transfusion was completed in 35% (30/86) of reactions prior to symptom onset. Transfusion was reattempted after resolution of symptoms in one instance or 1.2% (1/86) of the time. Transfusion reaction reports recommended premedication in 33.7% (29/86) of analyzed reactions. A small proportion, 7% (6/86), was taking regular antihistamine medication at the time of transfusion, all in the form of famotidine.

Of patients with a described history of ATRs, 70% (9/13) had historic transfusion reports available for review. In all, 20 reaction reports were reviewed, some of which were historical reports from before the beginning of our study period. Recommendations for blood product modification or patient premedication were made in 60% (12/20) of transfusion reports, with 20% (4/20) recommending volume reduction, 25% (5/20) recommending steroid premedication, and 55% (11/20) recommending antihistamine premedication. Recommendations for volume reduction or premedication prior to subsequent transfusion were present in 44% (4/9) of these patients, with 100% (1/1) volume reducing, 33.3% (1/3) premedicating with steroids, and 100% (3/3) premedicating with antihistamines. All patients had chronic illness; 85% (11/13) were oncology patients while one patient had sickle cell disease and the

other cirrhosis. All had undergone multiple transfusions and, at some point, been successfully transfused without allergic symptoms.

Discussion

We reviewed mild ATRs at a large academic medical center (VUMC) to better characterize the associated symptomatology with the goal of identifying what transfusionists might consider sufficiently concerning to be unwilling to continue a transfusion and abort it. In addition, we hoped to identify areas for possible improvement in the utilization of blood products and management of these patients.

We examined patients with mild ATRs, defined by allergic symptomatology without anaphylaxis or severe respiratory compromise. At our institution, the rate of ATRs has previously been reported as 0.6 per 1,000 transfusions.¹⁸ In our study, we found skin manifestations to be the most common presenting symptom in mild ATRs, with one-third of patients developing only dermatologic symptoms. Mild allergic symptoms are generally well tolerated and usually can be effectively treated with just antihistamine medication without aborting the transfusion. Patients with mild ATRs had a relatively low rate of respiratory symptoms (19%) such as mild wheezing or throat tightness (which was not unexpected since these symptoms are usually indicative of a more severe reaction).

Among the nonallergic symptoms observed, the most common symptom associated with mild ATRs in our study was tachycardia (37.8%), followed by dyspnea (28.9%), hypotension (17.8%), hypertension (13.3%), and nausea/vomiting (15.6%) (Table 1). The etiologies of these associated symptoms in mild ATRs remains unclear but is likely variable and in certain cases likely associated with the patient's underlying medical condition. Tachycardia could likely be associated with the increased heart rate of anemia, given that 82% of the patients who developed tachycardia were anemic, 64% of whom were tachycardic by pretransfusion vitals. All patients who developed tachycardia had been tachycardic at some point during the admission prior to transfusion. Although the CDC recommends classifying an ATR as severe if there is cardiac involvement, it may be too general to consider tachycardia in isolation as concerning for a cardiac etiology. Another potential etiology for tachycardia in patients with ATRs may be a sympathetic response to the anxiety of experiencing a transfusion reaction. Dyspnea and hypotension may similarly be associated with the high prevalence of anemia or be independent factors. The etiologies of the other associated symptoms remain unclear.

However, the importance of these analyses is that the relatively high prevalence of clinically concerning symptoms may be a contributing factor to transfusionists aborting transfusions associated with mild ATRs (at VUMC and likely elsewhere). The study may also suggest that transfusionists made the correct determination to abort at least some of these transfusions given the concerning associated symptoms and that we need to better clarify the kinds and contexts of such associated symptoms that might justify abortion of transfusion in mild ATRs.

The prevalence of atopic conditions in this patient population was not greater than in the general population except for a slightly higher history of drug allergy. Unfortunately, while drug reactions were reported at a rate higher than epidemiologic values in patients with ATR, they are one of the more subjective symptoms in clinical medicine and may not reflect true pathology. A similar study looking at risk factors for allergic reactions in platelet-transfused patients found allergic rhinitis and food allergy to be the most common conditions.¹⁰ We found allergic rhinitis to be common among our patient population (23%), but again at a rate no higher than what is expected in the general population. Moreover, various etiologies causing rhinorrhea may be falsely attributed to allergic rhinitis. The population we reviewed were only those having mild ATR; therefore, a link between atopy and anaphylactic reactions cannot be made based on our results. Based on our findings, a history of allergic disease was not felt to be associated with mild ATRs.

The total blood product wastage associated with mild ATRs in our study at VUMC was 6,892.3 mL at a cost of approximately \$12,507.96. This represents 0.15% of products transfused at our institution. In a culture focused on quality improvement and optimal product utilization, this represents an area of potential improvement. More than half of the patients went on to receive additional transfusions after mild ATRs. Of these, 34% required only one additional blood product. Employing optimal practices, these patients' symptoms could have been managed while the transfusion was paused, and the transfusion could have been completed if the symptoms resolved, which might have obviated additional transfusions and potential reactions. As 17% of patients with mild ATRs in this study had prior ATRs, prevention of further transfusions in this population represents an obvious preventative measure as pretreatment with medications has been shown to be ineffective.¹⁹⁻²²

Resumption of transfusion occurred in only one instance. This underscores the lack of understanding among clinical staff regarding the preferable option to pause the transfusion, treat the patient's symptoms, and complete the transfusion especially if there is symptom resolution. Given that 85% of patients in our study had

complete resolution of symptoms following treatment but only a single attempt at completing the transfusion was made, this presents an opportunity for mitigating blood product wastage and preventing additional blood product exposures. All patients had improvement of symptoms without progression to anaphylaxis, which is consistent with the observation that less severe allergic reactions generally do not evolve from mild ATRs, although continued patient monitoring is advised.

While we would not recommend premedication for patients following an initial mild allergic reaction due to its ineffectiveness at preventing recurrent mild ATRs, we do recognize a potential role for washing or premedication, including the use of both antihistamines and steroids in patients with a history of recurrent allergic reactions, especially if severity is moderate or severe.²³

A limitation of this study is the subjective nature of symptom reporting in the electronic medical record; however, these data are readily available for analysis and serve as an adequate surrogate for history taking in many situations. In addition, the use of epidemiologic data for rates of atopic disease as opposed to a control group may hinder accurate comparison as the general population and patients undergoing regular transfusion may have divergent clinical backgrounds.

Proper understanding and characterization of allergic symptoms are necessary for accurate identification and management of mild ATRs. With this understanding, clinicians can better predict ATRs, manage patients, and improve blood product wastage when mild ATRs occur.

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