



Clinical Chemistry Trainee Council

Pearls of Laboratory Medicine

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TITLE: Allergic Reactions to Blood Transfusion

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Hello, my name is Will Savage. I am Associate Medical Director in the Division of Transfusion Medicine at Brigham and Women's Hospital/Dana Farber Cancer Institute. Welcome to this Pearl of Laboratory Medicine on "Allergic Reactions to Blood Transfusion."

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Allergic transfusion reactions are a spectrum of acute hypersensitivity reactions to transfused blood. They occur during or very soon after a transfusion is complete. Typically, pruritus and/or urticaria are present in a localized area unrelated to the infusion site. In about 10% of reactions, the skin involvement is extensive, manifesting as coalescent eruptions over large parts or even the entire body. Flushing is a sign of histamine release and is common. Angioedema and dyspnea also occur in a large minority of allergic transfusion reactions, but these are typically mild. Angioedema usually involves a focal area, e.g. lips, eyelids. Dyspnea is often subjective without overt signs of respiratory distress. Nevertheless, life-threatening angioedema and respiratory failure do occur. Hypotension occurs in <1% of allergic transfusion reactions. Abdominal pain, nausea, and vomiting can also be signs. All of these manifestations are similar to other type I immediate hypersensitivity reactions.

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One way to classify allergic transfusion reaction manifestations is as mucocutaneous only or anaphylaxis. Anaphylaxis is defined as an acute, life-threatening illness in response to allergen exposure with involvement of the skin and/or mucosa plus respiratory compromise, hypotension, or gastrointestinal distress. Of course, "life-threatening" can be hard to define. Operationally, allergists often call a reaction with mucocutaneous manifestations and another organ system involved, anaphylaxis. The term "anaphylactoid" has been variably used to define mild cases of anaphylaxis that do not require extraordinary intervention or allergic reactions that do not have an IgE mediated mechanism. Many suggest that the term no longer be used because of its ambiguity and the fact that the mechanism is unknown in most cases.

The CDC hemovigilance criteria defines severity of reactions as severe or not severe, where severe is anaphylaxis, as I just described. The International Society of Blood Transfusion uses a mild, moderate, and severe definition, where moderate and severe are essentially mild and severe anaphylaxis.

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This is a photo of a typical urticarial eruption in response to a platelet transfusion. There were other lesions on the arms and back. These were accompanied by intense pruritus that was very uncomfortable for the patient.

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Allergic transfusion reactions are common. The best data on the incidence of these reactions comes from prospective studies of platelet transfusion. Generally, these show allergic reaction rates in the range of 2-4%. Most of these reactions are minor, meaning that they are limited to cutaneous findings and resolve relatively quickly. Note, however, that this does not mean that these reactions are inconsequential. They cause delays in transfusion, increase costs, and are uncomfortable for patients, as in the prior slide, despite being labeled “minor.” Reactions to RBC components are about 10 fold lower than platelets. This is associated with the reduced plasma content of RBC components. Data on reaction rates to plasma are less precise because plasma is used more frequently in settings that make it harder to identify allergic reactions, e.g. surgical and trauma situations. Nevertheless, the incidence is roughly the same as platelets. Most people only have an isolated allergic reaction. Recurrent reactions occur in a minority of people with allergic transfusion reactions.

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The mechanisms of allergic transfusion reactions are largely unknown, but there are many case reports that illustrate specific mechanisms. When thinking about mechanisms of these reactions, it's helpful to classify them as donor-, product-, and/or recipient-centric. Of course, in every reaction, there is a donor, product, and recipient involved, but it's useful to think about which element is pathologic.

On the donor side, case reports exist of donors with unusual, pathogenic antibodies that are passively transferred to recipients, thereby causing a reaction. Examples include case reports of donors with high levels of anti-peanut IgE, anti-penicillin antibody, anti-CD36 antibody, and anti-IgE antibody.

The best example of a product-specific issue is the observation that transfusions from pre-operative autologous blood donations can cause allergic transfusion reactions. This observation is an argument for a storage-related derangement that can lead to an allergic transfusion reaction, although no such mechanism has clearly been demonstrated.

For transfusion recipients, patients can make antibodies to plasma proteins, for example IgA. Anti-haptoglobin and anti-complement antibodies have also been described.

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Despite those examples of specific mechanisms, for most allergic reactions, a cause cannot be identified. In broad strokes, however, we know clinical risk factors for these “common” allergic transfusion reactions. Plasma seems to be the culprit. A study by Tobian and colleagues showed that the incidence of allergic transfusion reactions in patients with recurrent reactions decreased with decreasing amounts of plasma content. Concentrated platelets have about one-third the plasma of unmanipulated platelets and have about one-third the reaction rate. Washed platelets have over 90% of plasma removed, and the reaction rate is reduced by about 90%.

Another factor appears to be a recipient susceptibility for allergic transfusion reactions. Our recent study showed that among atopic diseases, aeroallergies in particular are a risk factor for allergic transfusion reactions. The odds ratio for an allergic reaction given a positive aeroallergen sensitization screen is 2.7. Furthermore, there is a direct, quantitative relationship between levels of aeroallergen-specific IgE and the frequency of reactions.

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Perhaps the most commonly talked about mechanism of allergic transfusion reactions is IgA deficiency. The concept is straightforward: someone lacking IgA gets sensitized through exposure and reacts when re-exposed to components containing IgA. The clinical data surrounding IgA deficiency are much less clear. Prevalence studies indicate that severe IgA deficiency with anti-IgA antibodies is ~1 in 1,200 people. The rate of severe allergic transfusion reactions is much lower. Furthermore, IgA deficiency is seldom implicated in fatal anaphylactic transfusion reactions. Why the discrepancy? It may be that anti-IgA antibodies play only a partial causal role in allergic transfusion reactions or they may be a surrogate marker for another risk factor. Additionally, anti-IgA that is IgE class may be the culprit, and currently no test can reliably determine IgE anti-IgA levels. Evidence is also derived from observations that passively transfused anti-IgA from donors with anti-IgA does not cause allergic reactions. Therefore, current IgA testing does not predict risk for allergic transfusion reactions.

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Regardless of the mechanisms of these reactions, we all want to prevent allergic transfusion reactions. The first and often overlooked method is to make sure that each transfusion is necessary. After all, a transfusion without benefit presents only risk to the patient. Assuming that the transfusion is required, the best way to prevent allergic transfusion reactions is to remove plasma by concentrating or washing, as appropriate. Additionally, platelets can now be manufactured in platelet additive solution, which leaves the platelet component with one-third the plasma of a standard platelet component. Plasma reduction is used only to prevent severe reactions or frequent, bothersome minor reactions. Plasma reduction is used in select circumstances only. It is time-consuming, shortens the lifespan of the component, and in the case of platelets, leads to decreased post-transfusion increments.

Many hypothesize that transfusion-related factors can contribute to allergic transfusion reactions, such as product age, infusion rate, or ABO matching. However, there is no clear evidence that giving fresher blood components, slowing infusion rates, or ensuring ABO matching affects the incidence of allergic transfusion reactions. Therefore, there is no evidence for transfusing products based on these attributes.

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The most common method for prevention of allergic transfusion reactions is transfusion premedication. Unfortunately, all available evidence, including two randomized controlled clinical trials, show that premedication with antihistamines does not prevent these reactions. Nevertheless, the practice of premedication is entrenched in most institutions. Premedication should be discouraged. On the other hand, antihistamines do alleviate symptoms when they occur. The situation is analogous to how albuterol is used to alleviate symptoms of asthma, but it is not used as a prophylactic medication in most circumstances.

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When an allergic transfusion reaction occurs, as with any transfusion reaction, the first step is to stop the infusion. Administration of antihistamines is warranted. Experimental data support a synergistic effect of H1 and H2 receptor antagonists used in combination. Glucocorticoids can prevent late phase reactions that can occur up to one day after the onset of symptoms. In the case of anaphylaxis, epinephrine is always the first choice drug. If an allergic reaction is minor and resolves quickly, the transfusion may be continued.

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In summary, allergic transfusion reactions are common and their incidence is related to how much plasma there is in the blood component. Most reactions are limited to skin findings, but they can be very bothersome to patients. Despite being very common, very little is known about what causes most allergic transfusion reactions. The most commonly employed strategy to prevent these reactions is premedication, but this does not work. Antihistamines only work for symptomatic relief, not as a premedication.

Slide 13: References**Slide 14: Disclosures****Slide 15: Thank You from www.TraineeCouncil.org**

Thank you for joining me on this Pearl of Laboratory Medicine on “Allergic Reactions to Blood Transfusion.” I am Will Savage.