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## Managing Blood Product Needs in Patients with Anti-IgA-Associated Anaphylaxis

**Introduction:** Anaphylactic and anaphylactoid reactions occur in one in 20,000 to 47,000 transfused components.<sup>1</sup> Reports to the FDA between 1976 and 1985, found that 8 (3.1%) of 256 transfusion-related deaths were caused by anaphylactic reactions.<sup>2</sup> Anaphylactic or anaphylactoid reactions related to antibodies to IgA occur less frequently, although this is the most common cause of transfusion-associated anaphylaxis in the US.<sup>3</sup> Since these reactions occur in IgA-deficient patients, techniques for managing these patients require IgA-deficient products such as washed red cells and platelets.

**Incidence:** The most common form of immune deficiency is isolated IgA deficiency (serum IgA less than 0.05 mg/dL). It occurs in approximately 1 in 700 individuals of European descent and about 1 in 18,500 Japanese.<sup>4,5,6,7,8</sup> The inheritance pattern can be either autosomal dominant or recessive. In addition, IgA deficiency may result from drug exposure, alcohol, chemicals such as benzene, or infectious agents such as toxoplasmosis, measles or rubella. It has been estimated that up to 40% of IgA-deficient individuals develop antibodies to IgA, putting them at risk for anaphylactic/anaphylactoid reactions when exposed to IgA-containing blood components.<sup>3</sup>

The incidence of IgA related anaphylactic/anaphylactoid reactions mentioned above is considerably less than what would be expected from the incidence of antibodies to IgA in blood donors. For example, Sandler *et al.*<sup>9</sup> found antibodies to IgA in 1 of 1,200 blood donors. The reasons for this difference are not clear. Not all patients with antibodies to IgA have a history of sensitization to IgA from pregnancy or previous transfusion, so absence of exposure history is not predictive of reaction risks. In addition, some non-IgA-deficient individuals develop autoantibodies to IgA that do not react with allogeneic IgA.<sup>10</sup>

**Antibody formation:** IgA is found primarily in secretions such as saliva, milk, respiratory and intestinal mucous. IgA antibodies are dimers composed of two heavy and two light chains. A "J" chain joins the heavy chains of the two subunits. IgA sub-classes are identified on the basis of amino acid sequence differences in the heavy chain and are designated as IgA1 and IgA2. Individuals lacking IgA may develop class-specific antibodies to IgA, while others may develop subclass specific antibody (anti-IgA1 or anti-IgA2) or allotype specific antibody (reacting against different IgA

- **IgA deficiency should be ruled out in cases of transfusion-associated anaphylaxis.**
- **Antibodies to IgA are the most common cause of transfusion-associated anaphylaxis in the US.**
- **It is important to recognize and confirm antibodies to IgA in patients with transfusion-associated anaphylaxis, because these patients will require life-long support with IgA-deficient blood products and plasma derivatives.**
- **IgA-deficient blood products include extensively washed cellular products and those collected from IgA-deficient blood donors.**

myeloma proteins). Subclass or allotype specific antibodies are considered to have "limited specificity" and are implicated in less severe allergic reactions. However, these "limited specificity antibodies" have caused severe<sup>11,12</sup> or even fatal<sup>12</sup> reactions. Class specific antibodies tend to be associated with more severe reactions.

Anaphylactic reactions generally are caused by IgE antibodies directed against IgA. Indeed, IgE anti-IgA mediated anaphylactic reaction following transfusion has been recognized in several patients with hypogammaglobulinemia or common variable immune deficiency who are being treated with IV immune globulin (IVIG).<sup>13,14</sup> IgE-anti-IgA has not been detected universally.<sup>15</sup> In addition, IgG anti-IgA has also been found with an anaphylactoid reaction.<sup>16</sup>

**Diagnosis:** Because the signs/symptoms of a transfusion-related acute allergic reaction are not specific, the suspected transfusion should be stopped. Signs and symptoms include pruritis, urticaria, angioedema, respiratory distress (caused by bronchospasm, laryngeal edema, or laryngospasm), abdominal cramping and diarrhea. The differential diagnosis includes hemolytic transfusion reaction, fluid overload, transfusion-related acute lung injury (TRALI), septic shock, and allergic reactions to other proteins, drugs, haptoglobin, complement and von Willebrand proteins, and symptoms related to the underlying disease. Environmental allergens such as latex, drugs, or food should also be investigated.

If antibodies to IgA are considered the likely cause, a pre-transfusion specimen should be tested for IgA levels and/or the presence of antibodies to IgA. It should be noted that many assays cannot detect low levels of IgA and it may be necessary

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to send specimens to reference laboratories (*e.g.*, American Red Cross). EIA testing detects IgA levels as low as 0.054 mg/dL. Ochterlony plates using radial immunodiffusion have a sensitivity of 5-7 mg/dL. If the EIA detects IgA, the individual is not considered IgA-deficient and the reaction is less likely to be mediated by antibodies to IgA. Subclass or allotype-specific antibodies to IgA as well as class specific antibodies to IgA may cause an anaphylactic reaction.<sup>17</sup> Immunoradiometric assays (IRMA)<sup>18</sup> and passive hemagglutination assays (PHAA)<sup>19,20,21</sup> can be used to detect IgG or IgM antibodies to IgA but may not detect IgE antibodies to IgA without modification. A negative result should be confirmed by a test capable of detecting IgE.<sup>21</sup> Unfortunately, these tests are not readily available.

**Treatment:** Epinephrine administration, airway management, and volume expansion are the key acute interventions. To prevent future reactions, patients should receive IgA-deficient blood components. Depending on the urgency of the transfusion, it may be necessary to transfuse IgA-deficient blood before the patient's IgA antibody status is known. Washing red blood cells with saline<sup>22</sup> three to six times removes IgA from RBC components. Platelet components must be obtained from IgA-deficient donors or washed. Washing platelets is less desirable because it impairs platelet function and there usually is substantial loss of platelets. Plasma products must be obtained from individuals known to be IgA-deficient. A blood product is considered IgA-deficient for the purpose of transfusion if the serum IgA is below 0.05mg/dL. Many blood centers have IgA-deficient donors who can be called upon to provide suitable blood products. In addition, the American Rare Donor Registry can be consulted.

Plasma derivatives such as IVIG, Rh immune globulin, Factor VIII concentrates and albumin may contain sufficient amounts of IgA to trigger reactions. Consequently it is important to consult the package insert prior to administering these products to susceptible patients. IgA-deficient immune globulin is available. A new strategy for "blocking" IgA antibodies has been proposed that involves *ex vivo* pretreatment of intravenous immunoglobulin preparations with autologous plasma.<sup>22</sup>

**Conclusion:** Transfusion-related anaphylaxis induced by antibodies to IgA is a potentially serious but rare event that must be differentiated from other causes of anaphylaxis. It occurs predominantly in IgA-deficient patients but has been reported in patients with normal IgA levels, including patients suffering from allergic reactions to other proteins. The best indicator of an IgA-mediated anaphylactic/anaphylactoid reaction in a clinical setting is the identification of antibodies to IgA in the patient. It is important to recognize and confirm this IgA deficiency among recipients, because these patients require lifelong support with IgA-deficient blood components.

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