Immunological transfusion reactions

Immunological transfusion reactions can be hemolytic or non-hemolytic in nature. Both types can be separated into acute (those occurring immediately after transfusion) and delayed reactions. The worst type of reaction is the acute hemolytic reaction, which can result in death of the animal.

Hemolytic immunological transfusion reactions

- **Acute hemolytic reaction**: An acute hemolytic reaction is due to a blood type incompatibility (i.e. there are antibodies in recipient serum against donor red blood cell antigens) and is a class II (antigen-antibody) hypersensitivity reaction. A disastrous acute hemolytic crisis is what is often pictured as the typical transfusion reaction, however, in reality, these reactions are quite uncommon, particularly in dogs and horses. These species lack naturally occurring antibodies to major red blood cell antigens and severe acute reactions are due to acquired antibodies, such as secondary to prior transfusions or pregnancy. The antigens involved in acute hemolytic reactions are DEA 1.1 and 1.2 in the dog and Aa and Qa in the horse (there has been one report of an acute hemolytic reaction in a DEA 1.1-negative, 1.2-positive Whippet administered numerous bags of DEA 1.1-negative blood, suggesting a reaction to a common blood group antigen (none of the known blood types) that was absent in the dog as well as a related sibling). In cats, an acute hemolytic reaction can occur on the first transfusion as naturally occuriring antibodies are found in this species. The most severe reaction occurs in type B cats administered type A or type AB blood.

  The severity and timing of an acute immune-mediated hemolytic reaction depends on the type of antibody involved (IgM or IgG), the temperature at which they bind to the antigen and how efficiently they fix complement. Hemolysis can be extravascular or intravascular, with consequences of intravascular hemolysis being more serious. With intravascular hemolysis, there is systemic activation of hemostasis (thus initiating DIC) and production of systemic hypotension (due to the release of vasoactive substances such as C3a, C5a, bradykinin), shock (due to cytokine release) and renal failure (from ischemic necrosis due to hypoxia, DIC and renal vasoconstriction).

  Clinical signs of a severe acute hemolytic reaction are, unfortunately, non-specific and include tachycardia, dyspnea, collapse, hypotension,

salivation, tremors, convulsions, weakness, vomiting and pyrexia. Acute intravascular hemolysis produces hemoglobinemia (as shown in the image on the left) and hemoglobinuria, which can occur with minutes of transfusion. Extravascular hemolysis is due to destruction of antibody-coated donor erythrocytes by the macrophages in the spleen and liver, leading to hyperbilirubinemia and bilirubinuria. Clinical signs are generally milder than those produced by intravascular hemolysis.

If an acute hemolytic reaction develops, the transfusion should be immediately stopped and supportive therapy instituted. This includes administration of intravenous fluids to combat hypotension and shock and maintain renal perfusion. Some authors also advocate the use of corticosteroids with or without low doses of dopamine. Treatment of DIC is also indicated (and controversial in itself). In general, acute hemolytic transfusion reactions can be **prevented** by crossmatching or using only matched typed blood. Remember, that all cats should be typed or crossmatched before their first blood transfusion (although depending on the breed, the likelihood of having a type B cat can be quite low).

- **Delayed hemolytic reaction**: Delayed hemolytic transfusion reactions are a result of extravascular hemolysis occurring within 3 to 21 days after transfusion. This reaction may occur in dogs that are administered incompatible blood on the first transfusion. It takes about 7 to 10 days to get an antibody response to the foreign red cells, thus after the production of antibody, there is accelerated removal of the donor erythrocytes and the transfusion does not last as long as it should. This also occurs in dogs when they are transfused with blood types to which they possess natural occurring antibodies (against DEA 3, 5 and 7) or have been sensitized to an antigen (that elicits a delayed hemolytic reaction, rather than the acute hemolytic reaction seen with antibodies against DEA 1.1 and 1.2) via previous incompatible transfusions, once an anamnestic response has been elicited.

  Delayed hemolytic reactions are usually mild and may not be recognized. This type of reaction should be suspected in a patient in which the post-transfusion hematocrit rapidly declines or does not stay elevated for as long as it was expected to, or that develops hyperbilirubinemia and/or bilirubinuria. The most common signs are fever, anorexia and jaundice. A positive direct Coombs test will also be seen.

Specific treatment for this type of reaction is generally not required. This type of reaction can be **minimized** by using matched typed or crossmatched blood (remember that the crossmatching procedure will not detect low titers of antibodies, therefore these reactions cannot be totally prevented). All dogs should be crossmatched after a second blood transfusion.

- **Neonatal isoerythrolysis**: This occurs when a female animal of one blood type is mated to a male of another. Neonates that inherit the blood group of the sire develop hemolytic anemia when they ingest colostrum containing antibodies against their and the sire's erythrocytes. This has been reported in cats, dogs, cows, pigs and horses. In cats, it occurs with type B queens mated to A or AB toms. In this situation, all kittens bearing the type A antigen will suffer a hemolytic anemia at birth after ingestion of colostrum containing **naturally occurring** anti-type A antibodies. In horses and dogs, this occurs in dams that have been **previously sensitized** to blood group antigens (types Aa and Qa especially in the horse and DEA 1.1 and 1.2 in the dog).

  Clinical signs include weakness, failure to thrive, hemoglobinuria and death (fading kitten/puppy/foal syndrome). Affected kittens can also suffer from tail tip necrosis. A Coomb's test on the neonate will be positive and a crossmatch between the dam's serum and neonate's erythrocytes will reveal the incompatibility (for more information, see mare-foal incompatibility). Neonatal immune-mediated thrombocytopenia has also been reported.

Non-hemolytic immunological transfusion reactions

- **Acute hypersensitivity**: Acute hypersensitivity reactions are usually due to anaphylactic (allergic or type I hypersensitivity) reactions. This is mediated by IgE antibodies which activate mast cells, which then release inflammatory and vasoactive mediators, that produce hypotension, increased vascular permeability, bronchiolar constriction, urticaria and pruritis. Another type of reaction is an anaphylactoid reaction, which is not mediated by IgE. The exact mechanism of this reaction is uncertain, but it is likely due to cytokines or other products which activate the same inflammatory and vasoactive mediators. Allergens in the donor blood include antibiotics or chemicals used in blood preparation, albumin and C4. Rarely, transfused IgE antibodies from the donor can initiate the reaction. This type of reaction is frequently seen with infusion of plasma (fresh, fresh frozen or frozen) and cryosupernatant. It has not been documented with infusion of cryoprecipitate.

This type of reaction can occur on the first tranfusion. Clinical signs occur rapidly after transfusion (within 1 to 45 minutes) and range from minor skin reactions (this is the most common reaction, consisting of pruritis, facial edema, wheals, urticaria) to more severe allergic reactions, including hypotensive shock, bronchoconstriction and cardiopulmonary arrest.

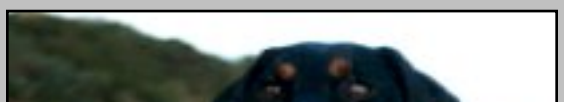
Treatment consists of stopping the transfusion. For mild reactions, administration of antihistamines and corticosteroids will rapidly alleviate the clinical signs. More severe signs require intensive shock therapy, including administration of corticosteroids and, possibly, epinephrine. This type of reaction can be minimized by pretreatment with antihistamines (in predisposed animals), slow infusion rates, not pooling products from multiple donors, and by being careful with selection of components (i.e. use cryoprecipitate instead of plasma when indicated).

- **Acute leukocyte/platelet hypersensitivity reactions**: These produce mild and transient fever (so-called febrile non-hemolytic transfusion reactions) and are the most common type of transfusion reaction observed with whole blood. In human patients, this reaction has only been observed with whole blood, red cell or platelet concentrates, and fresh plasma. It has not been observed with frozen plasma products (FFP or cryoprecipitate). The reaction is suspected when there is a temperature increase of at least 1 C with no other cause for the elevation. This reaction has been attributed to the presence, in the recipient's plasma, of antibodies reactive against antigens on donor leukocytes or platelets or to cytokines (TNF, IL-1, IL-6), that are actively produced by donor leukocytes and accumulate in the transfusion product with storage.

  These reactions can occur on the first transfusion, with fever being noted within the first 30 minutes (and can persist for up to 20 hours). Vomiting and tremors may also be seen. Severe lung injury due to acute respiratory distress syndrome (non-cardiogenic pulmonary edema, dyspnea and hypoxemia) has also been reported in rare human cases.

  In severe cases, the transfusion should be stopped. Antipyretics may be given. In milder cases, the transfusion rate can be slowed or stopped then restarted at a slower rate. Febrile reactions can be **minimized** by leukoreduction of the product prior to transfusion. This can be accomplished by the use of special filters in transfusion lines. One such filter has been evaluated in dogs and effectively reduced the number of transfused donor leukocytes in whole blood transfusions by 87 to 99%, without affecting post-transfusion red cell viability.

- **Delayed transfusion-related**



thrombocytopenia: Post-transfusion purpura is a rare condition in human patients characterized by a severe thrombocytopenia 1 to 2 weeks after blood or blood product transfusion. It is believed to be due to the development of platelet-specific antibodies that destroy both the transfused and the patient's own platelets. This has been reported in a dog with hemophilia A. The dog developed a severe thrombocytopenia (platelet count < 10,000/µl), on 2 occasions after being transfused (the first occurred 8 days after a second blood transfusion; the second, 5 days after cryoprecipitate infusions). On both occasions, the platelet counts normalized within 4 to 6 days of corticosteroid therapy (but the dog may have recovered spontaneously without treatment). No specific treatment is required.

- **Neonatal thrombocytopenic purpura**: This condition (similar to neonatal isoerythrolysis) has been recognized in pigs. Agglutinating antibodies against sire and piglet platelets have been documented in the dam. The piglets are generally born healthy, then develop thrombocytopenia after 5 to 9 days, with the nadir occurring at 10 to 13 days. Thrombocytopenia is due to increased platelet destruction and decreased platelet production. Clinical signs of cutaneous hemorrhage are seen. Death may result at 2 to 3 weeks of age. Surviving piglets appear clinically and hematologically normal by 16 weeks of age.Severe thrombocytopenia was discovered in a 1 day old Quarterhorse foal presenting for weakness and failure to suckle. His dam's serum contained antibodies that bound to his and a full brother's platelets.

- **Immunosuppression**: Donor lymphocytes in the transfused whole blood or blood product are believed to suppress immunity in the recipient. In extreme cases in human patients (especially with multiple transfusions), transfusion-associated graft versus host disease can result (this has not been reported with frozen plasma products). Immunosuppression or graft versus host disease can be reduced by leukoreduction or destruction of

immunocompetent donor lymphocytes (such as by radiation). This type of transfusion reaction has not been recognized in animals.