Abstract

Every transfusion of a blood component results in a physiologic reaction, but most reactions are nearly unnoticeable or have a minimal clinical consequence. It is important to be able to recognize potentially dangerous transfusion reactions early in their development and to take measures to minimize the damage that can occur. This article reviews the most significant reactions caused by administering different blood components. The pathogenesis, methods of avoidance, and treatment of each reaction are detailed.

As the availability of blood products and understanding of their use have grown, blood component therapy has become standard practice in veterinary medicine. Because different disease states result in a spectrum of hematologic deficiencies, fresh whole blood is rarely the most appropriate blood product to use. Donated fresh whole blood can be separated to yield specific blood components (e.g., packed erythrocytes, plasma, cryoprecipitate, platelet concentrates). By transfusing a patient only with the blood component that is indicated and by applying the techniques of blood typing, crossmatching, and appropriate donor selection, most transfusions can be performed safely and effectively. Even with meticulous planning, transfusion reactions can occur (see Box).

Transfusion Reactions

- Acute immunologic reactions
  - Acute hemolytic transfusion reaction
  - Allergic reactions
  - Febrile nonhemolytic transfusion reaction
  - Transfusion-related acute lung injury
- Delayed immunologic reactions
  - Delayed hemolytic transfusion reaction
  - Posttransfusion purpura
- Acute nonimmunologic reactions
  - Volume overload
  - Citrate toxicity
  - Hypothermia
  - Bacterial contamination
- Delayed nonimmunologic reactions
  - Infectious disease transmission

An understanding of transfusion medicine and transfusion reactions can minimize the frequency of reactions and their severity.
Canine Blood Types

There are eight commonly identified canine blood types, but as many as 12 may exist (Table 1).3,4

<table>
<thead>
<tr>
<th>Blood Type (Dog Erythrocyte Antigen)</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>42</td>
</tr>
<tr>
<td>1.2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>98–99</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
</tr>
</tbody>
</table>

It is rare to identify all the dog erythrocyte antigen (DEA) types of a donor and recipient before a transfusion, and it can be cost prohibitive. Because some DEA types are not very prevalent (Table 1) or do not stimulate a strong immune response, blood typing is generally limited to DEA 1.1 and 1.2 and some sources advocate typing for DEA 7.5–7 Dogs are believed to lack clinically relevant, naturally occurring antibodies against foreign erythrocyte antigens called alloantibodies. Some sources suggest that alloantibodies to DEA 7 exist, but this has been questioned.3,4 A first-time transfusion between two untyped dogs is unlikely to incite an acute transfusion reaction, even if they have different blood types.4

Feline Blood Types

Feline erythrocyte antigens are denoted with an AB system.6 An individual cat may have blood type A, B, or, very rarely, AB. In the United States, more than 99% of all cats have type A blood. Higher percentages of cats with type B blood are found in Europe, Japan, and Australia5,10 (Table 2).

<table>
<thead>
<tr>
<th>Location</th>
<th>Blood Type (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Northeastern US</td>
<td>99.7</td>
</tr>
<tr>
<td>Southeastern US</td>
<td>98.5</td>
</tr>
<tr>
<td>Southwestern US</td>
<td>97.5</td>
</tr>
<tr>
<td>West coast of the US</td>
<td>94.8</td>
</tr>
<tr>
<td>United States (total)</td>
<td>98.1</td>
</tr>
<tr>
<td>Australia (Brisbane)</td>
<td>73.3</td>
</tr>
<tr>
<td>England</td>
<td>97</td>
</tr>
<tr>
<td>Germany</td>
<td>94</td>
</tr>
<tr>
<td>France</td>
<td>85</td>
</tr>
<tr>
<td>Japan</td>
<td>90</td>
</tr>
</tbody>
</table>

Some breeds have a higher percentage of cats with type B blood10,11 (Table 3).
Cats with type B erythrocyte antigen have high levels of strong anti-A alloantibodies.

**Acute Immunologic Reactions**

Transfusion reactions are either acute or delayed and can result from immunologic or nonimmunologic causes.

**Acute Hemolytic Transfusion Reaction**

An acute hemolytic transfusion reaction (AHTR) results when a patient with preexisting antibodies to certain erythrocyte antigens is transfused with erythrocytes containing that antigen. This immunologic reaction is classified as type 2 hypersensitivity. Preexisting antibody (i.e., IgG or IgM) binds to the foreign erythrocyte antigen. This antigen-antibody complex then activates the complement cascade, resulting in intravascular hemolysis of the foreign erythrocyte.\(^4\,8\,12-15\)

If a dog that tests negative for a specific DEA is given blood that is positive for that antigen, the transfusion will not result in an AHTR, assuming the recipient has had no previous transfusions. If the same patient is again transfused with erythrocytes containing the DEA to which it has been sensitized, the second exposure can result in a life-threatening AHTR. DEAs 1.1, 1.2, and 7 are the blood types most likely to induce alloantibody production following a mismatched transfusion.\(^4\)

Enough erythrocytes and erythrocyte membrane fragments are present in fresh-frozen plasma and cryoprecipitate to cause an AHTR.\(^7\)

Because cats have endogenous alloantibodies to foreign erythrocyte antigens, an AHTR may occur with the first transfusion with the incorrect type of blood. The half-life of appropriately matched allogenic feline erythrocytes following a transfusion is 29 to 39 days. If type B blood is transfused into a cat with type A blood, the erythrocyte half-life is 2.1 days. Adverse reactions associated with this mismatch are considered relatively mild. Within minutes of starting such a transfusion, cats become listless, seem uncomfortable, and become tachycardic and tachypneic. Hemoglobinemia and hemoglobinuria may be noted.\(^8\) If type A blood is given to a cat with type B blood, the erythrocyte half-life is several hours and the reaction is severe and potentially fatal. These patients may hypoventilate or become apneic, vomit, develop diarrhea, vocalize, and develop arrhythmias. Hemoglobinemia and hemoglobinuria may occur. Because of the severe inflammatory response associated with a type AB-incompatible transfusion, signs of shock, systemic inflammatory response syndrome, multiorgan dysfunction syndrome, and disseminated intravascular coagulation can occur.\(^7\,8\) Acute renal failure can occur in humans who experience a type ABO blood mismatch causing an AHTR. Development of acute renal failure has been attributed to renal hyperperfusion, fibrin deposition, and direct tubular toxicity from free hemoglobin.\(^12\) Acute renal failure was not identified in cats subsequent to an experimentally induced AHTR, despite a similar constellation of clinical signs.\(^8\)

Most AHTRs can be avoided by taking a detailed history, blood typing donors and recipients, and crossmatching, when indicated. If an AHTR is suspected, steps should be taken to minimize the damage even before a definitive diagnosis of an AHTR can be made. The severity of the reaction is directly proportional to the volume of transfused mismatched blood. The transfusion should be stopped, and crystalloid and/or colloid solutions should be used to optimize blood pressure (BP) and maintain renal perfusion and urine output.\(^12\,15\) A central venous catheter and urinary catheter are useful in monitoring the adequacy of fluid therapy and assessing urine for the presence of hemoglobin. Urine output should be maintained at 1 to 2 ml/kg/hr. If the BP cannot be adequately maintained once the patient is fully volume loaded, vasoressor therapy should be considered. The mean arterial pressure must be kept above 60 to 70 mm Hg, which corresponds to a systolic arterial pressure of 80 to 100 mm Hg, to maintain appropriate renal perfusion.\(^13\) Heparin therapy may be indicated to minimize the prothrombotic state associated with severe inflammation, but an appropriate dose has not been uniformly agreed on. If hypoxemia (i.e., arterial hemoglobin oxygen saturation <94%; partial pressure
of arterial oxygen <70 mm Hg) is present, oxygen supplementation is indicated. Corticosteroids are not the standard of care in treating AHTRs in humans. Corticosteroid administration may minimize inflammation associated with AHTRs by decreasing interleukin (IL)-1 production, but this benefit is speculative.

Allergic Reactions

A wide range of acute allergic reactions can occur following transfusions. Most of these reactions are mild and manifested by cutaneous abnormalities such as erythema, urticaria, and pruritus, which are either self-limiting or easily treated (Figure 1 and Figure 2).

![Figure 1. Abdominal weals that developed during a transfusion.](image1)

![Figure 2. A wheal above the left eye of the same dog in Figure 1.](image2)

However, more clinically significant anaphylactic or anaphylactoid reactions can also occur, including hypotension, tachycardia, bronchoconstriction, vomiting, and diarrhea. A pure transfusion-related anaphylactic reaction has not been reported in the veterinary literature. An allergic reaction is a type 1 hypersensitivity reaction resulting from binding of antigen from the donor blood product to preformed IgE or IgG, which is bound to the recipient's mast cells and basophils. This causes the mast cells and basophils to degranulate, releasing vasoactive substances (i.e., histamine, leukotrienes, prostaglandins, cytokines).

Allergic reactions following fresh-frozen plasma and platelet transfusions tend to be more severe than those caused by erythrocyte products. This may imply that the severity of the reaction depends on the volume of plasma transfused and the amount of vasoactive substances in the stored plasma. During erythrocyte collection, some leukocytes contaminate the collection bag. These leukocytes degranulate during storage, releasing their vasoactive substances. When this blood is then used, an anaphylactic or anaphylactoid reaction can result. An anaphylactoid response is clinically indistinguishable from an anaphylactic reaction but differs in pathogenesis. An anaphylactoid response results from non-IgE-mediated mast cell or basophil degranulation, likely caused by the presence of complement-derived anaphylatoxins (i.e., C3a, C4a, C5a).

Cutaneous or mild gastrointestinal upset may be the first noted abnormality of an anaphylactic reaction; therefore, attention should be given to patients showing such signs. Anaphylactic reactions in dogs are manifested primarily by gastrointestinal signs of vomiting and diarrhea. Cats typically show respiratory distress, but severe pruritus, vomiting, and diarrhea may also be noted.
If an allergic reaction is suspected, the transfusion should be slowed or stopped. Diphenhydramine (2 mg/kg) should be given intramuscularly. If signs progress or do not improve, a short-acting steroid may be given, but there is not a consensus on an appropriate dose. If an anaphylactic reaction is suspected, epinephrine (1:1,000; 0.01 to 0.02 mg/kg SC, IM, or IV) should be administered to prevent bronchoconstriction and maintain blood pressure. Depending on the severity of the reaction, oxygen supplementation, intravenous fluid therapy, and vasopressors may be indicated.

Because an AHTR can appear similar to an allergic reaction, acute hemolysis should be ruled out. Evidence of hemoglobinemia or hemoglobinuria with a rapidly dropping packed cell volume (PCV) suggests a hemolytic transfusion reaction.

Febrile Nonhemolytic Transfusion Reaction

A febrile nonhemolytic transfusion reaction (FNHTR) is characterized by a 1°C or greater elevation in body temperature during or shortly following a transfusion that is not attributable to underlying illness or another transfusion reaction. FNHTRs are the most common adverse transfusion reactions reported in veterinary and human medicine. Despite the frequency of these reactions, they are usually self-limiting and of little clinical significance.

Most FNHTRs are caused by leukocyte antigens on donor leukocytes and platelets that react with specific antibodies in the recipient’s plasma. Transfusions of platelet concentrates are most likely to induce an FNHTR, but any blood product that contains platelets, leukocytes, or membrane fragments can cause this reaction. Leukocytes are often in blood products but are regarded as nonfunctional contaminants. During storage, leukocytes and platelets release pyrogenic cytokines IL-1β, IL-6, IL-8, and tumor necrosis factor-α. Consequently, the longer a blood product has been stored, the more likely it is to induce an FNHTR than is a fresh blood product of the same type.

Leukoreduction (i.e., removal of leukocytes from a donated blood product) has become common in human transfusion medicine. Based on a recent study, leukoreduction appears to be effective in veterinary patients as well. Several filter types are available for removing leukocytes at the time of donation or just before transfusion. Because leukocytes continue to elaborate pyrogenic cytokines during storage, it is advantageous to leukoreduce blood before storage rather than immediately preceding a transfusion.

Treating an FNHTR consists of slowing or temporarily stopping the transfusion and administering antihistamines and/or an NSAID to limit fever if it is clinically significant. Before proceeding with the transfusion, the clinician must be confident that fever is not a component of a more serious transfusion reaction.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a rare syndrome that can develop 1 to 6 hours following transfusion of a plasma-containing blood product. It is characterized by development of bilateral pulmonary edema, fever, and hypotension and is clinically indistinguishable from acute respiratory distress syndrome. In humans, TRALI is the second most common cause of transfusion-related fatalities, with a 5% mortality rate. TRALI has not been reported in the veterinary literature.

TRALI is caused by leukocyte antibodies from the donor plasma that react with the recipient’s leukocytes. TRALI should be suspected if the clinical history fits the syndrome and other causes of pulmonary edema, including cardiogenic pulmonary edema and volume overload, have been ruled out. The pulmonary fluid produced in TRALI has a high protein content, so it cannot be eliminated by diuretic therapy. In patients with TRALI, as in other cases of noncardiogenic pulmonary edema, the ratio of protein in the pulmonary fluid to that in blood is greater than 0.7. TRALI can be confirmed by documenting the presence of leukocyte antigen in donor plasma and demonstrating a positive reaction of donor plasma with recipient leukocytes via a crossmatch reaction. This level of confirmation may be impractical to routinely attain in veterinary patients.

The reaction typically lasts less than 96 hours. Therapy involves intravenous fluid and oxygen support as warranted by the severity of pulmonary dysfunction. Treatment with diuretics may be detrimental because of decreased intravascular volume and increased viscosity of the pulmonary fluid.

Delayed Immunologic Reactions

Delayed Hemolytic Transfusion Reaction

http://www.vetfolio.com/emergency-medicine/transfusion-reactions
A delayed hemolytic transfusion reaction (DHTR) develops when a patient is given blood containing a foreign antigen and the recipient then develops antibodies to that antigen. Dogs develop antibodies to a foreign antigen 4 to 14 days after transfusion. The newly formed antibodies adhere to the transfused cells, which are prematurely removed from the circulation. One of the hallmarks of a DHTR is extravascular hemolysis; therefore, hemoglobinuria does not occur. A DHTR is mild and can be clinically undetectable. An unexpected drop in PCV may be noted, often accompanied by a rise in serum bilirubin. Humans with DHTRs have described chills, back pain, and fever.

Because the only sign may be a premature decrease in PCV, it may be challenging to differentiate a DHTR from erythrocyte destruction due to an underlying disease such as immune-mediated hemolytic anemia, babesiosis, or *Mycoplasma haemophilus* infection. A positive Coombs' test is supportive of, but not specific for, a DHTR, especially in patients with immune-mediated hemolytic anemia.

Therapy is generally not indicated for a DHTR. The fall in PCV should be monitored because additional transfusions may be indicated if the rate of erythrocyte destruction is high, the inflammatory response may be significant, warranting supportive measures.

**Posttransfusion Purpura**

Patients that have been transfused with blood components containing whole platelets or platelet fragments may develop posttransfusion purpura (thrombocytopenia) following subsequent transfusions. This is a rare condition in humans and veterinary patients that develops following exposure to foreign platelet antigens. Thrombocytopenia typically occurs 7 to 14 days following a transfusion, and platelet counts can be low enough to result in spontaneous bleeding. Thrombocytopenia can resolve spontaneously in several weeks, but because catastrophic hemorrhage can occur early in the course of the disease, immunosuppressive steroid therapy is usually instituted early to hasten improvement.

**Acute Nonimmunologic Reactions**

**Volume Overload**

Volume overload can be caused by infusion that is too rapid or administration of an excessive volume of a blood product. Blood products are colloidal suspensions comprised of cells and/or plasma, so they do not rapidly diffuse from the intravascular space into the interstitial space as does crystalloid solution. Patients with cardiac disease or that are being diuresed for renal insufficiency must be transfused with caution. In addition, neonates and cats are less tolerant of intravascular volume expansion than are adult dogs. Patients with chronic anemia may present in a compensated euvolemic state, so rapid transfusion may result in hypervolemia. Volume overload may result in pulmonary edema and an increased respiratory rate, cough, dyspnea, or cyanosis. An acute increase in central venous pressure and/or arterial BP is helpful in diagnosing volume overload.

Volume overload can be avoided by transfusing at a rate and volume appropriate for the size and cardiovascular state of the patient. A central venous catheter can facilitate assessment of a patient's intravascular volume by measuring the central venous pressure. A sharp increase in central venous pressure (normal: 0 to 10 cm H$_2$O) during transfusion should prompt a rate reduction or discontinuation of the transfusion. If circulatory overload is suspected, a single dose of furosemide has been advocated to reduce intravascular volume by diuresis.

**Citrate Toxicity**

Citrate is the anticoagulant most commonly used in preservative solutions for blood products. Citrate binds calcium, preventing clot formation. It is metabolized to bicarbonate by the liver, skeletal muscle, and kidneys. This normal metabolism can be overwhelmed during large-volume, rapid transfusions or if significant liver dysfunction exists. Unmetabolized citrate can cause hypocalcemia. Hypomagnesemia can also result from citrate toxicity. Signs of hypocalcemia include nausea, arrhythmias, and tremors, leading to tetany. Electrocardiogram changes seen with hypocalcemia can include Q-T interval prolongation, bradycardia, and ventricular premature contractions. Suspected citrate-induced hypocalcemia can be confirmed by obtaining an ionized calcium level. Treatment involves slowing or stopping the transfusion and slowly infusing calcium gluconate (94 to 140 mg/kg IV for 20 to 30 minutes) or calcium chloride.

**Hypothermia**
Blood products that have been refrigerated or frozen should be warmed to body temperature before administration. Infusing large volumes of cold blood products can precipitate clinically significant arrhythmias and hypothermia-induced coagulopathy. Even small volumes of cold blood products can be detrimental if administered through a central line because transfused blood does not mix with enough warm blood before reaching the heart. Blood should be warmed to no more than 100.5°F (38°C) with an approved warming device to avoid overheating. Using a microwave oven or warm tap water is not an appropriate method of warming blood products because uneven and excessive heating can easily cause cellular damage and protein denaturation. Commercial blood warmers can warm the entire unit before administration, or a warmer that warms blood as it flows through the line can be used.

**Bacterial Contamination**

Transfusions of bacterially contaminated units of blood and blood products can cause severe sepsis and death. Contamination results from occult bacteremia of the blood donor, skin contamination at the time of donation, and contaminated collection devices. Platelet products pose the greatest risk because they are sometimes stored at room temperature (71.6°F [22°C]) for 3 to 5 days. Although stored whole blood and packed erythrocytes are generally refrigerated at 39.2°F (4°C) for up to 35 days, some bacteria can still thrive at this temperature. The organisms most commonly associated with erythrocyte contamination are *Yersinia enterocolitica*, *Serratia* spp, and *Pseudomonas* spp. The contaminants of platelet concentrates include *Staphylococcus*, *Streptococcus*, *Salmonella*, and *Serratia* spp. Most deaths from contaminated transfusions are due to contamination with gram-negative organisms.

It can be difficult to identify which units have been bacterially contaminated. Units of blood with dark discoloration, bubbles, or visible particulate matter may be contaminated. In addition, a low pH or glucose level or a positive Gram’s stain can suggest contamination, but these techniques are very insensitive. If a transfusion-transmitted bacterial infection is suspected, a sample from the suspicious unit should be gram-stained and cultured. The affected patient should be treated promptly with antibiotics and other therapeutic strategies appropriate for septic patients. Preventing bacterial contamination of blood components may include the following:

- Improving donor skin antisepsis
- Discarding the initial aliquot of donated blood to avoid skin contaminants and tissue plugs
- Limiting blood product storage times
- Using properly sterilized and stored collection equipment

**Delayed NonImmunologic Reactions**

**Infectious Disease Transmission**

The American College of Veterinary Internal Medicine recently published a consensus statement on screening canine and feline blood donors for infectious diseases. This consensus statement identifies a number of infectious diseases that can be spread via transfusions and makes recommendations for screening donors for those diseases. Some of those recommendations are included here.

Heartworm disease is found in most regions of the United States, and screening blood donors for this pathogen is common. Nevertheless, heartworm disease cannot be transmitted via transfusion from a donor that tests positive for microfilaria. The microfilaria must be ingested by a mosquito and then reintroduced into another dog or cat to complete their maturation and cause clinical heartworm disease. Heartworm testing of blood donors is suggested to maintain the health of the donor, not because there is a risk of transmitting heartworm disease to the recipient.

*Babesia* spp, the causative organisms of canine babesiosis, can be transmitted by transfusion. Babesiosis has been identified with high frequency in greyhounds and pit bulls, which are commonly used in donor programs. A report of *Babesia gibsoni* transmission due to a blood transfusion in Michigan was recently published. Blood donors, especially breeds at increased risk, should be screened for *Babesia* spp.

Canine donors should be screened for *Ehrlichia canis* by immunofluorescent antibody or point-of-care tests. Immunofluorescent antibody titers greater than 1:80 should be regarded as true positives, and animals with these titers should be excluded from donation; positive titers less than 1:80 should be considered possible false-negative results, and animals with these titers should be retested 2 to 3 weeks later or using a different method.
Leishmaniasis is an infectious disease caused by a protozoan and has been shown to be transmissible via blood transfusions. Foxhounds, which are most commonly infected with *Leishmania* spp, and dogs with histories of being in endemic areas should be screened for leishmaniasis.

No case of Lyme disease (*Borrelia burgdorferi*) transmitted by transfusion has been identified. It is not essential to test for this organism before blood donation.

Feline blood donors should test negative for FeLV, FIV, and *Mycoplasma haemofelis* (formerly *Haemobartonella felis*). *Bartonella henselae*, the causative agent of cat scratch fever, has been shown to cause myriad illnesses in cats, and the organism can be transmitted via transfusion.

Although it is impossible to completely eliminate transfusion-related disease transmission, the risk can be kept low by selecting healthy donors with known histories and screening for certain pathogens.

**Summary**

The usefulness of blood and blood product transfusions in small animal medicine is without debate. Greater availability of blood products has allowed their increased use outside of universities and referral hospitals. As the use of transfusions increases, so does the potential for associated adverse events. Understanding how transfusion reactions arise can facilitate their prevention and appropriate treatment.

**REFERENCE:**


