

# Transfusion Medicine in Small Animals

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## KEYWORDS

- Transfusion medicine • Red blood cells • Plasma • Platelets • Albumin • TRALI
- TACO • Transfusion reaction

## KEY POINTS

- Transfusion medicine can be life saving and can be performed in veterinary clinics.
- Blood donors should be appropriately screened to minimize disease transmission.
- Blood typing is strongly recommended before transfusion in both dogs and cats.
- Crossmatching can be performed using gel technology.
- Red blood cell transfusions are the treatment of choice for anemia. Use of plasma is indicated for the treatment of active bleeding caused by coagulopathy. Other uses of plasma are controversial.
- Platelet transfusions can be used in small animal patients with active bleeding secondary to thrombocytopenia or thrombocytopenia.
- The use of human serum albumin is associated with a high risk of reactions.
- Reactions, both non-immune mediated and immune mediated, are a risk of transfusions.

Transfusions have been used as a life-saving modality for hundreds of years. The first documented transfusion in any species occurred in 1665 when Richard Lower withdrew blood from one dog and replaced it with blood from another dog. However, it was not until the 1950s that the use of transfusion medicine became more prominent in veterinary medicine because of the availability of equipment and techniques.<sup>1</sup> In the past 60 years, veterinary transfusion medicine has made remarkable advances. However, as knowledge has grown and the availability of different blood products has increased, transfusion therapy has become more complex. Availability of expanded donor screening, typing modalities, and crossmatching techniques make choosing the right donor unit for each patient potentially more complicated. Increased

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Disclosures: The author has no funding sources or conflicts of interest to disclose.

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Vet Clin Small Anim 43 (2013) 735–756  
<http://dx.doi.org/10.1016/j.cvsm.2013.03.007>

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availability of different blood components gives the clinician more options to tailor therapy more appropriately while avoiding transfusion-related reactions. This article summarizes recent advances in veterinary transfusion medicine and provides the clinician with evidence to guide transfusion decision making.

## BLOOD DONOR SCREENING

In human medicine, individual blood units are screened for infectious diseases. A limited number of diseases are screened because of test availability and cost. Careful interview of donors is used to minimize risk of other diseases. In the veterinary field, it is usually cost prohibitive to test individual units. Therefore, a combination of careful interview and blood screening of the donor is used to minimize the risk of infectious disease transmission.

In 2005, the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on infectious disease testing for blood donors was published.<sup>2</sup> Since publication, polymerase chain reaction (PCR) assays have become more readily available for many diseases of concern.<sup>3</sup> When positive, PCR assays indicate that the organism has been identified in the blood stream and active infection is present. False-negatives are possible if the organism is present only in small amounts, because only a small sample of blood is examined. Several veterinary diagnostic laboratories offer donor-screening PCR panels, which typically include at least *Ehrlichia* spp, *Babesia* spp, *Anaplasma* spp, and *Mycoplasma hemocanis* or *Mycoplasma haemofelis*. When assessing which screening tests to perform, it is important to evaluate whether the diseases included are transmitted in blood, are present in asymptomatic donors, are geographically appropriate, and whether the test specificity and sensitivity for pertinent infectious diseases is acceptable. **Table 1** gives general recommendations of clinicopathologic screening for dogs and cats.

## ADVANCES IN BLOOD TYPING

### Dogs

Different blood antigens have been known to exist in dogs since 1910 and antigen groups have been described since the 1940s.<sup>4</sup> Although approximately 20 antigen specificities in 13 groups were originally identified by researchers, only 6 of these

Table 1 Recommended testing for canine and feline blood donors	
Canine Donors	Feline Donors
Blood type	Blood type
Complete blood count	Complete blood count
Chemistry panel	Chemistry panel
Fecal analysis	Fecal analysis
Heartworm antigen	FeLV
<i>Babesia</i> spp	FIV
<i>Ehrlichia</i> spp	<i>M haemofelis</i>
<i>Neorickettsia</i> spp	<i>Bartonella</i> spp
<i>Bartonella</i> spp	—
<i>M hemocanis</i>	<i>Ehrlichia</i> , <i>Anaplasma</i> , <i>Neorickettsia</i> spp (geographic)
<i>Leishmania</i> spp (geographic)	<i>Cytauxzoon felis</i> (geographic)
<i>Trypanosoma cruzi</i> (geographic)	
<i>Brucella canis</i> (breeding animals)	

Abbreviations: FeLV, feline leukemia; FIV, feline immunodeficiency virus.

antigens, dog erythrocyte antigen (DEA) 1.1, DEA 1.2, DEA 3, DEA 4, DEA 5, and DEA 7, can be routinely identified by typing.<sup>5-7</sup> A newer antigen, Dal, exists at high frequency in most dogs but is missing in some Dalmatians.<sup>8</sup> Antibodies against Dal *in vitro* seem to induce a strong agglutination reaction and could cause a severe transfusion reaction. Dal has been shown to be independent from known DEA antigens.<sup>9</sup> Dogs do not have natural antibodies to the DEA 1 system. It has been shown that natural antibodies are present in some dogs for DEA 3, DEA 5, and DEA 7, and in occasional dogs for less common antigens.<sup>7,9,10</sup> At present, a universal donor in dogs is considered to be negative for DEA 1.1, DEA 1.2, DEA 3, DEA 5, and DEA 7, and positive for DEA 4.

The DEA 1 system, with its allelic subtypes (DEA 1.1, DEA 1.2, and possibly DEA 1.3), is the most important because of its high degree of antigenicity. Dogs that are DEA 1.1 negative do not react to DEA 1.1-positive blood on initial transfusion because of lack of natural antibodies to this allele. However, the second time a DEA 1.1-negative dog is given DEA 1.1-positive blood, it may develop a severe hemolytic reaction.<sup>11</sup> Likewise, natural antibodies to DEA 3, DEA 5, and DEA 7 can result in transfusion reactions that are usually mild or delayed; also, a significantly shorter survival time of the transfused red blood cells (RBCs) may be seen.<sup>12</sup>

In order to identify dogs that are true universal donors, typing must be done through a commercial laboratory (Animal Blood Resources International) rather than through point-of-care blood typing tests. Specific blood typing is done with polyclonal antibodies using a tube agglutination method. A gel column test using a monoclonal antibody against DEA 1.1 was developed; however, this is no longer commercially available. Research is ongoing to develop gel methodology for other DEA antigens. Availability of testing for DEA 3 and DEA 5 has been variable in recent years.

In-house typing kits are available; however, these only test for the most antigenic type system, DEA 1.1. Although this is typically beneficial for the emergent patient, it should not be used as a sole method for blood screening prospective donors. The most common in-house typing kits are the DMS card test (CARD; DMS Laboratories, NJ) and the Quick test DEA 1.1 (CHROM; Alvedia, France), both of which use different monoclonal anti-DEA 1.1 antibodies. The benefits of the CHROM testing system is that it is not affected by the presence of autoagglutination (ie, the agglutinates do not move across the test strip and therefore do not interfere with typing).<sup>13</sup> With the tube agglutination method or the CARD, autoagglutination can prevent accurate typing.

A recent study compared the gel column test, CARD, and CHROM tests in both healthy dogs and those who were sick, and found identical results in 69 of 88 samples (78%). In 6 cases, the CHROM result was DEA 1.1 negative, whereas the gel and CARD both were positive. In 18 cases, the CARD result was different from both the gel and CHROM, reading positive in 15 and negative in 3. Because of the disparity of results in these systems, it is strongly recommended that blood typing for donors be confirmed by an outside laboratory.<sup>13</sup> For recipients, it is better to use a test that has false-negative results, because this leads to a true DEA 1.1-positive dog receiving a negative blood unit, which is safe, rather than a test with a high false-positive rate, which could lead to true DEA 1.1-negative dog receiving a positive transfusion (after which a transfusion reaction is more apt to occur).

## Cats

Cats are either type A, type B, or type AB. Recently, the MiK antigen has also been identified.<sup>14</sup> Note that there is no universal blood type in cats, and all cats must be tested before receiving any type of transfusion. Blood type is determined by 3 alleles,

with A being dominant over the rare ab, which is dominant over b. Cats with a genotype A/A, A/ab, or A/b are type A, whereas only cats with b/b are type B. Rare AB cats are genotypically ab/ab or ab/b.

The distribution of these blood types varies geographically, with the highest incidence of B reported in Australia (36% in Sydney).<sup>15</sup> It was originally reported that 97% of cats in the United States were type A and that only 0.3% of cats in the northeast part of the United States were type B.<sup>16</sup> However, a 2005 study from the Animal Medical Center of New York City revealed a 6% incidence of the B blood type.<sup>17</sup> The B blood type is more common in certain exotic cat breeds, including Devon rex (41%), British shorthair (36%), Cornish rex (31%), exotic shorthair (27%), and Scottish fold (19%), but is also seen in domestic breed cats.<sup>18</sup> Type AB has been reported to occur in less than 1% of the general cat population. However, this incidence may be higher because new methodologies seem better at identifying these cats.<sup>19</sup>

Type A cats may have weak anti-B alloantibodies that can cause shortened RBC survival if a B donor is used. However, type B cats have strong anti-A antibodies and can have a fatal reaction from as little as 1 mL of transfused type A blood.<sup>20</sup> Type AB cats have no alloantibodies against either type A or B blood in their sera; they should receive either AB or A blood products if they need a transfusion because of the strong anti-A antibodies present in B serum. Most cats have MiK antigen but, in cats that do not, naturally occurring antibodies can lead to a hemolytic transfusion reaction with a first-time transfusion.

Original typing for cats was done using serum from type B cats with strong anti-A antibodies to identify type A cats. Anti-B antibodies are weaker in A serum but lectin from *Triticum vulgare* reacts strongly with type B antigen.<sup>21</sup> At present, there are 2 commercially available in-house typing kits for cats (Rapid<sup>®</sup>-VetH Feline, DMS Laboratories, Flemington, NJ [CARD] and Quick test A+B, Alvedia, France [CHROM]). Both kits use monoclonal antibodies against type A and type B. In a recent study comparing typing methodologies in cats, the gold standard tube agglutination test, CARD, and CHROM gave identical results in 52 of 58 cats (89.7%). Overall, the CARD had 91.4% accuracy and CHROM had an overall accuracy of 94.8%. In 2 of the 6 cats with discordant resultants, feline leukemia (FeLV) infection was present.<sup>22</sup> It is recommended that B and AB cats be confirmed by a second method or through an outside laboratory.<sup>19,22</sup> At present, there is no in-house typing system available for the MiK antigen.

Blood typing is recommended before all transfusions in both dogs and cats. In an emergent situation in which time for blood typing is precluded, DEA 1.1-negative blood can be given to a dog of unknown type safely. However, typing and use of DEA 1.1-specific blood is recommended whenever possible to maximize the efficient use of canine blood donors that can be used. In cats, there are no universal donors and cats must always be blood typed before transfusion to prevent a life-threatening reaction.

## CROSSMATCHING

In-house crossmatching can be used when blood typing is not available. It can also be used in conjunction with blood typing results. In dogs, crossmatching is recommended if transfusion history is unknown, if a hemolytic reaction is noted during a first transfusion, if more than 7 days has lapsed between administration of transfusions, or if the donor DEA 7 type is unknown.<sup>7,23</sup> In the past, crossmatching was recommended in dogs that had previously been pregnant. However, a recent study showed that pregnancy does not seem to sensitize dogs to antigens on RBCs.<sup>8</sup> In cats, both typing and

crossmatching should be strongly considered before an initial transfusion, because of the identification of antigens such as MiK with naturally occurring antibodies and the potential for a potential fatal transfusion reaction (eg, when type A blood is given to a type B cat). In addition, because in-house typing methodologies are not perfect, both typing and crossmatching on the first transfusion helps to identify any missed type incompatibilities in cats.<sup>7</sup>

Crossmatching has historically been done using a manual procedure that includes both a wash and an incubation step. **Box 1** gives a description of the crossmatching technique.<sup>24</sup> The procedure is time consuming and interpretation has been shown to be operator dependent. Gel crossmatch technology has recently been developed. One benefit is that the gels can be saved to show to others for verification (vs blood typing cards, which dry up). Gel technology also requires less blood than a standard crossmatch (0.5 mL vs 2–3 mL). In addition, the gel crossmatch can be used even if the patient is autoagglutinating.<sup>25</sup> The gel allows agglutinates to be trapped in a matrix but free cells to sink to the bottom, allowing easier interpretation of compatibility. A gel system for companion animals is available for both major and minor crossmatches (RapidVet<sup>®</sup>-H, DMS Laboratories Inc., NJ) **Fig. 1**.<sup>9</sup>

### TRANSFUSION COLLECTION AND ADMINISTRATION

Whole blood can be collected for transfusion in many hospitals when proper bags and preservatives are available. Dogs and cats should be appropriately screened and a full physical examination should be performed before to each donation to ensure general health and lack of ectoparasites. If sedatives are necessary (typically required for cats), acepromazine should be avoided because of potential effects on platelet function. Blood is usually drawn from the jugular vein once the area has been aseptically prepped (to avoid contamination of the blood product). Dogs can safely donate 15 to 20 mL/kg, whereas cats can donate 10 to 15 mL/kg (lean body weight).

Blood should ideally be collected with the use of an anticoagulant preservative (eg, citrate-phosphate-dextrose-adenine [CPDA-1], Adsol) at a ratio of 1 mL of anticoagulant per 9 mL of blood.<sup>24</sup> Note that blood cannot be stored in syringes long-term,



**Fig. 1.** Gel crossmatch kit for use in both dogs and cats. (Courtesy of RapidVet<sup>®</sup>-H Feline/DMS Laboratories, Inc., Flemington, NJ; with permission.)

**Box 1****Crossmatching technique**

1. Obtain blood in both ethylenediamine tetraacetic acid (EDTA) tube (purple top) and in a nonadditive tube (red top) from both donor and recipient. If using a stored RBC unit, use one of the provided tags and empty the sample into a red-top tube to spin.
2. Centrifuge and separate plasma and serum from the RBCs. Save the removed serum in a separate tube. Discard the plasma from the EDTA tube.
3. Wash the RBCs from the EDTA tube (purple top).
  - a. Place the RBC in a second tube 12 × 75 mm and fill three-quarters full with saline.
  - b. Centrifuge for 1 minute, decant the saline, and repeat 3 times, removing the supernatant the last time.
4. Resuspend the cells to make a 2% to 4% solution (0.2 mL of blood in 4.8 mL of saline gives a 4% solution).
5. Label tubes to make the following mixtures:
  - a. Major crossmatch: 2 drops patient serum with 1 drop donor RBC suspension
  - b. Minor crossmatch: 1 drop patient RBC suspension with 2 drops donor serum
  - c. Control: 1 drop patient RBC suspension with 1 drop patient serum
6. Incubate for 15 to 30 minutes at 37°C.
7. Centrifuge for 15 seconds.
8. Interpretation of results:
  - a. If either hemolysis or hemagglutination is seen macroscopically, or if agglutination is seen microscopically, the donor is not a good match

*Modified from Lanevski A, Wardrop KJ. Principles of transfusion medicine in small animals. Can Vet J 2001;42:447–54.*

and should only be stored if collected aseptically into sealed, gas-diffusible blood bags.

The process of transfusion administration can potentially affect the survival of the RBCs, and technique, use of delivery system, and filter use must be correct when transfusing a patient. All blood products should be warmed to body temperature before administration. Plasma should be thawed by double bagging the product and placing in a warm water bath. Microwaves should not be used to thaw or warm blood products because of potential RBC or protein damage. RBCs should ideally be administered through a large-bore peripheral catheter (ideally >22 gauge). Initial administration of transfusions should be done slowly (eg, 0.5–1 mL/kg/h for the first 15 minutes) to monitor for an acute reaction, time permitting. Vital signs should be monitored every 15 minutes during the first hour and every 30 to 60 minutes thereafter. All transfusions should be administered within 4 hours, to prevent increased risk of bacterial contamination of the unit.<sup>7</sup>

In 2011, a study showed a significant decrease in the short-term probability of RBC survival in those canine blood transfusions administered with either a volumetric or syringe pump.<sup>26</sup> However, a similar study in cats showed no loss of RBCs with the use of a syringe pump and HemoNate filter.<sup>27</sup> As a result of these studies, the author recommends that canine packed RBCs (pRBCs) be given through an in-line blood filter but not through a fluid pump. Feline pRBCs can be given using a syringe and HemoNate filter.

If available, leukoreduction (the process by which white blood cells [WBCs] are removed from an RBC unit) can be considered. Leukocytes in stored pRBCs can lead to release of inflammatory compounds such as histamine and plasminogen activator inhibitor-1, potentially predisposing to transfusion reaction.<sup>28</sup> The benefit of leukoreduction is that it can decrease the incidence of nonhemolytic transfusion reactions and the immunomodulation that has been seen after transfusion in some human patients.<sup>28</sup> Leukoreduction can be performed either before storage or at the time of administration, and is also available for purchase through commercial blood banks as leukoreduced pRBC (Hemosolutions, Colorado Springs, CO).

The process of leukoreduction is now more readily available for canine blood, and has been shown to be associated with smaller increases in WBCs, fibrinogen, and C-reactive protein levels in recipients than with than nonleukoreduced transfusions.<sup>28</sup> A pilot study was recently done with feline RBC; however, the use of the neonatal leukoreduction filters resulted in loss of 8 mL of blood and may not be justified at this time.<sup>29</sup>

## BLOOD COMPONENTS

The appropriate use of blood components allows more specific treatment while avoiding the risks of giving the unnecessary parts of the blood.<sup>30</sup> Component therapy is a more efficient way of using blood resources, allowing 1 donated unit to be split into multiple products (which may then benefit more than 1 patient). For example, a chronically anemic FeLV-positive cat may only require RBCs rather than whole blood (WB), provided the patient is not coagulopathic or thrombocytopenic. Likewise, a coagulopathic patient secondary to long-acting anticoagulant toxicosis may not be clinically anemic, and may only require fresh frozen plasma (FFP) or frozen plasma (FP) rather than WB, thereby saving the RBCs for another patient.

Appropriate storage of blood components is also necessary to allow efficient and maximal use of blood products. For example, the storage of component therapy (eg, FFP and pRBCs) allows longer storage time (compared with WB alone).<sup>31,32</sup> Available blood products, storage times, and indications for use are summarized in **Table 2**.<sup>33–35</sup>

## RBC PRODUCTS

RBCs are indicated for the treatment of anemia. Anemia is defined as a deficiency of RBCs or hemoglobin (Hb). Anemic animals are usually pale, exercise intolerant, weak, tachypneic, and potentially tachycardiac and hypotensive (consistent with hemorrhagic shock). These clinical signs of anemia are related to decreased oxygen delivery ( $Do_2$ ), because Hb plays a significant role in delivering oxygen to cells. This is explained in the formula for  $Do_2$ :

$$Do_2 = \text{cardiac output} \times \text{oxygen content of blood (CaO}_2\text{)}$$

$$CaO_2 = [(PaO_2 \times 0.003) + (SaO_2 \times Hb \times 1.34)]$$

$$CO = \text{stroke volume} \times \text{heart rate}$$

SaO<sub>2</sub> is arterial oxygen concentration.

The transfusion trigger is the Hb level at which an animal's  $Do_2$  has decreased enough that anaerobic metabolism occurs. In critically ill humans, transfusions are recommended at a Hb level of 7 g/dL (approximate hematocrit [HCT] of 21%) unless

**Table 2**  
**Summary of Blood Components**

Blood Product	Definition	Composition	Stability	Indications for Use	Other Information	Dose
WB	Blood pulled from a donor with no processing	RBCs, WBCs, platelets, all components of plasma	In 1–6°C refrigerator, 28 d in CPDA-1, 30 d in ACD	Massive blood loss, need for multiple components	Platelets lose activity after refrigeration, must be used within 4–6 h if not refrigerated	Transfusion amount (mL) = $(PCV_{\text{desired}} - PCV_{\text{current}}) / PCV_{\text{donor}} \times \text{blood volume (mL/kg)} \times \text{wt (kg)}$ Blood volume dog = 88 mL/kg, Blood volume cat = 66 mL/kg
Packed RBCs	RBCs centrifuged and most of the plasma removed	RBCs, may have some WBCs	In 1–6°C refrigerator: 20 d in CPDA-1, 35 d in CPDA-1 with Optisol or Nutricel, 37 d in CPDA-1 with Adsol	Anemia	—	
Leukoreduced RBCs	Packed RBCs where WBC have been removed before storage	RBCs	37 d in CPDA in 1–6°C refrigerator	Anemia; leukoreduction may reduce immunomodulation and nonhemolytic febrile reactions	—	
PRP	Plasma and platelets separated from RBCs using a soft spin	Platelets, plasma	5 d in gas-diffusible bags with constant agitation at 22°C	Severe thrombocytopenia or thrombocytopathia with active hemorrhage or need for an invasive procedure	—	1 unit per 10 kg
Platelet concentrate	Further centrifugation of PRP to have a smaller volume or platelets obtained via plateletpheresis	Platelets, plasma	5 d in gas-diffusible bags with constant agitation at 22°C	Severe thrombocytopenia or thrombocytopathia with active hemorrhage or need for an invasive procedure	—	1 unit per 10 kg



Frozen platelets	Platelet concentrate created by plateletpheresis and then frozen using DMSO for platelet stability	Platelets	6 mo at $-20$ to $-30^{\circ}\text{C}$	Severe thrombocytopenia or thrombocytopenia with active hemorrhage or need for an invasive procedure	—	1 unit per 10 kg
Lyophilized platelets	Platelet concentrate created by plateletpheresis, aldehyde cross-linked for platelet stability and then lyophilized	Platelets	2 y in refrigerator	Severe thrombocytopenia or thrombocytopenia with active hemorrhage or need for an invasive procedure	—	Research product in development
FFP	Plasma separated from WB and frozen within 8 h; $<1$ y of age	Coagulation factors, anticoagulation factors such as antithrombin, alpha-macroglobulin, albumin	1 y in freezer maintained at $-20$ to $-30^{\circ}\text{C}$	Coagulation disorders resulting in active hemorrhage or as prophylaxis before invasive surgery in an animal with a known significant clotting factor deficiency	Potential use for treatment of severe necrotizing pancreatitis, DIC	10–30 mL/kg, higher dose for vWF
FP	Plasma separated from WB but not frozen completely within 8 h or plasma that has been frozen $>1$ y but $<4$ y	Contains stable coagulation factors II, VII, IX, X, albumin	5 y in freezer maintained at $-20$ to $-30^{\circ}\text{C}$	Coagulation deficiencies, specifically of II, VII, IX, or X resulting in active hemorrhage	—	10–15 mL/kg
Cryoprecipitate-poor plasma	Supernatant that remains after preparation of cryoprecipitate	Contains stable coagulation factors II, VII, IX, X, anticoagulant, and fibrinolytic factors, albumin	1 y from original collection date in freezer maintained at $-20$ to $-30^{\circ}\text{C}$	Coagulation deficiencies of II, VII, IX, or X resulting in active hemorrhage that does not require vWF	—	—

(continued on next page)

**Table 2**  
**(continued)**

<b>Blood Product</b>	<b>Definition</b>	<b>Composition</b>	<b>Stability</b>	<b>Indications for Use</b>	<b>Other Information</b>	<b>Dose</b>
Cryoprecipitate	The precipitate containing cold insoluble proteins, formed when FFP is slowly thawed and spun	Contains concentrated vWF, VIII, XIII, fibrinogen, and fibronectin	10 mo when stored at $-20^{\circ}\text{C}$ or colder	When active hemorrhage from specific deficiency in vWF and VIII, or as prophylaxis when invasive procedure needed for animal with known deficiency of one of these factors	—	1 unit per 10 kg
Albumin	Protein is extracted from pooled plasma	Albumin	3 y at $20\text{--}24^{\circ}\text{C}$	Treatment of hypotension or hypovolemia in the septic patient with severe hypoalbuminemia	Both canine and HSA available; only canine albumin should be used ideally in canine patients because of risk of reaction from human product	Albumin deficit = $0.3 \times \text{BW (kg)} \times 10 \times$ (albumin desired – current albumin)
IVIG	Pooled IgG extracted from multiple human B9 donors	IgG	36 mo in refrigerator at $1\text{--}6^{\circ}\text{C}$	Treatment of immune disease	Monitor carefully for type I, III reactions	0.5 g/kg

Abbreviation: ACD, Acid-citrate-dextrose.

the patient has clinically significant heart disease, in which case a level of 10 g/dL (approximate HCT of 30%) is recommended.<sup>36</sup> Although the appropriate veterinary transfusion trigger has not been well studied or identified, animal data suggest that an HCT of 15% to 18% may be a reasonable guideline.<sup>7,37</sup> However, animals with low volume or poor contractility may require a higher Hb to maintain  $DO_2$ .

Fresh WB (FWB) has been the most common blood product traditionally used in veterinary medicine, because it is readily available to clinicians (often from an in-house donor or pet). WB is indicated when the patient is anemic, has a blood volume loss of more than 50%, or when the patient requires multiple components of blood (eg, RBC, clotting factors, platelets).<sup>24</sup> If WB is used before refrigeration, it is a good source of functional platelets.<sup>38</sup> One 500-mL unit of FWB obtained from a canine donor is estimated to contain  $7 \times 10^{10}$  platelets. Once refrigerated, platelet function decreases dramatically (discussed later). Recent work in human trauma has shown that maintaining the ratio of plasma, platelets, and RBCs close to 1:1:1 significantly improves the outcome in cases with large-volume blood loss.<sup>39</sup>

The amount of WB to administer can be calculated using the following formula<sup>7</sup>:

$$\text{Transfusion amount (mL)} = (\text{PCV}_{\text{desired}} - \text{PCV}_{\text{current}}) / \text{PCV}_{\text{donor}} \times \text{blood volume (mL/kg)} \times \text{wt (kg)}$$

where PCV is packed cell volume.

pRBCs are indicated when blood volume is normal (eg, as shown clinically by a normal total protein) but the animal requires oxygen carrying capacity (eg, Hb). This is typically seen clinically when the anemia is caused by lack of production (eg, lack of erythropoietin, aplastic anemia), or a destructive process (eg, hemolysis).<sup>24</sup> Component therapy (eg, use of pRBC and FFP together) can be used to replace significant blood loss if the patient's platelet count is adequate and a WB donor is not available. The dose of pRBC can be calculated as listed for WB. When using pRBC with a PCV of approximately 60%, the formula:  $1.5 \text{ mL} \times \text{desired \% increase in PCV} \times \text{BW (kg)}$ , where *BW* is body weight, provides an accurate volume to administer.<sup>40</sup>

## PLASMA PRODUCTS

Plasma contains albumin, globulins, clotting proteins, and anticoagulants. It can be stored and separated into many products. Indications for plasma use are debated in both human and veterinary medicine.<sup>30,41</sup> Plasma has been proved to be effective in actively bleeding patients with documented coagulation factor defects.<sup>42</sup> When dosing plasma products, a general guideline is 10 to 20 mL/kg. For example, a dose of 10 to 20 mL/kg of FFP is recommended for coagulopathic patients suffering from factor deficiency from vitamin K antagonist rodenticide toxicity,<sup>35</sup> whereas slightly higher doses (15–30 mL/kg) are needed to provide adequate factors to reverse coagulopathy from von Willebrand disease (vWD) or hemophilia A in dogs.<sup>43</sup>

The use of adequate dosing of plasma has also been proved, in humans, to be critical in preventing the dilutional coagulopathy that occurs with massive RBC transfusions.<sup>39</sup> As previously mentioned, studies in both civilian and military human patients with trauma have shown that 30-day survival is increased when maintaining a 1:1 ratio of plasma to RBC transfusion in massively transfused patients.<sup>39,44–46</sup>

Plasma is often administered to patients with increased coagulation parameters (but no active bleeding) before invasive procedures. However, there are no studies in human or veterinary medicine proving plasma's efficacy in prevention of hemorrhage.<sup>42,47</sup> Most human studies evaluating liver biopsies have found no association between coagulation times and the risk of bleeding.<sup>48,49</sup> One human study showed a mild increase in risk of hemorrhage with hyperbilirubinemia and a severely increased international

normalized ratio (INR).<sup>50</sup> A single veterinary study showed that the risk of hemorrhage after liver biopsy was more associated with platelet count than either prothrombin (PT) or activated partial thromboplastin time (PTT). The author recommends that the use of prophylactic plasma only be reserved for those patients with significant coagulopathy or those with documented severe factor deficiency undergoing a significant procedure (eg, splenectomy).

The use of FFP for the treatment of both hypercoagulability and hypocoagulability associated with disseminated intravascular coagulation (DIC) is controversial.<sup>30</sup> A study of dogs with severe illness and decreased antithrombin (AT) levels showed maintenance of AT with administered FFP; however, AT levels were not maintained when FFP was given with concurrent heparin.<sup>51</sup> There have been no prospective studies of dose or timing of FFP administration with DIC.

Plasma has also been used in patients with severe pancreatitis to help replace alpha-macroglobulins and maintain albumin levels, because survival in humans is known to be decreased in patients with low alpha-macroglobulin.<sup>52</sup> However, no benefit was seen compared with the control group when plasma was given to human patients with pancreatitis, even though an increase in alpha-macroglobulin levels was seen.<sup>53</sup> However, the control group comprised patients receiving colloid support in the form of albumin; so it is unknown whether colloid support from the albumin may still be useful for patients with pancreatitis. In veterinary medicine, a recent canine retrospective study evaluated the use of FFP with pancreatitis<sup>54</sup>; no improvement in mortality was seen with plasma administration. However, albumin levels were not reported before or after treatment of either group.

Hypoalbuminemia is also a controversial indication for plasma transfusion. Low albumin levels have been correlated with increased mortality in both humans and animals.<sup>55,56</sup> Albumin plays a key role in the body, because it makes up 70% to 80% of colloid osmotic pressure (COP), acts as a primary carrier molecule (eg, for medications), is important for the removal of bacterial toxins and free radicals, acts as a buffer, helps maintain microvascular integrity, and reduces platelet aggregation.<sup>55</sup> Despite the numerous theoretic benefits, exogenous albumin supplementation has not been proved to improve survival in human or veterinary medicine. Several large meta-analyses have examined human trials of albumin administration and found no overall benefit.<sup>57,58</sup> In a large trial of 6997 people resuscitated with either crystalloids or 5% albumin, there was a trend toward worse outcome with the use of albumin in patients with trauma<sup>59</sup> and no benefit in patients with burns.<sup>57</sup> However, a current meta-analysis found evidence for benefit of resuscitation with an albumin-containing fluid in human patients with sepsis.<sup>60</sup>

If plasma is used to increase serum albumin, 22.5 mL/kg is needed to raise the serum albumin by 0.5 g/dL if there is no ongoing loss. However, in one canine study evaluating FFP transfusions, no increase in albumin level was seen with average administration rates of 15 to 18 mL/kg.<sup>41</sup> Concentrated albumin may be more effective in animals with severely low albumin and concurrent peripheral edema. Synthetic colloids may be as or more effective in raising the COP in hypoalbuminemic animals.

Available plasma products include FFP, FP, cryoprecipitate, cryoprecipitate-poor plasma (CPP), human serum albumin (HSA), canine albumin, and intravenous immunoglobulin (IVIG). Each is discussed later in further detail; readers are also referred to the article "Fluid Therapy for the Emergent Small Animal Patient" by Elisa elsewhere in this issue for additional information.

FFP is plasma that has been separated from RBCs and frozen within 8 hours of collection of the blood. It contains all the coagulation factors, along with anticoagulants, fibrinogen, fibronectin, albumin, and alpha-macroglobulin. FFP is considered fresh when frozen at  $-40^{\circ}\text{C}$  for 1 year.<sup>35</sup> Coagulation factors are defined as either

labile or nonlabile, based on their activity with storage. Labile clotting factors include factors V and VIII, whereas nonlabile factors generally include the vitamin K-dependent factors II, VII, IX, and X.

FP is plasma that has been separated from RBC and frozen greater than 8 hours after blood collection or when FFP is more than 12 months old but less than 5 years of age.<sup>7</sup> The labile coagulation factors and anticoagulants are not consistently active but the nonlabile coagulation factors (eg, vitamin K-dependent factors) are readily available, making it the transfusion treatment of choice for a coagulopathic patient secondary to long-acting anticoagulant rodenticide toxicosis. Likewise, it can potentially be used as source of albumin.

Cryoprecipitate is made by slow thawing and centrifugation of FFP. The supernatant is removed and the remaining slush/sediment, which contains cold insoluble proteins, is a concentrated form of factor VIII, von Willebrand factor (vWF), and fibrinogen. The cryoprecipitate can then be refrozen and is good for 10 months from the date of the initial blood draw.<sup>61</sup> Cryoprecipitate is the preferred treatment of prophylactic or active bleeding in dogs with hemophilia A or vWD.<sup>43,62</sup> Recommendations for dosing are 1 unit of cryoprecipitate for every 10 kg of body weight. Although FFP can also be used, the administration of cryoprecipitate allows a more concentrated amount of desirable factors versus the administration of much larger amounts of FFP to accomplish the same goal. Lyophilized (freeze-dried) canine cryoprecipitate is now commercially available (ABRI, Dixon, CA).

CPP is the supernatant removed in the process of making cryoprecipitate.<sup>7</sup> This plasma can be refrozen for 12 months and is a source of the nonlabile clotting factors II, VII, IX, and X; thus, CPP can be used to treat anticoagulant rodenticide toxicosis. It is also a source of albumin, although large amounts are required to increase the albumin. Dosing is similar to that for FFP or FP for coagulopathy.

Albumin can be extracted from plasma to make a concentrated product. Concentrated HSA has been used in both canine and feline patients with extremely low albumin levels (typically secondary to septic peritonitis, and so forth).<sup>63–65</sup> Doses for canine administration have been extrapolated from human medicine, and recommendations vary. A simple formula is  $1.5 \text{ g/kg}$  or the albumin deficit can be calculated as  $\text{grams} = 10 \times (\text{albumin desired} - \text{albumin current}) \times \text{kg} \times 0.3$ .<sup>66</sup> This volume should be started slowly to monitor for reactions and then slowly titrated based on the stability of the patient. Although several articles have shown safety with HSA in sick patients, 2 healthy dogs died when given HSA in a research trial; this was caused by severe type III hypersensitivity reactions and development of profound vasculitis and membranoproliferative glomerulonephritis.<sup>67</sup> In addition, a follow-up study showed that even sick, potentially immunocompromised canine patients developed significant antibodies to HSA after administration.<sup>68</sup> With the current availability of canine albumin, the use of a potentially antigenic human product is not recommended.

Canine albumin is available (ABRI, Dixon, CA) as a lyophilized product. Each bottle contains 5 g of albumin, and typically ranges from \$125 to \$175. Canine albumin dosing can be calculated as listed for human albumin. Canine albumin is generally considered to be safer than HSA because of less immunogenicity. Initial safety studies have shown no signs of reactions in 6 dogs who received the product weekly for 4 weeks.<sup>69</sup>

Human immunoglobulin (IVIG) is polyvalent immunoglobulin G (IgG) that has been extracted and pooled from the plasma from multiple donors. It has been used in veterinary medicine to treat multiple immune diseases, including immune-mediated thrombocytopenia (ITP), immune-mediated hemolytic anemia, nonregenerative anemias, cutaneous diseases, polyradiculoneuritis, myasthenia gravis, and sudden

acquired retinal degeneration.<sup>70–73</sup> As with HSA, it is derived from humans, so antibody formation and type III hypersensitivity reactions are risks with its use in veterinary patients.<sup>70</sup> Type I hypersensitivity reactions and hypercoagulability are additional risks. Dosing for IVIG is extrapolated from human medicine, and is currently recommended at 0.5 g/kg.<sup>70,72</sup>

Specific clotting factors and anticoagulants are also extracted from human plasma and made into concentrates but these products are not yet used or produced in veterinary medicine. Examples include concentrates of factor VII, VIII, IX, and antithrombin.<sup>74</sup>

## PLATELET PRODUCTS

Until recently, platelet transfusions were not viable, readily available options in veterinary medicine. Recent advances in platelet storage may make platelet transfusion more readily accessible to veterinarians, including the availability of lyophilized platelets. However, there are limited publications in veterinary medicine about triggers for prophylaxis or therapeutic efficacy of platelet products in actively bleeding patients.<sup>75–78</sup>

In humans, platelets are recommended for prophylaxis in any patient with a count less than 10,000/ $\mu\text{L}$ <sup>74,79</sup> and in patients who require an invasive procedure with counts less than 50,000/ $\mu\text{L}$ . Platelets are also recommended in patients with drug or hereditary impairments of platelet function that require an invasive procedure. In actively bleeding patients, the use of therapeutic platelet transfusions is also warranted with platelet counts less than 20,000/ $\mu\text{L}$ .<sup>74,79</sup> With ITP, the use of platelet transfusions is controversial because of the rapid destruction of any administered platelet unless the patient has evidence of life-threatening bleeding (eg, spinal cord bleed, bleeding into the brain).<sup>74</sup>

The risk of bleeding with severe thrombocytopenia is affected by the degree of anemia. RBCs scavenge nitric oxide, which leads to increases in platelet activity. In addition, high hematocrit values push platelets toward the endothelium and reduce sheer stress.<sup>80</sup> In cases of moderate thrombocytopenia and concurrent anemia, the risk of bleeding is potentially lessened with pRBC transfusion alone.

As previously discussed, FWB is the product most veterinarians have available to them to supply a limited number of platelets. A dose of 10 mL/kg of FWB is expected to raise the platelet count about 10,000/ $\mu\text{L}$ , which is generally considered to be minimal; however, this may be life saving with severe thrombocytopenia.<sup>75</sup>

The advantage of FWB is that no platelets are lost, compared with component therapy production. In addition, the platelets are less activated than platelets obtained via centrifugation for concentrate.<sup>76</sup> FWB at room temperature is considered safe for use for 4 to 8 hours. Refrigeration of human platelets, either in WB or in platelet concentrate, rapidly leads to platelet aggregation and activation. In addition, refrigerated platelet survival is half that of platelets held at room temperature.<sup>81</sup> This effect is caused by clustering of the vWF receptors in response to temperature, leading to increased clearance by hepatic macrophages.<sup>82</sup> No studies have been done of canine refrigerated platelets to confirm whether a similar response occurs.<sup>76</sup> However, refrigeration of FWB should be avoided if used primarily for platelet transfusion.

Fresh platelet concentrate has traditionally been made by using a soft spin of WB, which separates the platelets into the plasma component. This technique allows appropriate allocation of component therapy and minimizes the volume or component of transfusion products that the patient may be receiving unnecessarily. After a soft spin, the plasma is expressed into a separate bag, and this plasma is then known as platelet-rich plasma (PRP). The PRP is spun again to create a platelet concentrate and the plasma is removed and stored as FFP.<sup>7,74</sup> One unit of platelet concentrate is

the amount made from 1 unit (500 mL) of WB but contains fewer platelets. Studies have shown average *in vivo* platelet recovery of 80%.<sup>83,84</sup> The dose is normally calculated as 1 unit/10 kg.

Fresh platelet concentrate can also be made through plateletpheresis. In this process, blood is taken from the donor and split into components (using an apheresis machine). During plateletpheresis, platelets are retained and the remaining volume is returned to the donor. The process is time consuming for the donor; however, large amount of platelets can be collected in this manner (eg, typically  $1-4 \times 10^{11}$  platelets). This amount is typically 4 to 6 times the amount collected in a centrifuged platelet concentrate. Plateletpheresis also allows maximum sterility of the product. In addition, during plateletpheresis, there is negligible WBC and RBC contamination, minimizing potential transfusion reaction. Fresh platelets must be stored in gas-soluble bags at room temperature with constant agitation to remain active. Bacterial contamination is a concern at room temperature and storage is limited to 5 days.<sup>76,85,86</sup>

Frozen platelet concentrate is made by stabilizing apheresed platelets with 6% Dimethyl sulfoxide (DMSO) or with 2% DMSO and Thrombosol.<sup>83</sup> Canine platelet recovery (after freezing with 6% DMSO at  $-62^{\circ}\text{C}$  [ $-80^{\circ}\text{F}$ ]) was shown to be 70% with a half-life of 2 days versus 3.5 days for fresh platelets.<sup>87</sup> The platelets were effective in halting active bleeding in thrombocytopenic dogs.<sup>88</sup> A more recent study comparing 6% DMSO with 2% DMSO and Thrombosol showed only 49% and 44% platelet recovery, respectively. Platelet half-life was confirmed to be about 2 days.<sup>83</sup> Frozen platelet concentrate with 6% DMSO is commercially available in veterinary medicine (ABRI, Dixon, CA). Dosing is recommended at 1 unit/10 kg of body weight given over 4 hours (see package insert for further information).

Lyophilized platelets (LYO) are an experimental product still undergoing research. Canine LYO are not yet commercially available but research is ongoing. Platelets are stabilized using a mild aldehyde cross-linking of membrane proteins and lipids, and then lyophilized and reconstituted with preservation of platelet structure and function. LYO can be stored for up to 24 months in the refrigerator, and can be reconstituted with saline immediately before use.<sup>89</sup> Research studies on LYO have shown that they bind to collagen, vWF and damaged endothelium. Receptors are activated normally and bind fibrinogen.<sup>90</sup> These platelets also retain the ability to increase procoagulant activity.<sup>89</sup> In a study of dogs on cardiac bypass, infusion of the LYO product led to improvement in venous bleeding time that was most pronounced at 20 to 30 minutes after infusion.<sup>91</sup>

A prospective, multicenter trial studied the use of fresh platelet concentrate (FRESH) and LYO in 37 dogs with active bleeding and thrombocytopenia. In this study, 22 dogs received LYO and 15 received FRESH. The incidence of transfusion reaction was low in both groups, and there was no difference in hospitalization time or mortality between the groups. The use of LYO seemed to be safe in dogs but larger studies are needed to study efficacy.<sup>77</sup> LYO products may also be used as hemostatic agents even if platelet numbers and function are normal. In a recent study, 20 swine were subjected to liver injury and then treated with either a placebo or LYO. Overall, 80% survived in the LYO group, whereas only 20% survived in the placebo group. One pig had evidence of thrombi in other locations on necropsy, indicating the need for further evaluation before these products are used in clinical patients.<sup>92</sup>

## RISKS OF TRANSFUSION PRODUCTS

With administration of any type of blood product, the benefits and potential risks must be evaluated. Although potentially life saving, transfusions can result in acute or

delayed reactions. Reactions have been reported to occur in 8% to 13% of pRBC transfusions in dogs and cats.<sup>17,31</sup> **Table 3** shows a list of non-immune-mediated and immune-related transfusion reactions.

Transfusion-associated circulatory overload (TACO) and nonhemolytic febrile reactions are the most common reactions seen in dogs and cats.<sup>93,94</sup> Most blood products cause significant oncotic pull, which is more pronounced with those containing albumin (eg, WB, FFP), which can be useful in animals that have severe peripheral edema or in animals that are severely hypotensive; however, volume overload with resultant pulmonary edema is a potential risk in those animals that are already normovolemic. Blood pressure should be monitored while administering blood products and patients should be appropriately monitored for signs of volume overload (eg, tachypnea, weight gain, hemodilution, serous nasal discharge, development of pulmonary edema or pleural effusion).

Nonhemolytic febrile reactions are defined as a temperature increase of 1 to 2°C within 1 to 2 hours of a transfusion. Nonhemolytic reactions are usually caused by antibody reactions against donor leukocyte or platelet antigens and are greatly reduced when leukoreduction filters are used before storage of blood. It is important to monitor patients carefully, because fever may also be an early indicator of a more severe reaction (eg, hemolytic reaction, sepsis). If a nonhemolytic febrile reaction is suspected, slowing of the transfusion or drug administration may be warranted.

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality in human medicine. TRALI manifests clinically as respiratory distress with severe noncardiogenic edema within 24 hours of transfusion and is seen mostly in patients receiving multiple plasma transfusions.<sup>94</sup> In human medicine, the development of TRALI is associated with use of plasma from female donors, particularly those who are parturient. The use of plasma from male donors, plasma from women who have never been pregnant, or from plasma that has been screened for the presence of WBC antibodies greatly decreases the incidence of TRALI.<sup>94,95</sup> In veterinary medicine, it is unclear whether TRALI occurs. RBC alloantibodies do not seem to be increased in dogs with repeated pregnancies but WBC alloantibodies have not been studied.<sup>96</sup> The incidence of parturient canine blood donors is typically rare in veterinary medicine, so TRALI may also be rare.

Type I hypersensitivity can also occur with any type of blood product and includes pruritus and angioedema, and can progress to bronchoconstriction and hypotension.

<b>Table 3</b>	
<b>Types of transfusion reactions</b>	
<b>Immunologic Reactions</b>	<b>Nonimmunologic Reactions</b>
Allergic reactions (type I hypersensitivity)	Sepsis
Hemolytic reactions	Citrate toxicity: hypocalcemia
Nonhemolytic febrile reactions	TACO
TRALI	Hyperammonemia
TRIM	Hypothermia
Decreased RBC survival	Hypophosphatemia
—	Hyperkalemia
—	Infectious disease transmission

*Abbreviations:* TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; TRIM, transfusion-related immunomodulation.



It has recently been found that humans with preexisting allergic conditions such as atopy seem to be more at risk.<sup>94</sup>

## SUMMARY

Transfusion medicine may be life saving in the emergent or critically ill veterinary patient. Blood products are becoming readily available, and transfusions can be performed in many clinic settings. The appropriate use of transfusion medicine should balance the potential risks, albeit rare, associated with transfusions. Patients should be appropriately screened with blood typing and crossmatching before therapy, and component therapy should be used when possible. Ongoing research may provide even better cage-side typing, longer storage times for components, and a larger variety of products that are more specific for each species.

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