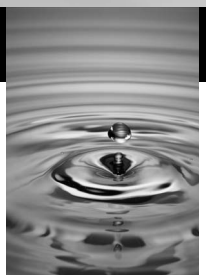
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



CHAPTER • 24

BLOOD TRANSFUSION AND BLOOD SUBSTITUTES

Ann E. Hohenhaus

Blood transfusions have many things in common with fluid therapy. Like crystalloid and colloid solutions, blood products are not used to treat disease; they are supportive therapies given to correct deficiencies in the patient until the underlying disease process can be treated. For example, a red blood cell transfusion is given to replace red blood cells lost as a result of a traumatic laceration. The transfusion of red blood cells increases the oxygen-carrying capacity of the blood, allowing for surgical repair of the laceration; it is not the primary treatment for hemorrhage. Likewise, sodium chloride is used to replace sodium, chloride, and water in a dehydrated patient with hypoadrenocorticism until adrenal hormones can be replaced.

The use of both blood transfusions and fluid therapy must be carefully assessed before inclusion in a patient's treatment plan, and the veterinarian should evaluate the risk/benefit ratio for each patient. Volume overload, electrolyte disturbances, and transmission of infection can occur from administration of pathogen-contaminated blood products or fluids.[18,46,91] Despite the potential negative effects of transfusion, most veterinarians view it as lifesaving therapy allowing the transfusion recipient to receive other necessary treatments such as surgery, chemotherapy, or medical care.[38]

Three major differences exist between the more commonly used fluids and blood products. The differences between crystalloid or colloid solutions and blood products are their immunogenicity, availability, and cost. The immunogenicity of blood products stems from the proteins and cellular material in the blood. Because crystalloid solutions lack proteins and cellular material, they are not considered immunogenic; however, certain colloid solutions such as hydroxyethyl starch have been reported to cause acute anaphylaxis in rare instances in humans.[70] The mechanism of this reaction is unknown.

Crystalloid and colloid solutions are readily available because they can be manufactured according to market demand. Only a living animal can produce blood, and production is limited to the donor's physiologic capability. The small number of commercial canine and feline blood banks that provide a convenient source of blood for the veterinary practitioner further limits availability of blood for transfusion (Box 24-1). Furthermore, blood products require a more regulated storage environment and have a significantly shorter shelf life than crystalloid or colloid solutions, making blood a less convenient product to stock and use in a veterinary hospital.

The actual costs associated with canine blood transfusions are not known, but in 1992, veterinarians estimated the cost of a 500-mL whole blood transfusion to range from $25 to more than $300.[38] The cost of 500 mL of lactated Ringer's solution is less than $1.

Despite the fact that the first documented transfusion was given to a dog in 1665 by Richard Lower at Oxford University, veterinary transfusion medicine scientifically and technologically lags behind its counterpart in human medicine.[54] Information in this chapter is based on animal studies whenever possible. When none is available, currently accepted guidelines from human medicine will be applied to the veterinary patient. The purpose of this chapter is to provide the reader with the following:

1. A basic understanding of the theory of blood component therapy
2. Information on the technical aspects of obtaining blood for transfusion
3. Suggestions for the administration and monitoring of transfusions
4. A description of the clinical applications of a veterinary blood substitute

BASICS OF BLOOD COMPONENTS

Blood, as it is collected from the donor, contains all the elements of blood: red blood cells, white blood cells, platelets, coagulation factors, immunoglobulins, and albumin. Whole blood can be transfused into the recipient as

Box 24-1 Veterinary Blood Banks

Animal Blood Bank
800-243-5759
www.animalbloodbank.com

"Buddies for Life"
248-334-6877
www.ovrs.com

Eastern Veterinary Blood Bank
800-949-3822
www.evbb.com

Hemopet
310-828-4804
www.hemopet.com

Midwest Animal Blood Services
517-851-8244
www.midwestabs.com

Penn Animal Blood Bank
215-573-PABB
http://www.vet.upenn.edu/research/centers/penngen/services/transfusionlab/pabb.html

Sun States Blood Bank
954-639-2231
www.ssabb.org

The Pet Blood Bank
800-906-7059
www.petshelpingpets.com

it is collected from the donor, but it is neither a specific therapy nor economical use of blood. The optimal method of preservation of blood for transfusion is to separate whole blood into its component parts. Appropriate use of blood components not only conserves the products but also allows the most specific and safe product to be used for each animal. When blood components are used instead of whole blood for transfusion, two dogs can benefit from 1 unit of whole blood. A plasma transfusion counteracts the anticoagulant effects of rodenticide intoxication in one dog, and red blood cells from the same donor can provide enhanced oxygen-carrying capacity in a second, anemic dog. Component transfusions also have been used in cats, but preparation of components is more difficult because of the small volume of blood collected from donor cats.[35,48,72]

Veterinarians need to become familiar with the use of blood components because blood components are the predominant products available through commercial blood banks. Component therapy requires planning to maintain an adequate blood inventory either through ordering blood from a blood bank or through acquiring and coordinating the equipment and donors for successful blood collection. Preparation of blood components from whole blood requires that the blood from the donor be collected into the anticoagulant-containing bag of a multibag plastic blood collection system. The whole blood then is separated into packed red blood cells (PRBCs) and plasma by differential centrifugation, and the plasma is transferred into one or more of the satellite bags via the sterile tubing linking the bags. The bags are separated, and PRBCs are stored in a refrigerator while plasma is frozen. Blood collected into glass bottles is not amenable to centrifugation and cannot be processed into components. Additionally, storage of canine blood in a glass bottle results in lower levels of 2,3-diphosphoglycerate and adenosine triphosphate (ATP) than blood stored in plastic bags; consequently, plastic bags are the preferred storage container for blood.[16] Most general practitioners do not have access to the type of centrifuge required to properly separate blood into components. It is possible to acquire a used centrifuge or request the local blood bank to process the blood collected by the veterinarian. However, production of components is not feasible for most veterinarians, and the technical aspects of component production are not included in this chapter but can be found elsewhere.[60,72]

The most commonly used blood products, their indications, and suggested dosages are described below. The dosage of a blood product depends on the physical state of the patient and the response of the patient to the treatment: in essence, the treatment is "to effect."

Whole Blood

Whole blood is the blood collected from the donor plus the anticoagulant. In veterinary medicine, no standards have been established for the volume of blood that constitutes 1 unit. When a human blood collection system is used for dogs, 450 ± 45 mL of blood is collected in 63 mL of anticoagulant and often is designated as 1 unit. Whole blood contains red blood cells, clotting factors, proteins, and platelets and is the product most commonly transfused into dogs and cats.[38] Once whole blood is refrigerated, the white blood cells and platelets become nonfunctional. As a starting point, the dosage for whole blood is 10 to 22 mL/kg.

Packed Red Blood Cells

PRBCs are the cells and the small amount of plasma and anticoagulant that remains after the plasma is removed from 1 unit of whole blood. If 450 mL of blood is collected, the volume of PRBCs obtained is approximately 200 mL. Because the plasma has been removed, the total volume transfused is less than 1 unit of whole blood but contains the same oxygen-carrying capacity as 450 mL of whole blood. In cats, the increase in packed

cell volume (PCV) after transfusion of 1 unit of PRBCs has been shown to be equivalent to the increase after transfusion of 1 unit of whole blood.[48] PRBCs are used only to treat clinically symptomatic anemia because they do not contain platelets or clotting factors. Red blood cell transfusions are administered to cats for a variety of reasons. Data on 126 cats administered whole blood or PRBCs indicated 52% were transfused for blood loss anemia, 38% for erythropoietic failure, and 10% for hemolytic anemia.[48] Similar reasons for transfusion of cats have been reported in Germany.[90] Dogs more commonly are transfused for blood loss anemia (70%) with 14% to 22% being transfused for hemolytic anemia and 8% to 14% for erythropoietic failure.[8,45] The initial dosage of PRBCs is 6 to 10 mL/kg, and transfusion is continued until the clinical signs of anemia are improved.

Fresh Frozen Plasma

Fresh frozen plasma is the plasma obtained from whole blood plus the anticoagulant, frozen within 8 hours of collection. When whole blood is centrifuged to produce plasma and PRBCs, the anticoagulant is collected in the plasma fraction. Fresh frozen plasma contains all clotting factors, which, if frozen at −30° C in a blood bank freezer, maintain activity for 12 months.[85] Fresh frozen plasma maintained in an upright freezer at −20° C maintains clotting factor activity for 6 months. When frozen, the plastic storage bag becomes brittle and if not carefully handled can crack, rendering the plasma unusable. For this reason, plasma is stored in special boxes to protect the plastic bag and must be handled carefully before transfusion. Fresh frozen plasma has been used to treat a wide variety of clinical patients. A retrospective analysis of fresh frozen plasma usage in dogs identified multiple indications for administration of fresh frozen plasma, including replacement of coagulation factors, albumin, α2-macroglobulin, and immunoglobulin despite the recommendation that fresh frozen plasma should not be used as a source of albumin, for volume expansion, or nutritional support.[53,62] Calculations suggest that 45 mL/kg of plasma would need to be given to increase albumin serum concentration by 1 g/dL.[84] In cases of coagulation factor deficiencies, plasma should be given to effect (i.e., until active bleeding ceases).[50] For the treatment of coagulation disorders, 6 to 10 mL/kg is the recommended starting dosage. Multiple doses may be required to control bleeding because of the short half-life of clotting factors, especially in patients with disseminated intravascular coagulation. Normalization of previously abnormal coagulation tests can be used as a guide for discontinuation of plasma therapy.

Cryoprecipitate

Cryoprecipitate is prepared by thawing fresh frozen plasma at 0 to 6° C. A white precipitate forms, the plasma is removed after centrifugation, and both aliquots are refrozen. The cryoprecipitate is a concentrated source of von Willebrand's factor, fibrinogen, and factors XIII and VIII (antihemophilia factor). It is useful in the treatment of deficiencies of these clotting factors and is handled in the same manner as fresh frozen plasma. Two studies have shown cryoprecipitate to be the blood product of choice for the treatment of von Willebrand's disease because it concentrates the larger, more hemostatically active von Willebrand's multimers into a smaller volume than fresh frozen plasma.[12,78] Cryoprecipitate is equivalent to fresh frozen plasma for the treatment of hemophilia A. The dosage is 1 unit per 10 kg body weight.[59]

Cryo-poor Plasma

Cryo-poor plasma is the plasma remaining after the cryoprecipitate is removed. Cryo-poor plasma contains factors II, VII, IX, and X, which make it useful for the treatment of rodenticide intoxication. Storage and handling of cryo-poor plasma is similar to fresh frozen plasma. The initial dosage is 1 unit per 10 kg of body weight.

Platelet-Rich Plasma

Platelet-containing components are prepared from fresh whole blood by centrifugation at a slower rate than is used for production of PRBCs and plasma.[60] The platelets are suspended in a small amount of plasma to facilitate transfusion. Storage of fresh platelets is impractical outside a blood bank, because it requires a temperature of 20 to 24° C in special plastic bags under continuous agitation.[1] It has been shown that transfused platelets are rapidly destroyed in human patients with immune-mediated thrombocytopenia, and because immune-mediated thrombocytopenia is a common cause of profound thrombocytopenia in dogs, most cases of thrombocytopenia-mediated hemorrhage may not be amenable to successful platelet transfusion. If a platelet transfusion is given, the dosage is the platelets collected from 1 unit of whole blood per 10 kg body weight.

Frozen Platelet Concentrate

Frozen platelets are collected from a single donor via plateletpheresis, and one bag contains 1×10^{11} platelets preserved in dimethyl sulfoxide (DMSO).[39] The bag also contains a small amount of fresh frozen plasma. Efficacy data on this product have not been published, but the manufacturer recommends this product be used for the treatment of immune-mediated thrombocytopenia. Because the product contains DMSO, it must be infused slowly, or bradycardia will result. The dosage is 1 unit of frozen platelets per 10 kg of body weight. This dosage should increase the platelet count 20,000/μL when a platelet count is obtained 1 to 2 hours posttransfusion.

Serum

The use of serum has been recommended for the treatment of kittens and puppies with failure of passive transfer.

Kittens treated with 5 mL subcutaneously or intraperitoneally three times in 24 hours achieved immunoglobulin G (IgG) concentrations comparable to kittens receiving colostrum.[52] Treatment of puppies with 22 mL/kg of serum given orally or subcutaneously at birth did not result in equivalent IgG and IgA concentrations when nursing puppies were compared with serum-treated puppies.[65] IgM was higher in the puppies treated with serum administered subcutaneously.

SOURCES OF BLOOD AND BLOOD PRODUCTS FOR TRANSFUSION

The most convenient source of blood for a veterinary clinic is a commercial blood bank. Currently, there are only a few commercial veterinary blood banks in the United States, and they cannot adequately supply all the small animal practices in the country with blood (see Box 24-1). Veterinary school blood donor programs may serve as an additional source of blood for the practitioner.[38]

Most small animal practitioners borrow a donor from an employee or maintain a blood donor on the premises.[38] Borrowing a donor from either an employee or a client is a frequently used, if less convenient, option and is less expensive than maintaining an in-hospital donor. Maintaining a donor on the premises is advantageous because they are readily available for donation and their health status and disease exposure can be controlled, but the expense associated with feeding, housing, and caring for a blood donor is significant.[36] Some institutions have instituted volunteer blood donor programs.[6,40] Donors are recruited from clients, employees, or the general public. Collecting blood from stray animals is unsafe because infectious disease exposure and health status are unknown.

BLOOD DONOR SELECTION

Identification of donor dogs and cats before blood is needed is essential to allow blood type to be determined and the health status of the donor to be assessed before blood collection, thus ensuring the safety of the blood being transfused. Recommendations on infectious disease screening for canine and feline blood donors recently have been published as a consensus statement. The recommendations are included in the sections below.[88]

Dogs

More than 50 years ago, the best blood donor was believed to be a large, quiet dog not requiring anesthesia during blood collection.[56] The current recommendation is unchanged. A canine blood donor weighing more than 27 kg can safely donate 450 mL of blood in one donation, allowing collection of blood into commercially manufactured blood collection bags designed to facilitate sterile processing of components. Dogs weighing 27 kg or more have been shown to consistently donate 1 unit of blood for 2 years at 3-week intervals.[67] Bags for collecting 225 mL of blood (Terumo Medical Corporation, Somerset, NJ) have successfully been used in dogs weighing 16 to 27 kg.[72] Dogs selected as donors also should have an easily accessible jugular vein to facilitate venipuncture.

Greyhounds have been promoted as ideal blood donors because of their gentle disposition, high hematocrits, and lean body type, which simplifies blood collection.[30] Many greyhounds are euthanized because of poor racing performance, and these dogs are available from racetracks, breeders, and rescue organizations.[22]

Veterinarians choosing greyhounds as blood donors should be aware of certain breed idiosyncrasies that will impact on the management of a greyhound donor. The greyhound idiosyncrasy most important in transfusion medicine is the high red blood cell count, PCV and hemoglobin concentration, and low white blood cell counts and platelet count compared with mixed breed dogs.[66,79] Greyhounds in Florida have a seroprevalence of babesiosis of 46%.[81] Because the geographic origin of greyhounds serving as blood donors cannot always be determined, all greyhounds being screened as donors should have serologic testing for *Babesia canis* performed, and dogs with positive titers should be excluded as donors. Greyhounds with negative titers against *B. canis* should have *B. canis* polymerase chain reaction (PCR) performed, and if the test is positive, the dog should be excluded as a donor.

In addition to the tendency of greyhounds to be asymptomatic carriers of *B. canis*, some other breeds of dogs should be used cautiously as blood donors because they are known to be asymptomatic carriers of infectious organisms transmitted by transfusion. American pit bull terriers and Staffordshire bull terriers recently have been recognized as carriers of *Babesia gibsoni*.[4,55] Use of these dogs as blood donors should be restricted to those dogs seronegative and PCR-negative for *B. gibsoni*. Leishmaniasis has been identified in American foxhounds.[32] Transfusion of *Leishmania infantum*–infected blood from American foxhounds resulted in clinical leishmaniasis in transfusion recipients.[64] All potential foxhound donors should be screened for *Leishmania* sp.

Although seven canine blood groups or blood type systems have received international standardization, typing sera are available for only five types (Box 24-2). Red blood cells can be negative or positive for a given blood type, except for the dog erythrocyte antigen (DEA) 1 system which has three subtypes, DEA 1.1, 1.2, and 1.3. Canine red blood cells can be negative for all three subtypes (a DEA 1-negative blood type) or positive for

Box 24-2 Blood Types in Dogs and Cats for Which Typing Antisera Currently Exist

Dogs	
Dog erythrocyte antigen (DEA)	1.1, 1.2
	3
	4
	5
	7
Cats	
Type	A
	B
	AB

any one of the three subtypes. Alloantibodies, occurring naturally and without previous sensitization from transfusion, do not appear to cause transfusion incompatibility in the dog.

The blood type of the ideal canine blood donor is not uniformly agreed on among transfusion experts. Of the five blood groups for which typing sera are available, a transfusion reaction has been attributed to antibody against DEA 1.1 induced by a DEA 1.1-positive transfusion in a DEA 1.1-negative recipient and to an antibody induced by a DEA 4-positive transfusion in a DEA 4-negative dog.[26,58] In theory, red blood cells expressing DEA 1.2 can sensitize a DEA 1.2-negative transfusion recipient, resulting in an acute hemolytic transfusion reaction if a second transfusion of DEA 1.2-positive blood is given. In a laboratory setting, antibodies against DEA 1.2 have been reported to cause transfusion reactions, but clinical reports of hemolytic transfusion reactions mediated by anti-DEA 1.2 antibodies are lacking. Approximately 45% of dog red blood cells are positive for DEA 7. It is believed DEA 7 is structurally related to an antigen found in common bacteria. A naturally occurring antibody against DEA 7 has been described in 20% to 50% of DEA 7-negative dogs and may result in accelerated removal of DEA 7-positive cells from a DEA-negative donor with anti-DEA 7 antibodies.[73] Based on this information, the recommendation has been made to select donors that are negative for DEA 1.1, 1.2, and 7. Others suggest the donor dog should also have red blood cells positive for DEA 4 to be designated as a universal donor.[33] Ninety-eight percent of dogs are DEA 4-positive, making it easy to find donors of this blood type. The importance of DEA 3 and 5 in blood donor selection remains to be determined.

One other feature that should be considered before selection as a blood donor is the dog's plasma von Willebrand factor concentration. Von Willebrand's disease is the most common inherited coagulopathy in dogs and has been reported in many breeds of dogs and in dogs of mixed breeding as well. Because of the high frequency of this disease in the canine population, plasma from a canine blood donor is likely to be used to transfuse a dog with von Willebrand's disease-induced hemorrhage, and a donor with a normal concentration of von Willebrand's factor is essential to replace the deficient coagulation factor.

CATS

The physical requirements for a feline blood donor are similar to those for a canine donor. The ideal feline donor is a large cat, more than 5 kg body weight, with a pleasant disposition. Easily accessible jugular veins facilitate collection of blood, and choosing a shorthair cat decreases the clipping required before phlebotomy.

It is essential to determine the blood type of potential donors. Only one feline blood group system has been identified with three blood types: A, B, and AB (see Box 24-2).[3] Unlike dogs, cats have naturally occurring alloantibodies against type A or type B cells.[24] Cats of blood type B have strong hemagglutinating antibodies of the IgM type against type A cells, and cats of blood type A have weak hemolysin and hemagglutinating antibodies of the IgM and IgG type against type B cells. The clinical significance of these alloantibodies is threefold in transfusion medicine. First and most importantly, a cat may have a transfusion reaction without sensitization from a previous transfusion; second, type A kittens born to a type B queen are at risk for neonatal isoerythrolysis[11]; and third, the antibodies are useful in determining the blood type of a cat.

Donors of both type A and type B blood must be available because there is no universal donor in cats. Incompatible transfusions result in shortened red blood cell survival in the transfusion recipient and potentially death; therefore the serologic compatibility between recipient and donor must be determined before every transfusion in cats.[24] Donors of type A blood are easy to find because more than 99% of the domestic cats in the United States are type A.[28] The prevalence of domestic cats with type B blood varies geographically. In the United States, the western states have the highest percentage of type B cats, 4% to 6%.[28] Australia has the highest reported percentage of type B cats in their domestic cat population, 73%.[3] In Europe, the frequency of blood type B in domestic cats varies from 0% in Finland to 14.9% in France.[27] Some purebred cats have a higher frequency of type B in their population.[25] The British shorthair and the Devon rex have been reported to have the highest proportion of type B individuals, approximately 50%. The Siamese, Oriental shorthair, Burmese, Tonkinese, American shorthair, and Norwegian forest cat breeds have not been reported to have any members with type B blood. Blood type AB is

extremely rare, occurring in 0.14% of cats in the United States and Canada.[31] Fortunately, a type AB donor is not required to successfully transfuse a type AB cat. Blood from a type A cat is adequate.

BLOOD DONOR SCREENING

Screening blood donors for infectious diseases transmitted by blood transfusion is an integral step in maintaining a safe blood supply. Infectious disease screening of canine and feline blood donors varies within the different geographic regions of the United States and with the breed of the blood donor. A consensus statement developed by a committee consisting of members of the Infectious Disease Study Group and the Association of Veterinary Hematology and Transfusion Medicine should serve as the guideline for donor screening.[88]

Infectious organisms known to be transmitted by blood transfusion include *B. canis, B. gibsoni*, *Haemobartonella canis*, and *Leishmania* sp.[18,51,64,76] All canine blood donors should be screened for *Ehrlichia canis* and *Brucella canis*, and if they test positive, they should be eliminated from the donor pool. Titers against *E. canis* less than 1:80 may be false positives and should be repeated in 2 to 3 weeks. Dogs with initially negative titers to *E. canis* can receive additional screening with a PCR test. Splenectomy of donor dogs to facilitate identification of *B. canis* and *H. canis* carriers is not recommended. In neutered dogs, a single negative test for *Brucella canis* is adequate. Based on travel history and breed, additional screening for *Trypanosoma cruzi*, *Bartonella vinsonii*, *B. canis*, *B. gibsoni*, *L. donovani*, and organisms previously classified as *Ehrlichia* spp. (*Anaplasma phagocytophilum* and *Anaplasma platys*) may be indicated.[88] Dogs should not donate if they are ill or have fever, vomiting, or diarrhea; using donors with these clinical signs has resulted in *Yersinia entercolitica* contamination of human units of blood.[19]

Outdoor cats should not be used as blood donors because restricting access to other cats can prevent most infectious diseases potentially transmitted to cats by transfusion. Potential donor cats should be screened for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV). Because FeLV infection can take up to 3 months to become patent, cats being considered as donors should be screened monthly for FeLV for 3 consecutive months. Testing for FIV antibodies can be performed simultaneously. *Bartonella henselae* is an emerging feline infectious disease and has been transmitted to cats by infected blood.[49] The use of cats with positive serology or cultures for *B. henselae* as blood donors is controversial. Because fleas are the vectors of agents potentially transmitted by transfusion, flea control is essential in donor cats. Cats that are infected with organisms formerly classified as *Haemobartonella* sp. (*Mycoplasma haemofelis* and *Mycoplasma haemonominutum*) also should be eliminated from the donor pool. Testing should include both light microscopy and PCR for *Mycoplasma* sp. Screening of donor cats for feline infectious peritonitis (FIP) is problematic because there is no reliable test to identify the FIP-causing coronavirus. Feline blood donors should be screened for infection with *Cytauxzoon felis* and the agents causing feline ehrlichiosis if they are known to have traveled to endemic locations.

BLOOD DONOR HEALTH MAINTENANCE

A safe blood supply begins with healthy blood donors. All blood donors should undergo a complete physical examination each time they donate blood. Complete and differential blood counts, biochemical profile, and fecal examination should be performed annually. Blood donors should be vaccinated on a schedule appropriate to the donor's geographic location and risk factors for contracting infectious diseases. Because the ideal feline blood donor lives in an indoor environment and is not exposed to other cats, the author believes vaccinations against FeLV, FIV, and FIP are unnecessary in donor cats. Heartworm testing should be performed and prophylaxis should be administered to donor dogs and cats on the schedule recommended for pets in the geographic region of the blood bank. Because many infectious diseases potentially transmitted by transfusion are vector-borne, control of ectoparasites in blood donors is critical to providing the safest blood possible.

EQUIPMENT AND SUPPLIES FOR COLLECTION OF BLOOD

Skin Preparation

Strict aseptic technique must be used during the blood collection process to prevent contamination. Whenever possible, solutions and equipment used for the collection process should be single-use products to prevent inadvertent contamination of blood.[37] After clipping the hair over the venipuncture site, the skin is surgically scrubbed. The ideal skin preparation regimen is yet to be determined in animals; however, in human blood donors, a 30-second, 70% isopropyl scrub followed by a 2% iodine tincture resulted in better skin surface disinfection than alcohol followed by chlorhexidine or green soap.[29] Venipuncture is accomplished while wearing sterile gloves and without touching the scrubbed area.

Anticoagulant Solutions

Several different solutions are available to anticoagulate and preserve blood for transfusion (Table 24-1). Anticoagulants provide no nutrients to preserve red cell

TABLE 24-1 Anticoagulants and Preservatives for Blood

Canine Blood	Ratio with Blood	Storage Time @ 0-6°C
Anticoagulant		
Heparin	625 U/50 mL blood	For immediate transfusion
3.8% sodium citrate	1 mL/9 mL blood	For immediate transfusion
Anticoagulant-preservative		
CPDA-1	1 mL/7 mL blood	20 days
ACD "B"	1 mL/7-9 mL blood	21 days
Additive solutions	100 mL/250 mL packed red blood cells	37-42 days
Feline Blood		
Anticoagulant		
Heparin	625 U/50 mL blood	For immediate transfusion
3.8% sodium citrate	1 mL/9 mL blood	For immediate transfusion
Anticoagulant-preservative		
ACD "B"	1 mL/7-9 mL blood	30 days
Additive solutions		Not evaluated

metabolism during storage. Blood collected in anticoagulants should be transfused immediately. Anticoagulant-preservative solutions have been designed to provide nutrients to maintain red blood cell function during storage.

CPDA-1

One common anticoagulant solution for preservation of canine red blood cells, citrate phosphate dextrose adenine (CPDA-1), is found in commercially prepared, multiple-bag systems. Maximal storage time for feline blood in CPDA-1 has yet to be determined but may be as long as 35 days.[7]

ACD

Acid citrate dextrose or anticoagulant citrate dextrose (ACD) formula B can be used to store either canine or feline blood.[17,57] It can be purchased in 500-mL bags and placed in syringes for collection of blood.

Additive Solutions

Additive solutions are contained in a multibag system containing citrate phosphate dextrose (CPD) or citrate phosphate dextrose 2 (CPD-2) as the anticoagulant. The additive solution is contained in a bag separate from the main bag and is added to PRBCs after the plasma is removed. Additive solutions that have been evaluated in dogs are Adsol (Fenwal Laboratories, Baxter Health Care Corporation, Deerfield, IL) and Nutricel (Miles Pharmaceutical Division, West Haven, CT).[87,89] Storage time of canine red blood cells with these solutions is approximately equal (5 weeks). Additive solutions have not been evaluated for storage of feline blood.

Leukoreduction Filters

White blood cells are responsible for some adverse effects of transfusion and do not contribute to transfusion efficacy (see "Adverse Effects of Transfusion"). An integral filter to remove white blood cells from whole blood is incorporated into some blood bag systems. One system has been evaluated using canine blood and effectively removed white blood cells without affecting red blood cell viability.[5]

COLLECTION OF BLOOD

Dogs

Dogs that have not previously donated blood may require sedation, whereas dogs that have previously donated often do not. If sedation is necessary, the author prefers butorphanol (0.1 mg/kg intravenously, 10 to 15 minutes before donation). This calms the donor but does not induce lateral recumbency. Some prefer to collect blood from dogs in lateral recumbency, especially if the femoral artery is used.[71] The choice is strictly a matter of personal preference and skill. Acepromazine is not recommended because it causes hypotension and platelet dysfunction.

The flow of blood into the bag can occur by gravity or suction. Blood collected by suction does not have a greater rate of hemolysis than that collected by gravity flow, and it can be collected more rapidly.[15] Suction collection of blood is facilitated using a device (Vacuum Chamber) manufactured by the Animal Blood Bank (Dixon, CA). This device requires an external vacuum source during collection of blood.

Cats

It is unusual to find a feline blood donor that does not require sedation during blood donation. The author prefers a combination of ketamine (10 mg) and diazepam (0.5 mg) intravenously for cats. Other protocols using midazolam and isoflurane have been described.[71] If the sedative agent is to be given intravenously, a peripheral vein (cephalic or medial saphenous) should be used to preserve the jugular veins for blood collection.

No commercially available system is manufactured for the collection of blood from cats because of the small volume of blood that can safely be withdrawn from a cat. Typically, anticoagulant can be withdrawn from a blood bag port using a syringe. It is placed in one or two large

syringes (25 to 60 mL) depending on the volume of blood to be collected (see Table 24-1). A large (19-gauge) butterfly needle is used for jugular venipuncture so that if a second syringe of blood is to be collected, the full syringe can be removed and the second syringe connected without a second venipuncture. By the definition of the American Association of Blood Banks, this is an "open" system, and blood collected in this manner should not be transfused more than 24 hours after collection.[83] Alternatively, the excess CPDA-1 can be expelled from the bag and cat blood collected directly into the bag.[68] A commercially available vacuum system can be used for collecting blood from cats, but some authors find this system less satisfactory than the syringe method.[44,71]

PRETRANSFUSION COMPATIBILITY TESTING

Selection and transfusion of compatible blood is one component of the process to provide a safe and efficacious red cell transfusion. The current recommendations are different for cats and dogs at the time of the first red cell transfusion. The recommendation for subsequent transfusions is the same in both species. Because each unit of red blood cells is antigenically distinct, the recipient may form antibodies after transfusion of any unit of blood. The immune system will take a minimum of 5 days to make antibodies against transfused red blood cells; consequently, a crossmatch should be performed if more than 4 days elapse between transfusions. Performing a crossmatch will not prevent an immune reaction to subsequent transfusions; it can only identify those units of blood with potential to cause acute hemolytic transfusion reactions.

Dogs

Because of the lack of clinically significant preformed alloantibodies in the dog, blood typing and crossmatching are not routinely performed before the first transfusion of DEA 1.1-negative donor blood. If DEA 1.1-positive blood were being transfused, it would ideally be given to a DEA 1.1-positive recipient. DEA 1.1 status can be determined by using the card typing system available from DMS Laboratories (Flemington, NJ). The typing kit contains all necessary equipment and reagents to determine DEA 1.1 blood type in minutes. Blood typing or crossmatching is not required before transfusion of canine plasma.

Cats

At the time of the first red blood cell transfusion, blood type should be performed on all cats because any breed of cat can be blood type B and transfusion of type A blood to a type B cat will result in an acute hemolytic transfusion reaction. Blood typing in the cat has been simplified by the availability of typing cards (DMS Laboratories; Fig. 24-1). A special situation with regard to blood typing and crossmatching exists in cats. When blood typing is unavailable, crossmatching will prevent an A-B mismatch transfusion in a cat. In cats, an incompatible major crossmatch, when crossmatching is performed with a known type A donor, strongly suggests the potential recipient is a type B cat because of the preformed alloantibodies that exist in all type B cat plasma regardless of transfusion status. If cat plasma is administered, it should be the same blood type as the recipient. If blood typing is not available, crossmatching the donor to the recipient cat will prevent a reaction because of A-B incompatibility.

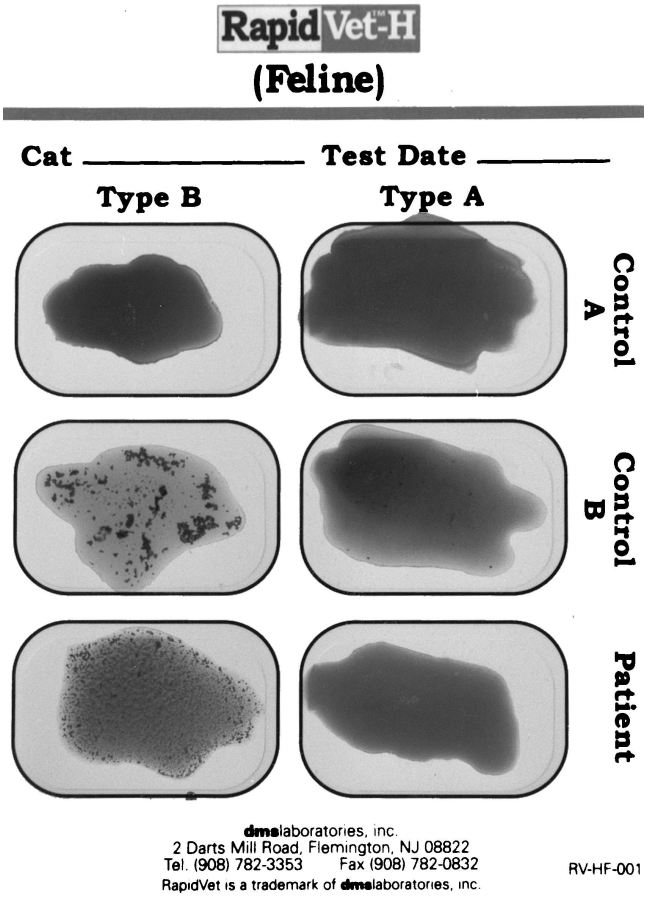


Fig. 24-1 A feline blood typing card. The patient is blood type B. (Courtesy of DMS Laboratories, Inc., Flemington, NJ.)

ADMINISTRATION OF BLOOD AND PLASMA

The person administering the blood should pay careful attention to the blood bag label before transfusion. The most common reason for an acute hemolytic transfusion

reaction in human patients is clerical error—the wrong unit of blood is released from the blood bank or a unit of blood is given to a patient who was not intended to receive a transfusion.[80] In veterinary medicine, it is crucial to confirm that the blood comes from the correct species of blood donor in addition to being typed and matched to the patient requiring a transfusion. The contents of the bag also should be examined for normal color and consistency. Bacterially contaminated blood often appears brown or purple because of deoxygenation, hemolysis, and formation of methemoglobin.[37]

Blood and plasma can be administered using several routes. Most commonly, blood is given intravenously. The diameter of the catheter used for transfusion is important in determining the rate of blood flow because blood flows more slowly through a small catheter; however, small diameter catheters have not been associated with increased risk of hemolysis during transfusion.[83]

The intraosseous route can be used successfully for administration of blood and plasma.[63] In normal dogs, 93% to 98% of red blood cells administered through an intraosseous catheter are found in the peripheral circulation within 5 minutes.[13] This rapid and simple method is especially useful in animals with vascular collapse and in extremely young puppies and kittens. Special intraosseous catheters are available, but a spinal needle, bone marrow aspiration needle, over-the-needle catheter, or even an ordinary hypodermic needle can be used. Sites for the placement of the intraosseous catheter include the trochanteric fossa of the femur, the medial tibia, and the iliac crest. Blood flows very rapidly through an intraosseous catheter, and rate of administration should be monitored closely. Plasma can be administered intraperitoneally in emergency situations, but red blood cells are slowly and poorly absorbed by this route, and it is not recommended for red blood cell transfusions.

A blood transfusion administration set should be used for any transfusion of blood or component because the incorporated filter removes blood clots and debris that could cause embolism. The filter typically used in veterinary medicine is 170 μm in size. For small-volume transfusions, an 18-μm filter that can be attached to intravenous tubing is useful. An 18-μm filter does not work well for large-volume transfusions because it rapidly becomes obstructed with debris, and flow slows. A blood administration set does not remove air from stored blood. Although glass bottles are convenient blood collection systems because they do not require an extrinsic vacuum source, the risk of an air embolism is increased when blood is collected into glass bottles. Glass bottles are not recommended for collection and storage of blood.

The American Association of Blood Banks explicitly states that medications should not be added to blood or components.[83] In addition, no fluid should be added to blood except 0.9% sodium chloride when it is necessary to decrease the viscosity of PRBCs. Fluids containing calcium such as lactated Ringer's solution may overcome the anticoagulant properties of citrate, resulting in coagulation of the blood. Solutions such as 5% dextrose in water are hypotonic and may induce hemolysis.

The recommended rate of transfusion of red blood cells depends on the status of the recipient. In massive hemorrhage, the transfusion should be given as rapidly as possible. In a normovolemic, stable transfusion recipient, some clinicians recommend a rate of 0.25 mL/kg for the first 30 minutes, after which the rate is increased if no reaction is seen.[82] In patients with heart disease, a rate of 4 mL/kg/hr should not be exceeded.[30] Plasma can be given more rapidly (4 to 6 mL/min).[47] Whatever the rate chosen, it should be rapid enough to complete the transfusion within 4 hours of initiation because of the risk of bacterial growth in blood maintained at room temperature for a prolonged period.

Control of delivery rate can be accomplished by use of infusion pumps to deliver a preset volume over a specific period. The use of infusion pumps must be limited to devices approved for use with blood because some infusion pumps can result in hemolysis of red blood cells as a result of excessive pressure.[77]

Because blood does not contain any antibacterial agents, it must be refrigerated until used to retard bacterial growth and maintain red blood cell viability. If the clinical status of the animal requires that the transfusion be given more slowly than over 4 hours, the blood can be split into smaller units with a transfer bag. One portion of the blood is transfused while the other is returned to the refrigerator until the first half of the transfusion is completed. In patients with cardiac disease at risk for volume overload, the risk can be minimized by use of PRBCs, which require infusion of a lower volume than whole blood. Diuretics can be administered before transfusion to decrease intravascular volume in cardiac patients.

Warming of blood before transfusion has been recommended to prevent hypothermia in the transfusion recipient. Warming of blood probably is only necessary if a large volume of blood is to be given or if the recipient is a neonate. For adult animals receiving a single unit of blood, the blood can be administered at refrigerator temperature. Warming blood has the potential for excessive heating, causing red blood cell membrane damage and hemolysis or bacterial growth if contamination is present. Blood warming devices that use dry heat, radio waves, microwaves, or electromagnetic energy are available, but cost often is prohibitive. Refrigerated human blood can be warmed quickly by admixing it with warm (45 to 60° C) 0.9% saline in a ratio of 1:1 without damage to red blood cells.[42] This method has not been tested for dogs or cats. Once blood is warmed to 37° C, it deteriorates rapidly and, if not used, should be discarded. Fresh frozen plasma must be thawed before transfusion. A method for thawing canine fresh frozen plasma in a

microwave oven has been described, but the author has found this unsatisfactory because of uneven heating by household microwave ovens.[41] Plasma can be thawed at room temperature, and if the thawing time needs to be shortened, the plasma can be placed into a plastic bag and thawed in a 37° C water bath. The plastic bag is necessary to prevent contamination of the infusion ports in the water bath. Plasma should be used within 4 hours of thawing.

Transfusion recipients should be monitored during transfusion to allow early detection of a transfusion reaction. Rectal temperature, heart rate, and respiratory rate should be recorded every 10 minutes during the first 30 minutes and then every 30 minutes thereafter. The patient should be monitored for vomiting, diarrhea, urticaria, and hemoglobinuria or hemoglobinemia. Changes in vital signs or clinical status may indicate a transfusion reaction. Patients developing volume overload will become tachypneic or dyspneic, and tachycardic.

Patients receiving large transfusions (≥1 blood volume in 24 hours) of stored blood may develop specific abnormalities. Consequently, patients receiving large transfusions should be monitored for changes in serum potassium, ionized calcium, and ionized magnesium concentrations, as well as hypothermia and coagulation abnormalities.[43]

Box 24-3 Classification of Transfusion Reactions

Acute Immunologic
Acute hemolytic reaction
Febrile nonhemolytic reaction
Urticaria

Acute Nonimmunologic
Electrolyte disturbances
- Hypocalcemia
- Hyperkalemia
- Hypomagnesemia

Embolism (air or clotted blood)
Endotoxic shock
Circulatory overload
Contamination of blood
- Bacteria
- Spirochetes
- Protozoa

Physical damage
- Freezing
- Overheating

Hypothermia
Dilutional coagulopathy

Delayed Immunologic
Delayed hemolytic
Posttransfusion purpura

Delayed Nonimmunologic
Infectious disease transmission
- Feline leukemia virus
- Feline infectious peritonitis
- Feline immunodeficiency virus
- Bartonellosis
- Babesiosis
- Hemotrophic mycoplasma
- Ehrlichiosis
- Leishmaniasis
- Brucellosis

Hemochromatosis

ADVERSE EFFECTS OF TRANSFUSION

Definition

An adverse effect of transfusion or transfusion reaction consists of the range of immunologic and metabolic changes that occur during or after administration of a blood product. Four classes of adverse effects of transfusion have been described (Box 24-3). Acute transfusion reactions occur during or within a few hours after a transfusion, and delayed transfusion reactions occur after the completion of the transfusion. The delay may be months to years. Reports describing adverse effects of transfusion in dogs and cats are limited to case reports and retrospective series.*

Acute Immunologic Transfusion Reactions

Acute immunologic transfusion reactions occur because antibodies that elicit an immune response are present in the plasma of either the donor or recipient. The sequelae of an acute immunologic transfusion reaction are rapid, often irreversible, and sometimes fatal. Current theories on the pathogenesis of acute hemolytic transfusion reaction in humans propose that hemolysis induces the release of cytokines such as tumor necrosis factor, interleukin-1 (IL-1), IL-6, and IL-8, complement, endothelium-derived relaxing factor (nitric oxide), and endothelin, resulting in the clinical syndrome of disseminated intravascular coagulation, shock, and acute renal failure.[10] The pathophysiology of acute hemolytic transfusion reaction in dogs and cats must differ in some manner from that described in humans because acute renal failure is not reported to be a feature in dogs and cats.[2,23,26,92]

The best example of an acute hemolytic transfusion reaction in veterinary medicine is the administration of type A red blood cells to a type B cat. In the recipient

*References 2,18,23,24,26,35,45,48,51,64,76,84,86,92.

cat, naturally occurring alloantibodies and complement bind to the transfused red blood cells and cause hemolysis. Clinical signs described in cats having an acute hemolytic transfusion reaction include fever, vomiting, lethargy, icterus, and death.[2] Results of laboratory testing often show a positive Coombs test, rapidly declining PCV, and increasing serum bilirubin concentration.

Dogs experiencing an acute hemolytic transfusion reaction show clinical signs similar but not identical to those observed in cats. Most affected dogs exhibit fever, restlessness, salivation, incontinence, and vomiting. Some dogs develop shock, and an occasional dog experiences acute death. Plasma and urine hemoglobin concentrations increase within minutes of transfusion. Incompatible cells are cleared from circulation in less than 2 hours. Dogs whose red blood cells lack the DEA 1.1 antigen that have previously been sensitized by transfusion of DEA 1.1-positive cells are at the greatest risk for an acute hemolytic transfusion reaction.[26]

Other acute immunologic transfusion reactions reported in dogs and cats include nonhemolytic fever and urticaria.[8,35,45,84] In humans, nonhemolytic fever is a result of antibodies against donor white blood cells, and urticaria occurs as a result of antibodies-against donor plasma proteins. Nonhemolytic febrile transfusion reactions do not require treatment, but antipyretics may be used if the patient is uncomfortable (Table 24-2). Urticaria is the most common reaction to plasma transfusion in dogs.[84] If urticaria caused by plasma administration is diagnosed, it should be treated with short-acting corticosteroids and antihistamines. The plasma transfusion then may be restarted at a slower rate and the recipient observed carefully.

DELAYED IMMUNOLOGIC TRANSFUSION REACTIONS

Delayed immunologic transfusion reactions are classified as delayed hemolytic, transfusion-induced immunosuppression, posttransfusion purpura, and graft-versus-host disease. These reactions are not preventable by crossmatching or blood typing. Delayed hemolytic transfusion reactions invariably occur in persons who have been previously sensitized to allogenic red blood cell antigens by transfusion or pregnancy. Even though compatible blood is given to a patient, the recipient may develop antibodies against any one of the hundreds of red blood cell antigens present on the transfused cells. An anamnestic response to the antigens on the transfused red blood cells results in a delayed hemolytic transfusion reaction that occurs 7 to 10 days after a transfusion and is a well-described complication of red cell transfusion in humans. It has not been reported in dogs, but there is

TABLE 24-2 Drug Dosages and Route of Administration for Use in Acute Transfusion Reactions

Type of Reaction	Drugs to Consider
Acute hemolytic	Methylprednisolone succinate 30 mg/kg, IV, once Dexamethasone sodium phosphate 4-6 mg/kg, IV, once
Febrile nonhemolytic	Aspirin 10 mg/kg, PO once
Urticaria	Diphenhydramine 2 mg/kg, IV, prn Prednisone 0.5-1 mg/kg every 12-24 hr PO
Hypocalcemia	Calcium gluconate (10% solution) 50-150 mg/kg, IV over 20-30 min Discontinue if bradycardia occurs. Repeat if hypocalcemia persists. Calcium chloride (10% solution) 50-150 mg/kg, IV over 20-30 min Discontinue if bradycardia occurs. Repeat if hypocalcemia persists.
Hypomagnesemia	Magnesium sulfate 0.75-1 mEq Mg^{2+}/kg IV over 24 hr Magnesium sulfate 0.15-0.30 mEq/kg IV over 5-15 min
Hyperkalemia	Regular insulin 0.5 U/kg, IV given with 50% dextrose 2 g/U of insulin prn Infuse 0.9% saline
Circulatory overload	Nitroglycerine paste (2%) $\frac{1}{4}$ to 1 inch applied to skin, once (monitor blood pressure, may cause hypotension) Furosemide 2-4 mg/kg, IV once Oxygen therapy
Dilution coagulopathy	Fresh frozen plasma 3-5 mL/kg until coagulation tests normalize.

IV, *Intravenous;* PO, *orally;* prn, *as needed.*

no reason it could not occur. Fever is the most common sign of a delayed hemolytic transfusion reaction in humans. Icterus also may be noticed 4 to 7 days after a transfusion.

The only delayed immunologic transfusion reaction that has been reported in veterinary medicine is post-transfusion purpura.[86] It occurred in a dog with hemophilia A that had previously received a transfusion. Five to 8 days after subsequent transfusions, thrombocytopenia and petechiation were evident. Blood collected during a thrombocytopenic episode was positive for platelet-bound IgG, indicating an immune mechanism for platelet destruction.

Acute Nonimmunologic Transfusion Reactions

Acute nonimmunologic transfusion reactions are caused by physical changes in the red blood cells during collection, storage, or administration.

Collection-associated Changes in Blood

Improper collection of blood can result in an adverse reaction to transfusion. Introduction of air when collecting blood into glass bottles increases the likelihood of venous air embolism. Venous air embolism causes sudden onset pulmonary vascular obstruction, a precordial murmur, hypotension, and death as a result of respiratory failure. Collection of blood from an inadequately screened donor can result in transmission of bacteria, spirochetes, or protozoa and eventually clinical signs of the associated disease in the recipient. Transfusion of blood contaminated by bacteria can cause shock, which is managed with volume expansion and pressor agents, as well as empirical antibiotic administration based on results of a Gram stain. Endotoxic shock results from transfusion of blood heavily contaminated with endotoxin-producing bacteria. Clinical signs in cats transfused with blood contaminated by bacteria include collapse, vomiting, diarrhea, and acute death, but most cats did not exhibit clinical signs after receiving bacterially contaminated blood.[37] Hypotensive shock developed in a dog that received a *B. canis*–infected transfusion.[18]

Storage-associated Changes in Blood

During storage, the ATP content of red blood cells decreases, and some cells undergo hemolysis resulting in leakage of potassium out of the cells into the storage medium. The increase in potassium in the storage medium is a contributing factor in the development of hyperkalemia in patients receiving large volume transfusions of stored blood. A large-volume transfusion of stored blood can cause hyperkalemia, but this is rare unless the patient has renal failure or preexisting hyperkalemia.[43] Hyperkalemia in a transfusion recipient is as it would be in any patient with hyperkalemia. The transfusion should be discontinued and 0.9% NaCl administered because 0.9% NaCl does not contain added potassium and will facilitate renal excretion of potassium. Intravenous administration of insulin, followed by administration of 50% dextrose and frequent monitoring of blood glucose and potassium concentrations until serum potassium concentration normalizes, is all that is necessary. Routine empirical administration of calcium to transfusion recipients cannot be recommended because of the risk of hypercalcemia and increased myocardial irritability, but animals with ionized hypocalcemia resulting from large transfusion should be treated with calcium gluconate or calcium chloride to effect.[14] Physical damage (such as freezing or overheating) to red blood cells during storage causes hemolysis. While being transfused, the patient exhibits hemoglobinuria and hemoglobinemia without evidence of other signs of an acute hemolytic transfusion reaction, such as fever, vomiting, or collapse. During storage of blood, formation of clots and other debris may occur and can result in embolism during transfusion.

Administration-associated Changes in Blood

In instances of large-volume transfusion, ionized hypocalcemia or ionized hypomagnesemia can result from the citrate used as an anticoagulant complexing with calcium or magnesium and lead to myocardial dysfunction and potential cardiac arrest and tetany.[46] Hypothermia is common after large-volume transfusion in veterinary patients, and use of warming blankets should be instituted whenever possible. Dilution of coagulation factors by large-volume transfusion of coagulation factor-depleted stored blood results in prolongation of coagulation times. In dogs receiving large-volume transfusions, prolongation of coagulation times is associated with a poor prognosis.[43] Administration of fresh frozen plasma is indicated to correct the coagulation abnormalities. Dogs and cats with chronic severe anemia or compromised cardiac and pulmonary systems are at greater risk for circulatory overload and pulmonary edema than are those without cardiopulmonary disease. Dogs and cats developing volume overload from transfusion are treated with oxygen supplementation, diuretics, and vasodilators. Improvement should be seen within 1 to 2 hours.

Delayed Nonimmunologic Transfusion Reactions

In humans, human immunodeficiency virus, hepatitis virus, and cytomegalovirus infections are documented as late effects of transfusion. The transmission of infection to a recipient cat from a donor cat infected with FeLV or FIV would be a veterinary example of a delayed nonimmunologic transfusion reaction. A recently described late complication of transfusion is hemochromatosis in a miniature schnauzer.[75] The dog received blood transfusions every 6 to 8 weeks for 3 years to treat chronic anemia. It was euthanized because of progressive liver

disease, and the diagnosis of hemochromatosis was confirmed by necropsy.

EVALUATION OF A PATIENT WITH A SUSPECTED TRANSFUSION REACTION

Immediate intervention is critical because of the life-threatening nature of acute hemolytic transfusion reactions. In all animals suspected of having some form of acute transfusion reaction, the transfusion should be stopped and samples of patient blood and urine obtained for baseline evaluation of biochemical, hematologic, and coagulation values. The unit of blood should be inspected to ensure it is from the appropriate species and is the intended unit based on the crossmatch or blood type. Urine can be visually inspected to determine the presence or absence of hemoglobin. A Gram stain and bacterial culture of the blood remaining in the blood bag should be done. Rectal temperature of the recipient should be compared with the pretransfusion value. A transfusion-associated fever is defined as an increase in 1° F over the pretransfusion temperature.[83] The cardiovascular system should be monitored by electrocardiogram and blood pressure measurement. Immediate evaluation of serum ionized calcium and potassium concentrations would be useful, but certain electrocardiographic changes suggest hypocalcemia (long QT interval with a normal heart rate) or hyperkalemia (decreased height of P waves, loss of P waves, or widening of the QRS complex with large T waves) if rapid measurement of serum electrolyte concentrations cannot be obtained. Venous access and blood pressure should be maintained by an infusion of a crystalloid solution such as lactated Ringer's solution or 0.9% NaCl. Intravenous administration of short-acting glucocorticoids may suppress some of the mediators of acute hemolytic transfusion reactions and lessen the clinical progression, but their efficacy in transfusion reactions has not been evaluated in veterinary patients. When the evaluation of a patient with a suspected transfusion reaction suggests that an acute hemolytic transfusion reaction is occurring, the blood typing and crossmatching must be repeated to determine whether a laboratory error is responsible for the reaction. When fever occurs without evidence of hemolysis and the Gram stain is negative for bacterial contamination, the transfusion may be restarted.

It is important to recognize the late effects of transfusion and not mistake them for another disease process. Delayed transfusion reactions usually are managed with supportive care. The only specific treatment for a delayed transfusion reaction consists of treating a transfusion-acquired infection appropriately.

PREVENTION STRATEGIES

A special effort is not necessary to prevent transfusion reactions. Simply by following the transfusion guidelines discussed here with reference to donor selection, blood typing, blood storage, and administration, most transfusion reactions can be prevented. Crossmatching detects antibodies in the plasma of the recipient or donor that may cause an acute hemolytic transfusion reaction. A transfusion reaction may still occur despite a compatible crossmatch. Crossmatching does not prevent sensitization to red blood cell antigens, which may result in a hemolytic reaction during future transfusions, because it detects only antibodies that are currently present in the donor or recipient. Crossmatching is a specific procedure designed to minimize acute transfusion reactions. It should be performed routinely in veterinary clinics.

Crossmatch Procedure

Performing a crossmatch is an intimidating but simple procedure, once all the equipment is assembled (Box 24-4). Several descriptions of the procedure have been published, all of which describe the same basic procedure with minor variations.[6,21,74] Not all protocols recommend the use of phosphate-buffered saline; others have an additional step at the end using species-specific Coombs reagent to increase test sensitivity, and some recommend that tubes be incubated at 4° C, 37° C, and 42° C. The following is the protocol the author uses:

1. Obtain EDTA-anticoagulated blood from the recipient and the potential donor or the tube segments of blood from the units being considered for transfusion.
2. Centrifuge both donor and recipient blood for 5 minutes at 1000 *g*.
3. Using pipettes, remove the plasma, and save in separate labeled tubes.
4. Wash the red blood cells by adding phosphate-buffered saline to the red cells to fill the tube. Resuspend the red cells in the saline by tapping the bottom of the tube with a finger.
5. Centrifuge the red cells and saline for 5 minutes at 1000 *g*. Pipette off saline, and discard.
6. Repeat steps 4 and 5 twice.
7. After third washing of the red cells in saline, resuspend the red cells to a 3% to 5% solution. It will appear bright cherry red.
8. For each potential donor, mix two drops of recipient plasma and one drop of donor red cell suspension for the major crossmatch. Mix gently.
9. For each potential donor, mix two drops of donor plasma and one drop of recipient red cell suspension for the minor crossmatch. Mix gently.
10. For the recipient control, mix two drops of recipient plasma and one drop of recipient red cell suspension. Mix gently.
11. Incubate the tubes at room temperature for 15 minutes.
12. Centrifuge the tubes for 15 seconds at 1000 *g*.
13. Observe the plasma for hemolysis.
14. Resuspend the centrifuged cells by shaking gently.
15. Observe the red blood cells for agglutination.

Box 24-4 Equipment for Performing Crossmatch

1 mL of EDTA blood from the recipient
1 mL of EDTA blood from the potential donor(s)
Tabletop centrifuge
3-mL test-tubes (sterility not required)
0.9% saline or phosphate-buffered saline
Disposable pipettes
Test-tube rack

Interpretation. Hemolysis or agglutination in a crossmatch indicates transfusion incompatibility. The degree of agglutination is graded 0 to 4+ (Box 24-5 and Fig. 24-2). Units of blood that are incompatible should not be used. If all available units are incompatible, the least reactive unit should be chosen. When the recipient control shows hemolysis or agglutination, the crossmatch cannot be interpreted. This is common in patients with hemolytic anemia.

Blood Type

Blood typing is important in preventing A-B mismatch transfusions in cats and preventing sensitization caused by giving DEA 1.1-positive blood to a DEA 1.1-negative dog. A reference laboratory can perform blood typing of dogs and cats, but this is not convenient in emergency situations. Commercially available blood typing cards for feline types A, B, and AB and canine type DEA 1.1 are available. The author has found that sick cats often are typed as AB when the cards are used but when retested in a reference laboratory are actually type A.

Box 24-5 Crossmatch Incompatibility

0	No agglutination
Trace	Microscopic agglutination
1+	Many small agglutinates admixed with free cells
2+	Large agglutinates mixed with smaller clumps
3+	Many large agglutinates
4+	Single agglutinate, no free cells

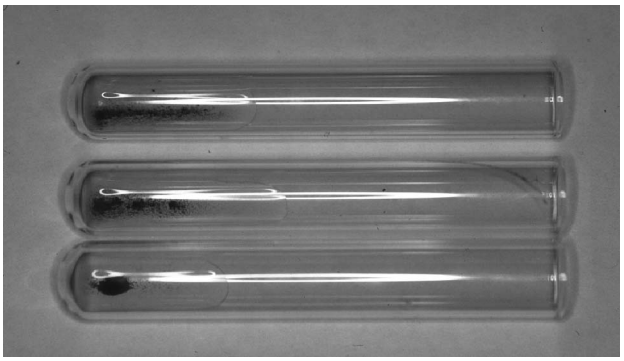


Fig. 24-2 Three tubes demonstrating increasing degrees of crossmatch incompatibility. From top to bottom, the tubes are graded 1+, 2+, and 4+.

VETERINARY HEMOGLOBIN-BASED OXYGEN-CARRYING FLUID (BLOOD SUBSTITUTE)

Previously, a red blood cell transfusion was the only therapy available to increase the oxygen-carrying capacity of the blood. Now another option is available. The Food and Drug Administration has approved a hemoglobin-based oxygen-carrying (HBOC) fluid, Oxyglobin (Biopure Corporation, Cambridge, MA), for use in the dog. Oxyglobin (hemoglobin glutamer-200 [bovine]) is ultrapurified, polymerized hemoglobin of bovine origin (13 g/dL) in a modified Ringer's lactate solution with a physiologic pH (7.8). The hemoglobin polymers range in molecular mass from 65 to 500 kD, with an average of 200 kD. The viscosity is low compared with blood (1.3 and 3.5 centipoise, respectively), and the solution is isosmotic (300 mOsm/kg) with blood. The concentration of methemoglobin, the inactive form of hemoglobin, is 10%. Oxyglobin can be stored at room temperature or refrigerated (2 to 30° C) for up to 3 years. Its intravascular half-life is dose dependent (18 to 43 hours, at a dosage of 10 to 30 mL/kg), as measured in healthy dogs. It is expected that more than 90% of the administered dose will be eliminated from the body in 5 to 7 days after infusion. The oxygen half-saturation pressure (P-50) of Oxyglobin is greater than that of canine blood (38 versus 30 mm Hg, respectively). This increase in P-50 facilitates offloading of oxygen from hemoglobin. The hemoglobin is packaged in the deoxygenated state in an overwrap that is impermeable to oxygen.

Complications of severe anemia result from poor oxygenation of tissues. Restoration of adequate tissue oxygenation typically is achieved by administering a blood transfusion. Improvement in the clinical signs of anemia results from a corresponding increase in hemoglobin concentration, which in turn increases the arterial oxygen content of the blood. The increased oxygen content of the blood supplied by Oxyglobin also relieves the clinical signs of anemia.

Oxyglobin has been tested in a multicenter clinical trial in dogs with moderate to severe anemia (PCV, 6% to 23%). Sixty-four dogs in need of blood transfusion were studied, including those with anemia caused by blood loss (n = 25), hemolysis (n = 30), or ineffective erythropoiesis (n = 9).[69] Thirty dogs were randomized to the Oxyglobin group and 34 dogs to an untreated

control group. Dogs in both groups were monitored for a decrease in hemoglobin concentration or deterioration in physical condition at which time they received additional oxygen-carrying support. If additional oxygen-carrying support was needed, Oxyglobin-treated dogs received PRBCs (n = 1), and untreated control dogs received Oxyglobin (n = 19). Treatment success was defined as the lack of need for additional oxygen-carrying support for 24 hours. The success rate in treated dogs (95%) was significantly greater than the success rate in control dogs (32%). This difference between treated and control dogs was significant, regardless of the cause of anemia.

Although Oxyglobin is not approved for use in cats, a retrospective study of its use in 72 cats recently has been published.[20] Oxyglobin was administered to these cats off-label and with owner consent. Anemia caused by blood loss, ineffective erythropoiesis, and hemolysis was the reason for Oxyglobin administration in all but two cats. The dose of Oxyglobin administered varied widely, but the mean (± SD) dose per infusion was 14.6 (± 13.1) mL/kg at a rate of 4.8 (± 6.2) mL/kg/hr. After infusion, the PCV decreased approximately 2% because of the dilutional effect of Oxyglobin, and the hemoglobin concentration increased approximately 1.5 g/dL.

The use of Oxyglobin as an oxygen-carrying solution eliminates some of the pretransfusion testing required with red blood cell transfusions. No reconstitution or preparation is necessary before infusion. Blood typing and crossmatching are not necessary because the red blood cell membrane, which is the major cause of transfusion incompatibility, has been removed during the manufacturing process. Repeated dosing of Oxyglobin was evaluated in the retrospective study of its use in cats. No allergic reactions were reported. A laboratory study of repeated dosing in dogs showed antibodies to Oxyglobin did form, but those antibodies did not decrease binding of oxygen to Oxyglobin and did not result in systemic allergic reactions.[34]

Adverse effects of treatment with Oxyglobin are similar in dogs and cats. After treatment, a transient discoloration (yellow, brown, or red) of the mucous membranes, sclera, urine, and sometimes skin occurs. Overexpansion of the vascular volume may occur, especially in normovolemic animals. Rates of administration greater than 10 mL/kg/hr in anemic, clinically ill dogs sometimes resulted in increased central venous pressure, with or without pulmonary edema or other respiratory signs of circulatory overload. Pleural effusion and pulmonary edema were found commonly in cats given Oxyglobin, but evidence was insufficient to directly link either to the administration of Oxyglobin.[20] In the clinical trial in dogs, vomiting occurred in 35% of the treated dogs. Diarrhea, fever, and death also were seen in approximately 15% of Oxyglobin-treated dogs; however, an association with Oxyglobin or the underlying disease could not be determined. These findings were most common in dogs with immune-mediated hemolytic anemia that received Oxyglobin.

The presence of Oxyglobin in serum may cause artifactual changes in the results of serum chemistry tests. Interference by Oxyglobin depends on the type of analyzers and reagents used but is not typical of hemolysis.[9,61] Blood samples for analysis should be collected before infusion. A list of valid chemistry tests by analyzer is included in the product labeling. Results of any clinical chemistry test performed on serum containing Oxyglobin should be interpreted with consideration of the validity of the test. In general, all tests using colorimetric techniques are invalid, but other methodologies also show some interference. No interference is seen with hematologic or coagulation parameters except when optical methods are used for measuring prothrombin time and activated partial thromboplastin time. Dipstick measurements (pH, glucose, ketones, protein) of urine are inaccurate when gross discoloration of the urine is present. The urine sediment is not affected.

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