Blood-Component Therapy: Selection, Administration and Monitoring

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Transfusion of blood products is a frequent necessity in small animal practice. Transfusion medicine has become more sophisticated with increased access to blood components, knowledge of blood types, and cross-matching requirements. Although potentially life saving, this procedure does carry some risk. In addition to selecting the appropriate blood product, several steps need to be completed to prepare the product for administration and the patient for receiving a transfusion.

Products

Whole Blood Products

Fresh whole blood (WB) is composed of red blood cells (RBCs), white blood cells, platelets, coagulation factors, and plasma proteins, including albumin and antithrombin III (AT III). The erythrocytes carry oxygen to the tissues while the plasma supports oncotic volume expansion and contains coagulation factors. Fresh WB should be transfused within 4 to 6 hours of collection because platelets and some clotting factors are rapidly inactivated during storage. It has been reported that a dose of 20 mL/kg will potentially raise the packed cell volume (PCV) about 10%.[1] Fresh WB is indicated when there is massive, acute hemorrhage, when a coagulation defect occurs, and/or when severe thrombocytopenia causing blood loss fails to respond to other treatments aimed at restoring the oxygen-carrying capacity of the circulating blood pool.

Stored WB provides RBCs and plasma proteins, including albumin and ATIII. Stored at 1°C to 6°C, it has a shelf life of 4 weeks. During storage, the concentration of coagulation factors V and VIII decrease, thus making it an inappropriate choice in patients with von Willebrand's disease and/or hemophilia A. Platelets do not survive refrigeration; therefore, stored WB is an inappropriate choice for patients with thrombocytopenia. As with fresh WB, a dose of 20 mL/kg will raise the PCV about 10%. The indications for stored WB are otherwise similar to fresh WB.

Packed RBCs

Widespread use of WB has decreased because of the availability of component therapy. Component therapy protects the patient by minimizing exposure to unnecessary factors and thus reducing the risk of reaction. It has the added benefit of maximizing treatments per donation. Packed RBCs (pRBCs) are prepared by centrifugation of fresh WB at 4,100 rpm for 10 minutes at 4°F (speed and times will vary depending on the centrifuge). This separates RBCs from the plasma portion. Separation of pRBCs from the plasma results in decreased colloid oncotic pressure compared with WB, as well as removal of coagulation factors. pRBCs are indicated for use in anemic patients that are normovolemic, do not require coagulation factors, and/or may be prone to volume overload (ie, those with documented heart disease). The PCV of the pRBCs is ~80%. This necessitates reconstitution with 10 mL of 0.9% saline per 30 to 40 mL of pRBCs to promote an adequate transfusion rate. Infusion of pRBCs increases the oxygen-carrying capacity by increasing the number of circulating erythrocytes. In the absence of continued blood loss, 1 mL/kg of pRBC will raise the PCV by 1%.[1]

Fresh-Frozen Plasma

Fresh- frozen plasma (FFP) is obtained from centrifuged WB with the RBCs removed and the plasma frozen within 6 hours of collection. The anticoagulant remains in the plasma portion. After 1 year of frozen storage, it contains therapeutic levels of von Willebrand's factor (vWF) II, VII, VIII, IX, and X.[2,3] FFP transfusion supplies hemostatic proteins, but minimizes the risk of red-cell sensitization or volume overload if WB was used.[1] It can be stored at −20°C for 1 year. After 1 year, it is reclassified as frozen plasma (FP) and can be stored for an additional 4 years. FFP is generally used as a supplement in various diseases with deficiencies of proteins, which are retained in it.

FFP has been used most commonly for coagulation-factor replenishment in patients with acquired or inherited coagulation disorders.[4,5] Examples of congenital factor deficiencies include von Willebrand's disease (vWD), hemophilia A (factor VIII deficiency), and hemophilia B (factor IX deficiency). Common causes of acquired factor deficiencies include liver failure, warfarin toxicity, and disseminated intravascular coagulopathy. vWD, the most common inherited bleeding disorder in dogs, is named for the reduced quantity of functional vWF. This deficiency creates impaired platelet adhesion during primary coagulation. The effect is an increased susceptibility to hemorrhage. The finding of a prolonged buccal mucosal bleeding time in a patient with hemorrhage, normal coagulation parameters, and a normal platelet count supports a diagnosis, but this must be confirmed with a vWF assay. There are 3 different classifications of canine vWD, based on the level of deficiency. Treatment decisions are based on the severity of the clinical signs (ie, hemorrhage). Plasma cryoprecipitate (follows) is the most effective treatment for patients with vWD, but

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FFP (6-10 mL/kg every 8-12 hours, as needed) can be used if cryoprecipitate is not available.[6] The vWF concentration can be checked post-treatment. A nontransfusion method of treating vWD is desmopressin acetate, a synthetic vasopressin, which stimulates vasopressin receptors to release intracellular stores of vWF.[6]

Hemophilia A is the most common inherited coagulation-factor deficiency in dogs and cats. Factor VIII helps activate factor X by activating factor IX in the presence of ionized calcium and phospholipid.[7] Factor VIII deficiency results in prolonged hemorrhage from damaged blood vessels because of defective fibrin formation. It has been most frequently described in German shepherds. A diagnosis of hemophilia should be considered in patients with unexplained hemorrhage and a normal prothrombin time (PT) but prolonged activated partial thromboplastin time (aPTT). FFP is the treatment of choice for hemophilia A, with the goal of treatment being to increase the factor VIII level above minimum hemostatic (therapeutic) values.[8] Factor VIII activity can be checked post-transfusion by using a modified aPTT test.

Hemophilia B is caused by a functional or absolute deficiency of factor IX. Once activated by factor XI, it complexes with factor VIII, calcium, and phospholipid. The deficiency results in a weakened platelet plug, which easily disintegrates. The aPTT is prolonged and the PT is normal. FP is the optimal choice for hemophilia B patients requiring therapy.[9]

FFP has also been suggested as an adjunct in the treatment of acute pancreatitis. Although controversial, it is based on the premise that during pancreatic inflammation, stores of antiproteases (ie, α-macroglobulin) are consumed to inhibit prematurely activated pancreatic proteases, which subsequently become depleted. The potential hope is to replenish depleted proteins and naturally occurring antiproteases such as AT III, antichymotrypsin, and α-macroglobulin. In people, it has been documented that the more severe the pancreatitis, the lower the serum concentration of α-macroglobulin.[10] Although the same correlation has not been documented in dogs, it has been shown that human patients with acute pancreatitis have significantly decreased serum α-macroglobulin concentrations.[11] Even though FFP was effective in supplementing serum concentrations of antiproteases during bouts of acute pancreatitis, there was no statistical improvement in the clinical outcome.[12,13] There have been no prospective studies evaluating the effectiveness of FFP in the treatment of canine acute pancreatitis.

FFP has been proposed as a source of immunoglobulin. In a study of 12 canine patients receiving FFP for immunoglobulin supplementation, it was undetermined whether FFP from routinely vaccinated donors provided sufficient immunoglobulin to have a beneficial effect in dogs with parvoviral infection, sepsis, or endotoxemia.[4] FFP can increase the serum immunoglobulin concentration in puppies and kittens with passive-transfer failure.[14]

The use of FFP as a source of albumin has been abandoned in human medicine. This is because of the availability of other supplements (ie, hydroxyethyl starch, dextran, and human albumin solution). The dose of FFP recommended for albumin supplementation is considerably higher than that for coagulation-factor replacement (45 mL/kg vs. 10-20 mL/kg). This dose should increase the serum albumin concentration by 1 g/dL.[1] Given the limited availability of FFP, other colloidal solutions should probably be the first line of treatment in hypoalbuminemic patients with no evidence of coagulation abnormalities.

The recommended dose of FFP for diseases other than pancreatitis is 10 to 20 mL/kg (roughly 1 unit of FFP is given for each 10 to 20 kg of body weight.) Plasma should not be diluted before administration. Unthawed FFP units must be handled delicately because there is a considerable risk of cracking the frozen plastic. FFP can be thawed at room temperature. If plasma is needed more acutely, then it can be sealed in a plastic bag and placed in a $<37°C$ water bath for thawing. This method usually takes 25 to 35 minutes. In an emergency, microwave thawing can be considered. Microwave thawing has been tested and found to be useful in thawing canine FFP with deteriorating coagulation factors I (fibrinogen), VIII, or vWF, and with PT and aPTT remaining unchanged.[15] First, the FFP units are placed in a warm-water bath to render the bag less brittle. Second, they are wrapped in an additional plastic bag and irradiated with microwaves for 10-second intervals. Between each exposure, the units are gently and briefly agitated. Finally, when only shards of ice are left intact, the bags are inverted several times until no frozen particles remain.[15]

FP is plasma processed from WB and frozen after 6 hours of collection, or FFP that has been stored for more than 1 year. FP differs from FFP because it is not a source of factors V or VIII, which are not preserved during delayed processing. This makes FP an inappropriate choice for patients with hemophilia A. However, FP does contain the vitamin K-dependent factors II, VII, IX, and X.

Cryoprecipitate

Cryoprecipitate is harvested by thawing FFP and separating out the cold-precipitated material.[16] Cryoprecipitate provides concentrated amounts of factors VIII, XI, XII, vWF, and fibrinogen. It is prepared from 1 unit of FFP thawed at 4°C. During thawing, the cryoprecipitate forms as a white precipitate in the plasma. The cryoprecipitate is separated from the liquid (cryopoor portion) plasma by centrifugation. The dose is 12 to 20 mL/kg every 10 to 12 hours, or 1 unit per 10 kg of body weight, until the active bleeding stops.[16] Indications for use are vWD, hemophilia A, and hypofibrinogenemia. Cryoprecipitate, like FFP, is best stored at $-20°C$ for up to 1 year.[17]

Hemoglobin-based Oxygen Carriers (Oxglobin®)

Oxyglobin® (Biopure) is hemoglobin (Hb)-based oxygen-carrying fluid that increases plasma and total Hb concentration, which in turn increases arterial oxygen content. Bovine Hb is polymerized to increase its duration of action. Because it is made only from Hb (ie, no RBCs or other antigenic parts), it holds an advantage over RBCs because there is no risk of infectious disease transmission, no need for blood-type determination or cross-matching, and because decreased viscosity provides increased microvascular flow, with more efficient release of oxygen at the tissue level.[18] The stable shelf life is up to 3 years at room temperature, and it is readily available. Oxyglobin® has excellent colloid and vasoactive properties. Because the colloid oncotic pressure (37 torr) is higher than hetastarch, it causes greater retention of fluid within the vascular space. The plasma half-life is 30 to 40 hours.[19] The initial dose recommended for dogs is 10 to 15 mL/kg (with a maximum rate of 5 mL/kg/h) to give temporary support of hemorrhage with hypoproteinemia, to provide support in anemia of chronic dis-

ease, or in patients with chronic blood loss. Because of an increased risk of volume overload (pulmonary edema or pulmonary edema) in cats, the lower initial dose used is 5 mL/kg. It can be repeated with careful monitoring. Possible adverse effects include antigenicity and volume overload. Many colimetric and optical tests are invalid, as well as urine dipsticks, after Oxyglobin® administration. Hb concentration, rather than packed cell volume (PCV), is measured before and after administration. Normal Hb in a canine is 13 to 18 g/dL and in a feline is 10 to 15 g/dL. The "effective" PCV is approximately Hb × 3.

Autotransfusion

Autotransfusion is the process of collecting autologous blood after a bleeding episode and after filtration, and infusing it back into the donor. It is indicated only when there is active bleeding into a major body cavity with no other source of RBCs available. It is contraindicated when blood is contaminated by excretory waste, infectious agents, or malignant cells. Its advantages include antigenic compatibility, no risk of disease transmission, and being normothermic, pH balanced, immediately available, and economical, especially in providing life-saving blood-replacement therapy. Disadvantages include a potential for hemolysis, formation of emboli, development of coagulopathy or disseminated intravascular coagulation, and sepsis.

Transfusion Administration

Preparation

Frozen or refrigerated blood products should be warmed to room temperature before administration. Excessive heating should be avoided because it precipitates and denatures proteins, destroys clotting factors, and decreases oxygen-carrying capacity of RBCs. Warming can also facilitate bacterial growth if the blood products are contaminated during the collection procedure.[20] Dogs that have received no previous blood transfusions and cats that have been blood typed and have received no previous blood transfusions should not need premedication before transfusion. All patients that have received previous blood transfusions should have a cross-match performed before subsequent transfusion. Diphenhydramine (0.5 mg/kg), administered subcutaneously or intramuscularly, may be given prophylactically.

Before initiating the transfusion, the bag should be checked to ensure that the correct unit is being administered to the correct patient and that it has a normal color and consistency. Do not transfuse the unit if it is dark, contains clots, or is abnormal in appearance.

Transfusion

All blood products should be administered through a commercially available blood-administration set. They contain a 270-μm filter to remove clots and debris formed during storage. In many cases, gravity flow will be enough for the administration of components, but infusion pumps can be used if they do not damage RBCs. Typically, individual infusion-pump manufacturers will specify whether they are safe for the administration of blood products.

The preferred route of blood transfusion is through an intravenous catheter, because all of the cells are transfused directly into circulation. A transfusion can also be administered to neonates through an intraosseus catheter with a 20-gauge needle. Within minutes, almost all of the RBCs are absorbed into circulation. The transfusion should be completed within 4 to 6 hours to prevent bacterial contamination. Transfusion reactions can occur even after only 1 mL of blood product is given and up to weeks later. The transfusion rate should be set at 0.25 mL/kg for the first 30 minutes. If no adverse affects are witnessed, then the rate can be increased to 0.5 mL/kg. Plasma can be administered at 4 to 6 mL/kg/h.

Transfusion Monitoring

For adequate monitoring during transfusion, pretreatment measurements are necessary. Pretreatment PCV, total solids (to monitor hemolysis), heart rate, respiratory rate, mucous membrane color assessment, and body temperature should be obtained and recorded. If possible, observation of urine color should be performed as well. Oxyglobin®-receiving patients should have total Hb measured. Obtaining a central venous pressure may be helpful to prevent volume overload in cardiac patients.

Every 15 minutes for the first hour of the transfusion, a heart rate, respiratory rate and body temperature should be measured. If no adverse affects are seen, the transfusion rate can be increased. After the first hour, the patient should be intermittently (ie, every 1 hour) observed for signs of any reaction (fever, hypotension, vomiting, diarrhea, discolored urine, apnea, or collapse). If any reactions are observed, then the transfusion should be discontinued immediately. Intravenous crystalloids should be administered, as well as blood-pressure measurement and urine-output monitoring. The transfusion bag should be Gram-stained and cultured to eliminate bacterial contamination as the reason for the adverse reaction.

If no adverse reactions are seen during the transfusion, then a PCV should be obtained 1 to 2 hours after completion of the transfusion. If FFP was administered for a coagulopathy, then a coagulation profile should be obtained to monitor for effect. The patient should be monitored for possible reactions (tachypnea, tachycardia, fever, vomiting, hypotension, etc) during the following 24-hour period because some acute reactions may not develop until then.

Transfusion Reactions

Transfusion reactions encompass a spectrum of metabolic and immunologic changes concurrent or subsequent to a transfusion. Transfusion reactions are classified into 4 groups, with the initial division based on immune-mediated versus nonimmune-mediated. These reactions are further subdivided into acute reactions that occur within hours versus delayed reactions that can occur up to a week or more (years) after a transfusion.[21] By understanding the underlying mechanisms, many reactions can be prevented or treated more succinctly.

Acute hemolytic transfusion reactions represent the most common acute immunologic transfusion reactions seen in veterinary patients. These reactions are associated with antibodies directed against RBC antigens.[20] Acute antigen—antibody-mediated hemolytic transfusion reactions are classified as type II hypersensitivities.[22] The severity and timing of an acute immune-mediated hemolytic transfusion reaction depends on the antibody class involved (IgG, IgM), the temperature at which

these antibodies bind to cell-surface antigen, and the degree of complement fixation.[23] Intravascular hemolysis leads to fibrin generation, circulation of micro-thrombi, and consumption of platelets, coagulation factors, and eventually disseminated intravascular coagulopathy. Released vasoactive substances cause arteriolar dilation with capillary permeability, which leads to hypotension.[22] Phagocytosis is stimulated by antibody-coated erythrocytes.[23] Clinical signs include hypotension, tachycardia, tachypnea, pyrexia, vomiting, and even death. Acute intravascular hemolysis results in hemoglobinemia and hemoglobinuria. Naturally occurring antibodies to dog erythrocyte antigens 1.1 and 1.2 are extremely rare in dogs, and therefore the likelihood of acute hemolytic transfusion reaction on initial transfusion is unlikely, although reactions have been reported.[24,25] Dogs that receive a transfusion or serial transfusions with more than 3 days between transfusions require cross-matching to minimize the likelihood of acute immunologic transfusion reaction. Cats do have preformed, circulating RBC isoantibodies against whatever cat erythrocyte antigen they lack, resulting in blood types A, B, and AB. The administration of type-specific transfusion almost eliminates the risk of acute hemolytic transfusion reaction for cats receiving their first transfusion.

Acute, febrile nonhemolytic transfusion reactions result from immune-mediated reactions against the donor leukocytes or platelets. Clinically, it is defined when an increase in body temperature of at least 1°C is observed, with no other cause of fever found.[26] When patient antibodies bind to donor platelets, leukocytes, or plasma proteins, an antigen–antibody reaction releases endogenous mediators (eg, interleukin-1) and causes pyrexia. This acute immunologic reaction occurs within 30 minutes and can continue for up to 20 hours.[26] Vomiting and tachypnea may be observed. The transfusion should be discontinued, and may be restarted at a slower rate.

Acute hypersensitivity reactions that are anaphylactic (response of patient antibodies against donor immunoglobulin A) or allergic (mediated by immunoglobulin E antibodies) are classified as type I hypersensitivities. These stimulate mast cells to produce vasoactive substances that cause urticaria (response of antibody to donor plasma proteins) and pruritis. These reactions are most commonly associated with the transfusion of plasma products, because they contain albumin, immunoglobulins, and other alloantigens. These reactions usually occur within the first 45 minutes, and are treated by discontinuing the transfusion and administering steroids or antihistamines.

Delayed immunologic transfusion reactions can occur even if compatible blood is given to a patient. This amnestic response logically occurs in patients that have been previously sensitized to RBC antigens. If a certain RBC type is given to a different cell type, then antibodies are generated by the bitch and transferred via colostrums; the end result is neonatal hemolytic anemia (isoerythrolysis), occurring after the initial days of nursing colostrum.[27] Another delayed immunologic reaction is post-transfusion purpura caused by antibodies from previous transfusions against recipient platelets. This reaction occurs approximately 1 week after the transfusion and can persist for as many as 2 months.[22] The thrombocytopenia and petechiation is usually self-limiting.

Nonimmunologic reactions can also occur. Damage to the RBCs by inappropriate storage and/or administration, including ATP depletion, temperature extremes, bacterial contamination, and physical damage can cause pretransfusion hemolysis, which is easily confused with intravascular hemolysis.[28,29]

Blood is an excellent media for bacterial overgrowth. Several Gram-negative organisms can use citrate as their carbon source to grow at low temperatures and cause endotoxin-mediated septic shock.[20,22,30] Activation of the complement, kinin, and coagulation systems, as well as defects of oxygen transport, myocardial function, metabolism, and peripheral perfusion lead to this syndrome.[20,22] Circulatory overload is caused by excessive and aggressive transfusions. An already compromised circulatory system caused by cardiac or renal disease can decompensate easily. Tachycardia, tachypnea/dyspnea, and coughing may precede congestive heart failure. A transfusion rate of 1 mL/kg/h has been suggested in these patients.[29,31] Subsequently, dividing the unit or product may prevent this process.

Hyperkalemia, a possible end result, is caused by RBC ATP decline leading to lysis, with subsequent leakage of potassium. This reaction is rare unless there is pre-existing renal failure or hyperkalemia. With a massive transfusion, citrate anticoagulant may chelate circulating calcium, causing ionized hypocalcemia with all the associated abnormalities.[20,31] This risk is increased in patients with liver disease because citrate is rapidly metabolized to bicarbonate in the liver.[20,29,31] WB, FFP, and platelet-rich plasma contain high amounts of citrate.[29] Pulmonary microemboli (thrombi or air) may cause tachypnea and dyspnea. Microthrombi may occur because of white blood cells, platelets, and fibrin forming microaggregates in stored blood.[29] Lastly, disease transmission caused by viruses, which is the most common transfusion reaction in human transfusion recipients, can occur, especially in immunocompromised patients. For example, *Ehrlichia* and *Babesia* organisms have been transmitted to recipient canines though blood transfusion.[29,32]

Conclusion

The goal of transfusion therapy is to replenish the specific cell line or noncellular blood product that is diminished. pRBCs are the best therapy to rapidly improve oxygen-carrying capacity and restoring red-cell mass. Clotting factor deficiencies should be supplemented with plasma and occur with appropriate monitoring. Prevention of transfusion reactions is essential. Case selection, appropriate component choice, stringent donor screening, and blood typing or cross-matching are all equally important. It is important to remember that hemolytic transfusion reactions cannot be prevented by the administration of antihistamines or glucocorticoids. Careful planning before the transfusion will help prevent reactions. The primary treatment is to discontinue the transfusion and decide on continued therapy.

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