Clinical Considerations in Transfusion Practice

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Helpful Hints:
Scattered throughout this text are the following symbols to help you focus on what is really important.

♣ This is a routine feature of the subject being discussed. We've tried to narrow them down.
♠ This is an important feature. You should remember this.
♥ Something serious will happen if you do not remember this.

The Crossmatch

The major and minor crossmatch are performed to assist in providing compatible red cell products and possibly alleviating adverse reactions to transfusion.

♣ The major crossmatch is performed to detect antibodies in the recipient’s serum that may agglutinate or lyse the donor’s erythrocytes.
♠ Conversely, the minor crossmatch detects antibodies in the donor plasma directed against recipient erythrocytes.

About the Minor Crossmatch

♣ The minor crossmatch test procedure mixes the red cells of the recipient with the plasma from the donor. After appropriate incubation, the cell/plasma mixture is centrifuged and observed for agglutination. This test was widely used in human medicine until the advent of antibody screening cells. The advent of antibody screening cells to donor blood screening protocols eliminated the need for the minor crossmatch.

What are antibody screening cells?

Antibody screening cells are commercially available red cells that are human blood type O. These cells have been tested for common clinically significant human blood group antigens (such as the Rh system, MNS, Lewis, P, Kell, and others.) Antibody screening cells are typically sold in sets consisting of three antigenically different red cell samples. When used in human medicine for donor screening protocols, the plasma of a blood donor is tested against a set of antibody screening cells. If the antibody screen is negative, it can be assumed that the blood from the donor being tested is free from antibodies to the human blood group antigens present on the antibody screening cells. If the antibody screen is positive, another panel of screening cells is tested against the donor plasma and the antibody is identified. Remember that whole blood is separated into components and a positive antibody screen and identification may only exclude the donor plasma from the donor pool for routine transfusion. If the antibody screen is negative, it is assumed that the plasma can be safely transfused to an ABO compatible recipient. It is for this reason that routinely there is no crossmatch performed on plasma...
products in human medicine.

So what about veterinary medicine? Currently, antibody screening cells are not available for veterinary use. This is why the minor crossmatch is so important. Remember that in the minor crossmatch, the red cells of the recipient are tested with plasma from the donor. This testing is performed to provide a safe transfusion, especially in the case that whole blood or plasma is used. In addition, think of the minor crossmatch in regard to the donor screening process: recipient red cells are acting as anti body screening cells. Indeed, these cells may or may not contain clinically significant antigens. But when a particular donor is tested against one or more samples of recipient red cells through the use of the minor crossmatch and found to be negative, a very general assumption can be made that there are no clinically significant antibodies in the donor plasma. Keep in mind that most blood donors will be qualified into a blood donor program for a time period of at least one year. It follows that there could be at least 4 blood donations per year with donor plasma being tested against at least one sample of recipient red cells for each donation. If the blood donor program is willing to accept this as a method of antibody screening donors, then it follows that plasma products may be transfused without a minor cross match being performed.

Concurrently, it is advantageous to reject potential donors from the blood donor program who have been previously sensitized to foreign red cell antigens. This assists in eliminating plasma from the blood donor pool that potentially carries antibodies to red cell antigens.

**Blood Transfusion Guidelines**

**Rationale for Therapy**

Whole blood is a mixture of cellular constituents suspended in a liquid transport medium. The cells have different functions. Erythrocytes carry oxygen and participate in host defense by surface adsorption and absorption of many materials, phagocytes control bacteria, platelets are required for hemostasis, and lymphocytes mediate immunity. The liquid medium also contains an array of dissolved substances: albumin, globulins, coagulation proteins, metabolic intermediates, electrolytes, organic anions, and trace elements. Practical techniques for separation and concentration of some of the cellular constituents of whole blood are within the capabilities of all major veterinary blood donor centers. Modern transfusion therapy should be based upon use of components to treat specific defects with concentrates of the deficient blood constituent. There are a number of rationales for the preferential use of blood components.

**Consideration of the Limited Resource**

The most cogent argument supporting component therapy is that blood is a precious resource considering its therapeutic potential and the logistics and costs required in obtaining and delivering blood products. Separation into components permits a single donation to meet the individual needs of more than several patients. Blood donor screening eligibility criteria should be sufficient to obtain a safe donation.

**Kinetic Considerations**

Following hemorrhage, homeostatic mechanisms restore the various blood constituents at differing rates, depending on the capacity for synthesis, endogenous consumption, degradation, and distribution in various physiologic compartments. The half-inactivation time of canine and feline red cells is in terms of months whereas the half-life of albumin is just three to four days. Surgical blood loss may require restoration of red cells. Albumin may not be required, as it will be restored within several days. Another consideration is tolerance. Loss of 50% of red cell mass is well tolerated in a healthy individual whereas loss of 50% of blood volume can be fatal unless rapidly corrected.

**Consideration of Adverse Effects**

Other rationale for supporting the use of blood components include the myriad of possible adverse effects that can result from transfusion of unnecessary blood constituents. Any transfusion reaction means that the transfusion is not performing the intended job and, importantly, has burdened a patient already burdened by the physiologic state requiring transfusion. Sensitization to blood cells can result in refractory results in subsequent transfusions. Transfusion of multiple units of whole blood sequentially in order to achieve a certain hematocrit may also produce pulmonary edema due to volume overload.

**The Decision to Transfuse**

All transfusion therapy can produce only transient improvement in the patient’s condition. Unless the patient is able to produce the deficit component endogenously, more transfusions will be necessary. Furthermore, transfusions dampen the physiologic response to deficiency of a blood constituent. For example, if a patient has a low red cell mass, tissue hypoxia results in increased erythropoietin production and the marrow responds with reticulocytosis. Red cell transfusion, in this patient, will result in diminished and delayed reticulocyte response. Several questions should be considered prior to transfusion.
Is blood transfusion really necessary?  
What is the patient’s particular need?  
Does the prospective benefit justify the risks of transfusion?  
What blood component will effectively meet this special need at the lowest cost?  
After transfusion: Did the transfusion result in the anticipated benefit for the patient?

Answers to these questions should be documented in the patient’s record. As a minimum for red cell transfusion, a pre-transfusion hematocrit and total protein should be followed by posttransfusion (24 hour) determinations.

Blood components may be conveniently classified according to their physiologic functions: oxygen transport, as an adjunct in intravascular volume maintenance, hemostasis and phagocytosis. In veterinary medicine, support of phagocytosis with granulocyte transfusions has not been accomplished. Volume replacement requires maintenance of colloid oncotic pressure (COP) through the use of colloids (hetastarch, pentastarch, dextrans, gelatin products) in addition to plasma. Albumin administered in the form of plasma to hypooncotic (hypoalbuminemic) patients not receiving concurrent colloidal support will rapidly equilibrate with third spaces.

**Transfusion to Increase Oxygen Transport**

There is no set hemoglobin or hematocrit concentration below which a patient needs red cells. Patients and patient care dictate when red cells are required. A patient who has lost one third of his red cell mass acutely will require increased oxygen carrying capacity. Patients with chronic processes may have dramatically low hematocrits and, if not stressed, not require additional oxygen carrying capacity. However, in general terms, in both the dog and the cat, administering red cells to meet oxygen transport needs should be considered when hemoglobin concentration is below 7 grams per deciliter (hematocrit of 21%). When considering transfusion in specific patients, the clinician should consider age, etiology and duration of anemia, presence of coexisting cardiac, pulmonary, or vascular conditions, and hemodynamic stability.

**Products Which Increase Oxygen Transport**

**Whole Blood** - Acute massive blood loss exceeding 20% of blood volume (appropriate blood volume is 90 mL/kg-canine, 70 mL/kg-feline), coagulopathy with massive blood loss, the hematocrit will increase over the baseline value immediately after transfusion and increase further within 24 hours with volume redistribution.

**Red Cells (RC, Packed Cells)** - RC are achieved when refrigerated whole blood is centrifuged in refrigeration and the plasma is removed. Because the hematocrit will approximate 70 - 80%, RC are often mixed with sterile saline or with an additive solution do decrease viscosity.

To determine the anticipated hematocrit in patients receiving red cells, calculate total blood volume (see Whole Blood above) and the total volume of the red cells (calculated from the pre-transfusion hematocrit). Determine the total blood volume after administering the transfusion (pretransfusion blood volume + volume of transfusion). Determine the new hematocrit by adding the volume of transfused red cells to the pretransfusion red cell volume. Anticipated post-transfusion hematocrit is the post-transfusion red cell volume divided by the post-transfusion total blood volume.

**Blood Substitutes: Alternatives to Blood and Blood Products**

**Red Blood Cell Substitutes**

Requirements for a successful red blood cell substitute:

1. It must work  
2. Have a long shelf life  
3. Be minimally immunogenic  
4. Be pathogen and endotoxin free  
5. Be readily available at a reasonable cost  
6. Must deliver and release oxygen to tissues under clinical conditions

Clinical indications for a red blood cell substitute:

1. Acute anemia  
2. Acute blood loss  
3. Preoperative therapy  
4. Intraoperative replacement  
5. Useful to provide oxygen as a radiosensitizer in treatment of neoplasia

Hemoglobin based solutions:

Hemoglobin based oxygen-carrying solutions are a form of blood substitute used to increase the oxygen content of blood
and improve oxygen delivery to tissues. Hemoglobin is carried in plasma. Hemoglobin in plasma increases the efficiency of
offloading oxygen from blood cells to tissues by facilitating diffusion of oxygen through the plasma. Hemoglobin based
solutions have long storage life and are useful immediately. These solutions are polymerized stroma-free hemoglobin
which are virtually free of red cell membranes and as such are minimally immunogenic. These solutions deliver and release
oxygen for 18 to 24 hours. There are effects on laboratory tests but effects are generally known, predicted, or minimal.
These changes depend on the instrument used. Serum urea nitrogen and electrolytes appear to be unaffected.
Administration of these solutions turns mucous membranes yellow to red to brown for at least several days.

Characteristics of a hemoglobin based oxygen-carrying solution approved for use in dogs (Oxyglobin® Solution) Biopure
Corporation, Cambridge, Massachusetts)

This product has a physiologic hemoglobin concentration of 13 g/dL and is delivered in isosmotic lactated Ringer’s
solution. The average molecular weight of this solution is 200kD with a range of 65 - 500 kD . In this solution the
oxygen affinity is dependent upon chloride ions. This is in contrast to red cell oxygen delivery which is dependent
upon 2.3-diphosphoglycerate (2,3-DPG). The solutions are universally compatible and are stable at room
temperature.

Indications for use - Oxyglobin® is useful in treating anemia due to any cause including hemolysis, blood loss due to
trauma, surgery, gastrointestinal or genitourinary hemorrhage, or rodenticide toxicity causing hemorrhage.

Administration and monitoring - The rate of delivery of Oxyglobin® is ≤ 10 mL/kg/hour in normovolemic canine
patients. The signs of improved oxygenation include stabilization of vital signs such as heart and respiratory rates. Of
course, the underlying cause of anemia must be treated. Mucous membranes and sclerae may transiently become
yellow to red or brown. Volume expansion must be monitored. Decreases in red cell mass (packed cell volume; hematocrit)
are predicted due to hemodilution. However, hemoglobin concentration rises.

Effects of low colloid oncotic pressure - noncardiogenic pulmonary edema, generalized edema, hypovolemia.

Plasma Substitutes
Hetastarch as a plasma expander - This is a synthetic polymer (a waxy starch amylopectin) produced by DuPont
Pharmaceuticals under the name Hespan®. It is six percent hetastarch in normal (0.9%) saline which almost iso-osmotic
(310 mOsm/L). Hespan has a twelve-month shelf life. Administration dosages vary depending on authors. Twenty-five
mLs/kg has a 7.5 - 8.4 day half inactivation time.

Safety and side effects - Hetastarch has low toxicity in humans and dogs. In nonoliguric renal failure renal function
may improve. There are no apparent effects on granulocyte function. Hemostasis may be significantly affected.
Platelet numbers and function may be reduced. The prothrombin (PT) and activated partial thromboplastin times
(APTT) may be prolonged. Anaphylactic reactions have been reported.

Advantages of colloid (hetastarch) therapy - Colloid oncotic pressure (COP) is improved. There is expansion of
plasma volume without increase in interstitial water content. The use of hetastarch compares well with albumin and
dextran containing solutions. It is safe for acute and long term usage. Single injections can increase plasma volume
and COP for greater than forty-eight hours.

Hetastarch is useful in hypoalbuminemic dogs and cats. Current dosage recommendations are 30 - 35 mLs/kg/day
with repeat usage depending on clinical judgement.

Contraindications of hetastarch - Hetastarch is contraindicated in cardiac insufficiency and in oliguric renal failure.
Hetastarch is contraindicated in hemorrhage due to von Willebrand’s disease and may be contraindicated when
hemostasis is compromised or may be compromised.

VetaPlasma® (Smith Kline Beecham)

VetaPlasma® is marketed as a colloidal plasma expander (it is NOT plasma) in a physiologic electrolyte solution
with a pH of 7.4. It is for intravenous use in dogs and cats. VetaPlasma® is oxypolygelatin with an average molecular
weight of 30,000 Daltons. It does not increase plasma viscosity. It may improve renal function but it is excreted
primarily (88%) though the kidneys. Vetaplasma® may cause anaphylactoid reactions. It has a relatively short half
inactivation time (2 - 4 hours) and is hypoosmotic (200 mOsm/L). There is minimal (but some) hemostatic
dysfunction with use of this product.

Compatible IV Solutions
- 0.9% sodium chloride injection may be used to facilitate infusion of blood products.
- No medications or any other solution should be added to blood products unless the product is approved by the US FDA
  or there is adequate documentation that the product is safe for use with blood products.
- Various intravenous solutions interfere with blood transfusion.
Lactated ringer’s solution contains enough calcium to overcome chelating agents in anticoagulant-preservative additive systems. This results clot formation in the infusion line.

5% dextrose in water causes red cells to clump in the infusion line, causing red cells to swell and hemolyze.

### Blood Administration Sets

- Blood administration sets are used for the infusion of blood products.
- The use of a blood administration set assists in preventing potentially dangerous artifacts from being infused to the recipient. These sets contain a filter that serves to retain clots and other microaggregate particles that form in stored blood. The size of the particle retained by the filter is directly related to the size of the filter.
- Blood administration sets should be used with all blood components including platelet concentrates. Deviations from the manufacturer’s instructions should be avoided as this may render the blood product ineffective. For example, using the inappropriate administration set for the infusion of platelet products could cause platelets to be inappropriately retained within the infusion set, defeating the purpose of transfusion.
- There are a variety of infusion sets commercially available. The manufacturer should be consulted regarding suggested use.

Remember: any blood set should be changed every 4 hours. This is due to the fact that overt bacterial contamination may occur after longer periods of time.

- Some blood administration sets are designed for transfusion of more than one unit of blood, but total use time should not exceed four hours.
- Blood administration sets should not be reused due to the threat of bacterial contamination.
- There are two types of Blood Administration Sets: Gravity Drip and Syringe Push.

#### Gravity Drip

Standard blood administration sets contain a filter with a pore size of 170 - 260 microns. The set should be primed according to the manufacturer’s directions with blood or blood-compatible fluid. For optimal flow rate, the filter should be fully wet and the drip chamber should be no more than half full during transfusion. Standard sets are typically used to transfuse whole blood, red cells, and plasma products. As the name implies, this set is attached to the blood product and the blood product is infused by gravity drip.

#### Syringe Push

Syringe push sets may be used for component infusion or in the transfusion of products with a volume of less than 100 mls. This blood administration set uses the smallest priming volume of all sets. These sets have a smaller drip chamber and shorter tubing length than gravity infusion sets. This is helpful in the transfusion of small volume products. Syringe push sets contain an in-line filter that is extremely small and it may go unnoticed. Blood products may be transfused in one of two ways using this infusion set. This set may be attached to a blood bag, the product drawn in to the attached syringe. The product is then "pushed" into the recipient. Alternately, this set may be attached directly to a syringe of blood for immediate transfusion. This may be useful in the transfusion of feline whole blood.

### Adverse Effects of Blood Transfusion

- The basic principle in transfusion therapy is the same as in all medical approaches, "primus non nocere" - first do no harm. Though transfusion fatality rate is small, deaths do occur, especially in cats, and morbidity varies significantly between institutions. Hemolytic reactions can be the most serious problem. Careful observation of clinical signs and appropriate laboratory evaluation of adverse effects of transfusion result in safe transfusion practices.

### Signs of Transfusion Reactions

- Febrile or allergic reactions may occur with fever or chills in the same manner as severe hemolytic reaction. For this reason, any adverse change in the patient’s condition should be considered a possible sign of adverse transfusion reaction and should be evaluated.

The essential elements that should take place when a transfusion reaction is suspected are:

1. Stop the transfusion.
2. The intravenous access should be kept patent for treatment if necessary.
3. The responsible clinician must be notified to evaluate the patient.

Individuals who have had multiple transfusion or who have had prior pregnancies are at greatest risk for febrile reactions. A patient who has had a febrile reaction is a greater risk for subsequent reactions. Premedication does not appear be markedly effective in these cases and does not eliminate the need for astute observation.

When a reaction is suspected, the administration set should be changed. This allows the 10 - 15 mls of blood remaining in the tubing to be discarded rather than infused in the patient.
Complication-Immediate Immnologic Effects

Hemolytic Reactions
Hemolytic reactions are most severe but are rare and are due to incompatible blood or intradonor incompatibility in multiple transfusions. Because cats have naturally occurring alloanti bodies in plasma (in particular, strong anti-A in type B cats), feline donor and recipient should be blood typed and cross matched prior to the transfusion. Feline AB mis-matched transfusions are ineffective and may cause life-threatening hemolytic transfusion reactions.

- It should be noted that hemolysis can be a nonimmunologic problem. Hemolysis usually results from physical destruction of cells by overheating or mixing nonisotonic solutions with red cells. **NO OTHER solutions should be infused through the transfusion site unless the transfusion is complete.**

**Signs**
Chills (shaking), fever, pain at needle site or along venous tract, nausea, vomiting, darkened urine, flank pain, and if progressive, signs of shock and/or renal failure.

**Precautions**
- If possible, identify donor and recipient blood types before transfusion is initiated. Perform compatibility testing.
- Transfuse blood slowly for first 15 - 20 minutes and/or initial 20% of the anticipated transfusion volume; remain with patient during this period.

**Response**
- In the event of a reaction:
  - Stop the transfusion.
  - Maintain intravenous line.
  - Notify the clinician.
  - Save donor blood to re-crossmatch with the patient’s blood.
- If possible:
  - Monitor blood pressure for shock.
  - Insert urinary catheter and monitor outputs hourly.
  - Send sample of patient’s blood and urine to the laboratory. Hemoglobinuria indicates intravascular hemolysis.
  - Observe for signs of hemorrhage resulting from disseminated intravascular coagulation (DIC).
  - Support therapies to reverse shock.

Febrile Reactions
Any increase of one degree (Celsius) or more must be considered a febrile reaction due to white cell, platelet or plasma protein antibodies.

**Signs**
Fever, chills

**Precautions/Response**
- Stop the transfusion immediately.
- Consider antiallergy therapy.

Allergic Reactions
Patient reacts to allergens in donor blood-red cells, platelets, granulocytes, plasma proteins-often complement-immunoglobulins.

**Signs**
Urticaria, dyspnea, laryngeal edema

**Precautions/Response**
- Give antiallergy therapy for prophylaxis in patients with allergic tendencies, although this is often ineffective.
- Stop the transfusion immediately.
- Epinephrine may be used for dyspnea or anaphylactic reaction.

Complication-Immediate Nonimmunologic Effects

Circulatory Overload
Circulatory overload is due to too rapid transfusion (even small quantities) or excessive quantity of blood (even if administered slowly).

**Signs**
Dyspnea, rales, cyanosis, dry cough, distended neck veins (if visible, may be palpable).

**Precautions/Response**
- Transfuse blood slowly.
- Prevent overload by using red cells or administering divided amounts of blood.
Use an infusion pump to regulate and maintain flow rate.
If signs of overload appear, stop the transfusion immediately.

**Hypothermia**
Hypothermia is most often initiated by administering chilled blood product too rapidly.

**Signs**
Chills, lowering temperature, irregular heart rate, possible cardiac arrest

**Precautions/Response**
◆ Use a warming device to warm the blood product.
◆ If patient exhibits chills (shaking) and if patient body temperature is subnormal (from baseline), stop the transfusion.

**Electrolyte Disturbances**
Electrolyte disturbances are rare but are often associated with patients with renal compromise.

**Signs**
Nausea, diarrhea, muscular weakness, flaccid paralysis, bradycardia, apprehension, cardiac arrest

**Precautions/Response**
◆ Use saline washed red cells or fresh whole blood for patients at risk.

**Citrate Intoxication (Hypocalcemia)**
Citrate intoxication occurs especially in cats and with the use products which contain excessive anticoagulant due to short draws.

**Signs**
Tetany, muscular cramps, hyperactive reflexes, seizure activity, laryngeal spasm, respiratory arrest

**Precautions/Response**
◆ Infuse blood slowly.
◆ If tetany occur, clamp infusion tubing immediately, maintain patent intravenous line, notify clinician.

**Complication-Delayed Immunologic Effects**

**Delayed Hemolytic Reaction**

**Signs**
Destruction of red cells and fever 10 to 15 days after transfusion. This is often an anamnestic response.

**Precautions/Response**
◆ Observe for post-transfusion anemia and decreasing benefit from successive transfusions.

**Graft vs. Host**
Graft vs. host is a rare complication following transfusion to severely immunosuppressed patients such as those being intensively treated for immune-mediated disease, or being immunosuppressed with chemotherapy or radiation. Graft vs. host occurs if immunocompetent donor lymphocytes engraft and multiply in immunodeficient patient. Engrafted donor cells react against "foreign" cells of host-recipient.

**Signs**
Fever, skin rash, hepatitis, diarrhea, bone marrow suppression

**Precautions/Response**
◆ In human medicine, blood products may be irradiated. Red cell, granulocyte and platelet function are unaffected. Eighty-five to 95% of lymphocytes are rendered incapable of replication.
◆ Treatment is supportive and symptomatic.

**Post-transfusion Purpura**
Post-transfusion purpura is a rare development if antiplatelet antibody. Post-transfusion purpura occurs most exclusively in multiparous dogs (rarely cats).

**Signs**
Petechiae, purpura, ecchymosis follow precipitous fall in platelet count about one week post-transfusion. The antibody destroys both transfused and native platelets.

**Precautions/Response**
◆ Immunosuppressive therapy
◆ If life threatening, in human medicine, plasma exchange is initiated.
◆ The problem is often self limiting in dogs.
Alloimmunization (Antibody Formation)
Patient reacts to allergens in donor blood-red cells, platelets, granulocytes, plasma proteins—often complement-immunoglobulins.

**Signs**
Increased risk of hemolytic, febrile and allergic reactions

**Precautions/Response**
✧ Occurs in patients receiving multiple transfusions. Thus, transfuse products from a limited number of donors and observe patient for signs of reaction.

Complication-Delayed Nonimmunologic Effects

Transmission of Infection

**Signs**
Icterus from hepatitis, fever, nonspecific discomfort or pain (often around chest wall or sternum), hypotension, vomiting, diarrhea

**Precautions/Response**
✧ Query blood bank for anything notable currently associated with donor.
✧ Educate owners as to potential infectious signs.

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