

# Practical Transfusion Medicine

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## KEY WORDS

- transfusion
- hemorrhage
- anemia
- red cells
- fresh frozen plasma
- cryoprecipitate

Red blood cell transfusion is needed whenever the red cell number becomes so depleted that oxygen-carrying capacity is insufficient to maintain adequate performance. The definition of “adequate” may vary. For example, an otherwise healthy animal with mild to moderate weakness after acute blood loss may be allowed to recover spontaneously. A severely ill patient with the same degree of anemia may recover more quickly with fewer complications if transfused. The temptation to arbitrarily transfuse at a given hematocrit (Hct) level must be avoided. Several factors are considered in determining when transfusion is necessary, including the cause and degree of anemia, the expectation of further loss or response to specific therapy or supportive care, and the time of onset of anemia. The decision to transfuse also depends on the overall evaluation of the patient, especially cardiac, pulmonary, and renal function. The availability of alternatives such as iron replacement after chronic blood loss, autologous transfusion, or (soon to be available) blood substitutes may avert the need for blood. When the Hct is less than 30%, ventricular function is depressed in animals; however, oxygen extraction and central venous PO<sub>2</sub> remain normal until the Hct reaches 20%.<sup>1</sup>

## HEMORRHAGIC SHOCK

Trauma or surgery with subsequent internal or external hemorrhage are common emergencies. Animals can withstand the loss of 25% to 30% of their total blood volume without replacement. Following a sudden loss of 20% of the blood volume, it takes 20 to 60 hours to restore lost volume through endogenous plasma replacement.<sup>2</sup> After severe hemorrhage concentrations of albumin and other serum proteins are de-

creased. Increased synthesis of albumin begins in approximately 48 hours, so initially preformed albumin moves to the circulation from the interstitial space. Erythropoietin levels begin to rise within about 6 hours. The Hct falls gradually over 2 to 3 days after acute blood loss. A linear fall in the Hct causes a logarithmic rise in erythropoietin concentration. In the case of hemorrhage into a body cavity, the blood initially clots and then is defibrinated, leaving most of the red cells intact. The plasma and about 50% of the red cells will reenter the circulation after several hours.

Assuming that initial attempts at resuscitation with crystalloid or colloid replacement have been unsuccessful, red cells must then be replaced. Historically, physicians and veterinarians have relied upon fresh or stored whole blood to replace losses. On first thought it seems logical that blood loss should be replaced with blood, but initial blood replacement should consist of packed red blood cells (PRBCs).<sup>3</sup> The movement of albumin from the interstitial space to capillaries will replace up to 50% of lost blood volume without the need for supplementary plasma. Because of their osmotic effect, PRBCs actively increase plasma volume by causing movement of interstitial plasma into the circulation. Rapid transfusion is necessary in life-threatening hemorrhagic shock. The amount of blood to be given depends on the amount of blood lost and patient response. An initial dose of PRBCs of 10 ml/kg can be given and the patient reassessed. If large volumes of fluids and PRBCs are given, it is important to watch for signs of volume overload such as distended or pulsating jugular veins, increased central venous pressure, or pulmonary edema.

In massive transfusions (defined as administration of a total estimated blood volume of red cells within 24 hours), loss of clotting factors and platelets as well as the effects of red cell storage lesions on oxygen delivery must be considered. Large reserves of platelets are present in the spleen of normal individuals. These can be released in times of increased need. It is common for platelet counts to be increased after moderate hemorrhage. Some of the drop in platelet count that occurs after large volumes of fluids or PRBCs is only dilutional. Platelet replacement is indicated only if bleeding is occurring, not just because the count is low. As fluid shifts reestablish equilibrium, an increase in platelet count and serum proteins occurs. Decreased platelet counts after only moderate hemorrhage and transfusion might indicate the presence of disseminated intravascular coagulation (DIC) or some

other underlying disease. Clotting factor depletion rarely occurs, but after massive transfusion with PRBCs, monitoring of prothrombin time (PT) and activated partial thromboplastin time (APTT), or at least activated clotting time (ACT), is useful to determine the need for replacement.

### HEMOLYTIC ANEMIA

Hemolysis (or abnormal shortening of the red cell life span beyond the ability of the marrow to compensate) may be caused by intrinsic red cell defects or by exogenous effects from substances in the plasma or damage to vessels. If a compatible red cell transfusion is given to a dog with an intrinsic red cell disorder such as a red cell enzyme deficiency, the survival of the transfused cells is normal. Hemolysis due to exogenous causes such as immune-mediated or infectious disorders or toxicity is much more common. Here transfused cells are destroyed as readily as the recipient's own cells. The general approach to treatment is to transfuse as needed to prevent tissue hypoxia and remove the cause when possible. Any drug known to cause hemolysis must be discontinued along with any others that are not essential.

### CHRONIC BLOOD LOSS

If the cause of chronic blood loss can be identified and removed and the patient is stable, iron replacement may prevent the need for transfusion. If the anemia is severe, especially if further losses are anticipated, transfusion with PRBCs is indicated. One source of chronic blood loss in both human and animal patients in intensive care wards is repeated blood sampling. This can be a major problem in small dogs and cats undergoing diagnostic testing. In addition, cats have a relatively small blood volume to body weight ratio compared to other species. Those drawing blood on a repeated basis should remember that less blood needs to be drawn from an anemic patient to obtain a needed volume of plasma or serum as proportionally more of the blood volume is plasma (e.g., 1 ml of blood from an anemic patient is mostly plasma, whereas in a normal animal approximately 40% of the blood volume is red cells).

### DECREASED RED CELL PRODUCTION

Although compensatory mechanisms allow patients to function at low Hct levels, periodic transfusions of PRBCs may be required for survival. Cats are especially prone to development of anemia with any illness, because of their normally short red cell life span. Many cats with undiagnosed illnesses are carrying retroviruses such as feline leukemia virus or feline

immunodeficiency virus that suppress the marrow.

If clinical signs of anemia such as tachycardia, tachypnea, and weakness are present at rest, transfusion is indicated. In animals, the Hct is rarely elevated to the normal range by transfusion; thus one need not be concerned about further suppression of hematopoiesis. Hemosiderosis from iron overload becomes a possibility after multiple transfusions since 1 mg of iron is supplied per milliliter of PRBCs. Additional iron supplementation, especially by parenteral means, should be avoided. Cross-matching becomes progressively more important in dogs receiving multiple transfusions since the risk of sensitization is greater.

### RED CELL TRANSFUSION

Red cells may be available as fresh or stored whole blood or PRBCs.<sup>3-5</sup> Since in most anemias the need is for red cells only, PRBCs are the treatment of choice. PRBCs have less adenine, citrate, sodium, ammonia, histocompatibility antigens, and antibodies than whole blood. Because the Hct of PRBCs is approximately 80%, saline is usually added to facilitate administration of small volumes in congestive heart disease and larger volumes in dehydration or hypovolemia.

Fresh whole blood may be indicated in actively bleeding, anemic animals with thrombocytopenia. For convenience, fresh whole blood is also used in cats or small dogs less than 5 to 6 kg. Although fresh whole blood may supply some platelets, stored whole blood does not contain viable platelets after 12 to 24 hours. If equipment and personnel are available to make components, there is no value in storing whole blood.

Various formulas have been derived to estimate the Hct increment expected in the recipient after red cell transfusion. This is assuming that transfused cells will survive normally and that the recipient has a normal blood volume. A simple rule of thumb is that a transfusion of whole blood at 20 ml/kg or PRBCs at 10 ml/kg will raise the Hct of the recipient by 10 percentage points. For routine transfusion in the treatment of anemia, it is not necessary to warm the blood after taking it from the refrigerator. An unopened bag of saline may be stored in a 37°C water bath and used to dilute PRBCs when a transfusion is needed. Warming of blood is indicated for neonatal transfusion and for administration to hypothermic patients. Hypothermia causes vasoconstriction and also interferes with platelet function. Warming should be done only with a water bath with a thermostat or a standard blood warmer. If blood is heated to a temperature greater than 50°C, hemolysis will occur. A blood administration set with a 170 µ filter is used to prevent clots from entering the recipient.

## ALTERNATIVES TO RED CELL TRANSFUSION: HEMOGLOBIN SOLUTIONS

Because of supply shortages and medical risks associated with blood transfusions, researchers have worked for many years to find an effective and safe substitute for blood.<sup>6</sup> Initial problems encountered with transfusion of hemolyzed blood were a short half-life (20 to 30 minutes), increased oxygen affinity, complement activation with activation of the coagulation pathway, renal and coronary vasoconstriction, and renal tubular damage. The cause of the complement activation and vascular changes was residual stromal elements in the solutions. Improvements in purification have increased the safety, and the removal of blood group antigens has eliminated the need for typing and cross-matching. Polymerization of the hemoglobin molecules has increased the half-life to approximately 48 hours. Bovine hemoglobin solutions, antigenically similar to human hemoglobin, have been utilized because the chloride ion performs the function of 2,3-diphosphoglycerate, resulting in a lower oxygen affinity than that of human hemoglobin. Bovine hemoglobin is also free of the viruses that are of most concern in human transfusions.

## PLASMA

Plasma, whether fresh, fresh frozen, frozen, or separated into cryoprecipitate and cryoprecipitate-poor plasma, can be an important adjunct to the treatment of many diseases. During World War II, plasma was used extensively as a volume expander, and it continued to be used for this purpose into the 1980s even though it was shown to be no better than crystalloid or colloid.

### Fresh Frozen Plasma

As more was learned about the value of crystalloids and colloids and the risks associated with plasma, its use as a volume expander declined. A conference at the National Institutes of Health in 1985 concluded that there was no justification for the use of plasma as a volume expander or nutritional supplement, although approximately 50% of fresh frozen plasma (FFP) transfusions in human hospitals were given for such reasons.<sup>7</sup> As defined in American Association of Blood Banks (AABB) Standards, FFP is separated from fresh whole blood by centrifugation and frozen to  $-30^{\circ}\text{C}$  within 6 hours of collection. The major use for FFP both in animals and humans is as a source of clotting factors.

When reasons for canine FFP transfusions were categorized at the School of Veterinary Medicine at Tufts University between 1987 and 1988, the most common

use was for treatment of DIC.<sup>8</sup> By the time DIC is clinically evident, clotting factors are severely depleted. Once a patient is bleeding, fibrinogen is low, and the PT and APTT are prolonged, replacement of clotting factors with FFP is needed in addition to supportive care. Besides coagulation factors, FFP contains antithrombin, a potent inhibitor of thrombin formation. Replacement of antithrombin helps prevent further thrombosis. If the underlying cause of DIC can be eliminated and bleeding is not evident, it is not necessary to "treat" the laboratory abnormalities; they can simply be monitored. In the most severe cases of DIC with excessive blood loss, replacement of red cells, clotting factors, and platelets may be needed. Fresh whole blood is indicated initially, with other components added later, if needed. Heparin is sometimes used in conjunction with FFP, and controversy exists as to when and how it should be used. There is general agreement that heparin used alone in the bleeding patient is risky and unlikely to be successful.

In hepatic failure production of clotting factors, especially the vitamin K-dependent factors, is decreased. If ascites or edema is present, the efficacy of FFP is less because factors diffuse into the fluid. In bleeding human patients with liver disease the standard dose of FFP (10 ml/kg) often fails to correct the PT and APTT.<sup>9</sup> Twice the standard dose has been suggested and should be repeated every 4 hours because of the short half-life of factor VII. In addition, the PT and APTT do not always correlate with the risk of bleeding after liver biopsy. Vitamin K may be of benefit to these patients. FFP has been used in treatment of hemophilia A and von Willebrand's disease, although cryoprecipitate is more appropriate. In these patients, unless bleeding has been extensive, it is advantageous to avoid transfusing red cells. This prevents or delays development of alloantibodies, which could interfere with future transfusions.

### Frozen Plasma

Frozen plasma (FP) is defined as that salvaged from whole blood stored in the refrigerator for longer than 6 hours before freezing or as FFP that has been stored from 1 to 5 years. FP may be used as a source of stable clotting factors such as the vitamin K-dependent factors (II, VII, IX, and X) but not for unstable factors such as VIII and V. Uses for FP include acute severe warfarin toxicity and hemophilia B. Plasma is sometimes used in animals as a source of albumin. When plasma was removed from normal dogs and replaced with crystalloid, hypoalbuminemic edema developed after 70% plasma dilution over a 3 hour period.<sup>10</sup> Albumin is difficult to supply in adequate amounts to re-

verse hypoalbuminemia. Approximately 60% of the total body albumin is located in the interstitial space, where the concentration is in equilibrium with that in plasma. If hypoalbuminemia develops, the calculated plasma albumin deficit represents only 40% of the whole body deficit. If albumin losses involve the kidney or gastrointestinal tract, the albumin supplied by transfusion is quickly lost. Acute reversible hypoalbuminemia, such as that associated with burns, might respond well to plasma transfusion. Otherwise, hypoproteinemia is better treated by parenteral or enteral alimentation or other nutritional support. In catabolic states infused albumin is metabolized as a calorie source. The additional sodium contained in plasma might also aggravate edema or ascites.

### Cryoprecipitate

Cryoprecipitate is a concentrated solution of factor VIII, von Willebrand's factor, fibrinogen, and fibronectin that is prepared from FFP by a slow thaw and separation of cryoprecipitate-poor plasma from the cryoprecipitate. It is used primarily to treat hemophilia A and von Willebrand's disease.<sup>3</sup>

### Administration of Plasma and Cryoprecipitate

When plasma is separated from PRBCs, the majority of the citrate remains in the plasma so it is general-

ly given over a 2 to 4 hour period. Because the dose is dependent on the degree of clotting factor deficit, pretransfusion and posttransfusion evaluation of the PT and APTT is indicated. An appropriate starting dose is one unit per 20 kg. If cryoprecipitate or FFP is to be given prior to surgery, the infusion should begin about 1 hour before anesthesia for maximum benefit; for example, factor VIII has a half-life of 6 to 8 hours so giving it several hours before surgery is obviously less beneficial.

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