

TAKING THE CONFUSION OUT OF TRANSFUSIONS

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BLOOD PRODUCTS & INDICATIONS

WHOLE BLOOD (WB)

This is blood which has been obtained unchanged from a donor. WB contains red cells, plasma, platelets, and white cells. The platelet component will reduce with time, and the longer between blood donation and use, the fewer effective platelets.

In a patient with blood loss, whole blood is the ideal product as you are replacing like for like. Anaemic patients will benefit from the red cells in the whole blood, but don't necessarily require the plasma and other components. Those with clotting factor deficiencies will also have these replaced by the plasma in the whole blood. In case of acute haemorrhage caused by thrombocytopenia in a sensitive area, such as the brain or lungs, then whole blood derived platelets may help arrest this bleeding. Protein will also be administered with the transfusion, but this is not the most efficient way to achieve a rise in oncotic pressure.

PACKED RED BLOOD CELLS (PRBCs)

PRBCs are formed when whole blood is centrifuged to concentrate the red cells in solution. This produces a red cell concentrated blood product with a packed cell volume (PCV) in the region of 60 - 65%. This product can typically be stored for 28 days in the fridge.

The main indication is replacing red cells, with less of a need for plasma. It is the most effective way to increase the packed cell volume which can be achieved by administering less volume than whole blood. A classic example of when PRBCs would be used, is in managing animals with immune-mediated haemolytic anaemia (IMHA), where circulating volume of blood is unaffected, just the oxygen carrying capacity (red cells).

FRESH FROZEN PLASMA (FFP)

FFP is produced when plasma is separated from the cellular component of blood. Fresh frozen plasma must be split from the red cells within 8 hours after the donation and remains "fresh" for a year in the freezer. The main benefit of FFP is that it contains all the clotting factors, including the labile factors. Labile factors are the more "sensitive" proteins which degrade if the plasma isn't separated quickly enough, or during storage in the freezer. The main labile factors are **Fibrinogen** (substrate for clot formation), **Factor V**, **Factor VIII** (Haemophilia A) & **von Willebrand Factor** (von Willebrand's disease). It has a shelf-life of one year, before it becomes frozen plasma, described below.

Any clotting factor deficiency is an indication for FFP, including Haemophilia A (Factor VIII), von Willebrand's disease, bleeding *Angiostrongylus* vasorum (Lungworm) infection and disseminated intravascular coagulation (DIC) management. FFP can also be used to increase oncotic pressure as it contains albumin, but again it can take significant volumes to raise the albumin levels.

FROZEN PLASMA (FP)

FP is the plasma component separated from the cellular component from blood. It either remained unseparated within an 8-hour period following collection or has been stored for over one year in the freezer. Unlike FFP, Frozen plasma does not consistently have labile factors in sufficient amounts and cannot be relied upon to replace these. After a year of storage FFP becomes FP. It has a shelf life in total of five years (one year as FFP and four as FP)

The non-labile factors include Factors II, VII, IX and X, which means that FP can be used for anticoagulant rodenticide toxicity, as well as Haemophilia B (Factor IX). It can also be used for oncotic support.

CRYOPRECIPITATE

Cryoprecipitate has been formed by thawing and centrifuging fresh frozen plasma. It is concentrated plasma and contains the labile clotting factors, ideal for Haemophilia A, and von Willebrand's disease.

CRYOSUPERNATANT (CRYOPOOR)

This has been formed by thawing and collecting the supernatant, essentially is the left-over part after forming cryoprecipitate. It contains non-labile factors and the protein component of the blood. As the relevant factors and albumin are still present, anti-coagulant rodenticide toxicity and low oncotic pressure can both be treated with this.

PLATELET RICH PLASMA

This is plasma which has the platelets concentrated within it. It is a trickier product to store as the bag requires frequent agitation at room temperature and should be used within a few days of collection to prevent the platelets clumping and becoming inactive. Platelets have a short half-life in circulation, and are only a short-term fix for active haemorrhage. The main indication is thrombocytopenia resulting in life threatening haemorrhage.

TRANSFUSION TRIGGERS

Unfortunately, there is no specific PCV value that can be used as a cut off. Instead, the rate at which the PCV declined to the current level is more influential for the need for transfusion. We can use our clinical exam and ancillary tests to evaluate whether the animal requires a transfusion or not. With anaemia, it is the oxygen carrying ability of the blood that is affected, and without the cells of the body receiving adequate oxygen they can't form ATP, manifesting as shock. The question that needs to be answered is whether this animal is having to compensate for the lack of red cells.

The key features on clinical exam are:

- Pale mucous membranes
- Tachycardia
- Tachypnoea
- Pulses are often hyperdynamic (or bounding)
- Mentation, as brain oxygenation becomes limited
- Lactate levels

BLOOD TYPES

CANINE

There are several blood types in dogs, all of which start with DEA (Dog Erythrocyte Antigen) and are numbered. The blood type of dogs reflects whether the erythrocytes are expressing the antigen on their surface or not. From a practical point of view, we only routinely type dogs as to whether they are DEA 1 positive (expressing the antigen) or negative (not expressing it), as DEA 1 is the most antigenic, and is more likely to give rise to a transfusion reaction.

Dogs are blood typed as either DEA 1 Positive, Negative or a Weak positive. This is based on how strong the line is on the blood typing kits and has clinical use.

Ideally, we would always provide type-specific blood. In an emergency, a dog that has never received a blood transfusion before, can receive either DEA positive or negative blood. If we give a Negative dog Positive blood, this will be less effective, lasting a shorter time in circulation as it will be destroyed quicker by the immune system.

If typing a recipient as weak positive, then we assume they have less antigen on their red cells and give them DEA negative blood.

FELINE

Cats can be one of three blood types; A, B or AB. Type A cats express one antigen on their erythrocyte surface, Type B cats express a different antigen on their erythrocyte surface and Type AB cats express both antigens on their surface. From approximately 8 weeks of age, cats will produce alloantibodies against blood types of the opposite of their own. These are antibodies against the opposite blood type despite never having been exposed to these antigens prior. Type A cats have a lower level of circulating anti-B antibodies. Type B cats have high levels of anti-A antibodies. Type AB cats do not have anti-A or anti-B antibodies.

This means that unlike dogs, **cats cannot be transfused with untyped blood** and recipients can only have blood from a donor with the same blood type. Cats given the “wrong” blood type, particularly Type A blood given to a Type B cat, can be fatal, even with less than 1 ml of blood administered.

Type AB cats are universal recipients and in theory can have donations from Type A or Type B cats as they don't have antibodies against either. However, the plasma that is transfused with the donor's red cells must be taken into account. Type B cats can have such high anti-A antibodies in circulation that the plasma that is administered to the recipient with the red cells during a whole blood transfusion can be enough that the recipient's own cells (which express the Type A antigen) are destroyed by the transfused plasma. For this reason, Type AB cats should have either Type AB or Type A blood, given the lower circulating anti-B antibodies in the donor blood.

XENOTRANSFUSION

Given that dog blood is often more easily available than cat blood, and as cats don't have naturally occurring anti-dog blood antibodies, then it can be safer to give a xenotransfusion than to give untyped cat blood. The transfusion of red cells from dogs to cats is a short-lived solution, as the dog red cells are broken down by the cat's immune system within 3 – 5 days. The aim of a xenotransfusion isn't a long-term fix, but it is to provide a life saving measure in critically anaemic cats, buying time to perform diagnostics to identify the cause of the anaemia, and to arrange a feline blood donation of the appropriate blood type. This isn't a risk-free approach and there can be side effects, including but not limited to anaphylaxis, hypersensitivity reactions and severe hyperbilirubinaemia. More details of the procedure are available in the veterinary literature.^{1,2}

CROSS MATCHING

Cross matching is the way in which we try and establish *ex vivo* whether there are antibodies present that will bind to the red cells between the donor and recipient, and therefore more likely to cause a transfusion reaction. There are two parts to this, major and minor. A **major** crossmatch is performed by combining the **donor's red blood cells** with the **recipient's plasma**. It is termed major as this is where the biggest incompatibility is likely to lie. A **minor** cross match is when the **donor's plasma** is combined with the **recipient's red cells**.

If there are antibodies which will target an antigen on the red cells, then the blood will agglutinate. There are commercial labs or kits that can be used to cross match a patient. These won't always be available, and an alternative is to perform centrifugation of the donor and recipients' blood and mixing with the opposite red cells/plasma to perform a rudimentary cross match. A paper on rabbit crossmatching describes the in-house techniques possible.³

If we've already blood typed our patient, then why would we bother cross matching? The reason is that the typing is only testing for one major antigen, and there will be many others that we can't easily test for that can result in an incompatibility. Cross matching is a crude method of evaluating for these potential incompatibilities. There are two antigens that you may hear of that we can't test for easily, but cross match should identify an incompatibility with, *Mik* in cats and *Dal* in dogs.

In an ideal world, cross matching would be performed before every transfusion, but as blood products, time and finances can be limited, then we reserve it to specific situations. In any animal that has had a previous transfusion, or may have done, then they should be cross matched as they may have formed antibodies to

antigens on the surface of red cells, they were previously exposed to. Cross matching is necessary if it has been **four or more days** since the first transfusion, in our hospital if it has been less than four days then we do not cross match. If the previous medical history of a pet is unknown, then it may be worth cross matching.

VOLUME

Deciding how much blood product to give is a key decision. We have some rough numbers that we use clinically.

- 2 ml/kg of whole blood is needed to raise the recipient's PCV by 1%
- 1 ml/kg of packed red cells is needed to raise the recipients PCV by 1%
- 22.5 ml/kg of fresh frozen plasma is needed to raise albumin by 5 g/l
- Plasma is needed at 10 – 20 ml/kg for clotting factor replacement

ADMINISTERING BLOOD PRODUCTS

It is important that **sterile technique** is used throughout collection and administration. To minimise bacterial contamination, transfusions should be administered **within four hours after removing from the refrigerator**. A new IV line should be placed, and it is important that any IV lines are only **flushed with saline**. The calcium in Hartmann's precipitates with the anticoagulant in blood products and can cause issues.

A full clinical exam should be performed to obtain **a baseline** from which to compare against. Transfusions should be administered through a specific giving set, or a blood filter must be added. It may be preferable to use drip rates rather than fluid pumps, as they have the potential to damage the red cells depending on the type of equipment you have. In cats, or small dogs, then removing the blood from the collection bag in a sterile manner, into a syringe and using a syringe driver is useful. This can also be used when you plan to administer larger volumes over a longer period, allowing each aliquot you've taken from the fridge to be used within 4 hours each time.

Blood should be administered slowly to begin with, with various approaches used. We often start the transfusion at 0.25 ml/kg for the first 10 mins, then 0.5 ml/kg for the next 10 mins, 1 ml/kg for the last 10 minutes. Provided there have not been any signs of a reaction, then the remainder of the transfusion volume is given over the remaining 3.5 hours.

The patient should be clinically examined frequently at the start of the transfusion, typically every 5 minutes. Monitoring for signs of allergy such as pruritus, facial swelling or urticaria. Increases in heart rate, respiration rate/effort and temperature are also key features. A transfusion record should be used to have a record of the procedure and to help identify trends. If there have been no transfusion reactions, then frequency of checks can be reduced.

Once the transfusion is complete, you can then attach a bag of saline 0.9% to flush the lines through. If you suspect a transfusion reaction, a sample of the donor blood can be submitted for culture or retrospective testing. If at any point you have a suspicion of a transfusion reaction, **stop the transfusion**. You can then perform a full assessment of the patient and have the option of restarting the transfusion at a slower rate.

If needed, blood can be given as a bolus rapidly, but there is a risk associated with this. This approach is reserved for those patients which are peri-arrest and there is concern they won't survive without immediate blood. Fortunately, this isn't encountered too commonly!

TRANSFUSION REACTIONS

The Association of Veterinary Hematology and Transfusion Medicine have an excellent set of guidelines regarding transfusion reactions and is a valuable resource.⁴

Acute haemolytic transfusion reactions are often seen when there is a blood incompatibility. This is a type II hypersensitivity reaction where antibodies against the red cell surface antigens cause lysis. This can cause shock secondary to the severe inflammatory response and potentially DIC. This is typically encountered during the transfusion or within 24 hours of administration. Signs include tachycardia, tachypnoea, hypotension, pyrexia, tremors, and haemoglobinuria. If this is suspected, the transfusion should be stopped, a haematocrit tube spun down to check for haemolysis and supportive care instituted. This may be more likely if the patient has been exposed to a transfusion prior. The blood bag should be kept in case retrospective testing is needed.

Delayed haemolytic reactions, are when blood is broken down following antibodies developing over several days to foreign antigens. This is the reason that xenotransfusions are short lived in cats. This means that the benefits of the transfusion do not last, and often the increased destruction of the red cells results in haemoglobinuria and/or icterus.

Febrile non-haemolytic transfusion reactions are when there is an increase in temperature from baseline by $> 1^{\circ}\text{C}$ with no haemolysis. It is thought to be caused by a reaction to donor white cells, platelets, or cytokines, and is the most common transfusion reaction seen. If mild, the transfusion can be stopped and restarted at a slower rate. The patient should be closely monitored to make sure it is not part of a more serious reaction.

Acute hypersensitivity reactions can also occur and are usually allergy mediated. Signs such as urticaria, pruritus and vomiting. They can be severe enough to cause anaphylaxis. Mild signs should respond to antihistamines, whereas more severe reactions will need to be may require adrenaline and fluid support.

Volume overload and the relative risk of this occurring should be considered prior to administering the transfusion allowing appropriate monitoring. Cats are sensitive to volume overload, particularly if anaemic. To receive the necessary quantity of red blood cells required, they may also have to take on volume which they don't. Point of care ultrasound (POCUS) of the heart, in particular the left atrium:aorta ratio can help screen these patients for signs of early overload or concurrent heart disease, allowing closer monitoring. Packed red cells would be preferable as they'll have less plasma volume administered. Splitting the transfusion into smaller syringes and delivering these lesser volumes over a longer period can also assist. Standing the syringes on their plunger end, allows the red cells to sediment, and you can aseptically discard a volume of plasma before resuspending the cells to form a more concentrated product prior to administration.

AUTOTRANSFUSION

If there is a major cavity bleed such as with a haemothorax or abdomen, then this blood can be collected and given back to the patient, termed an autotransfusion. The benefit of this form of transfusion is that there won't be any compatibility issues as we'd see with donor blood as it is the patient's own, allowing for a more rapid administration.

For an autotransfusion, you must be sure that the effusion in the cavity is only blood and not contaminated e.g. bacteria from a penetrating wound/gastrointestinal rupture, or leakage of bile/urine from an organ rupture in the case of trauma.

If the blood is in a cavity and has been for a length of time, then it can be collected aseptically and administered to the patient via a blood filter to catch any debris. In these circumstances, no anticoagulant is necessary as the clotting factors will have already been used up at the source of the bleed. It may be that there is an arterial or acute bleed, there hasn't been time for the body's natural anticlotting activity, such as intraoperative haemorrhage. If the bleed is this acute, then anticoagulant should be added to the syringes before collection, as you would for whole blood donations, and blood given back through a blood filter.

REFERENCES

- ¹Elkin, M *et al* 2023. Retrospective study of canine blood xenotransfusion compared with type-matched feline blood allotransfusion to cats: indications, effectiveness, limitations and adverse effects. *Journal of Feline Medicine and Surgery*, 25(7)
- ²Le Gal, A., Thomas, E.K. and Humm, K.R., 2020. Xenotransfusion of canine blood to cats: a review of 49 cases and their outcome. *Journal of Small Animal Practice*, 61(3), pp.156–162
- ³Cutler, S., Richardson, J., Eatwell, K. and Llewellyn, E., 2021. In vitro compatibility testing of rabbit and canine blood. *Journal of Veterinary Emergency and Critical Care*, 31(6), pp.742–748.
- ⁴Odunayo, A *et al* 2021. Association of Veterinary Hematology and Transfusion Medicine (AVHTM) transfusion reaction small animal consensus statement (TRACS). Part 3: Diagnosis and treatment. *Journal of Veterinary Emergency and Critical Care*, 31(2), pp.189–203.