Practical guide to using frozen and fresh frozen plasma in general practice

Why every practice should keep a bag in the freezer

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Introduction

Keeping stock at reasonable levels in a practice is vital to good business management balancing the need to have a product available against the costs of keeping stock that is not used and potentially may go out of date and need to be replaced (as well as subtle small costs of space, stock taking, disposal of out-of-date product etc.). Practices need, therefore, to make decisions about preparedness for 'what if' scenarios and have protocols in place.

The difficult question for many practices is how bizarre/uncommon should these scenarios be to warrant keeping a drug or treatment in stock or buying a specialist piece of equipment. This can only really be answered on an individual practice basis as it will depend on the type of cases seen as well as the likely ability of clients to want to pay if the treatment/investigation is expensive and the relationship with other local practices in terms of borrowing treatments or using equipment. It is also important to try and understand the value that a particular drug or treatment will have on morbidity and mortality of a particular condition and whether the patient could be referred onwards if necessary so not having calcium available if presented with a seizuring hypocalcaemic patient would be a significant issue in that patient's care.

To some extent what to stock will also be influenced by whether the practice undertakes any out-of-hours work as that is likely to affect the type and frequency of cases seen. Such calculations are complex as a range of factors need to be taken in to account for example, is it better to set a higher mark-up against a drug or treatment and accept that it may go out of date but when used the charges will cover these costs or the client end up paying for a courier or the practice losing a member of staff at a time when a critical patient is in need of care to collect a product from a neighbouring practice?

Ideally decisions should be made on an evidence base but this relies on a practice have a good understanding of the cases and clients they see as well as literature outlining the value added by a particular treatment or investigation. Whilst the former can usually be derived from the practice management system, the latter is often lacking in the veterinary literature.

Blood products

In the UK, canine blood products have been available for some time whereas feline products still need to be obtained on a named patient basis meaning that most cats receive feline whole blood. Figure 1 shows a 7 year old, female neutered Collie cross that developed a severe hepatitis and associated coagulopathy of unknown cause who developed active bleeding following venepuncture. Poppy's life was saved by the multiple plasma transfusions that were required as she recovered from her hepatitis. Although technically possible, importing feline blood products from abroad that is not usually a practical option. The remainder of this article will focus on the use of plasma in dogs but will reference the use in cats where specific literature is available

Unlike blood or packed red cells, plasma products have a much longer shelf life and can be easily stored within most practices. A single canine donation is usually split into a plasma component and packed red cells as this doubles the value of the donation. Except where large or massive transfusion (products in excess of patient's blood volume) is indicated (Jutkowitz *et al* 2002; Buckley *et* al 2009), in which case fresh whole blood may be a better alternative if available, relatively few patients need both packed red cells and plasma.

Canine plasma is available in four forms

- Fresh frozen plasma
- Frozen plasma
- Cryoprecipitate
- Cryo-supernatant

Fresh frozen plasma (FFP) is made from a fresh, anticoagulated, whole blood donation that has been separated into two parts, the packed red cell portion and plasma by centrifugation. In order for it to be called FFP, this process needs to have occurred within 8 hours of the donation being made (Wardrop, Brooks, 2001) though this is an area of ongoing research (Walton, Hale, Brooks, et al 2014). FFP contains labile clotting factors (fibrinogen, FV, FVIII, von-Willebrand's factor) as well as non-labile factors (FII, FVII, FIX, FX, FXI), immunoglobulins, albumin, lipids and electrolytes. It DOES NOT contain viable platelets.

Frozen plasma (FP) is the anticoagulated portion of centrifuged blood if the separation has occurred later than 8 hours from collection or FFP that has been stored past its expiry date. It contains the non-labile clotting factors (FII, FVII, FIX, FX, FXI) and variable amounts of labile clotting factors, immunoglobulins, albumin, lipids and electrolytes.

Cryo-precipitate (Cryo-P) is a plasma fraction which is separated from FFP by a process of controlled thawing and centrifugation. It is a concentrated product containing the labile clotting factors fibrinogen (factor I), factor VIII and von Willebrand's factor. One standard unit is approximately 60ml.

Cryo-supernatant (Cryo-S) is a plasma fraction which is separated from FFP by a process of controlled thawing and centrifugation; it is also referred to as cryo-poor plasma in some studies. It is the remaining fraction after cryo-precipitate has been produced. It contains plasma proteins including albumin and vitamin K dependant clotting factors II, VII, IX and X. The concentration of albumin in Cryo-S is slightly higher than in FFP. One standard unit is approximately 140ml.

How long do products last?

FFP lasts for 1 year from the date of production and a further 4 more years as FP. Frozen plasma lasts 5 years from the date of production and still retains significant haemostatic activity at this time (Urban, Couto, Iazbik, 2013). Other studies have also indicated good levels of labile coagulation factors after periods of greater than a year although the technique used for preparation varied between studies (Donahue and Fernandez 2019)

Storage

FFP or FP should be stored in a freezer at less than -18˚C (0˚F); freezer temperature should be monitored and recorded daily or electronic records reviewed at least weekly to ensure it remains below -18˚C.

Plasma should be kept in a separate drawer of the freezer or protected by a padded external cover/box as the bags become brittle when stored and can crack leading to possible contamination or leakage when thawed.

What can plasma do?

Plasma contains labile and non-labile clotting factors so there is a clear indication for use in bleeding associated with coagulopathy or declining clotting times to the point that bleeding is highly likely. Plasma also contains albumin and can be used in cases of hypoalbuminaemia although its effects on plasma albumin is relatively small. The effect of continuous rate infusion of cryo-supernatant on albumin and colloidal osmotic pressure (COP) has been investigated in dogs (Culler *et al* 2019) who demonstrated a rise in both albumin and COP that correlated to the rate of infusion. Plasma also contains acute phase proteins such as alpha-2 macroglobulin that has anti-protease activity.

FFP vs FP vs Cryo-P vs Cryo-S – when to use what?

Below are the components of each of these products; indications for their use are given in table 1.

FFP

FFP is most commonly used for dogs presenting with bleeding associated with inherited or acquired coagulation disorders (Fig. 3). It can also be used when labile clotting factors are not required as frozen plasma but is a more expensive option. The most common condition likely to be seen in primary care practice requiring FFP or FP is anticoagulant rodenticide toxicity. There are no accurate estimates of the frequency of anticoagulant rodenticide toxicity in the UK but figures from VPIS show they receive 800 - 1,000 enquiries per year about anticoagulant rodenticide toxicity in dogs (Fig. 4) and is their second most common enquiry. There are a number of other indications for using FFP in dogs (Table 1 and below) that would potentially include:

- Bleeding associated with *Angiostrongylus vasorum* infection.
- Management of cases with undiagnosed von Willebrand's disease (Stokol, Parry, 1998) that are bleeding following surgery, for example spaying.
- As part of the management of potential or actual bleeding in cases with known von Willebrand's disease undergoing emergency or elective procedures.
- Coagulopathies associated with adder bites.
- Coagulopathy associated with xylitol ingestion (Dunayer, Gwaltney-Brant, 2006).

- Haemophilia A (Stokol, Parry, 1998) or other inherited coagulopathies involving labile clotting factors.
- In the management of disseminated intravascular coagulopathy (DIC).
- As part of management of severe post-surgical bleeding where clotting factors have been consumed – in most circumstances fresh whole blood would be a better alternative.
- Prior to liver biopsy in a patient with prolonged clotting times.

The value of FFP in the management of pancreatitis has been questioned. In one study (Weatherton, Streeter, 2009) the outcome of dogs receiving FFP was worse than those not given FFP. However, as this was a retrospective review, illness severity was difficult to assign and it is possible that those dogs with more severe disease tended to be given plasma. Notwithstanding this, in recent years, there has been a change of use of FFP and FP focusing more on the management of coagulopathy and less on the management of septic, inflammatory events or as an albumin replacement (Snow, Ari Jutkowitz, Brown et al 2010, Logan, Callan, Drew et al 2001).

FP

Frozen plasma still contains factor VII that is one of the critical deficiencies in anticoagulant rodenticide toxicity so can be used in its management. Additionally, FP can be of value in:

- Vasculitis
- Management of effusions associated with protein losing enteropathy or nephropathy – a considerable amount of plasma is required to raise the albumin significantly and will provide relatively short term benefit unless the underlying disease process is being addressed.
- Pancreatitis and peritonitis where there is not active DIC-associated bleeding to augment α1-macroglobulin levels that have been overwhelmed by the inflammatory process.
- Neonates with inadequate maternal antibody transmission.
- Other causes of hypoglobulinaemia or afibrinogenaemia (Chambers G, 2012).
- Haemophilia B and other inherited coagulopathies involving non-labile factors.

The use and benefits of plasma as a colloid remain a controversial issue in veterinary and human medicine since a clear benefit over appropriate crystalloid therapy in most circumstances remains lacking and the potential for causing harm exists.

Why not just give whole blood?

In some circumstances fresh whole blood provides a suitable alternative to FFP and in some cases where there has been significant bleeding, it may provide additional benefits. However, where there has not been significant blood loss, then whole blood will unnecessarily increase the PCV that can result in viscosity issues. There is also a higher likelihood of an adverse reaction when transfusing whole blood compared to plasma. It should also be remembered that the number of platelets in whole blood is quite small and their half-life short (1-2 days) so fresh whole blood will have little additional benefit to packed reds cells in IMTP cases unless there is active bleeding.

Practical guidance for using plasma products

How do I decide when to give plasma?

A specific evidence base as to the most appropriate time to give plasma (Fig. 5) is lacking and would be difficult to develop. General guidelines are given in Table 1 on the use of plasma under each circumstance based mainly on recommendations in man (Limbruno et al 2006), standard veterinary textbooks and specialist opinion.

What are the costs?

Current prices (Pet Blood Bank, May 2019) are shown in Table 2. Not for profit organisations such as Pet Blood Bank ask that practices do not mark up their products hence it is important to have an appropriate fee structure for administration and monitoring a plasma transfusion.

Do I need specific signed owner consent?

Specific owner consent should be obtained and the potential adverse events associated with plasma transfusion explained. Whether plasma is viewed as a drug or a treatment depends on the circumstances under which it is being used. Advice from the Veterinary Medicines Directorate is as follows: "If plasma is being used as replacement therapy i.e. to top up after loss of blood, then we would not consider this to be cascade use. Any other use would be considered cascade use."

A suggested wording for owner consent would be: "I consent to the administration of plasma to my dog *******. I understand that an adverse reaction to plasma transfusion can occur and that in very rare cases it can be life threatening."

The inclusion of additional statements may be necessary if plasma was being used under the cascade although it does not fit in any of the standard treatment categories since canine plasma does not hold a license for use in either humans or animals.

How should plasma be thawed and how long does it take?

Frozen bags of plasma should be handled with care as they are brittle and can crack easily. If the plasma is needed urgently then the bag can be placed in a waterproof zip-lock bag as an outer sleeve to prevent contamination of the injection ports and placed in tepid water (<37˚C); temperature should be monitored with a thermometer and the water replenished as it cools to speed the thawing process (Fig. 6); ideally the plasma temperature should remain below 20 ˚C. If the need is less urgent then place the plasma in a zip lock bag in a box on a suitable surface away from direct heat allowing it to thaw at room temperature. Average time to thawing of a unit (200ml) of FFP in a water bath was 34.7 ± 1.4 minutes. This time factor has led to the development of microwave plasma defrosters that have been shown to defrost a 120ml unit in 2.7 ± 0.1 minutes and a 240ml unit in 3.9 ± 0.2minutes with minimal loss of clotting factor activity (Turner *et al* 2018)

What volume and how should plasma should I given?

As the risk of transfusion reaction is very low and there is no clear evidence of benefit, premedication with antihistamines such as chlorphenamine or glucocorticoids is not necessary. Rate of intravenous administration should be according to need. In a non-emergency situation initial transfusion rate of 0.5-1.0 ml/kg/hour for 20-30

minutes is appropriate with close observation of the patient for any signs of an adverse reaction. If no reaction is observed the remaining plasma can be given over the next 3-4 hours. Suitable monitoring forms normally accompany the plasma when it is delivered. A giving set with a filter should be used but in an emergency situation this is not essential.

• Check temperature, heart and respiratory rate prior to starting the transfusion and then every 10-15 minutes for the first half hour

• If no issues have arisen then check half hourly until an hour after the transfusion has been completed

• Measure total proteins 1-2 hours after transfusion has finished

• Assess buccal mucosal bleeding time, PT, APTT or other clotting parameters as appropriate after the procedure depending on the underlying disease and reason for the transfusion. On rare occasions, assessment during transfusion may be necessary.

In an emergency situation, the risk and consequences of a transfusion reaction need to be weighed against the benefits of giving the plasma rapidly. If the situation demands, the whole transfusion can be given over a 20-30 minute period. The patient must be closely monitored during this time and equipment and drugs necessary for dealing with a transfusion reaction, should it occur, be immediately available. There are various recommendations as to an appropriate amount of plasma to be given in people and dogs ranging from 5-30ml/kg. In general, 20ml/kg is a reasonable target dose that will reliably correct most coagulation disturbances. However, this would require more than one bag of plasma in dogs over 11-12 kg and can be cost prohibitive for large and giant breeds; in some cases, giving as much as you have or the owner can afford over 5ml/kg may be the only option along with other supportive care. Work has been undertaken to try and match the amount required with thromboelastometry data (Langhorn *et* al 2019). Thromboelastometry machines are expensive but more affordable patient-side options e.g. VCM Vet™ are becoming available. Where the disease process is active such as DIC, multiple transfusions may be required every 8-16 hours over a 1-3 day period which again can be cost prohibitive (20 kg dog with DIC requiring 12 hourly transfusions for 2 days would require 1600ml of plasma at a cost of around £0.80 - £1.25/ ml). Such rough calculations are important to make when commencing plasma transfusion to allow owners to make informed decisions about treatment as the value of a single bag of plasma in a large dog with active bleeding may be limited. Suggested dose rates from cryo-P are 6ml/kg and for cryo-S are similar to FFP or FP at 10-30ml/kg – higher doses are required for albumin replacement. Human albumin is an alternative source of albumin that can be used in dogs.

Is cross matching or blood typing necessary?

Plasma products supplied by commercial blood banks in the USA and the UK are all required by the regulatory authorities to be labelled according to the Dog Erythrocyte Antigen (DEA) 1.1 red blood cell. A number of recent articles have also highlighted the importance of other DEA groups particularly 7 and 4. The significance of these in terms of adverse reactions to plasma transfusion is unknown.

type of the donor. However, well processed plasma products contain less than 4% red cells (Swisher S N, Young LE, Trabold N, 1962) and immunisation (antibody formation) to the known DEA groups does not occur. Hence

type matching for plasma transfusion in well processed plasma products with no visible red cell contamination is unnecessary.

In dogs that have had previous blood products then cross matching may be advisable although the risk remains very low when using repeat plasma transfusions compared to red cells. This can be undertaken by an external laboratory for non-urgent cases but would need to be done in-house for emergencies.

In-House Cross Matching

1. Label 2 glass slides.
    a. Minor cross match – recipient red cell and donor plasma.
    b. Recipient control – recipient red cells and recipient serum.
2. On the slide place one drop of citrated recipient blood and 2 drops of plasma.
3. Rapidly mix with and applicator stick
4. Gently rock the slides from side-side and observe for 2 minutes.
5. Place a cover slip and examine at 40x or greater for agglutination within 5 minutes of mixing.
6. Rouleaux formation can be difficult to distinguish from agglutination where agglutination is weak - if this occurs repeat steps 2-5 using 0.1ml of anticoagulated blood mixed in 1.2ml of saline.

Can I refreeze part use bags or store in the fridge?

Current strong opinion is that part used bags of plasma should be discarded, however, plasma is a relatively expensive and scare resource so storage can be considered particularly if the remainder may be used on the same patient. If it is likely that only part of a bag is to be used then an appropriate aliquot can be removed from the bag and, so long as sterility has been maintained, then the remainder could be immediately refrozen and considered as frozen plasma with appropriate labelling. However, plasma bags do not have injection ports to allow an aliquot to be removed ensuring sterility is maintained in the remainder. Placing the unused plasma in a blood collection bag that contains no anticoagulant or emptying a 100 or 250 ml bag of crystalloids using sterile technique (gloves, sterile needle and syringe) and refilling with plasma would be possible – all such procedures are not without risk of contamination of the plasma. Work by Yaxley *et al* (2010) showed no difference in coagulation factors in samples that were refrozen after an hour compared to a sample from the same donation that had not undergone a freeze-thaw cycle. Grochowsky *et al* (2014) have shown that thawed plasma can be stored in the fridge for up to 2 weeks but this is associated with some loss of coagulation factors. However, for most clinics the cost of such a device is prohibitive.

Transfusion reactions

How often do they occur?

Significant transfusion reactions to plasma are rare, particularly in the first transfusion. In man, mild urticarial type reactions occur in 1% of patients. Severe and anaphylactic reactions occur with a frequency of less than 1 case per

100,000 transfusions (Liumbruno, Bennardello, Lattanzio et al 2009). No reliable figures are available in dogs but a conservative estimate to give to a client would be less than 1:1000 chance of a severe reaction.

What do they look like?

A variety of types of transfusion reaction can occur (Table 3). In the majority of cases one or more of the following signs are seen (Fig. 7):

- Fever
- Restlessness, tremor, vocalisation
- Tachypnoea
- Tachycardia and/or arrhythmia
- Vomiting and/or hypersalivation
- Angioedema
- Urticaria
- Collapse, seizure, coma, cardiopulmonary arrest

If I get a reaction what should I do?

Mild reaction

- Reduce (usually half rate of administration of plasma)
- Stop transfusion, allow temperature, pulse and respiration to normalise and restart at a lower rate (usually half)

Severe reaction

- Stop transfusion
- Decide whether to
- Wait for signs to subside and restart at 50% of the previous rate
- Abandon transfusion – balance severity of reaction with clinical need
- Use drug treatment if anaphylactic (hypersensitivity) type
    - Maintain BP with IVFT
    - Antihistamines – 5-10 mg of chlorphenamine IV
    - Glucocorticoids only if normotensive
        - Dexamethasone sodium phosphate 0.2-1mg/kg
    - Rarely IV adrenaline or ephedrine

Conclusions

Fresh frozen plasma, in particular, is an extremely valuable resource to have immediately available in primary care practice. When plasma is readily available the likelihood of at least one unit being required in a year even in a small practice is high. FFP is indicated in a variety of clinical situations particularly where there is a severe haemostatic disorder and can make the difference between life and death. Used prudently and in a timely fashion alongside other treatment modalities in a variety of critical cases, FFP has the potential to reduce morbidity, hospitalisation times and mortality. In many situations, using FFP is preferable to whole blood transfusion.

There is a lack of evidence to support other indications for the use of plasma in dogs and many of the published studies are retrospective and lack appropriate controls. Similar studies on the level of labile coagulation factors in FFP after prolonged storage are based on measurement rather than demonstration of similar clinical efficacy to FFP stored for shorter periods.

Figures and Illustrations

Figure 1 – Seven year old Collie cross – post acute hepatitis (courtesy Pet Blood Bank)

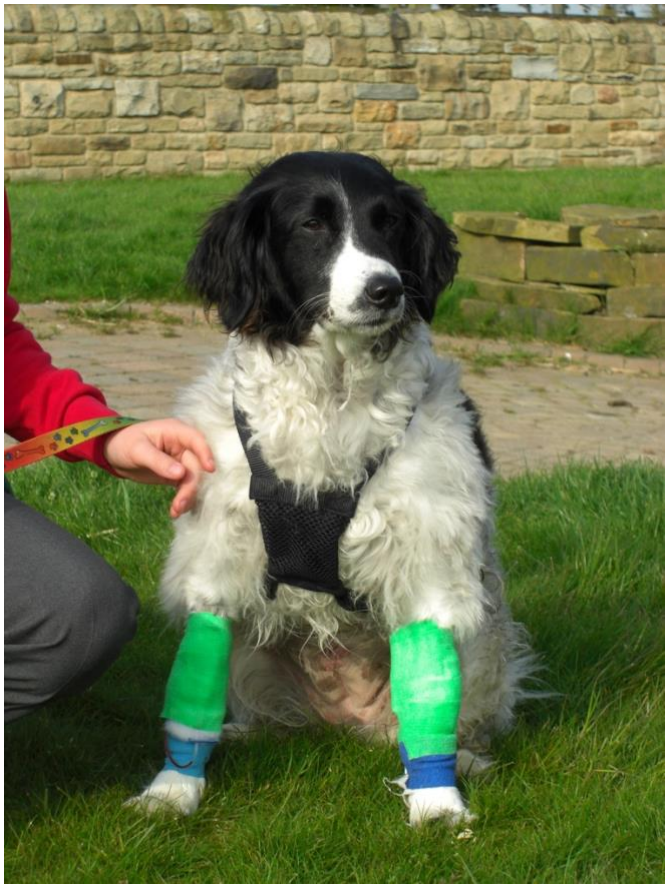

Figure 2 – Three year old, Labrador with severe, active, intrapulmonary haemorrhage associated with rodenticide toxicity

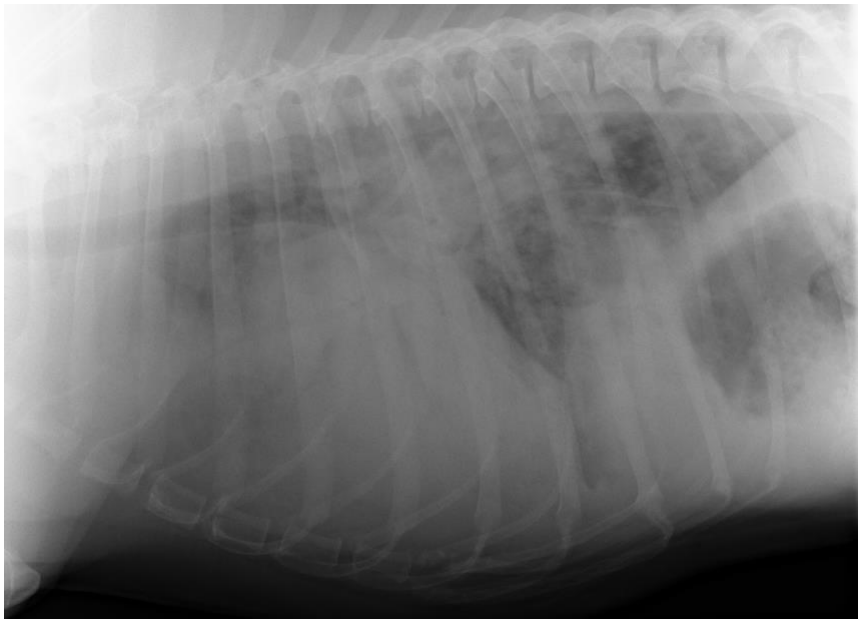

Figure 3- Ten year old Labrador with severe bleeding associated with Angiostrongylus vasorum

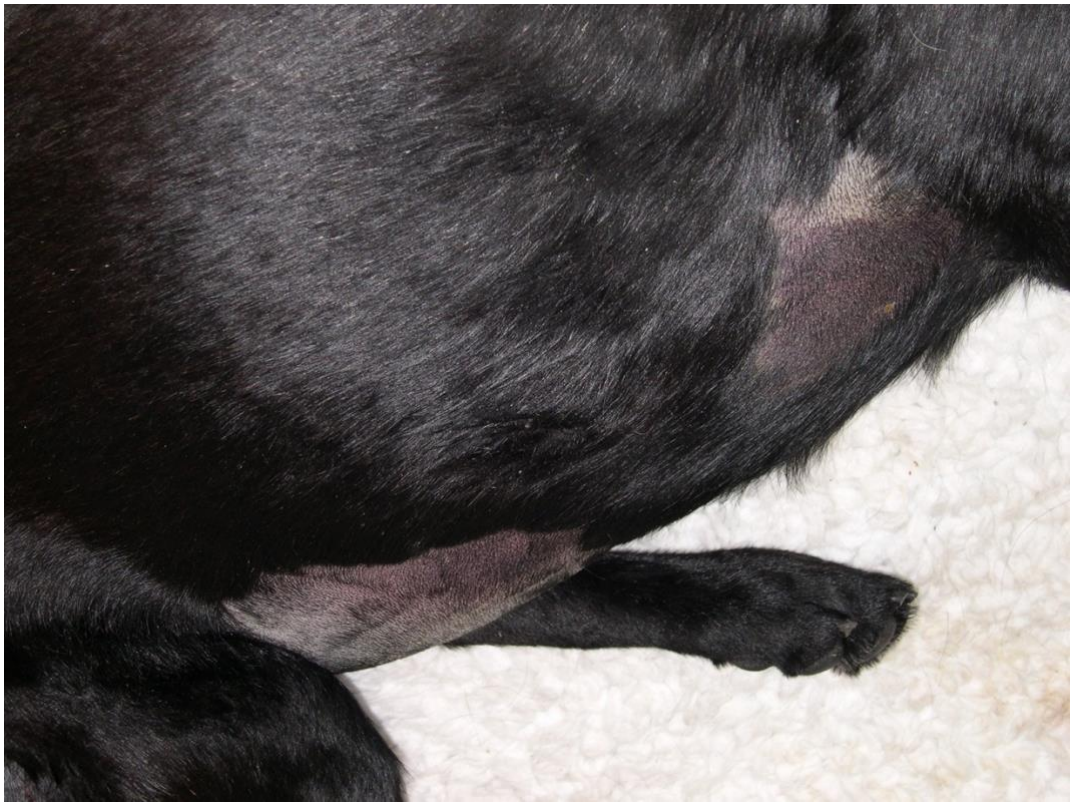

Figure 4

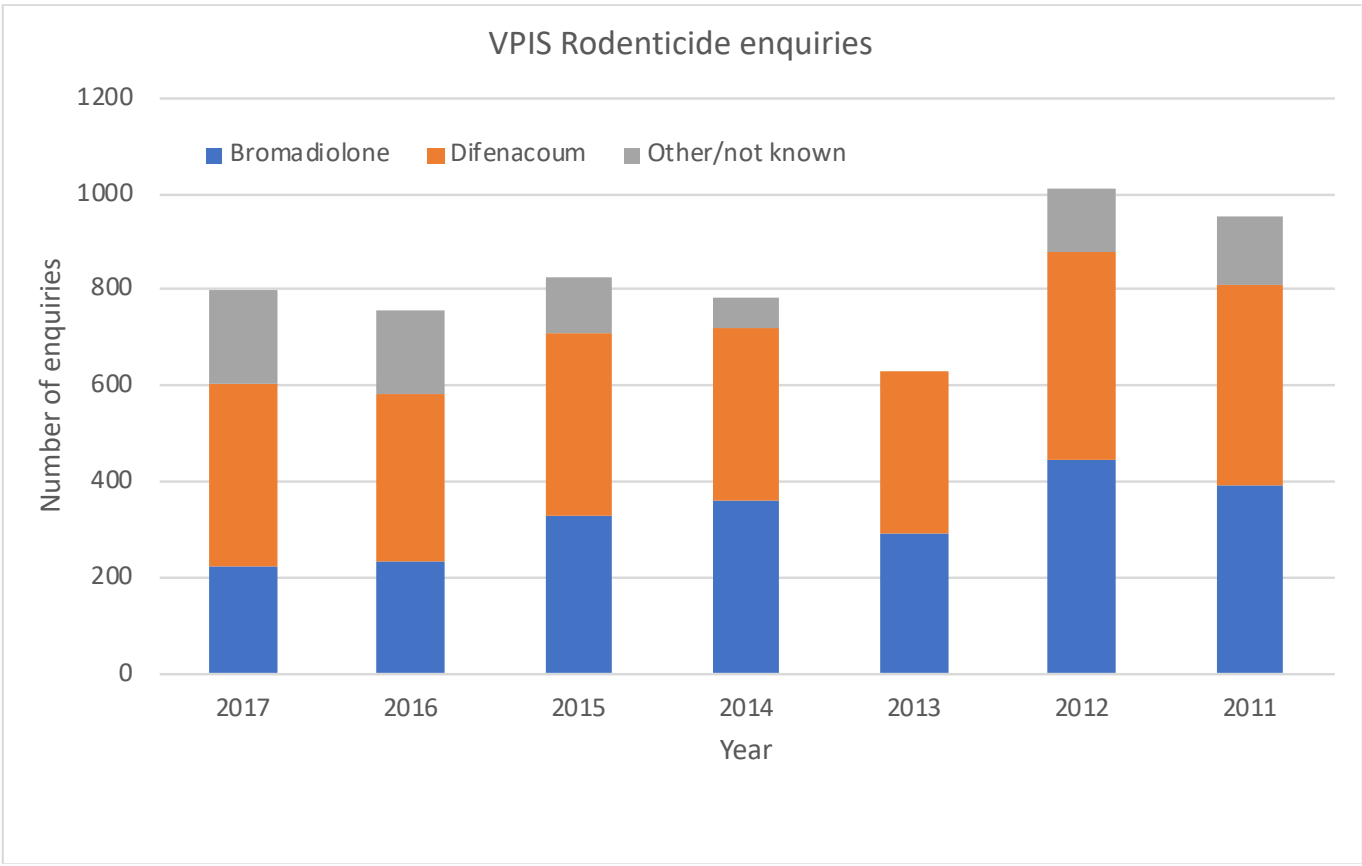

Figure 5 – Administration of FFP to an 11 year old Mn Jack Russell terrier with significant bleeding following liver biopsy

Figure 6 – Thawing FFP in a water bath

Figure 7 – Angioedema associated with transfusion reaction

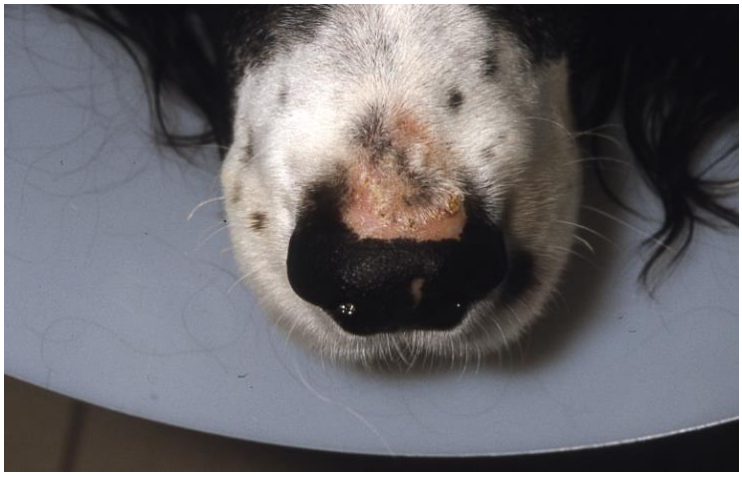

Table 1 – Indications for the use of plasma in dogs

General indication	Specific circumstances	FFP or FP	Category
Anticoagulant rodenticide toxicity	Active bleeding (Fig. 2) PT > 2X upper limit despite vitamin K PT < 2X upper limit especially if vitamin K has not been given or ingestion uncertain	FFP preferred Cryo-S	1 2 4
Bleeding due to Angiostrongylus	Active bleeding	FFP	1
Von Willebrand's disease (vWD)	Active bleeding Significant surgery planned (pre-operative transfusion)	FFP Cryo-P	1 1
Haemophilia A	As vWD	FFP, Cryo-P	
Haemophilia B	As vWD	,FFP, FP Cryo-S	
Adder bites	Marked or worsening petechiation/ecchymosis Minor petechiation/ecchymosis	FFP	1 2
Disseminated intravascular coagulopathy	Active bleeding Hypercoagulable state PT/APTT >2X upper limit Elevated FDPs, D-dimers; PT/APTT <2X upper limit	FFP	1 2 3 4
Post-surgical consumptive coagulopathy	Active bleeding	FFP	1
Liver biopsy	Bleeding post biopsy Clotting times >2x upper limit (pre-procedure transfusion)	FFP	1 3
Hypoproteinemia	With ascites Without ascites	FFP, FP or Cryo-S	3 4
Hypoglobulinemia	Active infection Neonate	FFP, FP	3 3

Vasculitis	Cutaneous petechiation ecchymosis	FFP, FP	2
Pancreatitis and peritonitis without DIC		FFP, FP	3/4
As a colloid		Cryo-S	2

Categorisation

1 – Plasma is strongly recommended

2 – Plasma may be appropriate but clear evidence of benefit is lacking

3 – Plasma has been suggested under these circumstances but evidence of benefit is lacking and other treatments are more appropriate in the first instance.

4 – Not currently recommended

Table – 2 Costs of canine plasma products (Pet Blood Bank)

Product	Cost (£) (ex. VAT)	Cost (£) (inc. VAT)
Canine fresh frozen plasma (200ml)	115.00	138.00
Canine fresh frozen plasma (100ml)	69.00	82.80
Canine frozen plasma (200ml)	66.16	66.19
Canine frozen plasma (200ml)	33.09	39.71
Canine Cryo-precipitate	203.33	244.00
Canine Cryo-supernatant	33.09	39.70

Table 3 - Immunological and non-immunological reactions to plasma transfusion

Immunological reactions	**Non immunological reactions**
Hypersensitivities including type I and II	Hypothermia (inadequately warmed product)
Acute lung injury (not recognised in canine patients at this time (Thomovsky and Bank 2014)	Citrate toxicity risk (hypocalcaemia) in very small patients or liver disease/failure
Febrile non-haemolytic transfusion reactions	Thrombosis
Immunosuppression	Bacterial contamination/sepsis
	Dilutional coagulopathy
	Volume overload
	Disease transmission

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