Fresh frozen plasma – why every practice should keep a bag in the freezer

Suspected rodenticide poisoning is a common presentation to primary care practices and is the second most common reason for seeking advice from the Veterinary Poisons Information Service. Keeping a unit of fresh frozen plasma (FFP) in the practice makes practical and commercial sense allowing rapid treatment of such cases as well as other coagulopathies, post surgical bleeding and dysproteinemias where appropriate. In many situations, plasma is a better choice than fresh whole blood not least as significant adverse reactions are rare. Furthermore FFP has a one year shelf-life and subsequent availability as frozen plasma (FP) for another 4 years means that likelihood of a unit being discarded is very low.

This article reviews the indications for using FFP and FP and provides answers to common questions about the use of plasma as well as providing a practical guide for its administration. Like many newer therapies, having FFP readily available in the practice will mean that it is used more frequently and in a more timely manner improving outcome for patients.

Key words: frozen, fresh, plasma, transfusion, coagulation, dog

Introduction
Keeping stock at reasonable levels in a practice is vital to good business management. The need to have a product available must be balanced against the cost of keeping unused stock that gets outdated and requires replacement (as well as subtle small costs of space, stock taking, disposal of out-of-date product etc.).

However, practices also need to be prepared for ‘what if’ scenarios. The question is how bizarre/rare should these scenarios be to warrant keeping a drug or treatment in stock or buying a specialist piece of equipment. In treatment terms, the likelihood of such an event happening should be matched against the critical need for a drug and the ease with which it can be obtained if not in stock (neighbouring practices, courier delivery) and this to some extent will be influenced by whether the practice undertakes any out-of-hours work. Such calculations are complex as a range of factors needs to be taken into account. For example, is it better to set a higher mark-up for a drug or treatment and accept that it may go out of date, but when used will the charges cover these costs? Or is it better to pay for a courier or lose a member of staff at a time when a critical patient is in the practice, in order to collect a product from a neighbouring practice?

Fresh frozen plasma is one such treatment; how likely is your practice to use a single unit of FFP within its shelf life? FFP has a long freezer (−18°C) life of one year and can provide life saving therapy to critical patients quickly and effectively if readily available. Like many treatments, having plasma available encourages use at an appropriate time improving success rather than it being a big hassle to get hold of and only ends up being used as a ‘hail Mary pass’ often with associated disappointing results. The added advantage of FFP is that at the end of its shelf life it does not have to be discarded but can be used as frozen plasma for another 4 years.

How do I assess a patient’s clotting ability?
There are a variety of tests that can be used to assess the clotting system (Fig. 1) including measurement of individual factors. However, for the majority of patients assessment is confined to:

Assessment of primary haemostasis

• Buccal mucosal bleeding time – tests primary haemostasis and the interaction between vascular endothelium and platelets including von Willebrand’s factor.

• Care should be taken if there are already indicators of reduced primary haemostasis such as thrombocytopenia or petechiation as bleeding can be difficult to stop.

• Platelet count – estimates number and morphology but does not indicate whether there is a defect in platelet function (thrombocytopenia).
Assessment of secondary haemostasis

- Activated clotting time (ACT) – assesses the intrinsic and common pathways.
- Activated partial thromboplastin time (APTT) – assesses the intrinsic and common pathways.
- Prothrombin time (PT) – assesses extrinsic and common pathways.
- Fibrinogen – reduced levels usually indicate consumptive process such as DIC but will also occur in advanced hepatic disease.
- Thrombin clotting time – prolonged if there is hypofibrinogenaemia, dysfibrinogenaemia or inhibition of thrombin by other substances e.g. heparin, FDPs or abnormal serum proteins.
- Fibrin degradation products (FDPs) – assesses whether there is increased fibrinolysis usually indicating DIC but will also be found with anticoagulant rodenticide toxicity, hepatic disease and thrombotic conditions.
- D-dimers – are a fibrin degradation product and an alternative to FDP measurement, values in the reference range have a good negative rule out (95%) for DIC.

What is the difference between fresh frozen plasma and frozen plasma?

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.

(Fig. 1 – Clotting cascade)

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 for more than a year. It contains the non-labile clotting factors (FII, FVII, FIX, FX, FXI) immunoglobulins, albumin, lipids and electrolytes.

How long does it 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).

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.

When should I use FFP?

FFP is most commonly used for dogs presenting with bleeding associated with inherited or acquired coagulation disorders (Fig. 2). 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 around 1,000 enquiries per year about anticoagulant rodenticide toxicity in dogs (Fig. 3). It is their second most common enquiry (>10,300 enquiries to date [ETD]) marginally behind NSAIDs (>11,500 ETD) and representing a significant percentage of total enquiries. 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.
- Diseases for which frozen plasma is indicated.

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).

When can I use frozen plasma?
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 aﬁbrinogenaeemia (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 fresh 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.

Practical guidance to using FFP and FP

How do I decide when to give plasma?
A specific evidence base as to the most appropriate time to give plasma (Fig. 4) is lacking and would be difficult to develop. General guidelines are given in Table 1 on the use of FFP or FP under each circumstance based on recommendations in man (Limbruno et al 2006), standard veterinary textbooks and specialist opinion.

How much does it cost?
Current prices (Pet Blood Bank, accessed Jan 27th 2014) 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 giving 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..."
Table 1: Indications for use of fresh frozen plasma (FFP) and frozen plasma (FP).

<table>
<thead>
<tr>
<th>General indication</th>
<th>Specific circumstances</th>
<th>FFP or FP</th>
<th>Category</th>
</tr>
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<tbody>
<tr>
<td>Anticoagulant rodenticide toxicity</td>
<td>Active bleeding</td>
<td>Preferred FFP</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>PT &gt; 2x upper limit despite vitamin K</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td>PT &lt; 2x upper limit especially if vitamin K has not</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>been given or ingestion uncertain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding due to Angiostrongylus</td>
<td>Active bleeding</td>
<td>FFP</td>
<td>1</td>
</tr>
<tr>
<td>Von Willebrand’s disease (vWD)</td>
<td>Active bleeding</td>
<td>FFP*</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Significant surgery planned (pre-operative transfusion)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>As vWD</td>
<td>FFP*</td>
<td></td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>As vWD</td>
<td>Either</td>
<td></td>
</tr>
<tr>
<td>Adder bites</td>
<td>Marked or worsening petechiation/ecchymosis</td>
<td>FFP</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Minor petechiation/ecchymosis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Disseminated intravascular coagulopathy</td>
<td>Active bleeding</td>
<td>FFP</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypercoaguable state</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PT/APTT &gt;2x upper limit</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated FDPs, D-dimers; PT/APTT &lt;2x upper limit</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Post surgical consumptive coagulopathy</td>
<td>Active bleeding</td>
<td>FFP</td>
<td>1</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Bleeding post biopsy</td>
<td>FFP</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Clotting times &gt;2x upper limit (pre-procedure transfusion)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>With ascites</td>
<td>Either</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Without ascites</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hypoglobulinemia</td>
<td>Active infection</td>
<td>Either</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Neonate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Cutaneous petechiation ecchymosis</td>
<td>Either</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatitis and peritonitis without DIC</td>
<td></td>
<td>Either</td>
<td>3</td>
</tr>
<tr>
<td>As a colloid</td>
<td></td>
<td>Either</td>
<td>4</td>
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</table>

**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

* Cryoprecipitate is the transfusion therapy of choice as it contains 5-10x the amount of active vWF and factor VIII.

Table 2: Approximate costs of FFP and FP (Pet Blood Bank).

<table>
<thead>
<tr>
<th>Product</th>
<th>Cost (£) (ex. VAT)</th>
<th>Cost (£) (inc. VAT)</th>
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<tbody>
<tr>
<td>Canine fresh frozen plasma (200ml)</td>
<td>175.43</td>
<td>210.52</td>
</tr>
<tr>
<td>Canine fresh frozen plasma (100ml)</td>
<td>105.71</td>
<td>126.85</td>
</tr>
<tr>
<td>Canine frozen plasma (200ml)</td>
<td>138.99</td>
<td>166.79</td>
</tr>
<tr>
<td>Canine frozen plasma (100ml)</td>
<td>83.40</td>
<td>100.08</td>
</tr>
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</table>

Figure 4. Fresh frozen plasma transfusion being given
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 FFP does not hold a license for use in either humans or animals.

How should plasma be thawed?

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. 5). 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.

In-house Cross Matching

1. Label 2 glass slides.
   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 applicator stick.
4. Gently rock the slides from side-to-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 a part used bag?

Current strong opinion is that part used bags of plasma should be discarded, however, plasma is a relatively expensive and scarce resource. 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.

How should it be 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 purchased plasma. 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.

How much should I give?

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 coagulopathy 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.
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.

### 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 at least one unit being required in a year even in a small practice is very 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.

**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. 6):

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

**If I get an adverse 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
  - Glucocorticoids only if normotensive
    ✓ Dexamethasone sodium phosphate 0.2-1mg/kg
    ✓ Rarely IV adrenaline

### Table 3. Immunological and non immunological types of transfusion reactions.

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

**Figure 6. Typical signs of an angioedema associated with an adverse reaction to transfusion (in this case to packed red cells).**

**Conclusions**

Fresh frozen plasma 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 very 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.

**References**


Pet blood Bank UK website: www.petbloodbankuk.org


1. What is the shelf life of fresh frozen plasma?
   A) 6 months
   B) 9 months
   C) 12 months
   D) 18 months
   E) 2 years

2. At the end of the shelf life fresh frozen plasma should be:
   A) Discarded into clinical waste
   B) Emptied down the sink and the bag discarded into general waste
   C) Can be considered as frozen plasma and shelf life extended by 1 year
   D) Can be considered as frozen plasma and shelf life extended by 4 years
   E) Can be still used on the next available patient as fresh frozen plasma

3. Which are the labile clotting factors?
   A) Factor V, VIII and von-Willebrand’s factor
   B) Factors I, II and X
   C) Factor VII, IX, X, XI
   D) Factor IX, X, XI
   E) Factor V and VII

4. How should frozen plasma be thawed out?
   A) In the microwave
   B) In hot water
   C) In tepid water (<37°C)
   D) At room temperature
   E) In tepid water or at room temperature

5. How much FFP is normally given?
   A) Given until albumin is above 20g/L
   B) 30-40mL/kg
   C) 10-20mL/kg
   D) 5-10mL/kg
   E) 4-5mL/kg

6. How common are severe plasma transfusion reactions in man?
   A) Common (1:10 → 1:100)
   B) Uncommon (1:100 → 1:1000)
   C) Rare (1:1000 → 1:10,000)
   D) Very rare (< 1:10,000)
   E) Almost never (< 1:100,000)

7. Which of the below is unlikely to be a sign of a transfusion reaction?
   A) Urticaria
   B) Tachycardia
   C) Facial oedema
   D) Salivation
   E) Coughing

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