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SPECIAL ARTICLE

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# Association of Veterinary Hematology and Transfusion Medicine (AVHTM) Transfusion Reaction Small Animal Consensus Statement (TRACS). Part 1: Definitions and clinical signs

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## Abstract

**Objective:** To use a systematic, evidence-based consensus process to develop definitions for transfusion reactions in dogs and cats.

**Design:** Evidence evaluation of the literature was carried out for identified transfusion reaction types in dogs and cats. Reaction definitions were generated based on

**Abbreviations:** AABB, American Association of Blood Banks; ACE, angiotensin-converting enzyme; AHTR, acute hemolytic transfusion reaction; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; AVHTM, Association of Veterinary Hematology and Transfusion Medicine; BNP, brain natriuretic peptide; CDC, Centers for Disease Control; CPDA, citrate phosphate dextrose adenine; DAT, direct antiglobulin test; DEA, dog erythrocyte antigen; DHTR, delayed hemolytic transfusion reaction; DIC, disseminated intravascular coagulation; DSTR, delayed serologic transfusion reaction; FFP, fresh frozen plasma; FNHTR, febrile non-hemolytic transfusion reactions; Hb, hemoglobin; HLA, human leukocyte antigen; HNA, human neutrophil antigens; HTR, hemolytic transfusion reaction; HyTR, hypotensive transfusion reactions; IAT, indirect antiglobulin test; IMHA, immune-mediated hemolytic anemia; LAH, left atrial hypertension; NETS, neutrophil extracellular traps; NHSN, National Healthcare Safety Network; NT-proBNP, N Terminal-proBNP; pRBCs, packed red blood cells; PCR, polymerase chain reaction; PTP, post-transfusion purpura; SHOT, serious hazards of transfusion; TACO, transfusion associated circulatory overload; TAD, transfusion associated dyspnea; TA-GVHD, transfusion associated graft versus host disease; TRALI, transfusion related acute lung injury; TTI, transfusion transmitted infection; WB, whole blood; XM, crossmatch

synthesis of human and veterinary literature. Consensus on the definitions was achieved through Delphi-style surveys. Draft recommendations were made available through industry specialty listservs and comments were incorporated.

**Results:** Definitions with imputability criteria were developed for 14 types of transfusion reactions.

**Conclusions:** The evidence review and consensus process resulted in definitions that can be used to facilitate future veterinary transfusion reaction research.

KEYWORDS
allergic reactions, anaphylaxis, Blood products, complications, morbidity

## 1 | INTRODUCTION

Transfusions are lifesaving but have risks. Reactions to blood products can either be acute or delayed and can range in severity from minor to life threatening. While transfusion reactions have been described in veterinary species, the definitions of these reactions have been variable.[1–3] Variability in definition impedes recognition and treatment in clinical practice and also impedes utilization of appropriate information in comparative prospective or retrospective studies.[4]

The Centers for Disease Control and Prevention (CDC), in collaboration with experts convened by American Association of Blood Banks (AABB), developed consensus definitions and a nationwide reporting module, which launched in 2009.[5] These national reaction definitions and reporting modules have led to large-scale studies, and improvements in transfusion practice.[6,7]

In 2018, an international committee of veterinary specialists convened in partnership with the Association of Veterinary Hematology and Transfusion Medicine (AVHTM) to develop consensus definitions and evidence-based recommendations for prevention, monitoring, diagnosis, and treatment for transfusion reactions in veterinary patients. The authors' hope is that this material will be the basis for further clinical research and for the potential development of a veterinary hemovigilance database.

In part 1 of this series, we define important terms and present each reaction type. For each reaction, we have included incidence, background human and veterinary literature, and areas for further research. In part 2 of this series, we provide evidence-based recommendations for prevention and monitoring of transfusion reactions and present a standard transfusion monitoring form. In part 3, we provide evidence-based recommendations for diagnosis and treatment of transfusion reactions and present clinical diagnostic and treatment algorithms.

## 2 | METHODS

The consensus project was initiated through the AVHTM. A call for volunteer contributors was made through the listserv and the group was convened. The committee includes members from 5 countries and 4 different areas of specialty certification (DACVIM, DACVCP, DACVECC, DECVECC). The members include those working in academia, private clinical practice, laboratory medicine, and blood banking. Many members have published extensively in the field of veterinary transfusion medicine.

The project was limited to transfusion reactions secondary to red blood cell, plasma, and platelet transfusions in dogs and cats. Reactions associated with human albumin, immunoglobulins, and antivenoms were not included. The reaction definitions from CDC's National Hemovigilance Module were used as the starting point.[7] Due to perceived clinical relevance, complications related to hyperammonemia and hypocalcemia due to citrate toxicity were included; similarly, reactions associated with xenotransfusion were included.

The group developed specific worksheet questions to review each reaction.[8] Comprehensive database searches were then performed including review of both human and veterinary literature. The reaction worksheet included search criteria, a review of the relevant veterinary and human literature, a proposed definition, clinical signs, diagnostic criteria, risk factors, evidence grade, and areas for further research. The committee discussed all reaction worksheets in an initial round of changes and suggestions. Delphi-style anonymous surveys were then used to refine the definitions and diagnostic criteria.[9] These draft definitions and recommendations were then presented to the AVHTM, ACVECC, and ACVIM discussion boards, and definitions further refined based on these comments and suggestions. [8,10]

## 3 | TERMS

Transfusion reactions can be classified based on etiology, time frame, and clinical signs. For the purposes of these guidelines, commonly used terms and definitions are listed in Table 1.

### 3.1 | Types and categories of reactions

Transfusion reactions are often presented as immunologic or nonimmunologic. However, this distinction is often not clear during the initial assessment of clinical patients. We have instead opted to present

**TABLE 1** Definitions used to discuss reactions associated with transfusion

| Term | Definition |
|---|---|
| Adverse Event | Any undesirable or unintended occurrence associated with transfusion. It includes all adverse reactions, incidents, near misses, errors, deviations from standard operating procedures and accidents |
| Adverse Reaction | Any unintended response in a patient associated with the transfusion of blood or blood components |
| Immunologic transfusion reaction | An adverse reaction to transfusion of blood or blood component due to response from the patient's immune system |
| Non-immunologic transfusion reaction | An adverse reaction to transfusion of blood or blood component caused by physical or chemical changes to the blood cells or product, contamination, or secondary to the volume infused |
| Acute transfusion reaction | Adverse reactions to blood, blood components, or plasma derivatives that occur within 24 hours of administration |
| Delayed transfusion reaction | Adverse reactions to blood, blood components, or plasma derivatives that occur beyond 24 hours of administration |
| Imputability | The probability that an identified probable cause was the actual cause of an adverse event after the investigation of the adverse transfusion event is completed |

reactions in order of published incidence. The true incidence of transfusion reactions is difficult to fully ascertain, in both people and animals, due to problems in bedside recognition and in reporting.[11] In one study in people, < 10% of actual transfusion reactions were reported to a hemovigilance system.[12]

The reactions covered, listed in order, include:

- Febrile Non-Hemolytic Transfusion Reactions (FNHTR) (Section 4)
- Respiratory Reactions (Section 5)
  - Transfusion Associated Dyspnea (TAD) (Section 5.1)
  - Transfusion Associated Cardiac Overload (TACO) (Section 5.2)
  - Transfusion Related Acute Lung Injury (TRALI) (Section 5.3)
- Allergic reactions (Section 6)
- Hemolytic Reactions (Section 7)
  - Acute Hemolytic Transfusion Reaction (AHTR) (Section 7.1)
  - Delayed Hemolytic Transfusion Reaction (DHTR) (Section 7.2)
- Delayed Serologic Transfusion Reaction (DSTR) (Section 8)
- Transfusion Transmitted Infection (TTI) (Section 9)
- Hypocalcemia/Citrate toxicity (Section 10)
- Transfusion Related Hyperammonemia (Section 11)
- Hypotensive Transfusion Reactions (HyTR) (Section 12)
- Post-transfusion purpura (PTP) (Section 13)
- Transfusion associated graft versus host disease (TA-GVHD) (Section 14)

## 4 | FEBRILE NON-HEMOLYTIC TRANSFUSION REACTIONS (FNHTR)

Fever is one of the most common adverse events associated with transfusion in veterinary studies. [1–3,13–18] Fever can be seen with many types of transfusion reactions including infection, hemolytic reactions, and transfusion-related acute lung injury (TRALI). It may also be present due to external warming or underlying patient infection. If these reactions and other possibilities are ruled out, an FNHTR is most likely.

| Febrile Non hemolytic Transfusion Reaction (FNHTR) | | |
|---|---|---|
| **Incidence** | **Dogs** | **Cats** |
| | 1.3%[19] | 3.7%[14] |
| | 3%[13] | 4%[15] |
| | 8.2%[3] | 5%[16] |
| | 12.3%[1] | 8.9%[20] |
| | 24.2%[2] | 10%[18] |
| | | 22.9%[17] |
| **Case Definition** | | **Imputability** |
| A FNHTR is an acute non-immunologic or immunologic reaction characterized by a temperature > 39°C (102.5°F) AND an increase in temperature of > 1°C (1.8°F) from the pre-transfusion body temperature during or within 4 hours of the end of a transfusion where external warming, underlying patient infection, AHTR, TRALI, and TTI have been ruled out. These occur secondary to donor white blood cell or platelet antigen-antibody reactions or due to transfer of proinflammatory mediators in stored blood products. | | **Definite**: Patient has no other condition that could explain the fever and hemolysis is not present<br>**Probable**: There are other potential causes, but transfusion is most likely<br>**Possible**: Other causes are likely, but transfusion cannot be ruled out |

### 4.1 | Background and human literature

The National Healthcare Safety Network (NHSN) on Hemovigilance defines an FNHTR as a fever over at least 38°C (100.4°F) AND increase of at least 1°C (1.8°F) from pre-transfusion values during or within 4 hours of the end of a transfusion OR rigors/chills in same time period AND absence of other causes. [7] The Australian Red Cross definition is similar but the time frame is within 24 hours of the transfusion.[21] While the > 1°C rise in temperature is not evidence-based, it has been universally accepted for human hemovigilance. [4]

In people, donor white blood cell or platelet antigen-antibody reactions are thought to be responsible for at least 70% of FNHTR.[22] Transfer of inflammatory cytokines produced in stored red blood cells by white blood cells is another cause. Patients receiving packed red blood cells (pRBCs) who have an FNHTR have been shown to have increased concentration of IL-6 and IL-8 although in these cases the cytokines were not increased in the blood units.[23]

In people, FNHTR are more common with platelet products and appear to be more common with non-leukoreduced red blood cells. In a recent human study using two hemovigilance databases, the overall per product rate of FNHTR was 0.17% after pre-storage leukoreduced packed red blood cell transfusions and 0.25% after platelet transfusions.[24] These numbers likely underrepresent the true incidence. In a retrospective case review study of 4857 human transfusions, 30 (0.62%) FNHTRs were identified but only 30% of these had been reported to the transfusion service. [11]

While FNHTR are not life threatening, they cause patient discomfort.[24] Because FNHTR is a diagnosis of exclusion, the development of a fever often leads to discontinuation of the transfusion and a series of diagnostic tests. Rule outs include underlying patient infection, acute hemolytic reaction, TRALI, and bacterial contamination of the blood unit. Direct antiglobulin test (DAT), human leukocyte antigen (HLA) testing, CBC and repeat blood typing are recommended. Blood cultures or PCR should also be considered if transfusion-transmitted infection is considered likely. There is currently no easy way to test for white blood cell antibodies.

### 4.2 | Veterinary literature

The definition of FNHTR has been variable in the veterinary literature. Studies have varied in whether they have differentiated FNHTR from other causes of fever, what temperature has been considered increased, how to define baseline, and over what timeframe during and after transfusion to monitor the temperature. Appendix A includes the definition of fever and incidence from relevant studies in dogs and cats.

### 4.3 | Areas for further research

Standardization of the timeframe and consideration of both temperature change and actual temperature value should improve case identification and study comparison in the future. However, diagnosis of FNHTR is complicated when the patient has an underlying reason for a fever, such as an immune, inflammatory, or infectious disease but then develops a new higher temperature. Testing for WBC antibodies is not widely available but would be useful in these situations. [22]

## 5 | ACUTE RESPIRATORY REACTIONS

Respiratory reactions are the most common overall cause of transfusion-associated mortality in people. Most respiratory reactions are either transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI). A new category, transfusion associated dyspnea (TAD), was developed to recognize other respiratory transfusion reactions in hemovigilance databases that could not immediately be categorized as TRALI or TACO.[4] In some studies, over half of TAD cases were later found to meet the criteria for another pulmonary transfusion reaction.[25] While TAD has not been used specifically in veterinary medicine, studies have reported respiratory distress after transfusion in dogs and cats without other descriptions and have been categorized as TAD below.

### 5.1 | Transfusion Associated Dyspnea

| Transfusion Associated Dyspnea (TAD) | | |
|---|---|---|
| **Incidence** | **Dogs**<br>2%[3] 3.9%[1]<br>6.3%[13] | **Cats** 0.4%[16]<br>2.4%[26]<br>7.4%[14] |
| **Case Definition** | **Imputability** | |
| Transfusion associated dyspnea is an acute transfusion reaction characterized by the development of acute respiratory distress during or within 24 hours of the end of a transfusion where TACO, TRALI, allergic reaction, and underlying pulmonary disease have been ruled out. | **Definite:** Patient has no other condition that could explain the clinical signs<br>**Probable:** There are other possible causes, but transfusion is most likely<br>**Possible:** Other causes are more likely, but transfusion cannot be ruled out | |

## 5.2 | TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD

| Transfusion Associated Circulatory Overload (TACO) | | |
|---|---|---|
| **Incidence** | **Dogs** 4.7%[2] | **Cats** 3%[20] |
| **Case Definition** | **Imputability** | |
| Transfusion-associated circulatory overload is an acute, non-immunologic reaction that is secondary to an increase in blood volume mediated by blood transfusion, characterized by acute respiratory distress and hydrostatic pulmonary edema. This reaction occurs during or within 6 hours of transfusion. It is associated with clinical, echocardiographic, radiographic, or laboratory evidence of left atrial hypertension or volume overload. These patients typically have a positive response to diuretic therapy. | **Definite:** Clinical signs of worsening respiratory signs, cough, dyspnea, orthopnea, pulmonary crackles;<br>AND<br>echocardiographic evidence includes left atrial enlargement, left ventricular dilation, or reduced ejection fraction;<br>AND/OR<br>radiographic evidence includes bilateral pulmonary infiltrates, pleural effusion, pulmonary edema, pulmonary venous congestion, or cardiomegaly;<br>AND/OR<br>laboratory evidence includes significantly elevated BNP, NT-proBNP or a BNP or NT-proBNP pre/post transfusion ratio of over 1.5x;<br>AND<br>no other explanation for circulatory overload.<br>**Probable:** Transfusion is likely contributing to circulatory overload, and either the patient has received other additional fluids, or, the patient has a history of cardiac insufficiency that could explain the circulatory overload, but transfusion is just as likely to have caused it.<br>**Possible:** The patient has a history of pre-existing cardiac insufficiency that most likely explains the circulatory overload. | |

### 5.2.1 | Background and human literature

The NHSN on Hemovigilance defines TACO as a new onset or exacerbation of 3 or more of the following within 6 hours of cessation of transfusion: acute respiratory distress (dyspnea, orthopnea, cough), increased BNP, increased central venous pressure, evidence of left heart failure, evidence of positive fluid balance, or radiographic evidence of pulmonary edema.[7]

While risk factors for TACO are not entirely understood, many have been suggested in people including administration of large volumes of blood, especially if rapid; blood transfusions in patients with chronic anemia; concurrent heart, respiratory, or renal disease, or systemic hypertension; patients treated with chronic loop diuretics; and patients that are already in a positive fluid balance.[27–30] In patients with normal kidney and cardiac function, massive transfusion is typically required to see signs of volume overload. Blood transfusion causing moderately increased blood volume in patients with compensated cardiac dysfunction or chronic kidney failure can result in pulmonary edema and respiratory distress. In patients with heart failure, pulmonary edema can occur without increases in total blood volume.[29] Patients with TACO typically have a positive response to diuretic therapy.[28,30,31]

The incidence of TACO ranges from <1% to 8% in human studies.[28] A 2018 study reported a transfusion-related mortality rate of 5% and named TACO the leading cause of death.[30]

Differential diagnoses for TACO may include transfusion-associated acute lung injury (TRALI), anaphylactic reactions, bacterial contamination of the blood unit, pulmonary thromboembolism, and hemolytic transfusion reactions with pulmonary complications.[32]

Diagnosing TACO may be difficult, as there are no pathognomonic signs or symptoms.[33] Clinical signs of volume overload may include new or worsening signs of respiratory disease including cough, dyspnea, orthopnea, or pulmonary crackles. Radiographs of the thorax may show bilateral pulmonary infiltrates, pleural effusion, pulmonary edema, pulmonary venous congestion, or cardiomegaly.[11,29,32] Echocardiographic findings indicating volume overload may include left atrial enlargement, left ventricular dilation, and a reduced ejection fraction.[11,28,29] While the use of pulmonary arterial catheters is becoming more infrequent, an increased pulmonary capillary wedge pressure measured by the use of a pulmonary arterial catheter would also provide evidence for circulatory overload.[29,30]

Significantly increased brain natriuretic peptide (BNP) or N Terminal-proBNP (NT-proBNP) concentration, or a BNP or NT-proBNP pre/posttransfusion ratio > 1.5, is the most well studied and convincing laboratory evidence of circulatory overload and hydrostatic pulmonary edema in TACO. [31] BNP concentrations < 200 pg/mL are associated with non-cardiogenic causes of pulmonary edema with specificity over 90% while normal natriuretic peptide concentration following transfusion is not consistent with a diagnosis of TACO. [32] Several novel biomarkers (tumorgenicity-2, cystatin C, growth differentiation factor 15, galectin-3) also show promise in diagnosing TACO.[31]

### 5.2.2 | Veterinary literature

The literature characterizing and defining TACO in dogs and cats is minimal.[3,34,35] A 2017 study evaluating transfusion reactions in dogs did not specifically define TACO and reported changes in respiratory status as an increase in the patient's respiratory rate or effort, or by a decline in pulse oximetry during or within 4 hours of transfusion.[1] In a 2014 study in dogs, volume overload associated with transfusion was defined as increased respiratory rate or effort, or diuretic administration at the clinician's discretion during or immediately after administration of transfusion. That study determined that the greatest risk factor

for volume overload during transfusion was related to the dose of blood product administered and found a 4.7% incidence of volume overload.[2] In a recent study, 3% of transfused cats were thought to have TACO but diagnostic criteria were not listed.[20]

### 5.2.3 | Areas for further research

While TACO is an uncommon but potentially life-threatening type of reaction in veterinary transfusion medicine, new studies are needed to better characterize the syndrome in veterinary patients. Biomarkers, as described in human studies, might be useful in defining this syndrome in veterinary medicine.

## 5.3 | TRANSFUSION-RELATED ACUTE LUNG INJURY

| Transfusion-associated lung injury (TRALI) | | |
|---|---|---|
| **Incidence** | **Dogs** 3.7%[36] | **Cats,** no published reports |
| **Case Definition** | **Imputability** | |
| Transfusion associated lung injury is an acute, immunologic reaction that is secondary to antigen-antibody interactions in the lungs. TRALI is characterized by acute hypoxemia with evidence of non-cardiogenic pulmonary edema on thoracic radiographs, during or within 6 hours of allogenic blood transfusion. Patients diagnosed with TRALI have no prior lung injury, no evidence of left atrial hypertension and no temporal relationship to an alternative risk factor for Acute Respiratory Distress Syndrome (ARDS). | **Definite:** Patient had no evidence of acute lung injury prior to transfusion;<br>AND<br>clinical signs of respiratory distress within 6 hours of the transfusion;<br>AND<br>no signs of left atrial hypertension;<br>AND<br>no alternative risk factors for Acute Lung Injury (ALI).<br>**Probable:** N/A<br>**Possible:** Evidence of other risk factors for acute lung injury (eg, pancreatitis, aspiration pneumonia, severe sepsis, shock) during or within 6 hours of the transfusion. | |

### 5.3.1 | Background and human literature

Transfusion-related acute lung injury is a devastating complication of transfusion in human patients and has emerged as a leading cause of transfusion-related mortality.[37–39] It was originally considered rare but has been increasingly recognized and reported after publications with international agreements on the definition of TRALI.[39,40]

Transfusion-related acute lung injury was first described in a 1985 trial of human surgical patients who developed hypoxemia and respiratory failure 1–6 hours after a blood transfusion.[41,42] None of the patients had hemodynamic overload consistent with TACO and about 72% required mechanical ventilation.[41] A large percentage of the donors had leukocyte antibodies, specifically anti-HLA type I antibodies.[39,41]

Consensus definitions of TRALI have been updated in 2019 and propose TRALI type I and TRALI type II definitions. [37 43 44 45] The 2019 definitions replaced the previous term "possible TRALI" with "TRALI type II" while the "delayed TRALI" (previously defined as patients with symptoms occurring within 24 hours) was no longer recognized as most cases of TRALI occur within 6 hours in human patients.[37]

TRALI Type I is defined as patients with no risk factors for ARDS and meeting the following criteria:

A Acute onset defined by
   I. Hypoxemia (P/F $\leq$ 300 or SPO2 < 90% on room air)
   II. Clear evidence of bilateral pulmonary edema on imaging (chest radiographs, chest CT or ultrasound)
   III. No evidence of left atrial hypertension (LAH) on echocardiography or use of pulmonary artery catheter, or if LAH is present, it is judged not to be the main contributor to the hypoxemia*
B Onset of pulmonary signs within 6 hours of transfusion (imaging can be documented up to 24 hours later)
C No temporal relationship to an alternative risk factor for ARDS

Other causes for ARDS, such as bacterial pneumonia, should be ruled out.

TRALI type II is defined as patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS (P/F 200–300), but whose respiratory status deteriorates and is judged to be due to a transfusion based on:

A. Findings as described in categories A and B of TRALI type I
B. Stable respiratory status in the 12 hours before the transfusion.

While the incidence of TRALI has not been well established in human patients, the reported ranges in literature varies from 0.004%-15.1% per patient transfused, with a higher incidence seen with plasma products.[46–48] TRALI ranges in severity, from mild to severe forms. Clinical features of TRALI in humans include dyspnea, fever, hypotension, tachypnea, tachycardia, frothy endotracheal aspirate and the need for mechanical ventilation to support oxygenation.[43] Signs often occur within 2 hours of transfusion.[43,49] While TRALI is a common cause of transfusion-associated mortality, only a small percentage of human patients with TRALI die (5-10%), compared to 30–40% of patients with other causes of ARDS.[50] Many patients experience significant morbidity, including prolonged need for mechanical ventilation and length of hospital stay.[50]

Plasma and platelet product transfusions carry the highest risk of TRALI in people, possibly because the bioactive mediators of TRALI are carried in plasma.[50,51] The bioactive mediators in TRALI are divided into antibody and non-antibody categories. Antibodies to human leucocyte antigen (HLA) class I and II and various neutrophil antigens (HNA) have been implicated in TRALI. [50] Non-antibody mediators that

accumulate during storage and have been associated with TRALI include bioactive lipids (lysophosphatidylcholines), soluble CD40 ligand, and aged cells. [50]

Multiparous women have been implicated in the pathogenesis of TRALI due to the high concentrations of HLA or HNA antibodies in their donated plasma volume. If the HLA antibody is cognate (recipient has a matched HLA antigen), then TRALI can develop although the presence of HLA antibodies is not an independent risk factor for the development of TRALI.[50] Approximately 50–89% of TRALI cases have been related to the presence of HLA or HNA antibodies in donor blood.[42,52,53] However, several studies have shown that the presence of HLA or HNA antibodies in donor blood is common and do not cause TRALI in a majority of cases, even when cognate antibodies are present.[52,54–56]

Neutrophils, monocytes, lymphocytes, platelets, neutrophil extracellular traps (NETS), the endothelium and other immune mechanisms might also play a role in the development of TRALI. Biological response modifiers may trigger activation and sequestration of recipient neutrophil granulocytes. Thus, in the "two-hit" model proposed for TRALI, the patient has primed neutrophils and endothelium as the "first hit".[52] Being a smoker, the presence of shock, having liver surgery, or having a positive fluid balance before transfusion and higher plasma IL-8 concentrations before transfusion have been identified as possible "first hit" risk factors.[50,57] Blood product transfusion serves as the "second hit" by fully activating the endothelium/neutrophils and leading to pulmonary neutrophil infiltration and edema.[52] A second model, the threshold model, proposes that factors in donor blood and recipient need to reach a threshold together.[52] In the threshold model, a critically ill patient is more likely to develop TRALI in the presence of low donor factor potency, compared to a non-critically ill patient.[52]

### 5.3.2 | Veterinary literature

There is minimal information on the incidence of TRALI in veterinary patients. A prospective study investigating the incidence of TRALI in dogs reported an occurrence of 3.7% (2/54) in enrolled subjects.[38] Both dogs had radiographic changes following fresh frozen plasma (FFP) transfusion that could be consistent with TRALI, although neither dog had acute respiratory distress, and echocardiograms were not performed. One of the 2 dogs died although the incidence of TRALI in this study was too low to determine a true mortality rate. Another case report describes a dog with bite wounds that developed acute respiratory distress after a whole blood transfusion. Changes appreciated on thoracic radiographs were suggestive of TRALI, but there was no mention of an echocardiogram and the clinical signs of respiratory distress began 8 hours after the transfusion had ended. The dog ultimately underwent mechanical ventilation but died after cardiopulmonary arrest.[58]

It is unknown how often multiparous female dogs are used as blood donors. A low incidence of multiparous female dog donors might theoretically contribute to the low incidence of reported TRALI in veterinary patients. However, one study demonstrated the lack of pregnancy-induced alloantibodies in dogs and suggested that multiparous female dogs should not be excluded from the donor pool.[59] There are no studies evaluating leukocyte or neutrophil antibodies in female dogs or cats.

### 5.3.3 | Areas for further research

The incidence of TRALI in veterinary medicine is currently thought to be rare. This may be because most female donors (at least in North America) are neutered and nulliparous. The presence of leukocyte and neutrophil antibodies in dogs and cats with prior litters should be investigated. An international effort to screen for TRALI, through large multicenter prospective studies, would provide more information on this condition in veterinary patients.

## 6 | ALLERGIC TRANSFUSION REACTIONS

| Allergic Reaction | | |
|---|---|---|
| **Incidence (includes urticaria, vomiting, and anaphylaxis)** | **Dogs**<br>0%[36]<br>0.3%[60]<br>0.47%[2]<br>3.3%[1]<br>4.2%[3]<br>6.6%[61] | **Cats**<br>0%[16,17,20,62,63]<br>0.9%[18]<br>1.1%[64]<br>3.2%[15]<br>3.7%[14] |
| **Case Definition** | **Imputability** | |
| An allergic transfusion reaction is an acute immunologic reaction that is secondary to a type I hypersensitivity response to an antigen within a blood product.<br>This reaction occurs during or within 4 hours of transfusion. It is characterized by clinical signs varying from transient and self-limiting to life-threatening anaphylaxis. Canine type I hypersensitivity reactions typically involve erythema, urticaria, pruritus and facial/extremity/genital angioedema. Gastrointestinal signs (vomiting, diarrhea), and hemoabdomen with progression to collapse can also be seen. Feline type I hypersensitivity reactions are typically respiratory (due to upper respiratory tract edema, bronchoconstriction, and excessive mucus production) although gastrointestinal signs and severe pruritus can also occur. | **Definite:** Occurs less than 1 hour after the start of the transfusion<br>AND<br>Responds rapidly to cessation of transfusion and supportive treatment<br>AND<br>The patient has no other conditions that could explain clinical signs.<br>**Probable:** Onset is between 1 hour after start and cessation of transfusion<br>OR<br>The patient does not respond rapidly to cessation of transfusion and supportive treatment<br>OR<br>There are other potential causes present that could explain clinical signs, but transfusion is thought to be the most likely cause.<br>**Possible:** There are other conditions that could readily explain why clinical signs are present. | |

### 6.1 | Background and human literature

Allergic transfusion reactions are caused by a type I hypersensitivity (IgE and mast cells) response to a blood product. Severity varies from transient self-limiting reactions to life-threatening anaphylaxis.[65,66] Reactions occur during the transfusion or within 4 hours of its cessation.[7] Diagnosis is usually based on clinical findings of cutaneous (angioedema, urticarial, pruritus), respiratory (stridor, dyspnea, wheezing, hypoxemia) or cardiovascular (hypotension and syncope) abnormalities.[7]

Generally, allergic reactions occur on the second exposure to an antigen, when primary exposure to the antigen resulted in the production of antigen-specific IgE or IgG.[65,67] The systemic response is rapid, with the release of inflammatory mediators often occurring within seconds to minutes. There appears to be a correlation between the time of onset of clinical signs and reaction severity.[65] Transfusion-associated allergic reactions are often triggered by plasma protein antigens, with IgA and haptoglobin described a causes in recipients lacking these proteins, although a specific allergen is generally not detected.[28,68–70]

Allergic reactions are one of the most common adverse reactions in human transfusion medicine, although their incidence rates vary markedly between studies, with mild reactions reported in between 1 in 4000 and 7 in 1000 human transfusions.[11,69,71] Anaphylaxis is much rarer, occurring at rates of 1 in every 20,000 to 30,000 transfusions.[69,71] The incidence varies between blood products, with reactions being more common in platelet and plasma transfusions than in packed red blood cell transfusions.[66,67,72] Factors associated with increased risk of allergic transfusion reactions include recipient hay fever,[73] recipient IgA or haptoglobin deficiency, [72] younger recipient age, [73] administration of non-leukoreduced blood products, [74] and the administration of apheresis plasma and platelets.[66,75]

Allergic reactions occurring during or shortly after a transfusion could also be due to an allergen other than the blood product such as a contact allergen or concurrently administered medication. Acute hemolytic transfusion reactions, TRALI, and bacterial blood product contamination could present in a similar manner to an anaphylactic reaction with hypotension and tachycardia and should be considered as differential diagnoses.

Increased tryptase concentrations are expected in patients that have had anaphylaxis or severe allergic reactions, but the half life is short at 2 hours.[72] A basophil activation test or urine eicosanoid metabolite measurement can also be used for diagnosis.[72,73] However, typical clinical signs are generally used to make a presumptive diagnosis.

### 6.2 | Veterinary literature

Allergic (type I hypersensitivity) reactions in dogs cause predominantly dermal (erythema, urticaria (usually generalized), pruritis and angioedema (often localized to head, extremities, and genitalia)) and gastrointestinal signs. More severe clinical signs consistent with anaphylaxis including hemoabdomen, coagulopathy, collapse, hypotension, and upper respiratory tract signs have been described in some cases.[76,77] In cats, respiratory and gastrointestinal signs predominate, although severe pruritus can occur. [76]

Allergic transfusion reactions have been reported in the veterinary literature and appear to be more common in dogs than cats and when plasma products are transfused, compared to pRBCs. Cutaneous signs of facial swelling, angioedema and pruritis are reported in both dogs and cats and there are reports of anaphylaxis in cats.[3,15,18,60] Vomiting is a recognized sign of an allergic reaction in both dogs and cats and vomiting is reported during the transfusion period in many studies. However, given the many possible reasons for vomiting, it can be difficult to determine if allergic transfusion reactions are the cause.[1,3,15] Similarly, dyspnea is reported in several studies with no definitive diagnosis determined, and anaphylaxis is one of several possible causes. [3,64]

### 6.3 | Areas for Further Research

The true incidence of allergic transfusion reactions in dogs and cats is unknown and large prospective studies are needed. Studies looking at possible predisposing factors such as age and prior allergies are also needed. The use of tryptase concentrations, the basophil activation test or urine eicosanoid metabolites for the diagnosis of allergic transfusion reactions could be investigated.

## 7 | HEMOLYTIC TRANSFUSION REACTIONS

Hemolytic transfusion reactions include AHTRs and DHTRs and can be immunologic or non-immunologic in nature. Immunologic HTRs are secondary to incompatibility of the transfused product and the recipient. The magnitude of an HTR depends on multiple immunological factors to include the class and subclass (in case of IgG) of the antibody, the ability of the antibody to activate complement, the blood group specificity of the antibody, the thermal range of the antibody, the number, density and spatial arrangement of the RBC antigen sites, the antibody concentration in the plasma and the amount of antigen (RBCs) transfused. [78] Non-immunologic HTRs occur due to thermal, osmotic, mechanical, or chemical factors that damage transfused blood cells, causing acute or delayed hemolysis. Ex vivo cellular damage may occur prior to transfusion as a result of bacterial contamination, prolonged storage, excessive warming, or erroneous freezing of blood unit. [79,80] Improper administration techniques, such as the addition of drugs or hypotonic intravenous fluids or trauma from extracorporeal devices may cause damage to RBCs. This ex vivo cellular damage may lead to acute or delayed hemolysis of the transfused RBCs in the patient.

## 7.1 | ACUTE HEMOLYTIC TRANSFUSION REACTIONS

| Acute Hemolytic Transfusion Reaction (AHTR) | | |
|---|---|---|
| **Incidence** | **Dogs** | **Cats** |
| | 0%[81] | 0.4%[16] |
| | 1%[3] | 2%[17] |
| | 2.4%[2] | 6.9%[20] |
| | 6.3%[1] | |

| Case Definition | Imputability |
|---|---|
| An acute hemolytic transfusion reaction is an acute, non-infectious, immunologic, or non-immunologic reaction that occurs secondary to accelerated destruction of transfused or recipient RBCs and is characterized by acute hemolysis.<br>Acute hemolytic transfusion reactions occur during or within 24 hours of blood product administration.<br>Causes of AHTRs can be divided into blood type incompatibilities and other causes of damage to transfused blood cells.<br>Blood type incompatibilities are immunologic acute hemolytic reactions that are type II hypersensitivity reactions due to major or minor incompatibilities between donor and recipient RBCs. A classic example would be in the case of a type A unit of blood given to a type B cat.<br>Non-immunologic causes of AHTRs may include thermal, osmotic, mechanical, or chemical factors that damage transfused blood cells. | Until direct or indirect antiglobulin or other confirmatory testing is available, the following diagnostic criteria must be met.Definite:New onset of evidence of hemolysis within 24 hours:<br>- Hyperbilirubinemia (1 or more of the following should be present- icterus, total serum or plasma bilirubin concentration above reference interval, bilirubinuria in cats, or ≥2+ bilirubin on a urine reagent strip in dogs).<br>- Hemoglobinemia (plasma discoloration, instrument-based indicators of hemolysis)<br>- Hemoglobinuria<br>- Spherocytosis in dogs<br>- Erythrocyte ghosts on a smear made immediately after blood collection.<br>AND<br>- Inadequate increase in PCV<br>With or without:<br>- New onset fever > 39.2°C (102.5°F)<br>- Tachycardia<br>- Hypotension (systolic blood pressure <90-100 mm Hg)<br>In the absence of serologic testing to identify a causative antibody, investigation for known (blood typing) and unknown (cross-matching) incompatibility as well as potential thermal, osmotic, mechanical, or chemical factors should be performed. |
| | **Probable:** There are other potential causes present that could explain acute hemolysis, but transfusion is the most likely cause<br>**Possible:** Other causes of acute hemolysis are more likely, but transfusion cannot be ruled out. |

### 7.1.1 | Background and human literature

The NHSN on Hemovigilance criteria for the diagnosis of AHTR are new onset of back/flank pain, chills/rigors, disseminated intravascular coagulation (DIC), epistaxis, fever, hematuria, hypotension, oliguria/anuria, pain/oozing at IV site or renal failure during or within 24 hours of transfusion. Two or more of the following should also be present- decreased fibrinogen, increased haptoglobin, increased bilirubin, increased lactate dehydrogenase (LDH), hemoglobinemia, hemoglobinuria, plasma discoloration consistent with hemolysis or spherocytes on blood film along with either a positive direct antibody test (DAT) or direct Coombs test for anti-IgG or anti-C3 plus positive elution test with alloantibody present on the transfused RBCs for immune-mediated reactions or negative serologic testing and confirmed the physical cause for non-immunologic reactions.[7]

In people, these reactions were historically responsible for the largest proportion of transfusion-associated deaths, but this has changed with improved compatibility testing. They are usually immunologic and usually caused by inadvertent administration of incompatible RBC transfusions secondary to blood typing compatibility errors. The transfusion of incompatible plasma products is a less common cause of AHTR. [82,83] Of the 355 transfusion-associated fatalities reported to the FDA from 1976 - 1985, 158 (48%) were classified as acute immunological HTRs and 6 (2%) were classified as acute non-immunological HTRs. Around 100 million units of RBCs were transfused in the USA during this time frame so the reported incidence of fatal acute immunologic and non-immunologic HTRs was low at approximately 1:1,100,000 units.[84] A more recent analysis of reactions reported to the NHSN on Hemovigilance found that in 2015, acute immunologic transfusion reactions occurred at a rate of 1:200,000 units transfused and acute nonimmunologic transfusion reactions occurred at a rate of 1:105,000 units. [12]

### 7.1.2 | Veterinary literature

The most common cause of AHTR in dogs and cats is mismatched transfusion, mainly due to erroneous recipient, donor or unit identification and labeling. Non-immunologic causes are infrequently reported in the veterinary literature.

*Canine Immunologic AHTRs*

Acute hemolytic transfusion reactions are uncommonly reported in dogs, likely due to both the lack of naturally occurring DEA 1 antibodies and due to improved compatibility testing. While the incidence of AHTR is thought to be low, variability in definitions makes it difficult to compare studies. Appendix B includes previously reported definitions of AHTR in the canine and feline literature.

An early case report described an AHTR resulting from DEA 1.1 incompatibility in a dog previously sensitized to DEA 1.1 from a transfusion given 3 years earlier. The dog developed a fever, pigmenturia, and lethargy within 2 hours of initiating the second transfusion. The donor blood was type DEA 1.1 positive, whereas the recipient's blood was type DEA 1.1, DEA 1.2, and DEA 7 negative.[85] A second case report describes alloimmunization of a DEA 4 negative dog resulting in increasingly severe acute hemolytic transfusion reactions following subsequent DEA 4 positive transfusions. The clinical picture and typing suggested development of anti-DEA 4 alloantibodies.[86] A third case report of an AHTR after a second DEA 1 negative transfusion in a dog suggested sensitization to a common unidentified antigen after the first blood transfusion.[87] In one retrospective case series, AHTR occurred in 2.4% (5/211) blood transfusions with one fatality.[2] In another retrospective study, AHTR were noted in only 0.04% (4/935) transfusions with one fatality.[3]

*Feline Immunologic AHTRs*

Naturally occurring alloantibodies are well described in cats and can lead to potentially fatal AHTR. Type B cats possess naturally occurring high-titered strongly hemolyzing and hemo-agglutinating anti-A antibodies, predominately of the IgM class.[88] The transfusion of Type A RBCs to Type B cats can result in rapid RBC destruction with an average half-life of 1.3 ± 2.3 hours depending on the alloantibody titer and destruction of all transfused RBCs within 24 hours.[88] A case report describes an AHTR in a type B Abyssinian cat shortly after transfusion of type A whole blood, characterized by only transient improvement in hematocrit, progressive lethargy, transient fever, icterus, and severe hemoglobinuria. Subsequent transfusions with type B blood were uneventful.[89] In another case report, a type B cat that was initially mistyped as AB developed recurrent anemia, hyperlactatemia, hyperbilirubinemia, hemoglobinemia, hemoglobinuria and a positive slide agglutination test with 24 hours of receiving a unit of type A whole blood.[90]

Natural occurring alloantibodies against the *Mik* antigen have been described in cats and an AHTR has been reported in a *Mik*-negative type A cat following inadvertent transfusion of *Mik*-positive type A blood.[91] In another report of an AHTR in a transfusion naïve type A cat following transfusion with type A whole blood, the nature of the offending alloantibody was unclear.[92] In a more recent study, 7 of 101 cats had AHTR and 3 of these had documented crossmatch (XM) incompatibility.[20]

*Non-immunologic AHTRs*

There are minimal descriptions of non-immunologic AHTR in veterinary species. One case series describes 4 dogs that developed hemolysis, hemoglobinuria, or both, during or within 24 hours of RBC transfusion. Two dogs died and 1 was euthanized due to severity and progression of clinical signs. Blood type and compatibilities were confirmed for each case, making immunologic reactions unlikely. Further investigation found no evidence of mechanical, chemical, or osmotic factors during product administration and blood smear and 16s bacterial RNA polymerase chain reaction results from the remaining lysed units failed to find evidence of bacterial contamination. Hemolysis of units secondary to inappropriate storage was suspected as other blood units in the clinic refrigerator had increased free hemoglobin. No further hemolyzed units or acute hemolytic reactions were seen after purchase of a dedicated refrigerator and improvement in temperature monitoring and storage conditions.[79]

### 7.1.3 | Areas for further research

The presence of clinically important naturally occurring alloantibodies is yet to be convincingly demonstrated in dogs. In both cats and dogs, previous immunization with mismatched blood products can lead to life-threatening AHTRs with subsequent transfusions.[86,87,93] The process by which these different alloantibodies are induced or enhanced by previous immunizing transfusions is poorly elucidated and it is unclear how they may impact future transfusion events.[81]

Further study is needed to further characterize naturally occurring and induced alloantibodies against canine DEA 3, DEA 5, DEA 7, and Dal, and feline *Mik* antigens and other as yet unrecognized antigens.

Future prospective studies evaluating the effect of XM on transfusion efficacy are warranted. In addition, the establishment of a more feasible and reliable XM test, appears to be of growing importance to prevent AHTR due to blood type incompatibilities in naïve and previously transfused cats. The clinical importance of the detected alloantibodies outside the AB and *Mik* system still needs to be determined.

Antibody screening is currently unavailable in veterinary medicine. Such testing would help distinguish AHTRs from ongoing hemolysis in the setting of pre-existing intravascular hemolytic disease as well as helping to differentiate immunologic from non-immunologic HTRs.

## 7.2 | DELAYED HEMOLYTIC TRANSFUSION REACTIONS

| **Delayed Hemolytic Transfusion Reaction (DHTR)** | | |
|---|---|---|
| **Incidence** | **Dogs, no published case reports** | **Cats** 64% with xenotransfusion of canine blood[48] |

| Case Definition | Imputability |
|---|---|
| A delayed hemolytic transfusion reaction is a delayed, non-infectious, immunologic or non-immunologic, reaction that occurs secondary to lysis or accelerated clearance of transfused RBCs.<br>Delayed hemolytic transfusion reactions occur 24 hours to 28 days after blood product administration.<br>Immunologic DHTRs are typically caused by a secondary immune response to the donor's RBCs.<br>Non-immunologic HTRs occur due to thermal, osmotic, mechanical, or chemical factors that damage transfused blood cells, causing delayed hemolysis. | **Definite**: Unexplained* decrease in PCV or hemoglobin >24 hours to 28 days after transfusion<br>AND<br>Delayed onset (24 hours - 28 days) of at least two indicators of red blood cell destruction (see AHTR definition)<br>AND<br>Evidence of RBC alloantibodies (for immunologic types) which developed between 24 hours and 28 days after transfusion<br>**Probable**: Unexplained* decrease in PCV or hemoglobin >24 hours to 28 days after transfusion<br>AND<br>delayed onset (24 hours - 28 days) of at least two indicators of red blood cell destruction (see AHTR definition)<br>**Possible:** Other causes of a decrease in PCV or hemoglobin 24 hours to 28 days after transfusion are likely, but transfusion cannot be ruled out. |

*cannot be explained by RBC loss or destruction secondary to the primary disease process

### 7.2.1 | Background and human literature

Immunologic DHTRs are classically caused by an anamnestic (secondary) immune response to the donor's RBCs, in which the recipient possesses low-titer antibodies from previous RBC antigen sensitization or has naturally occurring alloantibodies. Low-titer antibodies may be undetectable with routine XM and antibody screening. After subsequent exposure to the same RBC antigen with transfusion, the secondary immune response results in new antibody production, a significant rise in titer, and delayed hemolysis. A primary immune response can also result in delayed hemolysis of RBC. In this scenario, recipient antibodies are gradually formed over several days to weeks after the first exposure to a novel RBC antigen. Hemolysis occurs once sufficient antibody titers have been reached.

National Healthcare Safety Network (NHSN) on Hemovigilance defines a DHTR as a positive DAT for antibodies that develops between 24 hours and 28 days after cessation of transfusion. A positive elution test with alloantibody present on the transfused RBCs or a newly identified RBC alloantibody in recipient serum, and either an inadequate rise of posttransfusion hemoglobin level or a rapid fall in hemoglobin back to pretransfusion levels or the otherwise unexplained appearance of spherocytes is also needed for confirmation. A DHTR is probable if a newly-identified RBC alloantibody demonstrated between 24 hours and 28 days after cessation of transfusion but there is incomplete laboratory evidence to meet definitive case definition criteria.[7] The Serious Hazards of Transfusion hemovigilance scheme in the United Kingdom defines DHTRs as fever and other symptoms/signs of hemolysis more than 24 hours after transfusion, confirmed by a fall in hemoglobin or failure of increment, rise in bilirubin, or an incompatible XM not detectable before transfusion.[66]

Patients may have no apparent clinical signs with DHTRs or in more severe reactions, the clinical signs may be like an AHTR with fever, nausea or vomiting, tachycardia, hypotension, tachypnea/dyspnea, and pain. Red blood cell destruction may occur gradually with DHTRs as antibody synthesis increases over days. As the PCV falls, the patient may become more clinical for the anemia and display vague signs such as lethargy, weakness, or inappetence. Fever is associated with HTRs. The production of inflammatory cytokines is a consequence of the humoral and cell-mediated immunological reactions that mediate HTRs. Most hemolysis observed with DHTRs is extravascular as determined by involvement of the immunoglobulin IgG and the antibody specificities of the blood types.

The incidence of DHTRs in human and veterinary medicine is likely to be underestimated as many patients are asymptomatic and the drop in PCV may go undiagnosed or attributed to other etiologies. In human transfusion medicine, DHTRs are commonly associated with a secondary immune response and the majority of the DHTR publications revolve around sickle cell disease. There are case reports of DHTRs associated with naturally occurring alloantibodies in humans.[94–97]

### 7.2.2 | Veterinary literature

DHTR are reported in the veterinary literature following xenotransfusion of canine blood to the feline species. Early studies suggested that cats do not have detectable naturally occurring antibodies against canine RBCs as assessed by compatible pre-transfusion testing (slide autoagglutination and in vitro hemolysis tests).[98–100] These studies documented the production of antibodies against canine RBCs within 4–7 days of transfusion as evaluated by daily slide agglutination and in vitro hemolysis testing.[98–100] The lifespan of transfused radiochromium-labeled canine RBCs into 7 cats was determined to be an average of 3.6 days (maximum 5.4 days).[99] The average lifespan of compatible feline to feline transfused RBCs is 30 days.[101] Repeated xenotransfusion of canine blood to many of these cats > 6 days after initial transfusion resulted in severe anaphylactic reactions and death. Since these initial studies, case reports of successful xenotransfusion with no acute or delayed adverse reactions have been published.[102–105] Recent canine-to-feline xenotransfusion studies have revealed incompatible pre-transfusion major and minor XM testing suggesting the presence of naturally occurring alloantibodies in both species.[92,106] In a 2019 prospective canine-to-feline xenotransfusion study, DHTRs occurred in 25 of 39 (64%) cats with no significant difference between cats with compatible or incompatible pre-transfusion XM.[106] DHTRs occurred at a median of 2 days (range 1–6 days) after xenotransfusion in cats with incompatible major XM and

1 day (range 1–1.5 days) in cats that received major XM compatible blood.[106]

Delayed hemolytic transfusion reactions are described following feline AB-mismatched allogeneic transfusions. While Type B cats possess high-titer, strongly antigenic IgM antibodies, Type A cats have low alloantibody titers consisting of IgG and IgM classes. The transfusion of Type B RBCs into Type A cats can result in DHTRs with a mean half-life of 2.1 ± 0.2 days.[88]

Early canine blood group studies suggest that the presence of induced alloantibodies in dogs, such as those against DEA 3, 5 and 7, may be associated with accelerated clearance over three to five days in DEA 3, 5, or 7 negative dogs transfused with DEA 3, 5 or 7-positive RBCs, respectively.[107] The experimental data investigating DHTRs relevant to these DEA blood types is limited and complicated by changes in blood group nomenclature over the years. The presence of anti-DEA 7 antibodies in DEA 7-negative dogs ranges from 0% to 38%.[81,108,109] Further research documented that in 23% of DEA 7-negative dogs, low titers (<1:2 in 73% of samples) of warm, weakly agglutinating, mostly naturally occurring mostly IgM (69%) anti-DEA 7 antibodies were found. [110] The anti-DEA 7 antibodies evaluated in vitro showed no hemolytic activity, although titers were low and samples were collected in EDTA, which can inhibit complement-based lytic activity. In vivo evaluation of the transfusion of DEA 7-positive RBCs to the patients with naturally occurring anti-DEA 7 antibodies was not performed. After chromium-labeled DEA 7-positive RBCs were administered to dogs with anti-DEA 7 antibody, the labeled RBCs were absent after 4 to 5 days.[111] There are no reports of DEA 3, 5 or 7 related acute or delayed HTRs in clinical patients.

### 7.2.3 | Areas for further research

The incidence of DHTRs in veterinary medicine is unknown. Clinical recognition of delayed hemolysis days after a transfusion is challenging and may be complicated by lack of follow up, primary disease processes such as immune-mediated hemolytic anemia, or masking by the patient's regenerative response. Prolonged prospective clinical studies following pre- and post-transfusion clinicopathologic parameters (eg, PCV, serum total bilirubin) and pre- and post-transfusion XM compatibility to donor RBCs or DAT may expand our understanding of delayed immunologic transfusion reactions.

## 8 | DELAYED SEROLOGIC TRANSFUSION REACTIONS (DSTR)

| Delayed Serologic Transfusion Reaction (DSTR) | |
|---|---|
| **Incidence** | **No published reports in dogs or cats** |

| Case Definition | Imputability |
|---|---|
| A delayed serologic transfusion reaction is a delayed, immunologic reaction that is secondary to the development of new clinically significant antibodies against the transfused product without evidence of hemolysis. DSTRs occur 24 hours to 28 days after a transfusion. | **Definite:** Demonstration of new alloantibody formation between 24 hours and 28 days after a transfusion by either unexplained decrease in HCT/Hb > 24 hours to 28 days post transfusion AND positive DAT where DAT was negative prior to transfusion<br>OR<br>Serologic demonstration of a known RBC alloantibody after analysis of the transfusion history and known type incompatible blood transfusion (not currently available in veterinary medicine)<br>**Probable:** In the absence of a definite DSTR, a positive indirect coombs test with sensitized recipient sera against a sample of the donor's RBCs that caused the DSTR to develop. This may be time sensitive depending on the alloantibody involved and its concentration in the recipient circulation.<br>**Possible:** New alloantibody formation between 24hrs -28 days post transfusion without hemolysis, but other exposures or underlying conditions are present that most likely explain the conversion. |

### 8.1 | Background and human literature

Delayed serologic transfusion reactions are caused by alloimmunization to a RBC antigen that the recipient lacks. Reactions can be seen after a first transfusion due to naturally occurring alloantibody or as antibody first develops, or as an anamnestic response if a recipient is transfused again with the same antigen. Delayed serologic transfusion reactions were first recognized in 1995 and are sometimes termed "silent DHTRs." Delayed serologic transfusion reactions are defined as DHTRs as soon as hemolysis is detectable.

In people, DSTRs are well described with evidence of newly formed antibody to transfused antigen and no associated clinical signs. Identification involves serologic testing of both the donor and recipient blood and extensive serologic testing to detect new antibody is available.[112,] Definitive DSTRs can be diagnosed in patients that have a negative DAT pre-transfusion or a negative major cross match and indirect antiglobulin test (IAT) and a positive DAT and IAT 24 hours to 28 days following transfusion.[113] It can be more difficult to definitively diagnose a DSTR

in patients with a positive DAT as part of their underlying disease process, such as immune-mediated hemolytic anemia (IMHA).

Development of alloantibodies is mediated by many factors. Recipient considerations include phenotypic disparity between blood types of donor and recipient, recipient HLA presenting foreign antigen, genetic predisposition to "respond," health status at the time of antigen exposure, prior exposure including non-red cell exposure (platelets and leucocytes), and exposure during pregnancy or transfusion. Donor factors include genetic factors that may impact RBC storage characteristics, length of RBC storage, presence of contaminating white blood cells and platelets, and antigen dose.[114]

## 8.2 | Veterinary literature

There are occasional reports of DSTRs within the veterinary literature.[115] Canine and feline blood typing and cross matching literature describes alloimmunization that may represent DSTRs but are not defined specifically as DSTRs.[81,116,117]

Early studies demonstrated that positive DAT (and IAT against donor blood sample) developed 4–7 days following transfusion of DEA 1-positive red cells to a DEA 1-negative donor and the transfused red cells were sometimes removed from circulation prematurely without overt hemolysis.[107,118] The recipients developed anti-DEA 1 antibody and if exposed to this antigen again, an AHTR developed. The initial reaction could be defined as a DSTR or mild DHTR that on anamnestic response becomes a type II hypersensitivity hemolytic reaction or true AHTR.

Other DEA blood types have been defined as having naturally occurring antibody (DEA 3, 5 and 7) in antigen negative phenotypes and display varying degrees of reaction on exposure to DEA 3, 5 and 7 positive donated blood, respectively. As naturally occurring alloantibody – these reactions will show up post first transfusion (there is no prior transfusion or pregnancy required) as a delayed reaction. The most well defined of these is DEA 7[108,110,119]

DEA 6 and 8 are poorly defined and antisera is no longer available. It is suspected that they may also produce an alloantibody response in negative recipients receiving positive blood.[107,118,120]

DEA 4 has been further defined and is identified to produce an alloantibody that causes an acute reaction on re exposure. As a very commonly found antigen, recognition of this reaction is uncommon and poorly defined but is illustrated in one case report.[86] The case report can be interpreted to imply that antibody development to DEA 4 may take a few weeks consistent with a DSTR followed by an AHTR with subsequent exposure.

*Dal*, a common antigen in most dogs has been defined as lacking in a higher percentage of some breeds (Dalmatian, Doberman, Lhasa Apso and Shih Tzu).[121–123] Delayed alloimmunization occurs 4 days to a few weeks after transfusion of *Dal*-positive blood to a *Dal*-negative recipient.[121] In vivo characterization of the reaction that this causes on repeat exposure is yet to be demonstrated.

## 8.3 | Areas for further research

Recognition that DSTRs can occur in transfused animals may increase the number of cases reported. More comprehensive understanding of canine blood types is required to permit recognition and categorization DSTRs in canine transfusion medicine and will enable collection of relevant samples to better define alloantibodies. An international effort to reestablish a universal canine erythrocyte antigen naming system and collaborate to generate a library of sensitized sera is needed.[124]

# 9 | TRANSFUSION-TRANSMITTED INFECTION (TTI)

| **Transfusion-transmitted infection (TTI)** | | |
|---|---|---|
| **Incidence** | **Dogs – case reports only** | **Cats – 1%**[20] |
| **Case Definition** | **Imputability** | |
| A transfusion transmitted infection is an acute or delayed, non-immunologic reaction secondary to the transfusion of pathogen contaminated blood or blood components.<br>A TTI can occur hours to years after the transfusion due to the presence of the infectious agent in the blood/blood component unit collected from an infected donor, or from pathogen contamination of blood/blood component units during processing, storage or transfusion.<br>Clinical signs are highly dependent on pathogen transmitted and its pathogenicity for dogs and cats and the clinical status of the recipient. | **Definite**: ONE or more of the following:<br>I) laboratory evidence of a pathogen in a transfused blood product<br>AND/OR<br>evidence of the pathogen in the donor at the time of donation<br>AND/OR<br>evidence of the pathogen in an additional component from the same donation<br>AND/OR<br>evidence of the pathogen in an additional recipient of a component from the same donation;<br>II) AND<br>no other potential recipient exposure to the pathogen;<br>III) AND EITHER evidence that the recipient was not infected with the pathogen prior to transfusion.<br>IV) OR the identified pathogen strains are related by molecular or extended phenotypic comparison.<br>**Probable:** ONE or more of the following:<br>I) laboratory evidence of a pathogen in a transfused blood product<br>AND/OR<br>evidence of the pathogen in the donor at the time of donation<br>AND/OR<br>evidence of the pathogen in an additional component from the same donation | |

| Case Definition | Imputability |
|---|---|
| | AND/OR<br>evidence of the pathogen in an additional recipient of a component from the same donation;<br>**II) AND EITHER** evidence that the recipient was not infected with this pathogen prior to transfusion;<br>**III)** OR no other potential exposures to the pathogen could be identified in the recipient.<br>**Possible**: Temporally associated unexplained clinical illness consistent with infection, but no pathogen is detected in the recipient. Other, more specific adverse reactions are ruled out. |

## 9.1 | Background and human literature

A TTI is defined as laboratory evidence of a pathogen in the transfusion recipient with evidence that the recipient was not infected with the pathogen prior to transfusion. [7] Transfusion transmitted infection can arise from bacterial contamination of blood or blood components or from infectious pathogens carried by the blood donor. Bacterial contamination can arise from bacteria from the donor's skin during the collection procedure, unrecognized bacteremia in the donor, contamination from the environment or during the preparation of components, or contamination of ports during the thawing of frozen products in a water bath. [125] Bacterial infection is more common with platelets units (as these are stored at room temperature for preservation of function), previously frozen components thawed by immersion in a water bath such as frozen plasma units, and red cell components units as PRBC or WB units stored for several weeks. [125]

The concentration of bacteria in blood components just after collection is generally too low to detect or cause symptoms in the recipient. However, bacteria can multiply during component storage, particularly in room temperature platelet concentrates. [126]

Both gram-positive and gram-negative organisms have been implicated in transfusion transmitted bacterial infection in people, with serious morbidity and mortality occurring most frequently with gram-negative bacteria. [127] Organisms capable of multiplying at low temperatures and those using iron as a nutrient are most often associated with red cell contamination. [125] Bacterial sepsis account for at least 10% of transfusion-associated fatalities in people. [127]

Septic transfusion reactions usually present during or within 4 hours of transfusion. [128 129] Bacterial contamination is a differential diagnosis when transfusion recipients become febrile or hypotensive following transfusions. [130] Other clinical features suggesting bacterial contamination or endotoxin reaction include rigors, severe chills, tachycardia, nausea and vomiting, dyspnea, or circulatory collapse during or soon after transfusion. In severe cases, the patient may develop shock with accompanying kidney failure and DIC. [125 128]

## 9.2 | Veterinary literature

Reports of bacterial contamination of blood units in veterinary medicine are less frequently described than in human medicine, likely because fresh platelet transfusions are less common in veterinary medicine. Percentage of negative bacteriological units was high (94-100%) in studies on feline [131–136] and canine blood and plasma products [137–140].

Contaminants documented in veterinary blood units have included gram-negative (*Escherichia coli* [141] *Pseudomonas* spp., [141 142,143] *Serratia* spp.,[141,143,133,144] *Caulobacter* spp., [141] *Ralstonia* spp. [131]) and gram positive (*Enterococcus* spp., [141] *Propionobacterium* spp., [141] *Corynebacterium* spp., [141,145] *Leucobacter* spp., [141] *Bacillus* spp., [145] *Staphylococcus* spp.[131]) bacteria. In most reported cases of blood bacterial contamination, it could not be determined if the contamination occurred during blood collection or blood bag processing and storage. [143] However, contamination during blood collection may be more common. [133] In one study, a jar of alcohol-soaked cotton balls and a saline solution used during sedation and venipuncture of donors were found to be the sources of contamination. [144] Some authors have hypothesized contamination of the anticoagulant CPDA or contamination during the manipulations for microbiological evaluation. [131]

Infectious pathogens able to be transmitted by blood transfusion in veterinary medicine are reported in Table 2. These pathogens are documented: I) to be transmitted (experimentally or clinically) by blood transfusion or by intravenous blood injection in canine and feline patients; and/or II) to survive in stored blood units.

In the veterinary literature, few data are available on frequency of TTI and most publications are case reports. A study of 101 cats had a single incident of transmitted *Mycoplasma haemominutium*.[20] A study in dogs reported new infections in 11/211 (5.2%) receiving PRBC transfusion but these did not appear to be directly related to the blood units.[2]

The outcome of a contaminated transfusion is highly dependent on the number of organisms transfused, the type of organism and its pathogenicity for dogs and cats, the rate of transfusion, and the clinical status of the recipient. Immunosuppression of the blood recipient, including splenectomy, is a risk factor for development of a TTI. However, transfusion with a large load of endotoxin-producing gram-negative bacteria can cause rapid death in healthy individuals. In veterinary patients, the clinical outcome of transfusion of bacterial contaminated units has ranged from no reaction;[131,141,144] vomiting, collapse, diarrhea, icterus, panting, pyrexia/fever, abscess;[144] hypotensive shock syndrome;[149] and death. [144] In a case series of 15 *Serratia marcescens* contaminated units administered to 14 cats, 6 developed clinical signs of a transfusion reaction and 4 of these cats died. The most common clinical sign was vomiting. [144]

A study of canine WB units showed a low percentage of positive bacterial cultures but a higher percentage positive by qPCR testing.

**TABLE 2** Infectious pathogens documented as capable to be transmitted by blood transfusion in veterinary medicine

| Bacteria | Virus | Parasite |
|---|---|---|
| ***Haemobartonella canis*** [146,147] – dog<br>***Candidatus* Mycoplasma haematoparvum** [148] – dog<br>***Anaplasma phagocytophilum*** [192] – dog<br>***Rickettsia conorii*** [193] – dog<br>***Bartonella henselae*** [194,195] – cat***Mycoplasma haemofelis*** , [196] **'*Candidatus* Mycoplasma haemominutum'** [197] – cat | **FeLV** [198] (including FeLV provirus)[199] – cat<br>**FIV** [200] – cat | ***Babesia gibsoni*** [201,202,203] – dog<br>***Babesia canis*** [147,149] – dog<br>***Leishmania* spp.** [204–206] – dog<br>***Cytauxzoon* spp** [207,208] – cat |

FeLV: feline leukemia virus; FIV: feline immunodeficiency virus

Despite the bacterial positivity, no transfused recipient had an immediate or delayed adverse transfusion effect. [141] The acceptable level of contamination is unknown.

## 9.3 | Areas for further research

Further studies are needed to determine the most sensitive and specific methods to screen for blood donor infectious diseases and blood product contamination. In addition, further studies are needed to define a cutoff for acceptable bacterial load in products that would still allow transfusion.

# 10 | CITRATE TOXICITY/HYPOCALCEMIA

| Citrate Toxicity | |
|---|---|
| **Incidence** | **Case Reports only in dogs and cats** |
| **Case Definition** | **Imputability** |
| Citrate toxicity is an acute, non-immunologic reaction that is secondary to the transfusion of a large volume of blood, with citrate as the anticoagulant, and is characterized by a significant systemic hypocalcemia within hours of initiating transfusion. | **Definite:** Patients receiving massive transfusions with impaired hepatic function.<br>AND<br>compared to pretransfusion levels, a decrease in ionized calcium to <0.7 mmol/L;<br>AND<br>development of seizures, tremors, ptosis, vomiting (nausea), hypotension, QTc prolongation, salivation, tachycardia, salivation, or facial swelling.<br>**Probable:** Patients receiving massive transfusions with impaired hepatic function.<br>AND<br>compared to pretransfusion levels, a decrease in ionized calcium to between 0.71 and 0.8 mmol/L;<br>AND<br>development of vomiting (nausea), QTc prolongation, salivation, tachycardia, or facial swelling.<br>**Possible:** Patients receiving massive transfusions with impaired hepatic function.<br>AND<br>compared to pretransfusion levels, a decrease in ionized calcium to between 0.81 and 0.9 mmol/L;<br>AND<br>development of vomiting (nausea), QTc prolongation, salivation, tachycardia, facial swelling. |

## 10.1 | Background and human literature

Citrate is primarily metabolized by the liver, but with poor hepatic function or failure, the amount of citrate administered can exceed hepatic metabolic capacity and lead to calcium and magnesium chelation with resultant ionized hypocalcemia and ionized hypomagnesemia. Blood products that contain the greatest amount of citrate, such as fresh frozen plasma, will cause the greatest amount of calcium chelation.

Most patients that develop citrate toxicity have received massive transfusion, and the continued administration of citrate containing blood product enhances the severity of hypocalcemia. Additional complications associated with citrate toxicity include metabolic alkalosis, and hypernatremia, if sodium citrate is used as an anticoagulant. [150]

The severity of clinical signs is associated with the degree of hypocalcemia. In people, an ionized calcium of <0.9 mmol/L is associated with increased mortality and <0.8 mmol/L increases adverse cardiac effects. Ptosis can be the first clinical sign at 0.65-0.7 mmol/L and tremors and convulsions will develop at <0.4 mmol/L. Additional clinical signs include vomiting, nausea, hypotension, QTc prolongation,

salivation, tachycardia, salivation, or facial swelling.[151] Diagnosis is based on the presence of ionized hypocalcemia (or ionized hypomagnesemia), during or shortly after a transfusion, without another identifiable cause of the hypocalcemia.

## 10.2 | Veterinary literature

The evaluation of ionized calcium after transfusion and massive transfusion has been evaluated in laboratory animals and clinical patients receiving citrate and citrated blood products. The administration of citrate to dogs decreases the ionized calcium, ionized magnesium, and causes nausea and vomiting. At higher doses of citrate, dogs develop tachycardia, prolongation of the QT interval and QTc, T-wave inversion, depressed cardiac output, reddening of the pinna, facial swelling, and salivation. Most clinical signs of citrate toxicity start to resolve within one hour of stopping the citrate infusion, and are almost completely resolved within two hours. [152,153] A retrospective review of calcium disorders reported citrate toxicity after transfusion as the cause of hypocalcemia in 6% of cats and 4.7% of dogs. This study did not further define clinical signs or incidence related to number of transfusions.[154]

In 6/15 dogs undergoing massive transfusion, there was a significant decrease in ionized calcium and ionized magnesium.[61] The adverse reactions noted in this study included fever (3), vomiting (1), facial swelling (1), and delayed hemolysis (1).[61] A case report documented declining ionized calcium concentration following 5 units of pRBCs, 3 units of plasma, and 1.2 L of autotransfusion.[155] The use of autotransfusion alone does not appear to significantly decrease the ionized calcium.[156,157] The use of massive transfusion in cats is poorly reported. There were no clinically relevant changes in ionized calcium or magnesium in a report of one cat that received 3 units of blood.[158]

## 10.3 | Areas for further research

The incidence of citrate toxicity in veterinary medicine is likely uncommon but is difficult to determine as this reaction is poorly documented. Recognition that the condition occurs in transfused animals may increase the number of cases reported.

# 11 | TRANSFUSION-RELATED HYPERAMMONEMIA

| Hyperammonemia | |
|---|---|
| **Incidence** | **No published reports in dogs or cats** |
| **Case Definition** | **Imputability** |
| Hyperammonemia is an acute, non-immunologic reaction that is secondary to hyperammonemia and characterized by signs of development of encephalopathy (neurologic signs as ataxia, head pressing, circling, seizures and vomiting), during or immediately after (minutes to few hours) blood transfusion of stored blood or stored blood components. It is a potentially life-threatening reaction in patients with liver disease (liver failure, portosystemic shunt, premature neonates with immature functioning liver) who are unable to metabolize and excrete ammonia properly. | **Definite:** Laboratory evidence of hyperammonemia in the transfusion recipient; AND onset of signs of hepatic encephalopathy during or after a transfusion in a recipient with no evidence of signs of encephalopathy prior to the transfusion; AND laboratory evidence of hyperammonemia in transfused blood or blood components. **Probable**: Laboratory evidence of hyperammonemia in the transfusion recipient; AND onset of signs of hepatic encephalopathy during or after a transfusion in a recipient with no evidence of signs of encephalopathy prior to the transfusion. **Possible**: Onset of signs of hepatic encephalopathy during or after a transfusion in a recipient with no evidence of signs of encephalopathy prior to the transfusion. |

## 11.1 | Background and human literature

Human cellular blood products such as WB and PRBCs accumulate ammonia during storage due to cellular metabolism. [159–162] Ammonia rapidly accumulates in platelets concentrates stored at room temperature and also increases in plasma units stored at 4°C for 68 days and at -20°C for 5 and 8 months. [160,163] High ammonia concentrations in blood components could result in toxicity, particularly in recipients with hepatic dysfunction, as the healthy liver extracts 80% of the ammonia during first blood pass in people.[164] Clinical signs of transfusion related hyperammonemia include altered mental status with ataxia, dementia, head pressing, circling, and seizures after blood product administration.[165] Infants with transient hyperammonemia can experience seizures, coma, respiratory distress, apnea, lethargy, hypotonia, and intracranial bleeding.[166]

## 11.2 | Veterinary literature

Ammonia increases significantly during storage in canine PRBC units, in which mean values reached 466 mmol/L on day 28, 562 mmol/L on day 35 [167] and 1091 mol/L on day 42 of storage. [140] Storage of feline

WB [135,168] and PRBC units [134,135] resulted in mean values of 909 μg/dL and 1058 μg/dL respectively, after 35 and 42 days of storage. [135]

The clinical significance of blood unit related hyperammonemia in veterinary medicine is yet to be determined. Plasma ammonia concentration remained in the normal reference range in 5 anemic dogs without primary liver disease transfused with 5–10 mL/kg of stored pRBC. [167] A secondary source makes reference to hyperammonemia resulting in neurologic signs such as ataxia, dementia, head pressing, circling, seizures, and vomiting in veterinary patients.[169] However, there are no published reports of increased ammonia concentration and documented signs of hepatic encephalopathy in dogs or cats receiving stored blood products.

Risk factors for develop transfusion-related hyperammonemia are: using outdated blood products in which ammonia has accumulated; transfusion recipients with liver disease/hepatic dysfunction including portosystemic shunts that are unable to metabolize and excrete ammonia properly; [170] premature neonates with immature liver function; and recipients receiving large transfusion volumes and with hypoperfusion secondary to shock.[61]

### 11.3 | Areas for further research

Large scale measurement of ammonia in canine and feline blood components and in transfusion recipients is needed to better understand the clinical significance of hyperammonemia.

## 12 | HYPOTENSIVE TRANSFUSION REACTIONS (HYTR)

| Hypotensive Transfusion Reaction | | |
|---|---|---|
| **Incidence** | **Dogs - 0.9%[1]** | **Cats – no published reports** |
| **Case Definition** | **Imputability** | |
| A hypotensive transfusion reaction is an acute, non-immunologic reaction that is secondary to the infusion of stimulators of vasodilation and hypotension. It is characterized by the rapid onset of significant hypotension during or shortly after the completion of a transfusion, with the absence of other causes of hypotension, and improvement with cessation of the infusion. There is usually a decrease in systolic blood pressure of at least 30 mmHg from baseline. | **Definite:** The development of severe hypotension occurring between 15 minutes after starting the transfusion and 1 hour of stopping the transfusion; AND responds rapidly to stopping the transfusion and no other conditions explain hypotension;<br>**Probable:** The development of severe hypotension within 15 minutes of starting the transfusion and 1 hour after stopping the transfusion; AND the patient does not respond rapidly to supportive treatment, or there are other potential causes of hypotension.<br>**Possible:** The development of severe hypotension but other conditions or causes of hypotension could be identified. | |

### 12.1 | Background and human literature

Most HyTRs occur within minutes to hours of starting a transfusion, and are most commonly identified with red cell transfusions. [171–174] HyTRs develop following activation of coagulation factor XII, which causes the conversion of high-molecular-weight kininogen to bradykinin, leading to vasodilation and increased vascular permeability.[171] Bradykinin is primarily metabolized via angiotension-converting enzyme (ACE), and the use of ACE inhibitors before or during a transfusion has been associated with the development of HyTRs. [171,172,175] Additionally, the use of post-storage, bedside leukoreduced blood products that activate kinin-mediated pathways and increase bradykinin have been associated with an increased risk of developing HyTRs.[171,172,175] Hypotension can develop during other transfusion reactions (septic, AHTRs, TRALI, anaphylaxis/anaphylactoid), but are not classified as a HyTR. Although transient, HyTRs produce a dramatic decrease in blood pressure that improves with stopping the transfusion and supportive care. The hypotension usually recurs if a transfusion is restarted with the same blood product

Clinical signs of HyTRs are associated with severe hypotension, but can cause nonspecific findings, such as abdominal pain, nausea, dyspnea, tachypnea, and dizziness.[173] A diagnosis of HyTR occurs if: i.) there is a significant drop in blood pressure during a transfusion, or within 1 hour of stopping the transfusion, ii.) the systolic blood pressure decreases by 30 mmHg, or >25% reduction from baseline in pediatric patients, and iii.) an underlying cause cannot be identified.[173] Replacing an ACE inhibitor with a medication with a different mechanism of action prior to transfusion and using pre-storage, rather than post-storage, leukoreduction may decrease the risk of HyTRs.[171] Treatment for a HyTR consists of stopping the transfusion, treating the hypotension, and providing supportive care.[171,173] The use of post-storage blood product washing may also decrease the risk of HyTRs.[176]

### 12.2 | Veterinary literature

There are no published cases of HyTRs in dogs and cats. A decrease in blood pressure has been identified in clinical and research

transfusion settings but the hypotension was attributable to other causes.[149,177–179]

### 12.3 | Areas for further research

The incidence of HyTR in veterinary medicine is likely rare, but this is difficult to determine as the condition is poorly documented. Recognition that such a condition can occur in transfused animals may increase the number of cases reported.

## 13 | POSTTRANSFUSION PURPURA (PTP)

| Post-transfusion purpura (PTP) | | |
|---|---|---|
| Incidence | Dogs - Single case report[180] | Cats – no published reports |
| Case Definition | Imputability | |
| Post-transfusion purpura (PTP) is a delayed, immunologic reaction that is secondary to alloimmunization against platelet antigens. It is characterized by thrombocytopenia arising 5–12 days following transfusion of any platelet-containing blood product. | **Definite:** Patient has no other condition that could explain the thrombocytopenia<br>**Probable:** There are other possible causes but transfusion is most likely<br>**Possible:** Other causes are more likely but transfusion cannot be ruled out | |

### 13.1 | Background and human literature

Posttransfusion purpura (PTP) is a rare condition caused by alloimmunization against platelet antigens and is thus associated with patient antibodies directed against a platelet antigen that the patient lacks. Upon subsequent exposure to blood products containing the platelet antigen, PTP can develop. The vast majority of reported PTP cases in people involve antibodies directed against the human platelet antigen (HPA)-1a. Risk factors include previous red cell or platelet transfusions, or in man, previous exposure to fetal platelet antigens, seen in multiparous women.[181–184]

Although an alloantibody is involved, there is destruction of the patient's own platelets leading to thrombocytopenia. A number of mechanisms for this have been proposed: i) formation of immune complexes lead to destruction of autologous platelets, through an innocent bystander model ii) transfused platelet antigens adsorb onto the patient's own platelets, leading to immune-mediated destruction; iii) a platelet-specific autoantibody is produced along with the alloantibody, and destroys the patient's own platelets.[183]

Clinical signs are those typically seen with severe thrombocytopenia, such as petechial hemorrhages, epistaxis, or other bleeding from mucosal sites.[181] Diagnosis is based on the presence of a thrombocytopenia, often severe, within 5–12 days following a transfusion.[181] PTP is then confirmed by detection of circulating antibodies against platelet specific antigens, usually via ELISA or solid phase techniques. When platelet assays are unavailable, the diagnosis may become one of exclusion, where other conditions, such as disseminated intravascular coagulation, drug induced thrombocytopenia, autoimmune thrombocytopenia, or marrow failure are considered. Flow cytometry can also be used to assess the presence of platelet surface associated immunoglobulins.[161,181,184,185]

### 13.2 | Veterinary literature

Only one case of PTP has been documented in the veterinary literature. It involved a 5-year-old intact male German Shepherd with hemophilia A that developed thrombocytopenia (10,000 platelets/$\mu$L) 8 days after transfusion with 450 mL of fresh whole blood and 200 mL of fresh frozen plasma. Serum taken at the time of the thrombocytopenia had positive test results for platelet-binding IgG.[180]

### 13.3 | Areas for further research

The incidence of PTP in veterinary medicine is likely rare, but this is difficult to determine as the condition is poorly documented. Recognition that such a condition can occur in transfused animals may increase the number of cases reported.

## 14 | TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GVHD)

| Transfusion-associated graft vs. host disease (TAGVHD) | |
|---|---|
| Incidence | Research reports in dogs only[186] |
| Case Definition | Imputability |
| Transfusion-associated graft vs. host disease (TAGVHD) is an acute to delayed immunologic reaction that is secondary to donor lymphocytes engrafting on and eventually attacking host tissue. TAGVHD occurs 48 hours to 6 weeks following transfusion and has a high mortality rate in human patients (>90%).<br>The reaction is characterized by a skin rash, diarrhea, fever, hepatic dysfunction, and bone marrow hypoplasia. Liver and skin histopathology have a characteristic appearance. In humans, it is most common in immunocompromised individuals or when special circumstances cause transient immunosuppression. | **Definite:** Lymphocyte chimerism is identified in absence of other causes of chimerism<br>**Probable:** Lymphocyte chimerism is identified; other causes of chimerism exist<br>**Possible:** Chimerism negative or not investigated; other explanations more likely. |

## 14.1 | Background and human literature

Transfusion associated graft versus host disease (TA-GVHD) is a rare and often fatal complication of blood transfusion in people.[7,66] TA-GVHD was initially considered to occur only in immunocompromised individuals. However, more recent reports describe TA-GVHD in immunocompetent individuals in circumstances such as transfusion of blood from an HLA-homozygous donor to an HLA-heterozygous recipient who shares one haplotype, or due to transient immunosuppression.[187–189]

TA-GVHD is diagnosed by characteristic clinical signs (skin rash, diarrhea, hepatomegaly), laboratory findings (hepatic dysfunction, pancytopenia secondary to bone marrow hypoplasia) plus histological findings. Imputative diagnosis is considered when chimerism is demonstrated in blood or tissues.[7] A recent review suggests that milder or atypical cases of TA-GVHD are misdiagnosed or unrecognized.[189] Clinical signs develop between 48 hours to >6 weeks after cessation of transfusion; median time to develop the first symptom was 11 days in one systematic review. This condition is associated with a high mortality rate (>90%).[187,188,190]

## 14.2 | Veterinary Literature

There are no reported risk factors of TA-GVHD in veterinary patients. Press, et al speculate that it could become a concern with increasing frequency of stem cell transplantation in animals, and showed that irradiation of canine red cells did not cause significant morphological or biochemical alterations.[191]

One veterinary study repeatedly transfused un-irradiated leukocytes in dogs, and the dogs all developed GVHD. A parallel group was transfused with irradiated leukocytes on a similar schedule. The study revealed that certain doses of irradiation prevented the development of TA-GVHD.[186]

## 14.3 | Areas for further research

TA-GVHD is likely rare in veterinary medicine outside of experimental conditions. Awareness of this reaction could become important if stem cell transplantation becomes more frequent in veterinary patients.

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## Appendix A

### Veterinary Definitions and Incidence of Febrile Transfusion Reactions

| Study | Species | Incidence | Fever definition |
|---|---|---|---|
| Callan MB, et al. 1996[19] | Dogs | 1.3% | Fever is an elevation in body temperature by at least 1.1°C (2°F) during or within 4 hours post-transfusion. FNHTR not defined. |
| Hann L, et al. 2014[13] | Dogs | 3% | FNHTR is an increase in body temperature by ≥1.1°C (2°F) during or within 4 hours after transfusion without evidence of hemolysis |
| Holowaychuk MK, et al. 2014[2] | Dogs | 24.2% | FNHTR is a rectal temperature > 39.0°C [102.2°F) during or after pRBC transfusion. Exact timeline was not specified. |
| Bruce JA, et al. 2015[3] | Dogs | 8.2% | Rectal temperature > 1°C within 24 hours of receiving a transfusion. FNHTR not defined.<br>Excluded as a fever if the temperature was elevated prior to transfusion |

| Study | Species | Incidence | Fever definition |
|---|---|---|---|
| Maglaras CH, et al. 2017[1] | Dogs | 12.3% | Fever is an increase in rectal temperature ≥1.1°C (2°F) from baseline in previously normothermic patients, during or within the 4 hours following transfusion. Subjects that were hypothermic at the beginning of the transfusion were allowed to have an increase in body temperature >1.1°C (2°F) as long as the body temperature did not increase above the reference interval in the absence of external warming. FNHTR not defined |
| Klaser DA, et al. 2005[15] | Cats | 4% | Fever is an increase in rectal temperature by > 1°C (> 2°F). |
| Sylvane B, et al. 2018[17] | Cats | 22.9% | FNHTR is an increase of the body temperature before transfusion by 1°C during the transfusion without evidence of intravascular hemolysis. |
| McClosky ME, et al. 2018[16] | Cats | 5% | A febrile transfusion reaction is an increase in body temperature ≥ 2°F during or within 4 hours posttransfusion if active rewarming was not used. |
| Mansi ET, et al. 2019[14] | Cats | 3.7% | Fever is an increase in rectal temperature >1°C (1.8°F) from baseline in a previously normothermic or hyperthermic patient, during or within 4h of the end of the transfusion. Subjects that were hypothermic at the beginning of the transfusion were allowed to have an increase of more than 1°C (1.8°F) without classification of a fever as long as the body temperature did not increase above 39.2°C (102.5°F). |
| Martinez – Sogues, et al. 2020[18] | Cats | 10% | Fever is a rectal temperature increase >1°C(2°F) during or immediately after transfusion without any other explanation. |
| Humm KR, Chan DL 2020[20] | Cats | 8.9% | Fever is an increase in rectal temperature of greater than 1°C (1.8°F) from baseline at the beginning of the transfusion, non-pathological reasons for the increase, such as external warming and recovery from general anesthesia were removed. |

## Appendix B

### Veterinary Definitions of Acute Hemolytic Transfusion Reactions

| Study | Species | Acute hemolytic transfusion reaction definition |
|---|---|---|
| Callan et al. 1995[87] | Dogs | Increase in temperature, lack of increase in PCV and hemoglobinuria during and within a few hours of transfusion. |
| Giger et al. 1995[85] | Dogs | Fever, pigmenturia, lethargy and inadequate rise in PCV. |
| Melzer et al. 2003[86] | Dogs | Hemoglobinemia, inadequate rise in PCV within hours of transfusion. |
| Patterson J, et al. 2011[79] | Dogs | Hemolysis, hemoglobinuria or both during or immediately after transfusion. |
| Holowaychuk MK et al. 2014[2] | Dogs | Hemoglobinemia, hemoglobinuria, and rectal temperature > 39.0C (102.2°F) during or after transfusion. |
| Bruce et al. 2015[3] | Dogs | Suspected based on the presence of icterus (4/4 cases), inadequate rise in PCV (3/4 cases), lack of PCV response (1/4 cases), presence of fever (1/4 cases). |
| Goy-Thollot I, et al. 2017[81] | Dogs | Icterus, hypotension, hemoglobinuria and only transient increase in hematocrit during or after transfusion. |
| Maglaras CH, et al. 2017[1] | Dogs | Development of new or worsening hemolyzed serum or pigmenturia (eg, in a patient with extravascular immune-mediated hemolytic anemia that developed intravascular hemolysis associated with transfusion). If a patient had intravascular IMHA and hemolysis and did not clearly worsen or change during or after transfusion, it was not considered a complication. Because the data was retrospective, no attempt was made to differentiate immunologic from non-immunologic AHTR. |
| Giger U, et al 1990[89] | Cats | Signs of hemolysis including hemoglobinuria, icterus, a positive Coombs' test, rapidly declining PCV and marked hemoglobinuria within hours of transfusion. |
| Klaser DA, et al. 2005[15] | Cats | Pigmenturia, fever and tachypnea post-transfusion, PCV only transiently increased. |
| Euler et al. 2016[92] | Cats | Rapid return of PCV to pre-transfusion levels and evidence of intravascular hemolysis. |

| Study | Species | Acute hemolytic transfusion reaction definition |
|---|---|---|
| Sylvane B, et al. 2017[17] | Cats | Unexpected drop in the PCV or less than expected PCV after transfusion in association with elevated [Hb] after transfusion as well as clinical and laboratory abnormalities consistent with hemolysis. Expected increase in PCV after transfusion was defined as 1%/mL/kg of pRBCs. |
| McClosky ME, et al. 2018[16] | Cats | Fever, hemoglobinuria, hemoglobinemia, and a lack of increase in PCV during or within 24 hours of transfusion. |
| Koenig A, et al. 2020[90] | Cats | Acute intravascular hemolysis and rapid decline of the PCV. |