1   **Association of Veterinary Hematology and Transfusion Medicine (AVHTM) Transfusion**

2   **Reaction Small Animal Consensus Statement (TRACS) Part One: Definitions and Clinical Signs**

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30

31 **Abstract**

32 **Objective:** To use a systematic, evidence-based consensus process to develop definitions for transfusion

33 reactions in dogs and cats.

34 **Design:** Evidence evaluation of the literature was carried out for identified transfusion reaction types in

35 dogs and cats. Reaction definitions were generated based on synthesis of human and veterinary

36 literature. Consensus on the definitions was achieved through Delphi-style surveys. Draft

37 recommendations were made available through industry specialty listservs and comments were

38 incorporated.

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

40 **Conclusions:** The evidence review, and consensus process resulted in definitions that can be used to

41 facilitate future veterinary transfusion reaction research.

42 **Abbreviations**

43 **AABB** - American Association of Blood Banks

44 **ACE** - Angiotensin-Converting Enzyme

45 **AHTR** - Acute Hemolytic Transfusion Reaction

46 **ALI** - Acute Lung Injury

47 **ARDS** - Acute Respiratory Distress Syndrome

48 **AVHTM** - Association of Veterinary Hematology and Transfusion Medicine

49 **BNP** - Brain Natriuretic Peptide

50 **CDC** - Centers for Disease Control

51   **CPDA** – Citrate Phosphate Dextrose Adenine

52   **DAT** - Direct Antiglobulin Test

53   **DEA** - Dog Erythrocyte Antigen

54   **DHTR** - Delayed Hemolytic Transfusion Reaction

55   **DIC** - Disseminated Intravascular Coagulation

56   **DSTR** - Delayed Serologic Transfusion Reaction

57   **FFP** – Fresh Frozen Plasma

58   **FNHTR** - Febrile Non-Hemolytic Transfusion Reactions

59   **Hb** – Hemoglobin

60   **HLA** - Human Leukocyte Antigen

61   **HNA** - Human Neutrophil Antigens

62   **HTR –** Hemolytic Transfusion Reaction

63   **HyTR** - Hypotensive Transfusion Reactions

64   **IAT** - Indirect Antiglobulin Test

65   **IMHA** - Immune-Mediated Hemolytic Anemia

66   **LAH** - Left Atrial Hypertension

67   **NETS** - Neutrophil Extracellular Traps

68   **NHSN** - National Healthcare Safety Network

69   **NT-proBNP** - N Terminal-proBNP

70   **pRBCs –** Packed Red Blood Cells

71   **PCR** – Polymerase Chain Reaction

72   **PTP** - Post-transfusion purpura

73   **SHOT** - Serious Hazards of Transfusion

74   **TACO** - Transfusion Associated Circulatory Overload

75   **TAD** - Transfusion Associated Dyspnea

76   **TA-GVHD** - Transfusion Associated Graft Versus Host Disease

77   **TRALI** - Transfusion Related Acute Lung Injury

78   **TTI** - Transfusion Transmitted Infection

79   **WB** – Whole Blood

80   **XM** – Crossmatch

Introduction
81

82   Transfusions are lifesaving but have risks. Reactions to blood products can either be acute or

83   delayed and can range in severity from minor to life threatening. While transfusion reactions have been

84   described in veterinary species, the definitions of these reactions have been variable.[1–3] Variability in

85   definition impedes recognition and treatment in clinical practice and also impedes utilization of

86   appropriate information in comparative prospective or retrospective studies.[4]

87   The Centers for Disease Control and Prevention (CDC), in collaboration with experts convened

88   by American Association of Blood Banks (AABB), developed consensus definitions and a nationwide

89   reporting module, which launched in 2009.[5] These national reaction definitions and reporting modules

90   have led to large-scale studies, and improvements in transfusion practice.[6,7]

91   In 2018, an international committee of veterinary specialists was convened in partnership with

92   the Association of Veterinary Hematology and Transfusion Medicine (AVHTM) to develop consensus

93   definitions and evidence-based recommendations for prevention, monitoring, diagnosis, and treatment

94   for transfusion reactions in veterinary patients. The authors' hope is that this material will be the basis

95   for further clinical research and for the potential development of a veterinary hemovigilance database.

96   In part one of this series, we define important terms and present each reaction type. For each

97   reaction, we have included incidence, background human and veterinary literature, and areas for

98   further research. In part two of this series, we provide evidence-based recommendations for prevention

99   and monitoring of transfusion reactions and present a standard transfusion monitoring form. In part

100   three, we provide evidence-based recommendations for diagnosis and treatment of transfusion

101   reactions and present a clinical diagnostic and treatment algorithm

102   **Methods**

103   The consensus project was initiated through the AVHTM. A call for volunteer contributors was

104   made through the listserv and the group was convened. The committee includes members from five

105   countries and three different areas of specialty certification (DACVIM-IM, ACVCP, DACVECC). The

106   members include those working in academia, private clinical practice, laboratory medicine, and blood

107   banking. Many members have published extensively in the field of veterinary transfusion medicine.

108   The project was limited to transfusion reactions secondary to red blood cell, plasma, and

109   platelet transfusions in canine and feline patients. Reactions associated with human albumin,

110   immunoglobulins, and antivenoms were not included. The reaction definitions from CDC's National

111   Hemovigilance Module were used as the starting point.[7] Due to perceived clinical relevance,

112   complications related to hyperammonemia and hypocalcemia due to citrate toxicity were included;

113   similarly, reactions associated with xenotransfusion were included.

114   The group developed specific worksheet questions to review each reaction.[8] Comprehensive

115   database searches were then performed including review of both human and veterinary literature. The

116   reaction worksheet included search criteria, a review of the relevant veterinary and human literature, a

117   proposed definition, clinical signs, diagnostic criteria, risk factors, evidence grade, and areas for further

118   research. The committee discussed all reaction worksheets in an initial round of changes and

119   suggestions. Delphi style anonymous surveys were then used to refine the definitions and diagnostic

120   criteria.[9] These draft definitions and recommendations were then presented to the AVHTM, ACVECC,

121   and ACVIM discussion boards and definitions further refined based on these comments and suggestions.

122   [8,10]

123   **Terms**

124   Transfusion reactions can be classified based on etiology, time frame, and clinical signs. For the

125   purposes of these guidelines, commonly used terms and definitions are listed in Table One.

126   **Types and categories of reactions**

127   Transfusion reactions are often presented as immunologic or non-immunologic. However, this

128   distinction is often not clear during initial assessment of clinical patients. We have instead opted to

129   present reactions in order of published incidence. The true incidence of transfusion reactions is difficult

130   to fully ascertain, in both humans and animals, due to problems in bedside recognition and in

131   reporting.[11] In one study in humans, < 10% of actual transfusion reactions were reported to a

132   hemovigilance system.[12]

133   The reactions covered, listed in order, include:

134   Febrile Non-Hemolytic Transfusion Reactions (FNHTR)

135   Respiratory Reactions

136   • Transfusion Associated Dyspnea (TAD)

137   • Transfusion Associated Cardiac Overload (TACO)

138   • Transfusion Related Acute Lung Injury (TRALI)

139   Allergic Reactions

140   Acute Hemolytic Transfusion Reaction (AHTR)

141   Delayed Hemolytic Transfusion Reaction (DHTR)

142   Delayed Serologic Transfusion Reaction (DSTR)

143   Transfusion Transmitted Infection (TTI)

144   Hypocalcemia/Citrate toxicity

145   Transfusion Related Hyperammonemia

146   Hypotensive Transfusion Reactions (HyTR)

147   Post-transfusion purpura (PTP)

148   Transfusion associated graft versus host disease (TA-GVHD)

149

150   **Febrile Non-Hemolytic Transfusion Reactions (FNHTR)**

151   Fever is one of the most common adverse events associated with transfusion in veterinary

152   studies. [1-3,13-18] Fever can be seen with many types of transfusion reactions including infection,

153   hemolytic reactions and transfusion related acute lung injury (TRALI). It may also be present due to

154   external warming or underlying patient infection. If these reactions and other possibilities are ruled out,

155   a FNHTR is most likely.

156

Febrile Non hemolytic Transfusion Reaction (FNHTR)		
Incidence	**Dogs –** 1.3%[19] 3%[13] 8.2%[3] 12.3%[1] 24.2%[2]	**Cats –** 3.7%[14] 4%[15] 5%[16] 8.9%[20] 10%[18] 22.9%[17]
Case Definition	**Imputability**	
A FNHTR is an acute non-immunologic or immunologic reaction characterized by a temperature > 39°C (102.5F) AND an increase in temperature of > 1°C (1.8F) 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	
	Probable: There are other potential causes, but transfusion is most likely	
	Possible: Other causes are likely, but transfusion cannot be ruled out	

157

158

159   *Background and human literature*

160   The National Healthcare Safety Network (NHSN) on Hemovigilance defines a FNHTR as a fever

161   over at least 38°C (100.4 F) AND increase of at least 1°C (1.8 F) from pre-transfusion values during or

162   within 4 hours of the end of a transfusion OR rigors/chills in same time period AND absence of other

163   causes. [7] The Australian Red Cross definition is similar but the time frame is within 24 hours of the

164   transfusion.[21] While the > 1°C rise in temperature is not evidence based, it has been universally

165   accepted for human hemovigilance. [4]

166   In people, donor white blood cell or platelet antigen-antibody reactions are thought to be

167   responsible for at least 70% of FNHTR.[22] Transfer of inflammatory cytokines produced in stored red

168   blood cells by white blood cells is another cause. Patients receiving packed red blood cells (pRBCs) who

169   have a FNHTR have been shown to have increased levels of IL-6 and IL-8 although in these cases the

170   cytokines were not increased in the blood units.[23]

171   In people, FNHTR are more common with platelet products and appear to be more common

172   with non-leukoreduced red blood cells. In a recent human study using two hemovigilance databases, the

173   overall per product rate of FNHTR was 0.17% after pre storage leukoreduced packed red blood cell

174   transfusions and 0.25% after platelet transfusions.[24] These numbers likely underrepresent the true

175   incidence. In a retrospective case review study of 4857 human transfusions, 30 (0.62%) FNHTRs were

176   identified but only 30% of these had been reported to the transfusion service. [11]

177   While FNHTR are not life threatening, they cause patient discomfort.[24] Because FNHTR is a

178   diagnosis of exclusion, the development of a fever often leads to discontinuation of the transfusion and

179   a series of diagnostic tests. Rule outs include underlying patient infection, acute hemolytic reaction,

180   TRALI, and bacterial contamination of the blood unit. Direct antiglobulin test (DAT), human leukocyte

181   antigen (HLA) testing, CBC and repeat blood typing are recommended. Blood cultures and/or PCR should

182 also be considered if transfusion transmitted infection is considered likely. There is currently no easy

183 way to test for white blood cell antibodies.

184 *Veterinary literature*

185 The definition of FNHTR has been variable in the veterinary literature. Studies have varied in

186 whether they have differentiated FNHTR from other causes of fever, what temperature has been

187 considered elevated, how to define baseline, and over what timeframe during and after transfusion to

188 monitor temperature. Appendix A includes the definition of fever and incidence from relevant studies in

189 dogs and cats.

190 *Areas for further research*

191 Standardization of the timeframe and consideration of both temperature change and actual

192 temperature value should improve case identification and study comparison in the future. However,

193 diagnosis of FNHTR is complicated when the patient has an underlying reason for a fever, such as an

194 immune, inflammatory, or infectious disease but then develops a new higher temperature. Testing for

195 WBC antibodies is not widely available but would be useful in these situations. [22]

196 **Acute Respiratory Reactions**

197 Respiratory reactions are the most common overall cause of transfusion-associated mortality in

198 people. Most respiratory reactions are either transfusion associated circulatory overload (TACO) or

199 transfusion related acute lung injury (TRALI). A new category, transfusion associated dyspnea (TAD),

200 was developed to recognize other respiratory transfusion reactions in hemovigilance databases that

201 could not immediately be categorized as TRALI or TACO.[4] In some studies, over half of TAD cases were

202 later found to meet criteria for another pulmonary transfusion reaction.[25] While TAD has not been used

203 specifically in veterinary medicine, studies have reported respiratory distress after transfusion in dogs

204 and cats without other description and have been categorized as TAD below.

Transfusion Associated Dyspnea (TAD)		
Incidence	**Dogs**	**Cats**
	2%[3]	0.4%[16]
	3.9%[1]	2.4%[26]
	6.3%[13]	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	
	Probable: There are other possible causes, but transfusion is most likely	
	Possible: Other causes are more likely, but transfusion cannot be ruled out	

205

206 **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	Definite:	

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.	Clinical signs of worsening respiratory signs, cough, dyspnea, orthopnea, pulmonary crackles; **AND** echocardiographic evidence includes left atrial enlargement, left ventricular dilation, or reduced ejection fraction; **AND/OR** radiographic evidence includes bilateral pulmonary infiltrates, pleural effusion, pulmonary edema, pulmonary venous congestion, or cardiomegaly; **AND/OR** laboratory evidence includes significantly elevated BNP, NT-proBNP or a BNP or NT-proBNP pre/post transfusion ratio of over 1.5x;

	AND
	no other explanation for circulatory overload.
	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.
	Possible: Patient has a history of pre-existing cardiac insufficiency that most likely explains the circulatory overload.

207

208   *Background and human literature*

209   The NHSN on Hemovigilance defines TACO as a new onset or exacerbation of three or more of

210   the following within 6 hours of cessation of transfusion: acute respiratory distress (dyspnea, orthopnea,

211   cough), elevated BNP, elevated central venous pressure, evidence of left heart failure, evidence of

212   positive fluid balance, or radiographic evidence of pulmonary edema.[7]

213   While risk factors for TACO are not entirely understood, many have been suggested in humans

214   including: administration of large volumes of blood, especially if rapid; blood transfusions in patients

215   with chronic anemia; concurrent heart, respiratory, or renal disease, or systemic hypertension; patients

216   treated with chronic loop diuretics; and patients that are already in a positive fluid balance.[27–30] In

217   patients with normal renal and cardiac function, massive transfusion is typically required to see signs of

218   volume overload. Blood transfusion causing moderately increased blood volume in patients with

219   compensated cardiac dysfunction or chronic renal failure can result in pulmonary edema and respiratory

220   distress. In patients with heart failure, pulmonary edema can occur without elevations in total blood

221   volume.[29] Patients with TACO typically have a positive response to diuretic therapy.[28,30,31]

222   The incidence of TACO ranges from less than 1% to 8% in human studies.[28] A 2018 study

223   reported a transfusion-related mortality rate of 5% and named TACO the leading cause of death.[30]

224   Differential diagnoses for TACO may include transfusion-associated acute lung injury (TRALI),

225   anaphylactic reactions, bacterial contamination of the blood unit, pulmonary thromboembolism, and

226   hemolytic transfusion reactions with pulmonary complications.[32]

227   Diagnosing TACO may be difficult, as there are no pathognomonic signs or symptoms.[33] Clinical

228   signs of volume overload may include new or worsening signs of respiratory disease including cough,

229   dyspnea, orthopnea, or pulmonary crackles. Radiographs of the thorax may show bilateral pulmonary

230   infiltrates, pleural effusion, pulmonary edema, pulmonary venous congestion, and/or

231   cardiomegaly.[11,29,32] Echocardiographic findings indicating volume overload may include left atrial

232   enlargement, left ventricular dilation, and a reduced ejection fraction.[11,28,29] While the use of pulmonary

233   arterial catheters is becoming more infrequent, an elevated pulmonary capillary wedge pressure

234   measured by the use of a pulmonary arterial catheter would also provide evidence for circulatory

235   overload.[29,30]

236   Significantly elevated brain natriuretic peptide (BNP) or N Terminal-proBNP (NT-proBNP) level,

237   or a BNP or NT-proBNP pre/post transfusion ratio > 1.5, is the most well studied and convincing

238   laboratory evidence of circulatory overload and hydrostatic pulmonary edema in TACO. [31] BNP levels <

239   200 pg/mL are associated with non-cardiogenic causes of pulmonary edema with a specificity over 90%

240   while normal natriuretic peptide level following transfusion is not consistent with a diagnosis of TACO. [32]

241   Several novel biomarkers (tumorgenicity-2, cystatin C, growth differentiation factor 15, galectin-3) also

242   show promise in diagnosing TACO.[31]

243   *Veterinary literature*

244   The literature characterizing and defining TACO in dogs and cats is minimal.[3,34,35] A 2017 study

245   evaluating transfusion reactions in dogs did not specifically define TACO and reported changes in

246   respiratory status as an increase in the patient's respiratory rate or effort, or by a decline in pulse

247   oximetry during or within 4 hours of transfusion.[1] In a 2014 canine study, volume overload associated

248   with transfusion was defined as increased respiratory rate or effort, or diuretic administration at the

249   clinician's discretion during or immediately after administration of transfusion. That study determined

250   that the greatest risk factor for volume overload during transfusion was related to the dose of blood

251   product administered and found a 4.7% incidence of volume overload.[2] In a recent study, 3% of

252   transfused cats were thought to have TACO but diagnostic criteria were not listed.[20]

253

254   *Areas for further research*

255   While TACO is an uncommon but potentially life-threatening type of reaction in veterinary

256   transfusion medicine, new studies are needed to better characterize the syndrome in veterinary

257   patients. Biomarkers as described in human studies might be useful in defining this syndrome in

258   veterinary medicine.

259   **Transfusion-Related Acute Lung Injury (TRALI)**

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 six 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; **AND** clinical signs of respiratory distress within 6 hours of the transfusion; **AND** no signs of left atrial hypertension; **AND** no alternative risk factors for Acute Lung Injury (ALI).
	Probable: N/A
	Possible: Evidence of other risk factors for acute lung injury (pancreatitis, aspiration pneumonia, severe sepsis, shock, etc.) during or within 6 hours of the transfusion.

261   *Background and human literature*

262   Transfusion-related acute lung injury is a devastating complication of transfusion in human

263   patients and has emerged as a leading cause of transfusion-related mortality.[37–39] It was originally

264   considered rare but has been increasingly recognized and reported after publications with international

265   agreements on the definition of TRALI.[39,40]

266   Transfusion-related acute lung injury was first described in a 1985 trial of human surgical

267   patients who developed hypoxemia and respiratory failure 1-6 hours after a blood transfusion.[41,42] None

268   of the patients had hemodynamic overload consistent with TACO and about 72% required mechanical

269   ventilation.[41] A large percentage of the donors had leukocyte antibodies, specifically anti-HLA type I

270   antibodies.[39,41]

271   Consensus definitions of TRALI have been updated in 2019 and propose TRALI type I and TRALI

272   type II definitions. [37 43 44 45] The 2019 definitions replaced the previous term "possible TRALI" with

273   "TRALI type II" while the "delayed TRALI" (previously defined as patients with symptoms occurring

274   within 24 hours) was no longer recognized as most cases of TRALI occur within six hours in human

275   patients.[37]

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

277   A. Acute onset defined by

278   i. Hypoxemia (P/F ≤ 300 or SPO_2 < 90% on room air)

279   ii. Clear evidence of bilateral pulmonary edema on imaging (chest radiographs, chest CT or

280   ultrasound)

281   iii. No evidence of left atrial hypertension (LAH) on echocardiography or use of pulmonary artery

282   catheter, or if LAH is present, it is judged not to be the main contributor to the hypoxemia*

283   B. Onset of pulmonary signs within 6 hours of transfusion (imaging can be documented up to 24 hours

284   later)

285   C. No temporal relationship to an alternative risk factor for ARDS

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

287   TRALI type II is defined as patients who have risk factors for ARDS (but who have not been diagnosed

288   with ARDS) or who have existing mild ARDS (P/F 200-300), but whose respiratory status deteriorates and

289   is judged to be due to a transfusion based on

290   A. Findings as described in categories A and B of TRALI type I

291   B. Stable respiratory status in the 12 hours before the transfusion.

292   While the incidence of TRALI has not been well established in human patients, the reported

293   ranges in literature varies from 0.004%-15.1% per patient transfused, with a higher incidence seen with

294   plasma products.[46–48]. TRALI ranges in severity, from mild to severe forms. Clinical features of TRALI in

295   humans include dyspnea, fever, hypotension, tachypnea, tachycardia, frothy endotracheal aspirate and

296   the need for mechanical ventilation to support oxygenation.[43] Signs often occur within 2 hours of

297   transfusion.[43,49] While TRALI is a common cause of transfusion-associated mortality, only a small

298   percentage of human patients with TRALI die (5-10%), compared to 30-40% of patients with other

299   causes of ARDS.[50] Many patients experience significant morbidity, including prolonged need for

300   mechanical ventilation and length of hospital stay.[50]

301   Plasma and platelet product transfusions carry the highest risk of TRALI in people, possibly

302   because the bioactive mediators of TRALI are carried in plasma.[50,51] The bioactive mediators in TRALI are

303   divided into antibody and non-antibody categories. Antibodies to human leucocyte antigen (HLA) class I

304   and II and various neutrophil antigens (HNA) have been implicated in TRALI. [50] Non-antibody mediators

305   that accumulate during storage and have been associated with TRALI include bioactive lipids

306   (lysophosphatidylcholines), soluble CD40 ligand, and aged cells. [50]

307   Multiparous women have been implicated in the pathogenesis of TRALI due to the high

308   concentrations of HLA or HNA antibodies in their donated plasma volume. If the HLA antibody is cognate

309   (recipient has a matched HLA antigen), then TRALI can develop although the presence of HLA antibodies

310   is not an independent risk factor for the development of TRALI.[50] Approximately 50-89% of TRALI cases

311   have been related to the presence of HLA or HNA antibodies in donor blood.[42,52,53] However, several

312   studies have shown that the presence of HLA or HNA antibodies in donor blood is common and do not

313   cause TRALI in a majority of cases, even when cognate antibodies are present.[52,54–56]

314   Neutrophils, monocytes, lymphocytes, platelets, neutrophil extracellular traps (NETS), the

315   endothelium and other immune mechanisms might also play a role in the development of TRALI.

316   Biological response modifiers may trigger activation and sequestration of recipient neutrophil

317   granulocytes. Thus, in the "two-hit" model proposed for TRALI, the patient has primed neutrophils and

318   endothelium as the "first hit".[52] Being a smoker, shock, liver surgery, positive fluid balance before

319   transfusion and higher plasma IL-8 levels before transfusion have been identified as possible "first hit"

320   risk factors.[50,57] Blood product transfusion serves as the "second hit" by fully activating the

321   endothelium/neutrophils and leading to pulmonary neutrophil infiltration and edema.[52] A second

322   model, the threshold model, proposes that factors in donor blood and recipient need to reach a

323   threshold together.[52] In the threshold model, a critically ill patient is more likely to develop TRALI in the

324   presence of low donor factor potency, compared to a non-critically ill patient.[52]

325   *Veterinary Literature*

326   There is minimal information on the incidence of TRALI in veterinary patients. A prospective

327   study investigating the incidence of TRALI in dogs reported an occurrence of 3.7% (2/54) in enrolled

328   subjects.[38] Both dogs had radiographic changes following fresh frozen plasma (FFP) transfusion that

329   could be consistent with TRALI, although neither dog had acute respiratory distress and

330   echocardiograms were not performed. One of the two dogs died although the incidence of TRALI in this

331   study was too low to determine a true mortality rate. Another case report describes a dog with bite

332   wounds that developed acute respiratory distress after a whole blood transfusion. Changes appreciated

333   on thoracic radiographs were suggestive of TRALI, but there was no mention of an echocardiogram and

334   the clinical signs of respiratory distress began eight hours after the transfusion had ended. The dog

335   ultimately underwent mechanical ventilation but died after cardiopulmonary arrest.[58]

336   It is unknown how often multiparous female dogs are used as blood donors. A low incidence of

337   multiparous female dog donors might theoretically contribute to the low incidence of reported TRALI in

338   veterinary patients. However, one study demonstrated the lack of pregnancy induced alloantibodies in

339   dogs and suggested that multiparous female dogs should not be excluded from the donor pool.[59] There

340   are no studies evaluating leucocyte or neutrophil antibodies in female dogs or cats.

341   *Areas for further research*

342   The incidence of TRALI in veterinary medicine is currently thought to be rare. This may be

343   because most female donors (at least in North America) are spayed and nulliparous. The presence of

344   leukocyte and neutrophil antibodies in dogs and cats with prior litters should be investigated. An

345   international effort to screen for TRALI, through large multicenter prospective studies, would provide

346   more information on this condition in veterinary patients.

347   **Allergic Transfusion Reactions**

Allergic Reaction

Incidence (includes urticaria, vomiting, and anaphylaxis)	Dogs –	Cats –
	0%[36]	0%[16,17,20,62,63]
	0.3%[60]	0.9%[18]
	0.47%[2]	1.1%[64]
	3.3%[1]	3.2%[15]
	4.2%[3]	3.7%[14]
	6.6%[61]	

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. 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	**Definite:** Occurs less than 1 hour after the start of the transfusion **AND** Responds rapidly to cessation of transfusion and supportive treatment **AND** The patient has no other conditions that could explain clinical signs. **Probable:** Onset is between 1 hour after start and cessation

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.	of transfusion **OR** The patient does not respond rapidly to cessation of transfusion and supportive treatment **OR** There are other potential causes present that could explain clinical signs, but transfusion is thought to be the most likely cause.
	Possible: There are other conditions that could readily explain why clinical signs are present.

348

349   *Background and human literature*

350   Allergic transfusion reactions are caused by a type I hypersensitivity (IgE and mast cells)

351   response to a blood product. Severity varies from transient self-limiting reactions to life-threatening

352   anaphylaxis.[65,66] Reactions occur during the transfusion or within 4 hours of its cessation.[7] Diagnosis is

353   usually based on clinical findings of cutaneous (angioedema, urticarial, pruritus), respiratory (stridor,

354   dyspnea, wheezing, hypoxemia) and/or cardiovascular (hypotension and syncope) abnormalities.[7]

355   Generally, allergic reactions occur on the second exposure to an antigen, when primary

356   exposure to the antigen resulted in the production of antigen-specific IgE or IgG.[65,67] The systemic

357   response is rapid, with release of inflammatory mediators often occurring within seconds to minutes.

358   There appears to be a correlation between time of onset of clinical signs and reaction severity.[65]

359   Transfusion associated allergic reactions are often triggered by plasma protein antigens, with IgA and

360   haptoglobin described a causes in recipients lacking these proteins, although a specific allergen is

361   generally not detected.[28,68–70]

362   Allergic reactions are one of the most common adverse reactions in human transfusion

363   medicine, although their incidence rates vary markedly between studies, with mild reactions reported in

364   between 1 in 4000 and 7 in 1000 human transfusions.[11,69,71] Anaphylaxis is much rarer, occurring at rates

365   of 1 in every 20,000 to 30,000 transfusions. [69,71] The incidence varies between blood products, with

366   reactions being more common in platelet and plasma transfusions than in packed red blood cell

367   transfusions.[66,67,72] . Factors associated with increased risk of allergic transfusion reactions include

368   recipient hay fever,[73] recipient IgA and/or haptoglobin deficiency, [72] younger recipient age, [73]

369   administration of non-leukoreduced blood products, [74] and the administration of apheresis plasma and

370   platelets[66,75]

371   Allergic reactions occurring during or shortly after a transfusion could also be due to an allergen

372   other than the blood product such as a contact allergen or concurrently administered medication. Acute

373   hemolytic transfusion reactions, TRALI, and bacterial blood product contamination could present in a

374   similar manner to an anaphylactic reaction with hypotension and tachycardia and should be considered

375   as differential diagnoses.

376   Elevated tryptase levels are expected in patients that have had anaphylaxis or severe allergic

377   reactions, but the half life is short at 2 hours.[72] A basophil activation test or urine eicosanoid metabolite

378   measurement can also be used for diagnosis.[72,73] However, typical clinical signs are generally used to

379   make a presumptive diagnosis.

380   *Veterinary literature*

381   Allergic (type I hypersensitivity) reactions in dogs cause predominantly dermal (erythema,

382   urticaria (usually generalized), pruritis and angioedema (often localized to head, extremities, and

383   genitalia)) and gastrointestinal signs. More severe clinical signs consistent with anaphylaxis including

384   hemoabdomen, coagulopathy, collapse, hypotension, and upper respiratory tract signs have been

385   described in some cases.[76,77] In cats, respiratory and gastrointestinal signs predominate, although severe

386   pruritus can occur. [76]

387   Allergic transfusion reactions have been reported in the veterinary literature and appear to be

388   more common in dogs than cats and when plasma products are transfused, compared to pRBCs.

389   Cutaneous signs of facial swelling, angioedema and pruritis are reported in both dogs and cats and there

390   are reports of anaphylaxis in cats.[3,15,18,60] Vomiting is a recognized sign of an allergic reaction in both

391   dogs and cats and vomiting is reported during the transfusion period in many studies. However, given

392   the many possible reasons for vomiting, it can be difficult to determine if allergic transfusion reactions

393   are the cause.[1,3,15] Similarly, dyspnea is reported in several studies with no definitive diagnosis

394   determined, and anaphylaxis is one of several possible causes. [3,64]

395   *Areas for Further Research*

396   The true incidence of allergic transfusion reactions in dogs and cats is unknown and large

397   prospective studies are needed. Studies looking at possible predisposing factors such as age and prior

398   allergies are also needed. The use of tryptase levels, the basophil activation test or urine eicosanoid

399   metabolites for the diagnosis of allergic transfusion reactions could be investigated.

400   **Hemolytic Transfusion Reactions**

401   Hemolytic transfusion reactions include AHTRs and DHTRs and can be immunologic or non-

402   immunologic in nature. Immunologic HTRs are secondary to incompatibility of the transfused product

403   and the recipient. The magnitude of a HTR depends on multiple immunological factors to include the

404   class and subclass (in case of IgG) of the antibody, the ability of the antibody to activate complement,

405   the blood group specificity of the antibody, the thermal range of the antibody, the number, density and

406   spatial arrangement of the RBC antigen sites, the antibody concentration in the plasma and the amount

407   of antigen (RBCs) transfused. [78]   Non-immunologic HTRs occur due to thermal, osmotic, mechanical, or

408   chemical factors that damage transfused blood cells, causing acute or delayed hemolysis. Ex vivo

409   cellular damage may occur prior to transfusion as a result of bacterial contamination, prolonged storage,

410   excessive warming, or erroneous freezing of blood unit. [79,80] Improper administration techniques, such

411   as the addition of drugs or hypotonic intravenous fluids or trauma from extracorporeal devices may

412   cause damage to RBCs. This ex vivo cellular damage may lead to acute or delayed hemolysis of the

413   transfused RBCs in the patient.

414   **Acute Hemolytic Reactions**

415

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

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. Acute hemolytic transfusion reactions occur during or within 24 hours of blood product administration. Causes of AHTRs can be divided into blood type incompatibilities and other causes of damage to transfused blood cells. 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. 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: − 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). − Hemoglobinemia (plasma discoloration, instrument-based indicators of hemolysis) − Hemoglobinuria − Spherocytosis in dogs − Erythrocyte ghosts on a smear made immediately after blood collection. **AND** - Inadequate increase in PCV

	With or without: − New onset fever > 39.2°C (102.5F) − Tachycardia − Hypotension (systolic blood pressure <90-100mmHg) 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
	Possible: Other causes of acute hemolysis are more likely, but transfusion cannot be ruled out.

416

417   *Background and human literature*

418   The NHSN on Hemovigilance criteria for diagnosis of AHTR are new onset of back/flank pain,

419   chills/rigors, disseminated intravascular coagulation (DIC), epistaxis, fever, hematuria, hypotension,

420   oliguria/anuria, pain/oozing at IV site or renal failure during or within 24 hours of transfusion. Two or

421   more of the following should also be present- decreased fibrinogen, increased haptoglobin, elevated

422   bilirubin, elevated lactate dehydrogenase (LDH), hemoglobinemia, hemoglobinuria, plasma discoloration

423   consistent with hemolysis and/or spherocytes on blood film along with either a positive direct antibody

424   test (DAT) or direct Coomb's test for anti-IgG or anti-C3 plus positive elution test with alloantibody

425   present on the transfused RBCs for immune-mediated reactions or negative serologic testing and

426   confirmed physical cause for non-immunologic reactions.[7]

427   In humans, these reactions were historically responsible for the largest proportion of

428   transfusion-associated deaths, but this has changed with improved compatibility testing. They are

429   usually immunologic and usually caused by inadvertent administration of incompatible RBC transfusions

430   secondary to blood typing compatibility errors. The transfusion of incompatible plasma products is a less

431   common cause of AHTR. [82,83] Of the 355 transfusion associated fatalities reported to the FDA from 1976 -

432   1985, 158 (48%) were classified as acute immunological HTRs and 6 (2%) were classified as acute non-

433   immunological HTRs. Around 100 million units of RBCs were transfused in the USA during this time

434   frame so the reported incidence of fatal acute immunologic and non-immunologic HTRs was low at

435   approximately 1:1,100,000 units.[84] A more recent analysis of reactions reported to the NHSN on

436   Hemovigilance found that in 2015, acute immunologic transfusion reactions occurred at a rate of

437   1:200,000 units transfused and acute nonimmunologic transfusion reactions occurred at a rate of

438   1:105,000 units. [12]

439   *Veterinary literature*

440   The most common cause of AHTR in dogs and cats is mismatched transfusion, mainly due to

441   erroneous recipient, donor or unit identification and labeling. Non-immunologic causes are infrequently

442   reported in the veterinary literature.

443   Canine Immunologic AHTRs

444   Acute hemolytic transfusion reactions are uncommonly reported in dogs, likely due to both the

445   lack of naturally occurring DEA 1 antibodies and due to improved compatibility testing. While incidence

446   of AHTR is thought to be low, variability in definitions makes it difficult to compare studies. Appendix B

447   includes previously reported definitions of AHTR in the canine and feline literature.

448   An early case report described an AHTR resulting from DEA 1.1 incompatibility in a dog

449   previously sensitized to DEA 1.1 from a transfusion given 3 years earlier. The dog developed a fever,

450   pigmenturia, and lethargy within 2 hours of initiating the second transfusion. The donor blood was type

451   DEA 1.1 positive, whereas the recipient's blood was type DEA 1.1, DEA 1.2, and DEA 7 negative.[85] A

452   second case report describes alloimmunization of a DEA 4 negative dog resulting in increasingly severe

453   acute hemolytic transfusion reactions following subsequent DEA 4 positive transfusions. The clinical

454   picture and typing suggested development of anti-DEA 4 alloantibodies.[86] A third case report of an AHTR

455   after a second DEA 1 negative transfusion in a dog suggested sensitization to a common unidentified

456   antigen after the first blood transfusion.[87] In one retrospective case series, AHTR occurred in 2.4%

457   (5/211) blood transfusions with one fatality.[2] In another retrospective study, AHTR were noted in only

458   0.04% (4/935) transfusions with one fatality.[3]

459   Feline Immunologic AHTRs

460   Naturally occurring alloantibodies are well described in cats and can lead to potentially fatal

461   AHTR. Type B cats possess naturally occurring high-titered strongly hemolyzing and hemo-agglutinating

462   anti-A antibodies, predominately of the IgM class.[88] The transfusion of Type A RBCs to Type B cats can

463   result in rapid RBC destruction with an average half-life of 1.3 +/- 2.3 hours depending on the

464   alloantibody titer and destruction of all transfused RBCs within 24 hours.[88] A case report describes an

465   AHTR in a type B Abyssinian cat shortly after transfusion of type A whole blood, characterized by only

466   transient improvement in hematocrit, progressive lethargy, transient fever, icterus, and severe

467   hemoglobinuria. Subsequent transfusions with type B blood were uneventful.[89] In another case report, a

468   type B cat that was initially mistyped as AB developed recurrent anemia, hyperlactatemia,

469   hyperbilirubinemia, hemoglobinemia, hemoglobinuria and a positive slide agglutination test with 24

470   hours of receiving a unit of type A whole blood.[90]

471   Natural occurring alloantibodies against the *Mik* antigen have been described in cats and an

472   AHTR has been reported in a *Mik*-negative type A cat following inadvertent transfusion of *Mik*-positive

473   type A blood.[91] In another report of an AHTR in a transfusion naïve type A cat following transfusion with

474   type A whole blood, the nature of the offending alloantibody was unclear.[92] In a more recent study, 7 of

475   101 cats had AHTR and 3 of these had documented crossmatch (XM) incompatibility.[20]

476   Non-immunologic AHTRs

477   There are minimal descriptions of non-immunologic AHTR in veterinary species. One case series

478   describes four dogs that developed hemolysis, hemoglobinuria, or both, during or within 24 hours of

479   RBC transfusion. Two dogs died and one was euthanized due to severity and progression of clinical signs.

480   Blood type and compatibilities were confirmed for each case, making immunologic reactions unlikely.

481   Further investigation found no evidence of mechanical, chemical, or osmotic factors during product

482   administration and blood smear and 16s bacterial RNA polymerase chain reaction results from the

483   remaining lysed units failed to find evidence of bacterial contamination. Hemolysis of units secondary to

484   inappropriate storage was suspected as other blood units in the clinic refrigerator had increased free

485 hemoglobin. No further hemolyzed units or acute hemolytic reactions were seen after purchase of a

486 dedicated refrigerator and improvement in temperature monitoring and storage conditions. [79]

487 *Areas for further research*

488   The presence of clinically important naturally occurring alloantibodies is yet to be convincingly

489 demonstrated in dogs. In both cats and dogs, previous immunization with mismatched blood products

490 can lead to life-threatening AHTRs with subsequent transfusions.[86,87,93] The process by which these

491 different alloantibodies are induced or enhanced by previous immunizing transfusions is poorly

492 elucidated and it is unclear how they may impact future transfusion events.[81]

493   Further study is needed to further characterize naturally occurring and induced alloantibodies

494 against canine DEA 3, DEA 5, DEA 7, and Dal, and feline *Mik* antigens and other as yet unrecognized

495 antigens.

496   Future prospective studies evaluating the effect of XM on transfusion efficacy are warranted. In

497 addition, the establishment of a more feasible and reliable XM test, appears to be of growing

498 importance to prevent AHTR due to blood type incompatibilities in naïve and previously transfused cats.

499 The clinical importance of the detected alloantibodies outside the AB and *Mik* system still needs to be

500 determined.

501   Antibody screening is currently unavailable in veterinary medicine. Such testing would help

502 distinguish AHTRs from ongoing hemolysis in the setting of pre-existing intravascular hemolytic disease

503 as well as helping to differentiate immunologic from non-immunologic HTRs.

504 **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. Delayed hemolytic transfusion reactions occur 24 hours to 28 days after blood product administration. Immunologic DHTRs are typically caused by a secondary immune response to the donor's RBCs. 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 **AND** Delayed onset (24 hours - 28 days) of at least two indicators of red blood cell destruction (see AHTR definition) **AND** Evidence of RBC alloantibodies (for immunologic types) which developed between 24 hours and 28 days after transfusion	
	Probable:	

	Unexplained* decrease in PCV or hemoglobin >24 hours to 28 days after transfusion **AND** delayed onset (24 hours - 28 days) of at least two indicators of red blood cell destruction (see AHTR definition)
	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

505

506   *Background and human literature*

507   Immunologic DHTRs are classically caused by an anamnestic (secondary) immune response to

508   the donor's RBCs, in which the recipient possesses low-titer antibodies from previous RBC antigen

509   sensitization or has naturally occurring alloantibodies. Low-titer antibodies may be undetectable with

510   routine XM and antibody screening. After subsequent exposure to the same RBC antigen with

511   transfusion, the secondary immune response results in new antibody production, a significant rise in

512   titer, and delayed hemolysis. A primary immune response can also result in delayed hemolysis of RBC.

513   In this scenario, recipient antibodies are gradually formed over several days to weeks after first

514   exposure to a novel RBC antigen. Hemolysis occurs once sufficient antibody titers have been reached.

515   National Healthcare Safety Network (NHSN) on Hemovigilance defines a DHTR as a positive DAT

516   for antibodies that develops between 24 hours and 28 days after cessation of transfusion. A positive

517   elution test with alloantibody present on the transfused RBCs or a newly identified RBC alloantibody in

518   recipient serum, and either an inadequate rise of posttransfusion hemoglobin level or a rapid fall in

519   hemoglobin back to pretransfusion levels or the otherwise unexplained appearance of spherocytes is

520   also needed for confirmation. A DHTR is probable if a newly-identified RBC alloantibody demonstrated

521   between 24 hours and 28 days after cessation of transfusion but there is incomplete laboratory

522   evidence to meet definitive case definition criteria.[7] The Serious Hazards of Transfusion hemovigilance

523   scheme in the United Kingdom defines DHTRs as fever and other symptoms/signs of hemolysis more

524   than 24 hours after transfusion, confirmed by a fall in hemoglobin or failure of increment, rise in

525   bilirubin, and/or an incompatible XM not detectable before transfusion.[66]

526   Patients may have no apparent clinical signs with DHTRs or in more severe reactions, the clinical

527   signs may be like an AHTR with fever, nausea or vomiting, tachycardia, hypotension,

528   tachypnea/dyspnea, and pain. Red blood cell destruction may occur gradually with DHTRs as antibody

529   synthesis increases over days. As the PCV falls, the patient may become more clinical for the anemia

530   and display vague signs such as lethargy, weakness and/or inappetence. Fever is associated with HTRs.

531   The production of inflammatory cytokines is a consequence of the humoral and cell-mediated

532   immunological reactions that mediate HTRs. Most hemolysis observed with DHTRs is extravascular as

533   determined by involvement of the immunoglobulin IgG and the antibody specificities of the blood types.

534   The incidence of DHTRs in human and veterinary medicine is likely to be underestimated as

535   many patients are asymptomatic and the drop in PCV may go undiagnosed or attributed to other

536   etiologies. In human transfusion medicine, DHTRs are commonly associated with a secondary immune

537   response and the majority of the DHTR publications revolve around sickle cell disease. There are case

538   reports of DHTRs associated with naturally occurring alloantibodies in humans.[94–97]

539   *Veterinary literature*

540   DHTR are reported in the veterinary literature following xenotransfusion of canine blood to the

541   feline species. Early studies suggested that cats do not have detectable naturally occurring antibodies

542   against canine RBCs as assessed by compatible pre-transfusion testing (slide autoagglutination and in

543   vitro hemolysis tests).[98–100] These studies documented production of antibodies against canine RBCs

544   within 4-7 days of transfusion as evaluated by daily slide agglutination and in vitro hemolysis testing.[98–

545   100] The lifespan of transfused radiochromium-labeled canine RBCs into 7 cats was determined to be an

546   average of 3.6 days (maximum 5.4 days).[99] The average lifespan of compatible feline to feline transfused

547   RBCs is 30 days.[101] Repeated xenotransfusion of canine blood to many of these cats > 6 days after initial

548   transfusion resulted in severe anaphylactic reactions and death. Since these initial studies, case reports

549   of successful xenotransfusion with no acute or delayed adverse reactions have been published.[102–105]

550   Recent canine-to-feline xenotransfusion studies have revealed incompatible pre-transfusion major and

551   minor XM testing suggesting the presence of naturally occurring alloantibodies in both species.[92,106] In a

552   2019 prospective canine-to-feline xenotransfusion study, DHTRs occurred in 25 of 39 (64%) cats with no

553   significant difference between cats with compatible or incompatible pre-transfusion XM.[106] DHTRs

554   occurred at a median of 2 days (range 1-6 days) after xenotransfusion in cats with incompatible major

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

556   Delayed hemolytic transfusion reactions are described following feline AB-mismatched

557   allogeneic transfusions. While Type B cats possess high-titer, strongly antigenic IgM antibodies, Type A

558   cats have low alloantibody titers consisting of IgG and IgM classes. The transfusion of Type B RBCs into

559   Type A cats can result in DHTRs with a mean half-life of 2.1 +/- 0.2 days.[88]

560   Early canine blood group studies suggest that the presence of induced alloantibodies in dogs,

561   such as those against DEA 3, 5 and 7, may be associated with accelerated clearance over three to five

562   days in DEA 3, 5, or 7 negative dogs transfused with DEA 3, 5 or 7-positive RBCs, respectively.[107] The

563   experimental data investigating DHTRs relevant to these DEA blood types is limited and complicated by

564   changes in blood group nomenclature over the years. The presence of anti-DEA 7 antibodies in DEA 7-

565   negative dogs ranges from 0% to 38%.[81,108,109] Further research documented that in 23% of DEA 7-

566   negative dogs, low titers (<1:2 in 73% of samples) of warm, weakly agglutinating, mostly naturally

567   occurring mostly IgM (69%) anti-DEA 7 antibodies were found. [110] The anti-DEA 7 antibodies evaluated *in*

568   *vitro* showed no hemolytic activity, although titers were low and samples were collected in EDTA, which

569   can inhibit complement-based lytic activity. *In vivo* evaluation of the transfusion of DEA 7-positive RBCs

570   to the patients with naturally occurring anti-DEA 7 antibodies was not performed. After chromium-

571   labeled DEA 7-positive RBCs were administered to dogs with anti-DEA 7 antibody, the labeled RBCs were

572   absent after four to five days.[111] There are no reports of DEA 3, 5 or 7 related acute or delayed HTRs in

573   clinical patients.

574   *Areas for further research*

575   The incidence of DHTRs in veterinary medicine is unknown. Clinical recognition of delayed

576   hemolysis days after a transfusion is challenging and may be complicated by lack of follow up, primary

577   disease processes such as immune-mediated hemolytic anemia, or masking by the patient's

578   regenerative response. Prolonged prospective clinical studies following pre- and post-transfusion

579   clinicopathologic parameters (PCV, serum total bilirubin, etc.) and pre- and post-transfusion XM

580   compatibility to donor RBCs and/or DAT may expand our understanding of delayed immunologic

581   transfusion reactions.

582   **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 **OR** 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)

	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.
	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.

583

584   *Background and human literature*

585   Delayed serologic transfusion reactions are caused by alloimmunization to a RBC antigen that

586   the recipient lacks. Reactions can be seen after a first transfusion due to naturally occurring

587   alloantibody or as antibody first develops, or as an anamnestic response if a recipient is transfused again

588   with the same antigen.   Delayed serologic transfusion reactions were first recognized in 1995 and are

589   sometimes termed "silent DHTRs". Delayed serologic transfusion reactions are defined as DHTRs as

590   soon as hemolysis is detectable.

591   In humans, DSTRs are well described with evidence of newly formed antibody to transfused

592   antigen and no associated clinical signs. Identification involves serologic testing of both the donor and

593   recipient blood and extensive serologic testing to detect new antibody is available.[112,] Definitive DSTRs

594   can be diagnosed in patients that have a negative DAT pre-transfusion and/or a negative major cross

595   match and indirect antiglobulin test (IAT) and a positive DAT and IAT 24 hours to 28 days following

596   transfusion.[113] It can be more difficult to definitively diagnose a DSTR in patients with a positive DAT as

597   part of their underlying disease process, such as immune-mediated hemolytic anemia (IMHA).

598   Development of alloantibodies is mediated by many factors. Recipient considerations include

599   phenotypic disparity between blood types of donor and recipient, recipient HLA presenting foreign

600   antigen, genetic predisposition to "respond," health status at the time of antigen exposure, prior

601   exposure including non-red cell exposure (platelets and leucocytes), and exposure during pregnancy or

602   transfusion. Donor factors include genetic factors that may impact RBC storage characteristics, length of

603   RBC storage, presence of contaminating white blood cells and platelets, and antigen dose.[114]

604   *Veterinary literature*

605   There are occasional reports of DSTRs within the veterinary literature.[115] Canine and feline blood

606   typing and cross matching literature describes alloimmunization that may represent DSTRs but are not

607   defined specifically as DSTRs. [81,116,117]

608   Early studies demonstrated that positive DAT (and IAT against donor blood sample) developed

609   4-7 days following transfusion of DEA 1-positive red cells to a DEA 1-negative donor and the transfused

610   red cells were sometimes removed from circulation prematurely without overt hemolysis. [107,118]   The

611   recipients developed anti-DEA 1 antibody and if exposed to this antigen again, an AHTR developed. The

612   initial reaction could be defined as a DSTR or mild DHTR that on anamnestic response becomes a type II

613   hypersensitivity hemolytic reaction or true AHTR.

614   Other DEA blood types have been defined as having naturally occurring antibody (DEA 3, 5 and

615   7) in antigen negative phenotypes and display varying degrees of reaction on exposure to DEA 3, 5 and 7

616   positive donated blood, respectively. As naturally occurring alloantibody – these reactions will show up

617   post first transfusion (there is no prior transfusion or pregnancy required) as a delayed reaction. The

618   most well defined of these is DEA 7[108,119,120]

619   DEA 6 and 8 are poorly defined and antisera is no longer available. It is suspected that they may

620   also produce an alloantibody response in negative recipients receiving positive blood. [107,118,121]

621   DEA 4 has been further defined and is identified to produce an alloantibody that causes an acute

622   reaction on re exposure. As a very commonly found antigen, recognition of this reaction is uncommon

623   and poorly defined but is illustrated in one case report.[122] The case report can be interpreted to imply

624   that antibody development to DEA 4 may take a few weeks consistent with a DSTR followed by an AHTR

625   with subsequent exposure.

626   *Dal*, a common antigen in most dogs has been defined as lacking in a higher percentage of some

627   breeds (Dalmatian, Doberman, Lhasa Apso and Shih Tzu). [123–125]   Delayed alloimmunization occurs 4

628   days to a few weeks after transfusion of *Dal*-positive blood to a *Dal*-negative recipient.[123] *In vivo*

629   characterization of the reaction that this causes on repeat exposure is yet to be demonstrated.

630   *Areas for further research*

631   Recognition that DSTRs can occur in transfused animals may increase the number of cases

632   reported. More comprehensive understanding of canine blood types is required to permit recognition

633   and categorization DSTRs in canine transfusion medicine and will enable collection of relevant samples

634   to better define alloantibodies. An international effort to reestablish a universal canine erythrocyte

635   antigen naming system and collaborate to generate a library of sensitized sera is needed.[126]

636   **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. 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. 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: I) laboratory evidence of a pathogen in a transfused blood product **AND/OR** evidence of the pathogen in the donor at the time of donation **AND/OR** evidence of the pathogen in an additional component from the same donation **AND/OR**	

	evidence of the pathogen in an additional recipient of a component from the same donation;
	II) **AND**
	no other potential recipient exposure to the pathogen;
	III) **AND EITHER** evidence that the recipient was not infected with the pathogen prior to transfusion.
	IV) **OR** the identified pathogen strains are related by molecular or extended phenotypic comparison.
	Probable: ONE or more of the following:
	I) laboratory evidence of a pathogen in a transfused blood product
	AND/OR

	evidence of the pathogen in the donor at the time of donation
	AND/OR
	evidence of the pathogen in an additional component from the same donation
	AND/OR
	evidence of the pathogen in an additional recipient of a component from the same donation;
	II) AND EITHER evidence that the recipient was not infected with this pathogen prior to transfusion;
	III) OR no other potential exposures to the pathogen could be identified in the recipient.
	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.

637

638 *Background and human literature*

639   A TTI is defined as laboratory evidence of a pathogen in the transfusion recipient with evidence

640 that the recipient was not infected with the pathogen prior to transfusion. [7] Transfusion transmitted

641 infection can arise from bacterial contamination of blood or blood components or from infectious

642 pathogens carried by the blood donor. Bacterial contamination can arise from bacteria from the donor's

643 skin during the collection procedure, unrecognized bacteremia in the donor, contamination from the

644 environment or during the preparation of components, or contamination of ports during the thawing of

645 frozen products in a water bath. [127] Bacterial infection is more common with platelets units (as these are

646 stored at room temperature for preservation of function), previously frozen components thawed by

647 immersion in a water bath such as frozen plasma units, and red cell components units as PRBC or WB

648 units stored for several weeks. [127]

649   The concentration of bacteria in blood components just after collection is generally too low to

650 detect or cause symptoms in the recipient. However, bacteria can multiply during component storage,

651 particularly in room temperature platelet concentrates. [128]

652   Both gram-positive and gram-negative organisms have been implicated in transfusion

653 transmitted bacterial infection in humans, with serious morbidity and mortality occurring most

654 frequently with gram-negative bacteria. [129] Organisms capable of multiplying at low temperatures and

655 those using iron as a nutrient are most often associated with red cell contamination. [127] Bacterial sepsis

656 account for at least 10% of transfusion-associated fatalities in human. [129]

657   Septic transfusion reactions usually present during or within 4 hours of transfusion. [130] [131]

658   Bacterial contamination is a differential diagnosis when transfusion recipients become febrile or

659   hypotensive following transfusions. [132] Other clinical features suggesting bacterial contamination and/or

660   endotoxin reaction include rigors, severe chills, tachycardia, nausea and vomiting, dyspnea, or

661   circulatory collapse during or soon after transfusion. In severe cases, the patient may develop shock

662   with accompanying renal failure and DIC. [127] [130]

663   *Veterinary literature*

664

665   Reports of bacterial contamination of blood units in veterinary medicine are less frequently

666   described than in human medicine, likely because fresh platelet transfusions are less common in

667   veterinary medicine. Percentage of negative bacteriological units was high (94-100%) in studies on feline

668   [133–138] and canine blood and plasma products [139–142].

669   Contaminants documented in veterinary blood units have included gram-negative (*Escherichia*

670   *coli* [143] *Pseudomonas* spp., [143] [144,145] *Serratia* spp.,[143145135,146] *Caulobacte*r spp., [143] *Ralstonia* spp. [133]) and

671   gram positive (*Enterococcus* spp*.,* [143] *Propionobacterium* spp., [143] *Corynebacterium* spp., [143,147]

672   *Leucobacter* spp., [143] *Bacillus* spp., [147] *Staphylococcus* spp.[133]) bacteria. In most reported cases of blood

673   bacterial contamination, it could not be determined if the contamination occurred during blood

674   collection or blood bag processing and storage. [145] However, contamination during blood collection may

675   be more common. [135] In one study, a jar of alcohol-soaked cotton balls and a saline solution used during

676   sedation and venipuncture of donors were found to be the sources of contamination. [146] Some authors

677   have hypothesized contamination of the anticoagulant CPDA or contamination during the manipulations

678   for microbiological evaluation. [133]

679   Infectious pathogens able to be transmitted by blood transfusion in veterinary medicine are

680   reported in Table two. These pathogens are documented: I) to be transmitted (experimentally or

681   clinically) by blood transfusion or by intravenous blood injection in canine and feline patients; and/or II)

682   to survive in stored blood units.

683   In the veterinary literature, few data are available on frequency of TTI and most publications are

684   case reports. A study of 101 cats had a single incident of transmitted *Mycoplasma haemominutium.* [20]A

685   study in dogs reported new infections in 11/211 (5.2%) receiving PRBC transfusion but these did not

686   appear to be directly related to the blood units. [2]

687   The outcome of a contaminated transfusion is highly dependent on the number of organisms

688   transfused, the type of organism and its pathogenicity for dogs and cats, the rate of transfusion, and the

689   clinical status of the recipient. Immunosuppression of the blood recipient, including splenectomy, is a

690   risk factor for development of a TTI. [148–150] However, transfusion with a large load of endotoxin-

691   producing gram-negative bacteria can cause rapid death in healthy individuals. In veterinary patients,

692   the clinical outcome of transfusion of bacterial contaminated units has ranged from no reaction;[133,143,146]

693   vomiting, collapse, diarrhea, icterus, panting, pyrexia/fever, abscess;[146] hypotensive shock syndrome;[151]

694   and death. [146] In a case series of 15 *Serratia marcescens* contaminated units administered to 14 cats, 6

695   developed clinical signs of a transfusion reaction and 4 of these cats died. The most common clinical sign

696   was vomiting. [146]

697   A study of canine WB units showed a low percentage of positive bacterial cultures but a higher

698   percentage positive by qPCR testing. Despite the bacterial positivity, no transfused recipient had an

699   immediate or delayed adverse transfusion effect. [143] The acceptable level of contamination is unknown.

700   *Areas for further research*

701   Further studies are needed to determine the most sensitive and specific methods to screen for

702   blood donor infectious diseases and blood product contamination. In addition, further studies are

703   needed to define a cutoff for acceptable bacterial load in products that would still allow transfusion.

704   **Citrate toxicity/hypocalcemia**

705

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. **AND** compared to pretransfusion levels, a decrease in ionized calcium to <0.7 mmol/L; **AND** development of seizures, tremors, ptosis, vomiting (nausea), hypotension, QTc prolongation, salivation, tachycardia, salivation, or facial swelling.
	Probable: Patients receiving massive transfusions with impaired hepatic function. **AND** compared to pretransfusion levels, a decrease

	in ionized calcium to between 0.71 and 0.8 mmol/L; **AND** development of vomiting (nausea), QTc prolongation, salivation, tachycardia, or facial swelling.
	Possible: Patients receiving massive transfusions with impaired hepatic function. **AND** compared to pretransfusion levels, a decrease in ionized calcium to between 0.81 and 0.9 mmol/L; **AND** development of vomiting (nausea), QTc prolongation, salivation, tachycardia, facial swelling.

706

707

708   *Background and human literature*

709   Citrate is primarily metabolized by the liver, but with poor hepatic function or failure, the

710   amount of citrate administered can exceed hepatic metabolic capacity and lead to calcium and

711   magnesium chelation with resultant ionized hypocalcemia and ionized hypomagnesemia. Blood

712   products that contain the greatest amount of citrate, such as fresh frozen plasma, will cause the

713   greatest amount of calcium chelation.

714   Most patients that develop citrate toxicity have received massive transfusion, and the continued

715   administration of citrate containing blood product enhances the severity of hypocalcemia. Additional

716   complications associated with citrate toxicity include metabolic alkalosis, and hypernatremia, if sodium

717   citrate is used as an anticoagulant. [152]

718   The severity of clinical signs is associated with the degree of hypocalcemia. In humans, an

719   ionized calcium of <0.9 mmol/L is associated with increased mortality and <0.8 mmol/L increases

720   adverse cardiac effects. Ptosis can be the first clinical sign at 0.65-0.7 mmol/L and tremors and

721   convulsions will develop at <0.4 mmol/L. Additional clinical signs include vomiting, nausea, hypotension,

722   QTc prolongation, salivation, tachycardia, salivation, or facial swelling.[153] Diagnosis is based on the

723   presence of ionized hypocalcemia (and/or ionized hypomagnesemia), during or shortly after a

724   transfusion, without another identifiable cause of the hypocalcemia.

725   *Veterinary literature*

726   The evaluation of ionized calcium after transfusion and massive transfusion has been evaluated

727   in laboratory animals and clinical patients receiving citrate and citrated blood products. The

728   administration of citrate to dogs decreases the ionized calcium, ionized magnesium, and causes nausea

729   and vomiting. At higher doses of citrate, dogs develop tachycardia, prolongation of the QT interval and

730   QTc, T-wave inversion, depressed cardiac output, reddening of the pinna, facial swelling, and salivation.

731   Most clinical signs of citrate toxicity start to resolve within one hour of stopping the citrate infusion, and

732   are almost completely resolved within two hours. [154,155] A retrospective review of calcium disorders

733   reported citrate toxicity after transfusion as the cause of hypocalcemia in 6% of cats and 4.7% of dogs.

734   This study did not further define clinical signs or incidence related to number of transfusions.[156]

735   In 6/15 dogs undergoing massive transfusion, there was a significant decrease in ionized

736   calcium and ionized magnesium.[157] The adverse reactions noted in this study included fever (3), vomiting

737   (1), facial swelling (1), and delayed hemolysis (1).[157] A case report documented declining ionized calcium

738   concentration following 5 units of pRBCs, 3 units of plasma, and 1.2 L of autotransfusion.[158] The use of

739   auto-transfusion alone does not appear to significantly decrease the ionized calcium.[159,160] The use of

740   massive transfusion in cats is poorly reported. There were no clinically relevant changes in ionized

741   calcium or magnesium in a report of one cat that received 3 units of blood.[161]

742   *Areas for further research*

743   The incidence of citrate toxicity in veterinary medicine is likely uncommon but is difficult to

744   determine as this reaction is poorly documented. Recognition that the condition occurs in transfused

745   animals may increase the number of cases reported.

746

747   **Transfusion-related hyperammonemia**

748

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.

749

750   *Background and human literature*

751   Human cellular blood products such as WB and PRBCs accumulate ammonia during storage due

752   to cellular metabolism. [162–165] Ammonia rapidly accumulates in platelets concentrates stored at room

753   temperature and also increases in plasma units stored at 4°C for 68 days and at -20°C for 5 and 8

754   months. [163,166] High ammonia concentrations in blood components could result in toxicity, particularly in

755   recipients with hepatic dysfunction, as the healthy liver extracts 80% of the ammonia during first blood

756   pass in humans.[167] Clinical signs of transfusion related hyperammonemia include altered mental status

757   with ataxia, dementia, head pressing, circling, and seizures after blood product administration [168].

758   Infants with transient hyperammonemia can experience seizures, coma, respiratory distress, apnea,

759   lethargy, hypotonia, and intracranial bleeding.[169]

760   *Veterinary literature*

761   Ammonia increases significantly during storage in canine PRBC units, in which mean values

762 reached 466 mmol/L on day 28, 562 mmol/L on day 35 [170] and 1091 mol/L on day 42 of storage. [142]

763 Storage of feline WB [137,171] and PRBC units [136,137] resulted in mean values of 909 µg/dl and 1058 µg/dl

764 respectively, after 35 and 42 days of storage. [137]

765   The clinical significance of blood unit related hyperammonemia in veterinary medicine is yet to

766 be determined. Plasma ammonia concentration remained in the normal reference range in 5 anemic

767 dogs without primary liver disease transfused with 5-10 ml/kg of stored pRBC. [170] A textbook discusses

768 hyperammonemia resulting in neurologic signs such as ataxia, dementia, head pressing, circling,

769 seizures, and vomiting in veterinary patients.[172] However, there are no published reports of elevated

770 ammonia concentration and documented signs of hepatic encephalopathy in dogs and cats receiving

771 stored blood products.

772   Risk factors for develop transfusion-related hyperammonemia are: using outdated blood

773 products in which ammonia has accumulated; transfusion recipients with liver disease/hepatic

774 dysfunction including portosystemic shunts that are unable to metabolize and excrete ammonia

775 properly; [173] premature neonates with immature liver function; and recipients receiving large transfusion

776 volumes and with hypoperfusion secondary to shock.[157]

777 *Areas for Further Research*

778 Large scale measurement of ammonia in canine and feline blood components and in transfusion

779 recipients is needed to better understand the clinical significance of hyperammonemia.

780 **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;
	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.
	Possible: The development of severe hypotension but other conditions or causes of

	hypotension could be identified.

781

782   *Background and human literature*

783   Most HyTRs occur within minutes to hours of starting a transfusion, and are most commonly

784   identified with red cell transfusions. [174–177] HyTRs develop following activation of coagulation factor XII,

785   which causes the conversion of high-molecular-weight kininogen to bradykinin, leading to vasodilation

786   and increased vascular permeability.[174] Bradykinin is primarily metabolized via angiotension-converting

787   enzyme (ACE), and the use of ACE inhibitors before or during a transfusion has been associated with the

788   development of HyTRs. [174,175,178] Additionally, the use of post-storage, bedside leukoreduced blood

789   products that activate kinin-mediated pathways and increase bradykinin have been associated with an

790   increased risk of developing HyTRs.[174,175,178] Hypotension can develop during other transfusion reactions

791   (septic, AHTRs, TRALI, anaphylaxis/anaphylactoid), but are not classified as a HyTR. Although transient,

792   HyTRs produce a dramatic decrease in blood pressure that improves with stopping the transfusion and

793   supportive care. The hypotension usually recurs if a transfusion is restarted with the same blood product

794   Clinical signs of HyTRs are associated with severe hypotension, but can cause nonspecific

795   findings, such as abdominal pain, nausea, dyspnea, tachypnea, and dizziness.[176] A diagnosis of HyTR

796   occurs if: i.) there is a significant drop in blood pressure during a transfusion, or within 1 hour of

797   stopping the transfusion, ii.) the systolic blood pressure decreases by 30 mmHg, or >25% reduction from

798   baseline in pediatric patients, and iii.) an underlying cause cannot be identified.[176] Replacing an ACE

799   inhibitor with a medication with a different mechanism of action prior to transfusion and using pre-

800   storage, rather than post-storage, leukoreduction may decrease the risk of HyTRs.[174] Treatment for a

801   HyTR consists of stopping the transfusion, treating the hypotension, and providing supportive care.[174,176]

802   The use of post-storage blood product washing may also decrease the risk of HyTRs.[179]

803   *Veterinary literature*

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

805   identified in clinical and research transfusion settings but the hypotension was attributable to other

806   causes.[151,180–182]

807   *Areas for further research*

808   The incidence of HyTR in veterinary medicine is likely rare, but this is difficult to determine as

809   the condition is poorly documented. Recognition that such a condition can occur in transfused animals

810   may increase the number of cases reported.

811   **Posttransfusion Purpura (PTP)**

Post-transfusion purpura (PTP)		
Incidence	**Dogs -** Single case report[183]	**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	
	Probable: There are other possible causes but transfusion is most likely	
	Possible: Other causes are more likely but transfusion cannot be ruled out	

812

813 *Background and human literature*

814   Posttransfusion purpura (PTP) is a rare condition caused by alloimmunization against platelet

815 antigens and is thus associated with patient antibodies directed against a platelet antigen that the

816 patient lacks. Upon subsequent exposure to blood products containing the platelet antigen, PTP can

817 develop. The vast majority of reported PTP cases in people involve antibodies directed against the

818 human platelet antigen (HPA)-1a. Risk factors include previous red cell or platelet transfusions, or in

819 man, previous exposure to fetal platelet antigens, seen in multiparous women.[184–187]

820   Although an alloantibody is involved, there is destruction of the patient's own platelets leading

821 to thrombocytopenia. A number of mechanisms for this have been proposed: i) formation of immune

822 complexes lead to destruction of autologous platelets, through an innocent bystander model ii)

823 transfused platelet antigens adsorb onto the patient's own platelets, leading to immune-mediated

824 destruction; iii) a platelet-specific autoantibody is produced along with the alloantibody, and destroys

825 the patient's own platelets.[186]

826   Clinical signs are those typically seen with severe thrombocytopenia, such as petechial

827 hemorrhages, epistaxis, or other bleeding from mucosal sites.[184] Diagnosis is based on the presence of a

828 thrombocytopenia, often severe, within 5-12 days following a transfusion.[184] PTP is then confirmed by

829 detection of circulating antibodies against platelet specific antigens, usually via ELISA or solid phase

830 techniques. When platelet assays are unavailable, the diagnosis may become one of exclusion, where

831 other conditions, such as disseminated intravascular coagulation, drug induced thrombocytopenia,

832 autoimmune thrombocytopenia, or marrow failure are considered. Flow cytometry can also be used to

833 assess the presence of platelet surface associated immunoglobulins.[164,184,187,188]

834 *Veterinary literature*

835   Only one case of PTP has been documented in the veterinary literature. It involved a 5-year-old

836   intact male German Shepherd with hemophilia A that developed thrombocytopenia (10,000

837   platelets/μL) 8 days after transfusion with 450 mL of fresh whole blood and 200 mL of fresh frozen

838   plasma. Serum taken at the time of the thrombocytopenia had positive test results for platelet-binding

839   IgG.[183]

840   *Areas for further research*

841   The incidence of PTP in veterinary medicine is likely rare, but this is difficult to determine as the

842   condition is poorly documented. Recognition that such a condition can occur in transfused animals may

843   increase the number of cases reported.

844   **Transfusion associated graft versus host disease (TA-GVHD)**

Transfusion-associated graft vs. host disease (TAGVHD)	
Incidence	Research reports in dogs only[189]
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%).	Definite: Lymphocyte chimerism is identified in absence of other causes of chimerism
	Probable: Lymphocyte chimerism is identified; other causes of chimerism exist
The reaction is characterized by a skin rash, diarrhea,	Possible: Chimerism negative or not investigated; other explanations more likely.

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.	

845

846 *Background and human literature*

847 Transfusion associated graft versus host disease (TA-GVHD) is a rare and often fatal complication of

848 blood transfusion in people. [7,66] TA-GVHD was initially considered to occur only in immunocompromised

849 individuals. However, more recent reports describe TA-GVHD in immunocompetent individuals in

850 circumstances such as transfusion of blood from an HLA-homozygous donor to an HLA-heterozygous

851 recipient who shares one haplotype, or due to transient immunosuppression.[190–192]

852 TA-GVHD is diagnosed by characteristic clinical signs (skin rash, diarrhea, hepatomegaly), laboratory

853 findings (hepatic dysfunction, pancytopenia secondary to bone marrow hypoplasia) plus histological

854 findings. Imputative diagnosis is considered when chimerism is demonstrated in blood or tissues.[7] A

855 recent review suggests that milder or atypical cases of TA-GVHD are misdiagnosed or unrecognized.[192]

856 Clinical signs develop between 48 hours to >6 weeks after cessation of transfusion; median time to

857 develop the first symptom was 11 days in one systematic review. This condition is associated with a high

858 mortality rate (>90%).[190,191,193]

859 *Veterinary Literature*

860   There are no reported risk factors of TA-GVHD in veterinary patients. Press, et al. speculate that it could

861   become a concern with increasing frequency of stem cell transplantation in animals, and showed that

862   irradiation of canine red cells did not cause significant morphological or biochemical alterations.[194]

863   One veterinary study repeatedly transfused un-irradiated leukocytes in dogs, and the dogs all developed

864   GVHD. A parallel group was transfused with irradiated leukocytes on a similar schedule. The study

865   revealed that certain doses of irradiation prevented the development of TA-GVHD.[189]

866   *Areas for further research*

867   TA-GVHD is likely rare in veterinary medicine outside of experimental conditions. Awareness of this

868   reaction could become important if stem cell transplantation becomes more frequent in veterinary

869   patients.

870

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1356 **Table One: 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

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1360   **Table Two** Infectious pathogens documented as capable to be transmitted by blood transfusion in

1361   veterinary medicine.

Bacteria	Virus	Parasite
Haemobartonella canis [148,149] – dog	**FeLV** [201] (included FeLV provirus)[202] – cat	*Babesia gibsoni* [204 205,206] – dog
Candidatus **Mycoplasma haematoparvum** [150] – dog	**FIV** [203] – cat	*Babesia canis* [149,151] – dog
Anaplasma phagocytophilum [195] – dog		*Leishmania* **spp.** [207–209] – dog
Rickettsia conorii [196] – dog		*Cytauxzoon* **spp** [210,211] – cat
Bartonella henselae [197,198] – cat		
Mycoplasma haemofelis, [199]		
'*Candidatus* **Mycoplasma haemominutum'** [200] – cat		

1362   *FeLV: feline leukemia virus; FIV: feline immunodeficiency virus*

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1365   **Appendix A: Veterinary Definitions and Incidence of Febrile Transfusion Reactions**

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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. Excluded as a fever if the temperature was elevated prior to transfusion
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.

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1370   **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.
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.

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