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Xenotransfusion of canine blood to cats: a review of 49 cases and their outcome.

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Abstract

Objectives: To describe the use of a xenotransfusion protocol, the outcome of xenotransfusion in recipient cats and to assess owner memory of the xenotransfusion.

Methods: Cats administered xenotransfusions in two hospitals between January 2016 and July 2018 were included. Adherence to xenotransfusion protocol, cause of anaemia, blood type, packed cell volume (PCV), transfusion volume, transfusion reactions, PCV 12 hours after transfusion and survival to discharge were recorded. Owners of surviving cats were questioned to assess if they remembered that a xenotransfusion had been performed.

Results: Forty-nine cats underwent the xenotransfusion protocol. The most common causes of anaemia were surgical blood loss (n = 17), immune-mediated haemolytic anaemia (n = 14) and neoplasia (n = 14). Median PCV before transfusion was 10%. Six cats (12%) had febrile non-haemolytic transfusion reactions. Median PCV 12 hours after transfusion was 25%. Ten cats (20%) died or were euthanased within 24 hours of xenotransfusion. A delayed haemolytic transfusion reaction occurred in 25 of 39 (64%) cats manifesting as icterus in 15 cats after a median of 1.9 days and haemolytic serum in 19 cats after a median of 2 days. Of the 18 cats alive at 1 week after discharge, 15 (83%) were still alive at a median of 173 days after xenotransfusion. All owners contacted remembered that their cats had received a xenotransfusion.

- 25 **Clinical significance:** Xenotransfusion of canine blood to cats is possible but haemolysis should be expected
- 26 between 1 and 6 days post transfusion. Repeat transfusion with feline blood is often required.

27 Introduction

28 Xenotransfusion of canine blood to cats is a recognised veterinary technique, having been used to treat
29 anaemic cats in emergencies when compatible feline blood was not available (Oron et al. 2017, Bovens &
30 Gruffydd-Jones 2013). Although in vitro data suggest that transfusion of cats with dog blood could cause an
31 acute haemolytic transfusion reaction (Euler et al. 2016, Priolo et al. 2018), no severe acute adverse
32 reactions have been reported in cats receiving a single canine blood transfusion (Bovens & Gruffydd-Jones
33 2013, Klainbart et al. 2018). However, delayed haemolytic transfusion reactions are frequent and fatal
34 anaphylaxis has been described following repeated xenotransfusion (Hessler et al. 1962, René 1968, Lautié
35 et al. 1969, Bovens & Gruffydd-Jones 2013). Despite this, canine to feline xenotransfusion has regained
36 popularity because of the withdrawal of Oxyglobin from the market and the relative difficulty of sourcing
37 feline blood donors. Although there have been some recent clinical reports of successful xenotransfusion
38 (Oron et al. 2017, Weingram et al. 2014, Klainbart et al. 2018), large studies and literature regarding the peri-
39 transfusion time period, long-term follow-up and owner awareness of the significance of xenotransfusion
40 are lacking.

41

42 Indications for feline transfusion with feline blood products have been well described (Barfield & Adamantos
43 2011), but no protocol has been described to help clinicians decide when xenotransfusion is appropriate.
44 Reported clinical indications for xenotransfusion include previous transfusion reaction to feline blood (Euler
45 et al. 2016), insufficient time to blood type the recipient (Oron et al. 2017), non-readily available compatible
46 feline blood products (Oron et al. 2017, Weingram et al. 2014, Euler et al. 2016, Klainbart et al. 2018),
47 financial constraints (Weingram et al. 2014, Klainbart et al. 2018) and life-threatening emergencies (Oron
48 et al. 2017, Euler et al. 2016, Klainbart et al. 2018).

49

50 The aims of this study were to describe a xenotransfusion protocol and assess adherence to this protocol, to
51 describe the clinical situations in which xenotransfusion was used, to determine crossmatch compatibility
52 between canine donors and feline recipients and its relevance, to describe the short- and long-term

53 outcomes of cats administered a xenotransfusion, and to determine whether owners remembered that their
54 cat had received a xenotransfusion and that repeat xenotransfusion was contraindicated.

55

56 Material and methods:

57 This was a prospective observational study. All cats receiving a xenotransfusion at two university teaching
58 hospitals between January 2016 and July 2018 were enrolled in the study. In case of unavailability of
59 appropriate feline blood products or donors, a xenotransfusion protocol was applied, that required fulfilment
60 of set criteria (document 1, Supporting Information). If the clinicians involved in the case considered the cat
61 likely to die within 6 hours without blood product administration due to the severity of their clinical signs they
62 were considered potential candidates for transfusion. In the absence of suitable feline blood products, the
63 clinicians then had to ensure the cat had never been administered dog blood previously and obtain informed
64 consent for xenotransfusion from the owners. A member of the hospital Transfusion Medicine Service had to
65 review the case and agree to the patient's suitability for xenotransfusion. The owners were then informed of
66 the risks of sudden death, rapid haemolysis and likely requirement for a subsequent transfusion with feline
67 blood products. They were also informed that xenotransfusion could not be repeated. For the cats that were
68 discharged, written instructions that reiterated this information were given to the owners.

69

70 Adherence to the xenotransfusion protocol, recipient signalment, pre-transfusion PCV, cause of anaemia,
71 xenotransfusion volume and survival to discharge were recorded. Blood type, PCV after transfusion and
72 creatinine before and after transfusion were recorded when clinically possible. The recipients and donors were
73 typed using a commercial immunochromatographic test (respectively Lab test QuickTest A + B and dog
74 erythrocyte antigen (DEA) 1, Alvedia, Limonest, France). One millilitre of packed red blood cells per kilogram
75 was transfused for every percentage point of PCV increase desired, generally aiming for a PCV after transfusion
76 of 25%, although the decision was left to the attending clinician. When sufficient recipient blood was available,
77 both major and minor crossmatches were performed. Crossmatches were performed by trained personnel
78 using washed erythrocytes and a standard slide crossmatch technique as previously described (Tocci & Ewing

79 2009) although, due to the emergent situations in which the xenotransfusions were performed, crossmatch
80 results were not available before administration.

81

82 A standard transfusion monitoring sheet was used during the transfusion, to record temperature, pulse,
83 respiration rate, mucous membrane colour, capillary refill time, urine colour (if applicable), appearance and
84 demeanour at least hourly starting with a baseline before starting the transfusion. The transfusion was
85 administered via syringe and in-line filter (Hemo-Nate) on a syringe driver at 1 mL/kg/hour for the first
86 30 minutes and then increased to allow each syringe of blood to be given over no longer than 6 hours, with
87 further syringes being administered as required to provide the volume desired by the attending clinician. After
88 the end of the transfusion the patient was monitored as required by the attending clinician with a minimum
89 of once daily full physical examination including body temperature, pulse and respiration assessment until
90 discharge from hospital. Recipient PCV was measured 12 hours after the end of the xenotransfusion when
91 possible. Acute development of urticaria, angioedema or pruritus during the transfusion was recorded as a
92 suspected allergic reaction. If a recipient had an increase in rectal temperature of greater than 1°C from
93 baseline at the beginning of the transfusion, non-pathological reasons including external warming and
94 recovery from general anaesthesia were considered. If no such reason was found, then recipient serum and
95 packed red blood cell supernatant (obtained via centrifugation of haematocrit tubes) were checked for
96 haemolysis (as was recipient urine, if available) and, if present, a haemolytic transfusion reaction was
97 suspected. If absent, the blood product was cytologically examined for bacteria and cultured. If abnormalities
98 were noted the transfusion was stopped and a suspected septic transfusion was recorded. If neither a septic
99 nor an acute haemolytic transfusion reaction were suspected, then a febrile non-haemolytic transfusion
100 reaction was recorded. In these cases, the transfusion was stopped temporarily, the patient was monitored
101 and the transfusion was restarted if the temperature normalised. Transfusion-associated circulatory overload
102 was recorded if a cat developed respiratory distress (defined as increased effort and respiratory rate >40
103 breaths per minute) during or within 24 hours after the transfusion, echocardiography performed by the
104 attending clinician demonstrated an enlarged left atrium (with a left atrium-to-aorta ratio >1.5) and the

105 respiratory distress resolved with treatment with furosemide. Other causes of respiratory distress, including
106 transfusion-related acute lung injury were investigated if transfusion-related circulatory overload was not
107 diagnosed. A delayed haemolytic transfusion reaction was recorded if a patient developed haemolysed serum
108 and/or haemoglobinuria, an increase in total bilirubin or bilirubinuria and concurrent decrease in PCV more
109 than 24 hours after transfusion that could not be explained by any concurrent disease process. Serum
110 creatinine concentration was measured at approximately 24 hours and 5 days after transfusion (deemed the
111 time when a delayed haemolytic transfusion reaction was likely) at the attending clinician's discretion, to
112 assess for acute kidney injury secondary to the haemoglobinaemia caused by a haemolytic reaction.

113

114 For cats that survived to discharge, referring veterinary practices were contacted and asked for an update on
115 the cats in the study. For those that were still alive, owners were contacted with a standardised telephone
116 questionnaire (document 2, Supporting Information) incorporating five set questions with progression to the
117 next question only if xenotransfusion was not mentioned in the previous answer. The number of questions
118 (from 1 to 5) asked to prompt mention of xenotransfusion was recorded. The owners were then asked if any
119 warning had been given to them regarding future treatments and also if their cat had fully recovered from its
120 disease.

121

122 Ethical approval was granted for this study by the university teaching hospital Ethics and Welfare committee
123 (ref: SR2017-1162).

124

125 **Statistical analysis**

126 Statistical analyses were performed using the statistical software Tanagra version 1.4.50 (Lyon, France,
127 2003). Data were analysed and presented as median \pm range. Data were assessed for normality using the
128 Shapiro-Wilk test. Paired t tests were used to examine whether creatinine values were significantly different
129 before and after xenotransfusion and chi squared test or Fisher's exact test was used to assess the

130 association of the results of crossmatch with transfusion reactions. Differences were considered significant
131 at a P value <0.05.

132

133 Results

134 **Population**

135 Forty-nine cats received a xenotransfusion between January 2016 and July 2018 and were included in this
136 study. The protocol was followed in all cases. Twenty-three were neutered females, three were entire females
137 and 23 were neutered males. Twenty-eight were domestic shorthair cats, four were domestic long hairs, four
138 were British shorthairs, three were Bengals, two were Persians, two were Siamese, two were ragdolls and one
139 each was Burmese, Chantilly-Tiffany, Tonkinese and Abyssinian. Median age was 8.0 years old [range 0.6 to
140 16.5 years].

141

142 The most common reasons for anaemia were surgical blood loss (17 of 49, 34.7%) with the xenotransfusion
143 either given intra- (five of 17 cases) or post-operatively (12 of 17 cases), immune-mediated haemolytic
144 anaemia (IMHA, eight regenerative IMHA and six non-regenerative; 14 of 49, 28.6%) and neoplasia (14 of 49,
145 28.6%). There was one case each of inflammatory bowel disease, coagulopathy of undetermined cause, acute
146 kidney injury and oral ulcerations (feline eosinophilic granuloma). Nine cats (nine of 49, 18.4%) had received
147 a feline blood transfusion of feline packed red blood cells before the xenotransfusion.

148

149 **Blood tests**

150 Thirty cats were blood type A (61.2%), 14 were type B (28.6%) and three (6.1%) were type AB. Two cats were
151 not blood typed (one was administered a xenotransfusion during cardiopulmonary resuscitation and one was
152 deemed at risk of imminent cardiopulmonary arrest and died within 2 hours of starting the xenotransfusion).
153 Median PCV before transfusion was 10% [Range 4 to 16%].

154

155 Crossmatches between the feline recipients and the donated dog blood were performed in 29 cases. Major
156 crossmatches were incompatible in 20 of 29 cases (69.0%) and minor crossmatches were incompatible in eight
157 of 26 cases (30.8%) (with three minor crossmatches being non-interpretable due to the recipient being saline
158 agglutination positive). Both major and minor crossmatches were incompatible in six of 29 cases (20.7%) and
159 both crossmatches were compatible in seven of 29 cases (24.1%). Major and minor crossmatches only were
160 incompatible in 14 of 29 cases (48.3%) and two of 29 cases (6.9%), respectively.

161

162 **Transfusion**

163 Thirty-five cats (35 of 49, 71.4%) received DEA-1-positive packed red blood cells and 14 received DEA-1-
164 negative packed red blood cells (14 of 49, 28.6%). The median volume transfused was 14.6 mL/kg [range 2.6
165 to 28.0 mL/kg]. Six cats (six of 49, 12.2%) had a febrile non-haemolytic transfusion reaction during the
166 xenotransfusion. For two of these cats, the xenotransfusion was stopped (for 20 minutes in one case and
167 2 hours in the other) and was then continued when their temperature normalised. For one cat, the reaction
168 occurred towards the end of the transfusion and it was not restarted because the temperature remained
169 elevated. The occurrence of febrile non-haemolytic transfusion reaction was not significantly different
170 between cats with a compatible or incompatible crossmatch ($P = 0.75$). No other acute transfusion reactions
171 were noted.

172

173 **Short-term outcome**

174 PCV after transfusion was obtained in 39 cases. Five cats died or were euthanased during the xenotransfusion
175 (one was undergoing cardiopulmonary resuscitation when the xenotransfusion started, two were euthanased
176 due to the results of diagnostics that were performed during this time (biliary carcinoma and pulmonary
177 thromboembolism) and two did not stabilise, leading to the recommendation for euthanasia). Three cats were
178 euthanased before the 12-hour PCV check because of poor prognosis associated with the primary disease
179 (gastro-intestinal large granular lymphocytic lymphoma, ulcerative gastropathy and subcutaneous
180 haemangiosarcoma) and two cats survived but did not have a PCV reported 12 hours after the

181 xenotransfusion. Median PCV was 25% [range 10 to 50%], when evaluated at a median of 12 hours [range 4
182 to 14 hours] after xenotransfusion. Two cats (one with gastric lymphoma and one with diffuse splenic and
183 hepatic neoplasia) went home between 12 and 24 hours after xenotransfusion to be euthanased by their
184 referring veterinary surgeons.

185

186 Of the remaining 39 patients (39 of 49), a delayed haemolytic transfusion reaction occurred in 25. Haemolytic
187 serum was noted in 19 of 25 cats after a median of 2 days [range 1 to 6 days], and icterus or icteric serum in
188 15 of 25 cats after a median of 1.9 days [range 1 to 6 days]. Nine cats had both haemolysed and icteric serum.
189 Of the 14 cats without delayed haemolytic transfusion reaction, nine died or were discharged from the hospital
190 for euthanasia at home due to their underlying disease within 48 hours of the end of the xenotransfusion. The
191 remaining five were hospitalised for at least 6 days after xenotransfusion without developing overt
192 haemolysis, but one of them did receive a feline packed red blood cell transfusion 3 days later. Of the 25 cats
193 that developed a delayed haemolytic transfusion reaction, 14 (of 25) were discharged from the hospital,
194 among which one was discharged within 48 hours after xenotransfusion for euthanasia at home and two of
195 them died or were euthanased within a week. Overall, 14 cats (of 39) were administered a cat blood
196 transfusion after a median of 4 days [range 1 to 6 days].

197

198 Of the 20 cats with incompatible major crossmatch, 12 (12, 60%) developed a delayed haemolytic transfusion
199 reaction compared to three out of nine cats (33.3%) that were major crossmatch compatible. Two of the eight
200 cats with incompatible minor crossmatch and 10 of 18 (55.6%) cats with compatible crossmatch developed a
201 delayed haemolytic transfusion reaction (Table 1). Major or minor crossmatch did not apparently differ in the
202 occurrence of delayed haemolytic transfusion reaction (respectively $P = 0.24$ and $P = 0.28$). Delayed haemolytic
203 transfusion reactions occurred at a median of 2 days [range 1 to 6 days] after xenotransfusion in patients with
204 incompatible major crossmatch and 1 day [range 1 to 1.5 days] in cats that received compatible blood on major
205 crossmatch. Incompatibility on major crossmatch did not significantly affect the time between xenotransfusion
206 and development of a delayed haemolytic transfusion reaction ($P = 0.26$). However, time between

207 xenotransfusion and discharge for the crossmatched patients was a median of 2 days [range 0 to 16 days] and
208 21 of 29 (72.4%) patients were discharged or died before 6 days after xenotransfusion.

209

210 Twenty-three cats of the original population of 49 (46.9%) were discharged from the hospital. Five of these 23
211 cats (21.7%) died or were euthanased within a week after xenotransfusion: two were diagnosed with
212 leukaemia, two with hepatic and splenic neoplasia and one with gastric lymphoma. Of the remaining 18 cats
213 which survived more than 1 week after xenotransfusion, 11 (61.1%) had had a delayed haemolytic transfusion
214 reaction. However, five of seven cats that did not develop a delayed haemolytic transfusion reaction were
215 discharged before 7 days after xenotransfusion. Ten of the 18 surviving cats (55.6%) were administered a cat
216 blood transfusion after a median of 4 days [range 2 to 6] after xenotransfusion.

217

218 **Creatinine**

219 Creatinine measurements before and 1 day after xenotransfusion were available for 20 cats and at
220 approximately 5 days after xenotransfusion (median 4 days [range 2 to 10]) for 13 cats (Table 2). Median
221 value was 142 $\mu\text{mol/L}$ [range 54 to 800 $\mu\text{mol/L}$] before and 108 $\mu\text{mol/L}$ [range 52 to 824 $\mu\text{mol/L}$] at 1 day and
222 100 $\mu\text{mol/L}$ [range 50 to 1099 $\mu\text{mol/L}$] at approximately 5 days after xenotransfusion.

223

224 Urine specific gravity was available for 12 cases before xenotransfusion. Among the 22 cats for which a
225 creatinine measurement was recorded before xenotransfusion, seven were azotaemic (creatinine
226 $>140 \mu\text{mol/L}$). Six of these azotaemic cats had a urine specific gravity of less than 1.035 (Table 2).

227

228 **Long-term outcome**

229 Eighteen cats (18 of 49, 36.7%) were still alive 7 days after xenotransfusion. Of these 18, nine (50.0%)
230 received a xenotransfusion for surgical blood loss, six (33.3%) for IMHA, two for neoplasia (11.1%) and one
231 for inflammatory bowel disease (5.6%). One cat, diagnosed with mesenteric and splenic large cell lymphoma,

232 was euthanased 10 days after xenotransfusion due to lack of response to chemotherapy, and one was
233 euthanased 184 days after xenotransfusion due to a relapse of IMHA.

234

235 All surviving cats' owners were contacted, at a median of 173 days [range 157 to 570 days] after
236 xenotransfusion. One cat was lost to follow-up, so 15 owners were questioned. A median of two questions
237 [range 1 to 5] was necessary for the owners to mention the xenotransfusion, with all owners stating that
238 their cat had received a xenotransfusion by question 5. Nine owners (of 15, 60.0%) remembered their cat
239 could not receive a repeat xenotransfusion. Eight cats were reported to be recovered from their primary
240 disease, all of which had received a xenotransfusion for surgical blood loss.

241

242 Discussion

243 This study is the first to examine the long-term outcome of a large number of clinical feline recipients of
244 canine blood. The most common reason for xenotransfusion administration was surgical blood loss. The
245 urgency and unpredictability of these situations explains the use of xenotransfusions, because it was not
246 possible to find a cat donor sufficiently rapidly. The hospitals involved in this study do not have access to in-
247 house donors or a national cat blood bank (as is common for many veterinary surgeons around the world),
248 and so organising a feline donation relies on contacting an owner with a cat on the donation list and
249 arranging a donation for a mutually convenient time which can be many hours or even days after the urgent
250 need for blood has arisen (Doolin et al. 2017).

251

252 The high level of adherence to the protocol minimised potential unnecessary use of xenotransfusion and
253 suggests that xenotransfusions were only used in urgent situations where the cat was thought likely to die
254 within the next 6 hours. Canine to feline xenotransfusion described previously also mainly involved life-
255 threatening situations (Oron et al. 2017, Euler et al. 2016, Klainbart et al. 2018); although lack of affordability
256 of cat blood is also a suggested indication (Weingram et al. 2014, Klainbart et al. 2018). The protocol
257 described in this study could be used by any clinician to help decide whether a xenotransfusion is

258 appropriate, with objective parameters and specific indications. In the protocol described here, the
259 attending clinician needed to review the case with a member of the Transfusion Medicine Service and both
260 had to agree to the patient's suitability for xenotransfusion, but in primary care practice this step could be
261 substituted with a colleague, meaning that each case is carefully considered for suitability.

262

263 The proportion of cats developing a febrile non-haemolytic transfusion reaction in this study was
264 comparable to that reported in a previous smaller study of xenotransfusions in which 10% (two of 20) of cats
265 developed hyperthermia, although it was unclear whether other possible transfusion reactions that could
266 cause an elevated temperature had been excluded (René 1968). Interestingly, similar febrile non-haemolytic
267 transfusion reaction rates of 13 and 29%, for crossmatch compatible and non-crossmatched blood
268 respectively, were reported in a recent prospective study of cat blood administration to cats (Sylvane et al.
269 2018) but other studies have a much lower rates of 2.2 to 2.5% (Castellanos et al. 2004, Weingart et al. 2004,
270 Klaser et al. 2005, Roux et al. 2008, McClosky et al. 2018). Given the latter studies were retrospective or
271 surveys, it is possible that febrile non-haemolytic transfusion reactions were overlooked and that there is
272 little difference in febrile non-haemolytic transfusion reaction rate between cat and dog blood
273 administration to cats. In a recent study (Sylvane et al. 2018), febrile non-haemolytic transfusion reactions
274 did not appear to be associated with crossmatch incompatibilities between donor and recipient blood; our
275 findings were similar, although further studies with more crossmatched cases would be required for
276 confirmation.

277

278 Two cases were euthanased during xenotransfusion because they failed to stabilise and, although the signs
279 they displayed were not suggestive of an acute transfusion reaction, they could have been secondary to the
280 xenotransfusion and were difficult to interpret in a critical patient.

281

282 Our results may under-report the incidence of delayed haemolytic transfusion reaction because nine of 14
283 cats in which it was not detected died or were discharged from hospital within 48 hours of the

284 xenotransfusion. Furthermore, of the remaining five cats without signs of a febrile non-haemolytic
285 transfusion reaction (which were hospitalised for at least 6 days post-xenotransfusion), one cat diagnosed
286 with IMHA was administered a cat blood transfusion 3 days after xenotransfusion, which suggests
287 haemolysis might have been overlooked or that haemolysed serum or haemoglobinuria was not displayed by
288 this patient.

289
290 Delayed haemolytic transfusion reactions occurred after a mean of 2.3 days but there was evidence of
291 haemolysis as early as 1 day after the end of xenotransfusion administration in nine cases. The latest day
292 that evidence of haemolysis was first apparent was 6 days after xenotransfusion. Incompatibilities between
293 donors and recipients did not predict the development of a delayed haemolytic transfusion reaction or
294 influence the time between the xenotransfusion and the occurrence of a delayed haemolytic transfusion
295 reaction although in vitro results of major crossmatch between a canine donor and a feline recipient suggest
296 a potential high risk of acute transfusion reactions (Priolo et al. 2018). Haemolysis following xenotransfusion
297 can therefore occur much earlier than suggested by previous studies in which haemolysis was reported to
298 occur at day 4 to 7 (Bovens & Gruffydd-Jones 2013).

299
300 Creatinine monitoring was only available in a limited number of cases but showed azotaemia was frequent
301 after xenotransfusion. Most of the azotaemic cats had a urine specific gravity of less than 1.035 suggesting
302 renal azotaemia. Unfortunately, specific gravity was not measured concurrent with creatinine measurement
303 after xenotransfusion and so whether any azotaemia detected was genuinely renal in origin cannot be
304 determined, although by this point the cats had been hospitalised for several days and were monitored for
305 hydration or volume deficits and should have been normally hydrated. No significant difference in creatinine
306 levels was apparent after xenotransfusion which would suggest that marked acute kidney injury did not
307 occur secondary to haemoglobinaemia due to a delayed haemolytic transfusion reaction. However,
308 assessment of kidney injury with creatinine alone is suboptimal. Ideally, concurrent measurement of urine

309 specific gravity and sediment analysis would have been performed as recommended by the IRIS acute kidney
310 injury guidelines (Cowgill 2012).

311

312 All the non-surviving cats in this study died or were euthanased because of their underlying disease process
313 with long-term follow-up showing no evidence of complications of xenotransfusion after the delayed
314 haemolytic transfusion reactions at 1 to 6 days. It is impossible to state definitively that the xenotransfusions
315 did not contribute to mortality in this study, but the reasons for death or euthanasia given by the attending
316 clinicians described underlying disease process progression.

317

318 Owners received verbal instructions when they gave consent for the xenotransfusion and a written warning
319 was handed to them with their discharge because it has been shown to increase retention of information in
320 human medicine (Johnson et al. 2003). Follow-up showed that owners generally remembered that their cat
321 had had a xenotransfusion, but that they were less reliably aware that a repeat xenotransfusion was not
322 advisable. Strict protocols and excellent communication between veterinary practices therefore need to be
323 in place to make sure that repeat xenotransfusion is avoided.

324

325 Although there are clearly concerns about the use of xenotransfusion, most prominently the high frequency
326 of delayed haemolytic transfusion reactions meaning that many cats in this study required a further feline
327 blood transfusion and the previously described risk of death with repeat transfusion (Bovens & Gruffydd-
328 Jones 2013), there can be benefits to xenotransfusion administration in certain circumstances. First, in
329 emergencies, the period between a xenotransfusion and likely delayed haemolytic transfusion reaction
330 provides the clinician with the opportunity to source compatible feline blood if necessary. In cats with
331 adequate regeneration, a second transfusion of feline blood may not be required, as was the case in seven
332 of 18 cats that survived over a week after discharge. Secondly, administration of a xenotransfusion may
333 allow further investigations to be pursued, if the prognosis of the cat is expected to be poor or for owners to
334 have more time to consider their options, including euthanasia in terminal cases. Clinicians may also have

335 ethical concerns about using feline blood products in patients with a guarded prognosis due to the generally
336 accepted greater impact donation has on cats compared to dogs (Taylor & Humm 2016). This could well have
337 been relevant in this study given 31 of 49 cats had died by day 7 after xenotransfusion.

338

339 There were several limitations to this study. Although well defined, identification of acute and delayed
340 transfusion reactions required appropriate monitoring. A standardised protocol was used during the
341 xenotransfusion, to maximise recognition of acute transfusion reactions. However, delayed transfusion
342 reactions could have been overlooked because some patients died or were discharged from the hospital
343 before the 7 days previously reported as the latest time a delayed haemolytic transfusion reaction could
344 occur after xenotransfusion (Bovens & Gruffydd-Jones 2013). Also, as this was a clinical study, blood
345 sampling allowing identification of icteric or haemolysed serum did not occur in a standardised fashion,
346 although it was generally performed daily. The minimum monitoring was a once daily full physical
347 examination; however, these cases were critically ill initially and received very close monitoring during this
348 critical period in all cases.

349

350 Additionally, some tests were only performed on a subset of our cohort (crossmatches and creatinine
351 measurements). These tests were not imposed in the protocol due to the limited availability of blood in
352 these critical patients and were left at the clinician's discretion. Therefore, further studies with more cases
353 are required to investigate the trends outlined here.

354

355 It is also worth noting that there are no standardised guidelines regarding transfusion reactions in veterinary
356 medicine. Therefore, a delayed haemolytic transfusion reaction was diagnosed in this study using compatible
357 clinical signs. In human medicine, delayed haemolytic transfusion reaction is classed as definitive by the
358 Centres of Disease Control and Prevention when development of novel antibodies can be demonstrated
359 after transfusion in conjunction with a rapid decrease in PCV back to pre-transfusion levels (U.S. Centers for
360 Disease Control and Prevention 2018). Antibodies were not measured in our cases, but the clinical signs seen

361 in the patients were compatible with a delayed haemolytic transfusion or haemolysis (rapid decrease in PCV
362 and development of jaundice which self-resolves) as described by the CDC (U.S. Centers for Disease Control
363 and Prevention 2018).

364

365 In conclusion, this study demonstrates that xenotransfusion of canine blood to cats is a potentially life-saving
366 procedure in emergencies when feline blood products are not available. No acute adverse reactions other
367 than febrile non-haemolytic transfusion reactions (which are short-lived and self-limiting) were seen in this
368 study. Delayed haemolytic transfusion reactions are to be expected between 1 and 6 days after
369 xenotransfusion. Close monitoring of cats that receive a xenotransfusion is therefore advised because feline
370 blood products may be rapidly required.

371

372 The protocol used here was followed by clinicians and could be easily adapted for use in other clinics. For
373 some veterinarians the need for the administration of a xenotransfusion will never arise, but for those
374 working without access to feline blood banks or stored feline blood products, this information should
375 increase confidence that xenotransfusion can be performed. It also allows understanding of the adverse
376 effects that can arise, meaning owners can be fully informed and appropriate patient monitoring performed.
377 Finally, our study shows that the long-term outcome for these cats appears to be associated with their
378 primary disease and those who recover from this have no notable adverse effects that could be directly
379 attributed to xenotransfusion.

380

381 **Table 1.** Occurrence of reaction depending on crossmatch results

	Total	FNHTR	Haemolysis	Icterus	Icterus + haemolysis	No haemolysis	No icterus	No icterus or haemolysis	Discharge/Death after (median in days post transfusion)
Major and minor cross matches incompatible	6	2	0	2	0	3	1	1	2 [0 to 3]
Major cross match incompatible	14	2	8	6	4	5	4	2	2.5 [0 to 16]
Minor cross match incompatible	2	0	0	0	0	2	2	2	5 [0 to 10]
Compatible minor and major cross matches	7	1	3	1	1	2	3	2	2.5 [0 to 7]
FNHTR Febrile non haemolytic transfusion reaction									

382

383

384 Table 2. Creatinine measurements pre and post-xenotransfusion

	Creatinine pre-xenotransfusion ($\mu\text{mol/L}$)	USG	Creatinine 1-day post-xenotransfusion ($\mu\text{mol/L}$)	Creatinine post-xenotransfusion ($\mu\text{mol/L}$)	Number of days post-xenotransfusion measurement taken
Cat 1	270		238	1099	4
Cat 2	726	1.011	824		
Cat 3	219	1.026	228	603	5
Cat 4	800	1.014	741	671	5
Cat 5	69		125		
Cat 6	155		172		
Cat 7	57		68	50	2
Cat 8	252		321		
Cat 9	73	1.032	64	69	3
Cat 10	339	1.02	114	68	6
Cat 11	74	1.023	61		
Cat 12	144	1.038	108	100	2
Cat 13	94	1.018	98	79	6
Cat 14	66		97		
Cat 15	155	1.012	214		
Cat 16	142		96		
Cat 17	181		69	75	2
Cat 18	455	1.018	242	212	2
Cat 19	81		64	181	2
Cat 20	76	1.032	52		
Cat 21	88			57	10
Cat 22	54	1.025		120	4

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