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This is the author's accepted manuscript of an article published in Journal of Feline Medicine and Surgery.

The final publication is available at SAGE Journals via <https://doi.org/10.1177%2F1098612X17750333>.

The full details of the published version of the article are as follows:

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JOURNAL TITLE: Journal of Feline Medicine and Surgery.

PUBLICATION DATE: 24 January 2018 (online)

PUBLISHER: SAGE Publications

DOI: 10.1177%2F1098612X17750333

Feline primary erythrocytosis: a multicentre case series of 18 cats

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ABSTRACT

Case series summary: a retrospective multicentre case series of feline primary erythrocytosis (PE) was evaluated. The aim was to gain better understanding of disease presentation and progression to guide management and prognostication. Case records were assessed for evidence of increased packed cell volume (PCV >48%), sufficient investigation to rule out relative and secondary erythrocytosis, and follow-up data for at least twelve months or until death. Eighteen cats were included in the case series. No significant trends in signalment were noted. Seizures and mentation changes were the most common presenting signs (both n = 10). Median PCV was 70% (median total protein concentration of 76g/l) with no other consistent haematological changes. Sixteen cats survived to discharge. Phlebotomy was performed initially in 15/16 surviving animals and performed after discharge in 10/16. Hydroxyurea was the most common adjunctive therapy, used in 10/16 cats. Of the 16 patients surviving to discharge, 14 patients were still alive at the conclusion of the study (survival time > 17 months post-discharge), with the two non-survivors having lived for five years or more after diagnosis. PCV when stabilised did not correlate with resolution of clinical signs.

Relevance and novel information: in contrast to perceptions, feline PE was generally well-managed via a combination of phlebotomy and medical therapy, with evidence of prolonged survival times. The use of hydroxyurea enabled cessation or repeat phlebotomies.

Key words: polycythaemia, haematology, seizures, phlebotomy, hydroxyurea

44 INTRODUCTION

45 Feline primary erythrocytosis (PE), also known as polycythaemia, is a rare myeloproliferative disorder
46 resulting in increased red blood cell mass.⁽¹⁾ It is caused by an erythropoietin-independent clonal
47 expansion of a single haematopoietic stem cell⁽¹⁾ and in humans is considered a form of
48 myeloproliferative neoplasm.⁽²⁾

49 Excessive erythropoiesis is suspected to be caused by mutations in the erythropoietic signalling
50 cascade, resulting in constitutive downstream activation.⁽³⁾ In humans, the main mutation responsible
51 for primary polycythaemia (PP) is well-characterised. Ninety-eight percent of human PP is linked to
52 mutations in Janus Kinase 2 (JAK2), a tyrosine kinase,⁽⁴⁾ of which 95% are a valine to phenylalanine
53 substitution⁽⁵⁾ in exon 14 of the JAK2V617F gene.^(6,7,8) An identical mutation has also been identified in
54 a dog with PE.⁽⁹⁾

55 Affected animals may present acutely with severe signs, often including seizure activity,^(1,10) and may
56 require intensive initial support. Clinicians therefore need to provide rapid information to owners
57 regarding the morbidity and mortality of this condition. Current knowledge of feline PE is based on
58 isolated case reports and whilst prognosis is given as 'guarded', survival times of up to six years have
59 been reported.⁽¹⁾

60 The aim of this case series was to collate the largest set of data on feline PE so far, and thereby provide
61 a comprehensive description of the disease course and possible treatment options to guide
62 practitioners.

63 CASE SERIES SUMMARY

64 Patient records of client-owned cats diagnosed with feline PE from January 2006 to October 2015
65 were requested from veterinary hospitals across the UK. Five centres provided a total of eighteen
66 cases: Royal Veterinary College, London (10 cases); Willows, Solihull (4 cases); Animal Health Trust,
67 Newmarket (2 cases); Vets Now, Glasgow (1 case); Goddard's Veterinary Group, London (1 case).

68 Diagnosis of PE was based on marked increase in PCV (>48%)⁽¹⁾ with exclusion of relative erythrocytosis
69 or other secondary causes, such as underlying diseases resulting in hypoxia (e.g. cardiac disease) or
70 the potential for inappropriate erythropoietin production (e.g. productive renal tumour)⁽¹¹⁾.

71 Histories, initial clinical examination and laboratory results were reviewed. Treatment protocols and
72 further clinicopathological results were assessed during the period of hospitalisation. Follow-up
73 information was obtained via email or telephone requests, including details of further treatment, on-
74 going clinical signs, changes in haematological values, and survival at time of data collection.

75 Signalment

76 Eight cats were female and 10 were male, all were neutered. The median age was 5 years and 7
77 months (range 35 – 126 months). Median body weight was 4.63 kg (range 2.6-6.4 kg). The majority of
78 patients were domestic short haired cats (15/18). One cat had been successfully treated for immune-
79 mediated haemolytic anaemia (IMHA, suspected primary) one year prior to presentation, and one cat
80 had been treated for eosinophilic granuloma complex many years previously: neither were receiving
81 medication at time of diagnosis. The remainder were reported as having unremarkable previous
82 medical histories. A summary of the cases can be found in the online supplementary material
83 (Appendix 1).

84 Presenting signs and clinical examination

85 Presenting clinical signs are detailed in Table 1. Neurological signs were the most common presenting
86 complaint, affecting 16/18 patients, followed by gastrointestinal signs (6/18). The median average
87 duration of clinical signs prior to presentation was 2 days (range 1 - 167 days). Physical examination
88 findings are listed in Table 2, with the most notable finding being congested mucous membranes.

89 Clinicopathological data (at presentation)

90 Median PCV at presentation was 70% (range 64 - 83%) with a total protein (TP) concentration of 76g/l
91 (range 51 - 90g/l). All cases with an available complete blood cell count demonstrated increased red
92 blood cell concentration, haemoglobin concentration and haematocrit. Low mean cell haemoglobin
93 (9/15) and lymphopenia (10/15) were the other frequent changes seen on haemogram (for more
94 information, see Appendix 2). Evidence of increased erythrocyte production (e.g. anisocytosis,
95 polychromasia, and rubricytosis) was frequently seen on blood smear analysis.

96 Serum biochemistry results were predominantly within reference limits (10/17).^(a) Increased
97 creatinine kinase (CK) activity was present in eight animals (range 525 – 103351 IU/l, reference interval
98 [RI]: 52 - 506) and three cases had increased urea concentration (range 12.7 - 25.0 mmol/l, RI: 6.1 -
99 12.0). Four cats (unknown number tested) were reported to have evidence of hypoglycaemia on
100 patient-side testing: unfortunately numerical values were not recorded. Arterial blood gas analysis
101 was only performed in two patients, neither of which revealed hypoxemia.

102 Further laboratory testing included erythropoietin (EPO) assay (n = 11), retroviral testing (n = 8),
103 thyroxine assay (n = 1), urinalysis (n = 8) and urine culture (n = 2). EPO levels were within given
104 laboratory reference intervals in 7/11 cats, low in 2 cats and not reported in 2 patients. Seven out of
105 eight cats were negative on in-house lateral flow immunochromatography retroviral testing (result
106 not reported in 1 patient) and T4 level was within reference limits for the single cat tested. The only
107 abnormalities documented on urinalysis were microscopic haematuria in 4 cats and growth of
108 *Escherichia coli* from the urine of one cat. Non-invasive blood pressure was measured in 6 cats: all
109 were normotensive (range 95-142 mmHg).

110 Diagnostic imaging

111 A summary of diagnostic imaging modalities and findings is presented in Table 3. Two cats were
112 euthanased prior to full diagnostic imaging but underwent full post-mortem examination. No
113 abnormal findings on imaging or post-mortem were considered sufficient to cause secondary PE via
114 increased EPO production (appropriate or inappropriate). For example, renal lesions documented on
115 ultrasound were not considered consistent with pathology likely to induce excessive EPO production.
116 Similarly, degrees of cardiac functional impairment were considered minimal, and certainly
117 insufficient to cause hypoxaemia, in all cats. No thoracic abnormalities were documented on imaging
118 in any cats.

119 Initial management and outcome

120 One cat was euthanized on the day of presentation due to severity of clinical signs (collapse and
121 respiratory distress) and one cat was treated purely for seizures, with erythrocytosis only diagnosed
122 retrospectively. Stabilisation of the erythrocytosis was therefore attempted in 16 cats.

123 All 16 cases underwent phlebotomy under sedation within 24 hours of presentation. Median volume
124 of blood removed was 12.5ml/kg (range 4.5-17.9 ml/kg). Eight cats required a second phlebotomy
125 during hospitalisation to achieve clinical stabilisation and sufficient PCV reduction (aiming for PCV <50-
126 55%). Median total volume of blood removed was therefore 19.5ml/kg (range 4.6-27.5 ml/kg). No
127 adverse events were reported.

128 Three cats commenced treatment with hydroxyurea (HU) during the initial hospitalisation period.
129 Dosages varied from 32mg/kg per os (PO) once daily to 100mg/kg PO every five days. Anti-epileptic
130 medication was started on presentation in five cats: levetiracetam (n = 3), phenobarbital (n = 1), or
131 both drugs (n = 1). One cat underwent splenectomy.

132 Sixteen of 17 cats survived to discharge. The remaining cat was euthanized after two days of
133 hospitalisation due to owner concerns over reported poor prognosis and quality of life with on-going
134 treatment. The average time of hospitalisation was six days (range: 1 - 16 days).

135 On-going treatment

136 A variety of treatments were used to reduce PCV and manage clinical signs of PE long-term, as shown
137 in Table 4 (a more detailed outline of treatment modalities is provided in Appendix 3). Treatment was
138 usually deemed successful by the attending veterinarian when no clinical signs were seen with a PCV
139 <60%.

140 Phlebotomy post-discharge was performed in 10/16 cats over a median time frame of 16.4 months
141 (range 3-44 months), although one cat (Case 2) only had a single phlebotomy performed 44 months
142 post-discharge. The median number of phlebotomies performed post-discharge was 7 (range 1-37),
143 with an average interval of 6.5 weeks (range 1.5-16 weeks). One cat (Case 11) underwent 37
144 phlebotomies over a period of 18 months, gradually increasing in interval from weekly (1.5-5ml/kg)
145 up to monthly (3-6ml/kg), and was able to undergo conscious draining on a number of occasions owing
146 to amenable temperament. Six cats eventually maintained a stable PCV without further phlebotomies
147 after a variable period of time (range 3-24 months). Mild side effects were intermittently reported,
148 including difficulty to extract blood due to increased blood viscosity and progressive sclerosis of
149 jugular veins.

150 Ten cats received treatment with HU, most commencing in the first month after diagnosis. Initial doses
151 ranged from 9mg/kg PO once daily to 113mg/kg PO every five days,^(b) with titration dependent on
152 sequential PCV and haematology results. The median stable dose was 22mg/kg PO every other day
153 (range 10mg/kg SID to 45mg/kg every other day). All cats receiving HU were able to stop phlebotomy
154 treatment, either immediately or within five months of starting therapy.

155 Side effects of HU were reported in 6/10 treated cases. Methaemoglobinaemia was reported in three
156 cats, with symptoms including dyspnoea, tachypnoea, and cyanosis. These cats had received doses at
157 the upper end of the dose range (>100mg/kg per dose), with signs seen after first dose administration.
158 Symptoms responded to oxygen supplementation and N-acetylcysteine administration. Dose
159 reduction and S-adenosylmethionine were effective in preventing recurrence. Evidence of oxidative
160 damage to haemoglobin was documented in 3 cats (Heinz bodies ranged 30-48%). Four cats also
161 demonstrated evidence of myelosuppression, with neutropenia in three cats and thrombocytopenia
162 in one case. Neutropenia was mild in 2 cats ($2.46 \times 10^9/l$ and $2.21 \times 10^9/l$, RI 2.50 - 12.50) and moderate
163 in 1 cat ($1.78 \times 10^9/l$). The cats with mild neutropenia were receiving 35-45mg/kg on alternate days,
164 whilst the cat demonstrating moderate neutropenia was receiving 12.5mg/kg daily.
165 Thrombocytopenia was moderate in the affected cat ($56 \times 10^9/l$, RI: 200-600), who was receiving
166 20mg/kg HU daily. In all cases, concentrations normalised after reduction of HU dose (either by 50%
167 or by moving to alternate day dosing).

168 Hirudotherapy (leech treatment) was attempted in three cats. In one patient (Case 3), treatment
169 appeared to cause pain and triggered seizure activity. In the other patient (Case 7), hirudotherapy was
170 performed twice with no obvious side effects, but provided insufficient reduction in PCV. Six cases
171 required anti-epileptic therapy, which was continued long-term in three cats due to on-going seizure

172 activity. Phenobarbital was used in two cases, levetiracetam in three cases (one discontinued after
173 two months) and both drugs in Case 12: this cat was receiving no additional treatment for
174 erythrocytosis. One patient (Case 3) was prescribed aspirin (0.5mg/kg PO once daily) due to
175 development of thrombocytosis.

176 On-going monitoring

177 All cats surviving to discharge had at least 17 months of follow-up data. Fifteen patients demonstrated
178 reduction of PCV from presentation over the course of treatment (mean reduction 16%, range 3 -
179 32%). Details of PCV changes for Case 9 were not available. There was no standardised frequency of
180 monitoring.

181 Thrombocytosis (PLT >800x10⁹/l) was reported in three cases. One cat exhibited intermittently
182 increased platelet concentration from diagnosis onwards for the two and a half years of follow-up
183 data available, up to a maximum of 1176x10⁹/l. Two cats developed intermittent thrombocytosis five
184 months post-discharge, rising to a maximum of 1360x10⁹/l.

185 Leucocytosis occurred in two of the 16 surviving cases. One case (Case 17) developed a transient mild
186 lymphocytosis (8.4x10⁹/l, RI: 0.2-5.4) two years after diagnosis. This patient was found to have
187 concurrent *Toxoplasma gondii* infection. Case 1 developed marked, inappropriate rubricytosis with
188 the presence of circulating erythroblasts and occasional abnormal myeloid precursors 60 months post-
189 discharge, raising suspicions of a leukaemic transformation. The patient developed marked weight
190 loss and polyphagia and was euthanased due to concerns regarding prognosis and quality of life.

191 Long-term Survival

192 One case (Case 1) was euthanased 5 years after diagnosis due to potential leukaemia, and a further
193 cat (Case 2) died 4.75 years post-diagnosis, with comorbidities including chronic kidney disease and
194 senile behavioural changes. Of the 14 remaining cases, all were alive at the time of data collection.
195 Survival time post-discharge is shown in Table 4.

196 Continued clinical signs were reported in five cases: seizures (n = 3), periodic mentation changes (n =
197 1), and development of hind limb ataxia (n = 1). The ataxic patient was additionally diagnosed with
198 toxoplasmosis, and so it is possible that residual clinical signs were not related to PE. A total of seven
199 cats achieved a PCV below 50%. Of these, two experienced continued seizures. Of the nine cats with
200 a stable PCV >50% three experienced on-going clinical signs, whilst the remaining six cats were
201 asymptomatic. The mean PCV of cats with long-term clinical signs was 46%, compared to 62% for those
202 with no long-term signs. All cats with on-going clinical signs were perceived to still have a good quality
203 of life by their owners.

204 **DISCUSSION**

205 Neurological signs have previously been reported as a common presenting complaint in erythrocytotic
206 cats.^(1,10,11) Incidence in this case series was 14/16 cats, slightly higher than previous estimations of 50-
207 87%.^(1,10) Erythrocytosis is therefore a possible, if rare, differential for acute onset seizures in the cat.
208 The suspected aetiology is cerebral hypoglycaemia⁽¹²⁾ or hypoxia with possible ischaemic episodes, as
209 cerebral blood flow is known to be reduced in humans once PCV exceeds 46-52%.⁽¹³⁾

210 Imaging and laboratory findings were similar to those reported in the literature.^(1,11) A number of the
211 most common changes included increased CK activity, hypoglycaemia and left ventricular
212 hypertrophy. Increased CK activity may be caused by ischaemic myopathy or thrombotic events.
213 Hypoglycaemia is known to occur with increased PCV due to decreased plasma volume for glucose

214 transport,⁽¹²⁾ and post-sampling due to increased glucose metabolism in vitro by erythrocytes.⁽¹⁴⁾
215 Point-of-care glucometers have been documented to give lower results than reference analysers,
216 however these differences tend to be of minimal clinical significance, and therefore may not account
217 for the hypoglycaemia documented here.⁽¹⁵⁾ Low fructosamine values are likely to be more reflective
218 of true chronic hypoglycaemia than direct glucose measurements in PE patients. There is known to be
219 a significant overlap in EPO values between normal cats and those with both primary and secondary
220 erythrocytosis.⁽¹⁶⁾ EPO assay is therefore deemed to be of limited use in diagnosing PE. Mild ventricular
221 hypertrophy was present in four cats (31% of those undergoing echocardiography), and may be
222 incidental, or could reflect compensatory hypertrophy due to increased cardiac work-load due to
223 increased blood viscosity.

224 Phlebotomy has always been the key treatment of an acutely presenting erythrocytotic patient,⁽¹³⁾
225 rapidly improving clinical signs. The average amount of blood removed to achieve in this case series
226 was 19.5ml/kg, equating to a reduction in PCV of approximately 15%.⁽¹⁷⁾ Intermittent phlebotomy can
227 be continued long-term, with frequency determined by regular monitoring of PCV and clinical signs.
228 Potential side effects of phlebotomy include hypoferritaemia, hypoproteinaemia, sedation risks,
229 venous thrombosis⁽³⁾ and patient stress, in addition to financial and time investment by the owner.

230 If phlebotomy is required at an unacceptable frequency or side effects are noted, medical therapy in
231 the form of HU should be considered. HU is a ribonucleotide reductase inhibitor, reducing cellular
232 proliferation by interfering with the de novo synthesis of deoxyribonucleotides.⁽¹⁸⁾ HU also inhibits
233 recycling of methaemoglobin back to haemoglobin and can result in a significant increase in
234 methaemoglobin levels, usually maintained at 1%.⁽¹⁹⁾ Dyspnoea occurs when this level exceeds 25%.⁽¹⁹⁾
235 Additionally, inhibition of DNA synthesis can cause reversible bone marrow suppression.⁽¹¹⁾ The data
236 from this case series suggests that lower doses at a more regular frequency are associated with
237 reduced incidence of symptomatic methaemoglobinaemia. Starting cats on daily or alternate day
238 dosing and maintaining long-term dose at less than 20-30mg/kg HU PO per day (or alternate day
239 dosing) is therefore advisable.

240 Previous literature has advised to aim for a stable PCV of less than 50%.⁽¹⁾ This was only achieved in
241 7/16 of patients in this study, however 6/9 remaining cats were asymptomatic long-term. The average
242 stable PCV was in fact higher in cats without on-going clinical signs than those with continued signs.
243 It is therefore not possible to suggest a new therapeutic target from this data, however it would
244 appear that PCV <50% is an unnecessarily low goal.

245 Only two cats appeared to achieve remission, defined in human medicine as clinical and
246 haematological resolution without intervention for at least three months.⁽²⁰⁾ At present, a clear
247 dialogue should be maintained with the owners to discuss the difference between achieving clinical
248 and haematological control of the disease when deciding thresholds for intervention.

249 This study suggests that feline PE has a good prognosis for survival, with survival times of up to, and
250 possibly exceeding, 5 years. Cats also maintain a good quality of life, with the patients in this case
251 series either becoming asymptomatic or experiencing readily controlled clinical signs (e.g. seizures
252 managed with anti-epileptic medication).

253 Human literature reports 3-19% incidence of progression of PV to acute leukaemia, and 5-14%
254 incidence of transformation to myelofibrosis.⁽²¹⁾ One cat demonstrated possible malignant
255 transformation, however this was not confirmed with bone marrow examination. Longer-term follow-
256 up data would be required to determine the risk of malignant transformation.

257 A notable difference between feline PE and the most common form of human PP is the absence of
258 consistent trilineage hypercellularity in cats. Thrombocytosis and leucocytosis were documented in
259 this case series in only a handful of patients, with neither abnormality occurring concurrently. This
260 casts doubt on the likelihood of the prominent human JAK2V617F mutation as the underlying genetic
261 cause. However, erythrocytosis is known to occur as the only haematological abnormality in a subset
262 of gain-of-function JAK2 mutations affecting exon 12 as opposed to exon 14.^(21,22) This is believed to
263 be the genetic cause of PP in approximately 3% of human patients.⁽²³⁾ Congenital erythrocytosis,
264 suspected to be caused by a truncated EPO receptor,^(4,24) also causes pure erythrocytosis, however the
265 signalment of patients in this study is not supportive of a congenital basis for feline PE. JAK2 is now a
266 target for novel medical treatments for polycythaemia. Ruxolitinib, a JAK1 and JAK2 inhibitor, appears
267 to be well-tolerated, and a study comparing efficacy in humans with HU therapy has recently been
268 completed (the RELIEF trial).⁽¹³⁾

269 CONCLUSIONS

270 This study provides information to aid practitioners in diagnosing and managing cases of feline
271 erythrocytosis. Importantly, it should be noted that the historic term 'polycythaemia' is a misnomer:
272 'erythrocytosis' is a more accurate name, reflecting the lack of multilineage hypercellularity in this
273 species.

274 In contrast to previous literature, this case series suggests a good outcome for treated cats in the
275 medium to long-term. Phlebotomy is required for immediate cytoreduction and can be combined
276 with, or supplanted by, medical therapy. Elucidation of the underlying cause of feline erythrocytosis
277 would likely result in novel targets for treatment, possibly with improved reduction in PCV and
278 reduced adverse effects. This would require genetic comparison between affected and unaffected
279 animals. Extrapolation from human medicine suggests that JAK2, with a possible focus on exon 12,
280 could prove fruitful ground for further investigation.

281

282 FOOTNOTES:

283 **a. Quoted reference intervals are those of the Diagnostic Laboratory Services from the Royal**
284 **Veterinary College**

285 **b. Reformulated hydroxyurea capsules and a liquid formulation are available, which can facilitate**
286 **administration of smaller doses**

287

288 SUPPLEMENTARY MATERIALS (Appendices):

289 APPENDIX 1: summary of feline PE cases (n = 18)

290 APPENDIX 2: common haematological changes in feline PE cases

291 APPENDIX 3: long-term treatment and survival data for feline PE cases

292

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Clinical sign	Number affected (/18)
Seizures	10
- generalised	- 8
- focal	- 2
Altered mentation	10
Tremors/twitching	6
- facial	- 6
- pelvic limbs	- 1
Ataxia	6
Circling	5
Weakness	5
Respiratory distress	5
- mild	- 2
- moderate	- 3
Vomiting	3
- haematemesis	- 2
Ptyalism	3
Polyphagia	3
Blindness	2
Personality changes	2
Pelvic limb stiffness	2
Pica	2
Diarrhoea	1
Haematochezia	1
Inappetence	1
Polydipsia	1
Weight loss	1

Table 1: Presenting clinical signs in feline PE cases

Physical examination finding	Number affected (/18)
Congested mucous membranes	11
Hyperthermia (range 39.2°C - 41.4°C)	4
Reduced / absent menace response	4
Hippus	2
Delayed pupillary light reflexes	1
Nystagmus	1
Bruising	1
Peripheral venous dilation	1
Cutaneous erythema	1

Table 2: Physical examination findings on presentation in feline PE cases

Imaging modality	Number (/18)	Findings
Abdominal ultrasound	16	Unremarkable = 7 Chronic nephropathy = 4 Enteropathy = 3 Hepatopathy = 2 Splenomegaly = 2
Thoracic radiography	14	Unremarkable = 14
CT	2	Unremarkable = 1 Chronic nephropathy = 1
Echocardiography	13	Unremarkable = 9 Mild left ventricular hypertrophy = 4 Borderline left atrial enlargement = 2
MRI	2	Hippocampal oedema / necrosis = 2 (likely secondary to seizure activity)

Table 3: Imaging modalities and findings in feline PE patients

Case	Maintenance treatment	Stable PCV (%)	Able to stop treatment	Continued clinical signs	Perceived quality of life	Survival time (months)
1. 5y DSH (FN)	HU	30 - 50	Yes	None	Good	64 (PTS)
2. 8y DSH (MN)	HU	59	Yes	None	Good	57 (died)
3. 5y4m DLH (MN)	Phlebotomy, anti-epileptics, aspirin	37	Yes	Seizures	Fair	>40 (alive)
6. 6y1m DSH (MN)	Phlebotomy	60-70	No	None	Good	>30 (alive)
7. 2y11m BSH (MN)	HU, phlebotomy, anti-epileptics	38	No	Seizures	Good	>25 (alive)
8. 5y DSH (MN)	HU, phlebotomy, anti-epileptics	62	No	Intermittent lethargy and disorientation	Good	>19 (alive)
9. 8y11m DSH (MN)	Phlebotomy, clopidogrel	(Unknown)	No	None	Good	>17 (alive)
10. 6y DSH (FN)	HU	48	No	None	Good	>17 (alive)
11. 5y Maine Coon (FN)	Phlebotomy	40-50	Yes	None	Good	>62 (alive)
12. 6y DSH (MN)	Anti-epileptics	(Unknown)	N/A	Seizures	Good	>22 (alive)
13. 6y9m	HU	(Unknown)	Unknown	None	Good	>55

DSH (MN)						(alive)
14. 4y6m DSH (FN)	HU, anti-epileptics	55-60	No	None	Good	>24 (alive)
15. 8y7m DSH (FN)	HU	55-60	No	None	Good	>22 (alive)
16. 6y DSH (FN)	HU	54	No	None	Good	>47 (alive)
17. 10y6m DSH (MN)	HU	48	No	Ataxia	Fair	>44 (alive)
18. 4y DSH (FN)	HU, phlebotomy	(Unknown)	No	None	Good	>27 (alive)

Table 4: Long-term follow up data of feline PE cases. Cases 4 & 5 did not survive to initial discharge and are therefore not included.

Case	Presenting signs	Physical examination findings	Initial PCV / TP	Initial treatment	Survival to discharge	Maintenance treatment	Able to cease treatment	Survival time (months)
1. 5y DSH (FN)	Facial twitching, manic behaviour (1d)	Congested mucous membranes, depressed	68 / 70	Phlebotomy	Yes	HU	Yes	64 (PTS)
2. 8y DSH (MN)	Seizures, twitching, circling, polydipsia, polyphagia (4d)		76 / 90	Phlebotomy	Yes	HU	Yes	57 (died)
3. 5y4m DLH (MN)	Seizures, hyperaesthesia, polyphagia, vomiting, diarrhoea (4d)	Mild urinary retention	69 / 77	Phlebotomy	Yes	Phlebotomy, anti-epileptics, aspirin	Yes	>40 (alive)
4. 3y10m DSH (MN)	Collapse, respiratory distress (2d)	Congested mucous membranes, obtundation, diffuse pulmonary crackles	83 / 76	None	No	N/A	N/A	N/A
5. 4y1m DSH (FN)	Seizures, ataxia (1d)	Obtundation, dehydration	78 / -	Phlebotomy	No	N/A	N/A	N/A
6. 6y1m DSH (MN)	Seizures, weakness (1d)	Obtundation, heart murmur	70 / 67	Phlebotomy	Yes	Phlebotomy	No	>30 (alive)
7. 2y11m BSH (MN)	Seizures (28d)	Tachypnoea, circling, proprioceptive deficits	67 / 60	Phlebotomy	Yes	HU, phlebotomy, anti-epileptics	No	>25 (alive)
8. 5y DSH (MN)	Stupor, facial twitching (2d)	Blind, gallop rhythm	76 / 90	Phlebotomy	Yes	HU, phlebotomy, anti-epileptics	No	>19 (alive)
9. 8y11m DSH (MN)	Stiffness, haematochezia	Heart murmur, increased	67 / 78	Phlebotomy	Yes	Phlebotomy, clopidogrel	No	>17 (alive)

	(2d)	bronchovesicular sounds							
10. 6y DSH (FN)	Weight loss, haematemesis, pica (6d)	Unremarkable	64 / 70	Phlebotomy	Yes	HU	No	>17 (alive)	
11. 5y Maine Coon (FN)	Ataxia, circling (1d)	Unilateral menace deficit	65 / 51	Phlebotomy	Yes	Phlebotomy	Yes	>62 (alive)	
12. 6y DSH (MN)	Focal seizures, aggression (7d)	Aggressive	71 / -	None	Yes	Anti-epileptics	N/A	>22 (alive)	
13. 6y9m DSH (MN)	Seizures (1d)	Dull, congested mucous membranes	80 / -	Phlebotomy	Yes	HU	Unknown	>55 (alive)	
14. 4y6m DSH (FN)	Seizures, ataxia, ptyalism, facial twitching (41d)	Congested mucous membranes, hyperthermia	65 / 69	Phlebotomy	Yes	HU, anti-epileptics	No	>24 (alive)	
15. 8y7m DSH (FN)	Circling (1d)	Dyspnoea, generalised erythema	70 / 76	Phlebotomy	Yes	HU	No	>22 (alive)	
16. 6y DSH (FN)	Seizures, head tremors (1d)	Congested mucous membranes, abdominal pain	70 / 72	Phlebotomy	Yes	HU	No	>47 (alive)	
17. 10y6m DSH (MN)	Pelvic limb ataxia, haematochezia, haematuria (167d)	Muscle atrophy, plantigrade stance	55 / 70	Phlebotomy	Yes	HU	No	>44 (alive)	
18. 4y DSH (FN)	Pelvic limb ataxia, weakness, lethargy	Heart murmur, stiffness, tachypnoea	75 / -	Phlebotomy	Yes	HU, phlebotomy	No	>27 (alive)	

Appendix 1: summary of feline PE cases

Parameter	Change and frequency	Median value (range)	Reference intervals (SI units)
RBC	↑ (15/15)	17.30 (13.40 - 22.36)	5.0 - 10.0 ($\times 10^{12}/l$)
HGB	↑ (15/15)	21.5 (18.2 - 27.5)	8.0 - 15.0 (g/dL)
HCT	↑ (15/15)	65.9 (54 - 84.5)	24.0 - 45.0 (%)
MCH	↓ (9/15)	12.6 (9.7 - 15.1)	13.0 - 17.5 (pg)
Lymphocytes	↓ (10/15)	1.42 (0.17 - 4.4)	2.5 - 12.4 ($\times 10^9/l$)

Appendix 2 : Common haematological changes in feline PE cases. Machine used: Advia 2021i. Reference intervals used: QMHA laboratory. RBC: red blood cell count, HGB: haemoglobin concentration, HCT: haematocrit; MCH: mean cell haemoglobin

For Peer Review

Case Number	Phlebotomy		Hydroxyurea					Other medication	Stable PCV	Clinical signs	Perceived quality of life	Survival time (months)
	Number post-discharge	Interval post-discharge (weeks)	Overall time post-discharge (months)	Stopped or on-going	Initial dose	Maintenance dose	Side effects					
1	0	N/A	0	Stopped	113mg/kg q4d	23-45mg/kg EOD Stopped after 46mo	Initial MMB, Heinz bodies, transient mild neutropaenia	None	30-50	None	Good	64
2	1	(Once)	44	Stopped	100mg/kg q5d	30mg/kg EOD	Initial MMB	None	59	None	Good	58
3	5	2-3	4	Stopped	N/A	N/A	N/A	PB	37	Seizures	Fair	>40
6	18	6	29	On-going	N/A	N/A	N/A	None	60-70	None	Good	>29
7	5	2	3	Stopped	35mg/kg EOD	19mg/kg EOD	Heinz bodies, transient mild neutropaenia	PB	38	Intermittent seizures	Good	>25
8	5	10	13	On-going	15mg/kg SID	20mg/kg SID	None	None	62	Intermittent lethargy and disorientation	Good	>19
9	Unknown	Unknown	Unknown	Unknown	N/A	N/A	N/A	None	Unknown	None	Good	>17
10	2	6	3	Stopped	10mg/kg SID	10mg/kg SID	None	Renal diet	48	None	Good	>17
11	37	1-2	14mo	Stopped	N/A	N/A	N/A	None	40-50	None	Good	>62
12	0	N/A	0	N/A	N/A	N/A	N/A	PB, leve	Unknown	Intermittent	Good	>22

											seizures	
13	Unknown	Unknown	24	Stopped	100mg/kg q5d	25mg/kg SID Stopped after 24mo	Initial MMB	None	Unknown	None	Good	>55
14	0	N/A	0	N/A	10mg/kg SID	10mg/kg SID Stopped after 4mo	None	None	55-60	None	Good	>24
15	4	16	18	On-going	10mg/kg SID	9mg/kg BID	None	Meloxicam	55-65	None	Good	>22
16	0	N/A	0	N/A	17mg/kg SID	17mg/kg EOD	Transient moderate thrombocyto- paenia	None	54	None	Good	>47
17	0	N/A	0	N/A	15mg/kg SID	15mg/kg SID	None	None	48	Ataxia	Fair/good	>44
18	6	8	12	Stopped	32mg/kg q3d	13mg/kg SID	Transient moderate neutropaenia	None	Unknown	None	Good	>27

Table 1: Long-term treatment and survival date for feline PE cases. Cases 4 & 5 were euthanased prior to discharge and therefore are not included.
 Key: EOD = every other day, leve = levetiracetam, MMB = methaemoglobinaemia, PB = phenobarbital, SID = once daily