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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

INTRODUCTION

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

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

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

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

CASE SERIES SUMMARY

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

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

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

Signalment

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

Presenting signs and clinical examination

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

Clinicopathological data (at presentation)

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

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

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

Diagnostic imaging

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

Initial management and outcome

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

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

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

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

On-going treatment

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

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

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

Side effects of HU were reported in 6/10 treated cases. Methaemoglobinaemia was reported in three cats, with symptoms including dyspnoea, tachypnoea, and cyanosis. These cats had received doses at the upper end of the dose range (>100mg/kg per dose), with signs seen after first dose administration. Symptoms responded to oxygen supplementation and N-acetylcysteine administration. Dose reduction and S-adenosylmethionine were effective in preventing recurrence. Evidence of oxidative damage to haemoglobin was documented in 3 cats (Heinz bodies ranged 30-48%). Four cats also demonstrated evidence of myelosuppression, with neutropenia in three cats and thrombocytopenia in one case. Neutropenia was mild in 2 cats ($2.46x10^9$/l and $2.21x10^9$/l, RI 2.50 - 12.50) and moderate in 1 cat ($1.78x10^9$/l). The cats with mild neutropenia were receiving 35-45mg/kg on alternate days, whilst the cat demonstrating moderate neutropenia was receiving 12.5mg/kg daily. Thrombocytopenia was moderate in the affected cat ($56x10^9$/l, RI: 200-600), who was receiving 20mg/kg HU daily. In all cases, concentrations normalised after reduction of HU dose (either by 50% or by moving to alternate day dosing).

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

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

On-going monitoring

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

Thrombocytosis (PLT >800x10^9/l) was reported in three cases. One cat exhibited intermittently increased platelet concentration from diagnosis onwards for the two and a half years of follow-up data available, up to a maximum of 1176x10^9/l. Two cats developed intermittent thrombocytosis five months post-discharge, rising to a maximum of 1360x10^9/l.

Leucocytosis occurred in two of the 16 surviving cases. One case (Case 17) developed a transient mild lymphocytosis (8.4x10^9/l, RI: 0.2-5.4) two years after diagnosis. This patient was found to have concurrent *Toxoplasma gondii* infection. Case 1 developed marked, inappropriate rubricytosis with the presence of circulating erythroblasts and occasional abnormal myeloid precursors 60 months post-discharge, raising suspicions of a leukaemic transformation. The patient developed marked weight loss and polyphagia and was euthanased due to concerns regarding prognosis and quality of life.

Long-term Survival

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

CONCLUSIONS

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

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

FOOTNOTES:

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

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

SUPPLEMENTARY MATERIALS (Appendices):

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

APPENDIX 2: common haematological changes in feline PE cases

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

REFERENCES:

1. Giger U. Polycythemia and erythrocytosis. In: Ettinger SJ and Feldman EC (eds). *Textbook of Veterinary Internal Medicine.* 7th ed. St Louis: Elsevier, 2010. pp 279-283

2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 19;127(20): 2391-2405

3. McLornan D, Percy MJ and McMullin MF. JAK2v617F: A single mutation in the myeloproliferative group of disorders. *Ulster Med J* 2006; 75(2): 112-119

4. Bento C, Percy MJ, Gardie B, et al. Genetic basis of congenital erythrocytosis: mutation update and online databases. *Hum Mutat* 2014; 35(1): 15-26

5. Percy MJ and McMullin MF. The V617F JAK2 mutation and the myeloproliferative disorders. *Hematol Oncol* 2005; 23(3-4): 91-93

6. Griesshammer M, Gissliner H and Mesa R. Current and future treatment option for polycythemia vera. *Ann Hematol* 2015; 94: 901-910

7. Alvarez-Larrán A, Angona A, Martínez-Avilés L, et al. Influence of JAK2 46/1 haplotype in the natural evolution of JAK2V617F allele burden in patients with myeloproliferative neoplasms. *Leuk Res* 2012; 36(3): 324-326

8. Hermouet S and Vilaine M. The JAK2 46/1 haplotype: a marker of inappropriate myelomonocytic response to cytokine stimulation, leading to increased risk of inflammation, myeloid neoplasm, and impaired defense against infection? *Haematologica* 2011; 96: 1575-1579

9. Beurlet S, Kried P, Sansonetti A, et al. Identification of JAK2 mutations in canine primary polycythemia. *Exp Hematol* 2011; 39(5): 542-545

10. Hasler A and Giger U. Serum erythropoietin values in polycythemic cats. *J Am Anim Hosp Assoc* 1996; 32: 294-301

11. Evans L and Caylor K. Polycythemia vera in a cat and management with hydoxyurea. *J An Anim Hosp Assoc* 1995; 31: 434 - 437

12. Sarkar S and Rosenkrantz T. Neonatal polycythemia and hyperviscosity. *Semin Fetal Neonat M* 2008; 13(4): 248-255

13. Falchi L, Newberry K and Verstovsek S. New therapeutic approaches in polycythemia vera. *Cl Lymph Myelom Leuk* 2015; 15(S1): S27-33

14. Billinton C, Casciato D, Choquette D, et al. Artifactual hypoglycemia associated with polycythemia vera. *JAMA* 1981; 249(6): 774-775

15. Wess G and Reusch C. Capillary blood sampling from the ear of dogs and cats and use of portable meters to measure glucose concentration. *JSAP* 2008; 41(2): 60-66

16. Cook SM and Lothrop Jr CD. Erythropoietin concentrations measured by radioimmunoassay in normal, polycythemic and anaemic dogs and cats. *JVIM* 1994; 8(1): 18-25

17. Barosi G, Mesa R, Finazzi G, et al. Revised repsonse criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consenses project. *Blood* 2013; 121(23): 4778-4781

18. Saban N and Bujak M. Hydroxyurea and hydroxamic acid derivatives as antitumour drugs. *Cancer Chemoth Pharm* 2009; 64: 213-221

19. Kunos C, Radivoyevitch T, Ingalis S and Hoppel C. Management of 3-aminopyridine-2-carbxaldehyde thiosemicarbazone-induced methemoglobinemia. *Future Oncol* 2012; 8(2): 145-150

20. Finch N, Syme H and Elliott J. Risk factors for development of chronic kidney disease in cats. *JVIM* 2016; 30(2): 602-610

21. Scott L, Tong W, Levine R, et al. JAK2 exon 12 mutation in polycythemia vera and idiopathic erythrocytosis. *New Engl J Med* 2007; 356: 459-468

22. Bernardi M, Ruggeri M, Albiero E, et al. Isolated erythrocytosis in V617F negative patients with JAK2 exon 12 mutations: report of a new mutation [letter]. *Am J Hematol* 2008; 84(4): 258-260- doi: 10.1002/ajh.21357

23. Levine R, Pardanani A,Tefferi A and Gilliland DG. Role of JAK 2 in the pathogenesis and therapy of myeloproliferative disorders. *Nat Rev Cancer* 2007; 7: 673-683- doi:10.1038/nrc2210

24. Whitcomb WH, Peschle C, Moore M, et al. Congenital erythrocytosis: a new form associated with an erythropoietin-dependent mechanism. *Br J Haematol* 1980; 44(1): 17-24

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 ($x10^{12}$/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 ($x10^{9}$/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

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