COMPANION OR PET ANIMALS

Fat-soluble vitamin deficiency and subsequent coagulopathy in a cat with exocrine pancreatic insufficiency

Alexander James Barnes, 1 Kathryn Gates, 1 Jodi Kuntz 2

SUMMARY
This report describes the clinical signs, diagnostic findings and treatment of a female spayed Domestic Shorthair with exocrine pancreatic insufficiency (EPI) who presented in shock due to severe gastrointestinal haemorrhage secondary to coagulopathy caused by vitamin K-dependent clotting factor deficiency. Diagnostics revealed a prolonged prothrombin time, activated partial thromboplastin time, low trypsin-like immunoreactivity and gross evidence of pancreatic atrophy. Gastrointestinal haemorrhage resolved quickly with transfusion of fresh frozen plasma and vitamin K supplementation. Following treatment with oral pancreatic enzyme supplementation, the cat was found to have resolution of gastrointestinal signs, improved body condition and normalisation of clotting times. Fat-soluble vitamin levels were below the expected range and improved following treatment. This is the second report of coagulopathy in a cat with EPI and the first to describe fat-soluble vitamin deficiency that improved with pancreatic enzyme supplementation.

BACKGROUND
Exocrine pancreatic insufficiency (EPI) has a well-established association with fat-soluble vitamin deficiency in humans. The pancreatic enzyme phospholipase A2 is required for the hydrolysis of phospholipids, which form the membrane of lipid-containing micelles in the intestine. Without it, dietary fat and the fat-soluble vitamins within the micelle cannot be absorbed, resulting in steatorrhoea and reduced availability of these vitamins.5 Altered fat-soluble nutrient absorption has been well documented in human patients with cystic fibrosis, up to 90% of which require pancreatic enzyme replacement and 78% of which have shown prolongation in clotting times.2 3 Human patients with EPI have also demonstrated vitamin K deficiency in up to 63% of cases, despite conventional therapy.4 Two different studies demonstrated differences in vitamin A levels in dogs with EPI when compared with controls, but neither evaluation of clotting times or vitamin K levels.5 6 However, there has been no systematic evaluation of vitamin deficiency and the effects of its supplementation in feline patients specifically and a lack of a well-described connection between vitamin K deficiency and EPI in veterinary patients in general. To date, the only peer-reviewed literature addressing this issue is a case report of a cat with EPI and vitamin K-responsive coagulopathy. The current report aims to compare and contrast these cases and describe what we know about vitamin K and other fat-soluble vitamin deficiencies in EPI.

CASE PRESENTATION
A 9-year-old female spayed Domestic Shorthair (DSH) with a history of pancreatitis (diagnosed via feline pancreatic lipase (fPLI) and ultrasound on two occasions over 22 months) and suspected inflammatory bowel disease was presented to its primary care veterinarian for a 5-day history of progressive hyporexia, vomiting and diarrhea. Physical exam revealed moderate diffuse muscle wasting and a dull hair coat. Serum chemistry panel showed elevations in alkaline phosphatase (162 U/L, RI 12–59 U/L), alanine aminotransferase (272 U/L, RI 27–158 U/L), aspartate aminotransferase (AST; 80 U/L, RI 16–67 U/L) and blood urea nitrogen (BUN; 71 mg/dL, RI 16–37 mg/dL, BUN/crea 54.6). A complete blood count (CBC) showed a neutrophilic leukocytosis with a normal haematocrit (Hct) and platelet count. The patient was treated with subcutaneous fluids and continued prednisolone.

The following day, the patient presented for haemorrhage from the site of subcutaneous fluid administration and was hospitalised overnight on intravenous fluids. The next morning, a packed cell volume (PCV) and total protein (TP) was 9% and 4.6 g/dL, prompting referral. On presentation, she was laterally recumbent, obtunded, hypothermic (temperature: 35.2°C), and had active haemorrhage from the site of subcutaneous fluid administration and the current indwelling intravenous catheter. Compared with an exam 1 year prior, she had lost 1.18 kg and was significantly muscle wasted. A CBC showed a normocytic, normochromic, non-regenerative anaemia (Hct 5.6%, RI 30.3%–52.3%; reticulocyte 17.7 K/uL, RI 3–50 K/uL), thrombocytopenia, and prolongations of prothrombin time (PT) and activated partial thromboplastin time (aPTT) (table 1). Initial stabilisation included dexmethasone SPb (0.19 mg/kg IV), diphenhydraminec (2.29 mg/kg subcutaneously), famotidinea (0.57 mg/kg intravenously), vitamin K,c (phytonadione) (2.29 mg/kg subcutaneously once, then 2.38 mg/kg PO q 12 hours) and sucralfatea (95.41 mg/kg PO q 8 hour). Packed red blood cells (pRBC) (type A, 15.62 mL/kg) and fresh frozen plasma (FFP) (15.62 mL/kg) were given over 8 hours. Following transfusions, the PCV/TP was

---

1 Department of Emergency and Critical Care, ACCESS Specialty Animal Hospital, Culver City, California, USA
2 Department of Internal Medicine, ACCESS Specialty Animal Hospital, Culver City, California, USA

Correspondence to: Dr Alexander James Barnes; barnes.alex@gmail.com

Received 3 December 2019
Revised 24 December 2019
Accepted 20 January 2020

© British Veterinary Association 2020. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ.

To cite: Barnes AJ, Gates K, Kuntz J. Vet Rec Case Rep 2020;8:e001019. doi:10.1136/vetreccr-2019-001019
**INVESTIGATIONS**

One year later, the patient presented in acute haemorrhagic shock. Initial findings included hypothermia (32.8°C), pale mucous membranes, weak pulses, hypotension and muscle wasting. A CBC revealed a normocytic, normochromic, regenerative anaemia (Hct 8.6%, RI 30.3%–52.3%; reticulocytes 121.8 K/uL, RI 3.0–50.0 K/uL), neutrophilia (27.66 K/uL, RI 1.48–10.29), monocytosis (0.79 K/uL, RI 0.05–0.67 K/uL) and thrombocytopenia (73 K/uL, RI 151–600 K/uL). Serum biochemistry panel showed an elevated BUN (56 mg/dL, RI 16–36 mg/dL, BUN/crea 56) and hypoalbuminaemia (2.0 g/dL, RI 2.3–3.9). PT and aPTT were both markedly prolonged (table 1). FeLV/FIV SNAP ELISA was positive for feline leukaemia virus and negative for feline immunodeficiency virus. Abdominal ultrasound revealed a 5 cm mid-jejunal intussusception, scant peritoneal effusion and regional lymphadenopathy surrounding the intussusception with no visible pancreatic tissue. The patient was treated with crysaloids, pRBCs (10.2 mL/kg) and FFP (7.35 mL/kg). Repeated clotting times were improved and PCV/TP increased to 21% and 5.8 g/dL (table 1). On exploratory laparotomy, the jejunum was hypermotile with segments of bowel telescoping on themselves temporarily without persistent intussusception, there was diffuse small intestinal thickening and mesenteric lymphadenopathy, and no visible pancreatic tissue. Gastric, duodenal, jejunal, ileal, liver and mesenteric lymph node biopsies were collected. Given bicytopaenia and positive FeLV status, bone marrow aspirate and biopsy samples were collected.

Following surgery, the patient was treated with intravenous fluids1 (2.9 mL/kg/hour), pantoprazole1 (1 mg/kg intravenously q 12 hours), dexamethasone SP (0.1 mg/kg intravenously q 24 hours), ampicillin/sulbactam1 (30 mg/kg intravenously q 8 hours), phytanadione (2.0 mg/kg subcutaneously q 24 hours), hydromorphone1 (0.1 mg/kg intravenously q 4–6 hour), sucralfate (60.6 mg/kg PO q 8 hour), and vitamin A1 (5000 IU PO q 24 hours). After 16 hours of surgery, clotting times had normalised (table 1), but PCV/TP had decreased to 12%/6.0 g/dL prompting transfusion of additional pRBCs (10.29 mL/kg). The PCV/TP rose to 19%, 6.0 g/dL and remained stable until discharge. The patient was discharged with pancreatic enzyme supplementation1 (¼ teaspoon on each meal), sucralfate (30 mg/kg PO q 8 hour), omeprazole1 (1 mg/
the bone marrow. FeLV antigen by IFA of a bone marrow sample
periportal infiltrate, and lymph node biopsy showed reactive
enteritis, liver biopsy revealed mild chronic lymphoplasmacytic
inflammation. Owners reported that she had a good appetite with no
vomiting or diarrhoea. Her body weight remained stable and the
PCV rose to 26%. Feline trypsin-like immunoreactivity (fTLI),
cobalamin (B12), and folate levels were submitted and confirmed
EPI, hypocobalaminaemia and hyperfibrinolysinaemia (table 2).
No medications were added and omeprazole, amoxicillin/clavula-
nate and sulphate were discontinued. One week later, samples
were submitted for fat-soluble vitamin level testing. Results were
consistent with hypovitaminosis D. No reference intervals exist
in cats for vitamins A, E or beta-carotene, but results are listed
inside (table 2).

**DISCUSSION**

In cats, previously documented etiologies of EPI include chronic
pancreatitis, congenital pancreatic hypoplasia/aplasia, infection
(Eurytrema procyonis), pancreatic duct obstruction, amyloidosis,
neoplasia, trauma and intestinal enteropeptidase deficiency.

While EPI has previously been regarded as a rare disease in
cats, the frequency of its diagnosis has increased since the de-
velopment of the fTLI assay. The fTLI is currently considered the
most useful test in the diagnosis of feline EPI.

The diagnosis of feline EPI may be delayed due to the clinical
presentation differing from that of dogs. A retrospective study of
150 cases of feline EPI diagnosed via fTLI demonstrated that the
most common clinical sign was weight loss (>90%), unformed faeces
(62%), poor hair coat (50%) and anorexia (45%). In contrast, dogs
experience much higher rates of diarrhoea (95%) with lower rates of hypoglycaemia or anorexia (12%).

None of the cats in this retrospective study were noted to demonstrate clinical
cogaulopathy, although statistics regarding clotting time
were not reported.

Given the paucity of studies regarding feline EPI-associated
cogaulopathy, it may enhance our understanding of this condi-
tion to compare the patient in this report to the previous report.
The diagnosis of EPI in the previous report was confirmed via
histopathological diagnosis of pancreatic duct fibrosis and acinar
atrophy. The patient in this report had no identifiable pancreatic
tissue at the time of surgery. In the current report, the fTLI
was used for the diagnosis of EPI. As this provides a marker of
pancreatic function, rather than structure alone, it is considered
the gold standard for diagnosis of EPI. Furthermore, the current
report describes a patient that was significantly older at the time of
presentation than the previous report. The previous patient was
7-months old at the time of presentation, had a recent history of
ovariohysterectomy (OHE), and presented with signs including
weight loss, polyphagia and oily stool. Aside from changes to the
stool, no other clinical signs suggestive of pancreatitis were
described. In addition, that patient underwent multiple tests not
performed in the current case report including examination of
faecal proteolytic assay, evaluation of plasma turbidity following
oral corn oil administration, intravenous glucose tolerance test,
measurement of plasma insulin by radioimmunoassay and bacte-
rical culture of duodenal juice. These tests were not repeated in
the current report as they have fallen out favour due to inferior
sensitivity and specificity when compared with the fPLI.

The patient described in the current report appeared to have
recurrent pancreatitis (both ultrasonographic changes and
elevated fPLI) and progressive loss of pancreatic tissue over a
period of 16 months documented through serial ultrasound
examinations. This progression suggests that chronic
pancreatitis may be the inciting cause of pancreatic atrophy
and subsequent EPI. The patient in the previous report was a juvenile
(7 months) and displayed no signs of pancreatitis until shortly
prior to diagnosis, making chronic pancreatitis a less likely cause
of pancreatic acinar atrophy. Similarities between the cases
include prolonged clotting times (PT, aPTT) that were respon-
sive to vitamin K and FFP as well as hypocobalamimia.

In human patients with EPI, fat-soluble vitamin deficiency
has been well documented. Despite this, there has only been
one study to date that documented the prevalence of vitamin
K deficiency (63%) in this patient population. The frequency
with which these patients experience prolonged clotting times
or significant hemorrhagic complications is also currently
unknown. Information regarding trauma or previous surgical
intervention in these patients was unavailable. The incongruity
between vitamin K deficiency and haemorrhage in these patients

| Table 2 | Summary of gastrointestinal testing |
|-----------------|-----------------|-----------------|
| **Time of EPI** | **6-month** | **Reference intervals** |
| **diagnosis** | **recheck** | **(ug/mL)** |
| TLI | 3.50 | 4.10 | 12–82 ug/L |
| PLI | 1.4 | 0.0–3.5 ug/L |
| Cobalamin | <150 | <150 | 276–1425 ng/L |
| Folate | >24 | 12.5 | 8.9–19.9 mmol/L |
| Vitamin D | 54 | 198 | 127–335 mmol/L |
| Vitamin A | 109 | 151 | No established interval |
| Vitamin E | 1.03 | 11.8 | No established interval |
| Beta-carotene | <0.500 | <0.250 | No established interval |

EPI, exocrine pancreatic insufficiency; PLI, pancreatic lipase; TLI, trypsin-like immunoreactivity.

kg PO q 12 hours), amoxicillin/clavulanate (14.2 mg/kg PO q
8 hours), phystadone (0.75 mg/kg PO q 24 hours), vitamin
B12, as well as, her previously prescribed prednisolone and
tylosin powder. Histopathology of the gastrointestinal tract
found mild–moderate chronic- active lymphoplasmacytic
inflammation. Six days after surgery, the patient returned for recheck exam-
ination. Owners reported that she had a good appetite with no
vomiting or diarrhoea. Her body weight remained stable and the
PCV rose to 26%. Feline trypsin-like immunoreactivity (fTLI),
cobalamin (B12), and folate levels were submitted and confirmed
EPI, hypocobalaminaemia and hyperfibrinolysinaemia (table 2).
No medications were added and omeprazole, amoxicillin/clavula-
nate and sulphate were discontinued. One week later, samples
were submitted for fat-soluble vitamin level testing. Results were
consistent with hypovitaminosis D. No reference intervals exist
in cats for vitamins A, E or beta-carotene, but results are listed
inside (table 2).

At a 6-month recheck, the owners reported normal stool
appearance and quantity, no vomiting or diarrhoea. Her body weight remained stable and the
PCV rose to 26%. Feline trypsin-like immunoreactivity (fTLI),
cobalamin (B12), and folate levels were submitted and confirmed
EPI, hypocobalaminaemia and hyperfibrinolysinaemia (table 2).
No medications were added and omeprazole, amoxicillin/clavula-
nate and sulphate were discontinued. One week later, samples
were submitted for fat-soluble vitamin level testing. Results were
consistent with hypovitaminosis D. No reference intervals exist
in cats for vitamins A, E or beta-carotene, but results are listed
inside (table 2).

**OUTCOME AND FOLLOW-UP**

Six days after surgery, the patient returned for recheck exam-
ination. Owners reported that she had a good appetite with no
vomiting or diarrhoea. Her body weight remained stable and the
PCV rose to 26%. Feline trypsin-like immunoreactivity (fTLI),
cobalamin (B12), and folate levels were submitted and confirmed
EPI, hypocobalaminaemia and hyperfibrinolysinaemia (table 2).
No medications were added and omeprazole, amoxicillin/clavula-
nate and sulphate were discontinued. One week later, samples
were submitted for fat-soluble vitamin level testing. Results were
consistent with hypovitaminosis D. No reference intervals exist
in cats for vitamins A, E or beta-carotene, but results are listed
inside (table 2).

Additionally, repeated PT and aPTT were normal
inside (table 2).

At a 6-month recheck, the owners reported normal stool
appearance and quantity, no vomiting or diarrhoea. Her body weight remained stable and the
PCV rose to 26%. Feline trypsin-like immunoreactivity (fTLI),
cobalamin (B12), and folate levels were submitted and confirmed
EPI, hypocobalaminaemia and hyperfibrinolysinaemia (table 2).
No medications were added and omeprazole, amoxicillin/clavula-
nate and sulphate were discontinued. One week later, samples
were submitted for fat-soluble vitamin level testing. Results were
consistent with hypovitaminosis D. No reference intervals exist
in cats for vitamins A, E or beta-carotene, but results are listed
inside (table 2).

**Table 2** Summary of gastrointestinal testing

| **Time of EPI** | **6-month** | **Reference intervals** |
| **diagnosis** | **recheck** | **(ug/mL)** |
| TLI | 3.50 | 4.10 | 12–82 ug/L |
| PLI | 1.4 | 0.0–3.5 ug/L |
| Cobalamin | <150 | <150 | 276–1425 ng/L |
| Folate | >24 | 12.5 | 8.9–19.9 mmol/L |
| Vitamin D | 54 | 198 | 127–335 mmol/L |
| Vitamin A | 109 | 151 | No established interval |
| Vitamin E | 1.03 | 11.8 | No established interval |
| Beta-carotene | <0.500 | <0.250 | No established interval |

EPI, exocrine pancreatic insufficiency; PLI, pancreatic lipase; TLI, trypsin-like immunoreactivity.
may be due to measurement of serum vitamin K levels failing to account for vitamin K stores in the liver, bone marrow and adipose tissue. However, it is unclear whether vitamin K-deficient feline patients are at higher risk for coagulopathy than human patients. The patient in the previous report underwent OHE 30 days prior to signs of coagulopathy, prompting speculation that consumption of existing vitamin K stores may have induced coagulopathy noted at the time of presentation. The patient in the current report had received subcutaneous and fluids prior to the first coagulopathic event and had no known trauma prior to the second event. The elevation in BUN in association with anaemia during the second crisis is supportive of gastrointestinal haemorrhage, likely associated with the ultrasonographically identified intussusception. Although the BUN elevation during the first crisis was most likely also explained by gastrointestinal haemorrhage, other aetiologies cannot be definitively excluded. These findings suggest that feline patients with EPI may be at risk for spontaneous haemorrhage even if trauma is definitively excluded. The fact that multiple coagulopathic events separated by significant lengths of time is unique to this report. This may be explained by a number of factors. First, the authors cannot definitively conclude that occult trauma did not occur in the weeks to months preceding the coagulopathic events. Second, administration of oral vitamin K supplements following the first event may have increased stores of vitamin K for an extended period of time before clotting factors became deficient. Finally, the vitamin K level in the diet may have contributed to chronic supplementation.

Findings of hypocobalaminaemia and hyperfolataemia in this case were consistent in both reports. In previous studies of feline EPI, hypocobalaminaemia was present in up to 77% of cases. Although the patient in the previous report was persistently hypocobalaminaemic, cobalamin levels did increase to near-normal levels with pancreatic enzyme supplementation alone. The patient in the current report was hypocobalaminaemic following discontinuation of supplementation, warranting long-term supplementation. Cobalamin deficiency may have contributions from deficiency in intrinsic factor (produced exclusively in the pancreas in cats rather than the gastric mucosa in dogs and humans), a lack of pancreatic proteases required to liberate cobalamin from R-protein in the duodenum (preventing binding to intrinsic factor) and cobalamin consumption secondary to bacterial overgrowth (SIBO). In this case, persistent hypocobalaminaemia is likely multifactorial and may be partially explained by ileal disease. Hyperfolataemia in this case may be explained by SIBO or ileal mucosal disease.811

In veterinary medicine, serum vitamin K level analysis is not commonly performed by any commercial laboratory. However, measurement of other fat-soluble vitamins (A, D and E) is available. While the previous report of EPI-associated coagulopathy demonstrated resolution of coagulopathy with appropriate pancreatic enzyme supplementation, there was no documentation of fat-soluble vitamin deficiency. In this report, fat-soluble vitamin levels were measured after initiation of pancreatic enzyme replacement therapy and again 6 months later, at which time all levels increased. For vitamin D, the only vitamin with an established reference range, the level normalised with treatment. Hypovitaminosis D is one of the more common deficiencies in human EPI patients, which may primarily due to EPI or may reflect concurrent intestinal disease (commonly associated with hypovitaminosis D).8 Although no reference intervals exist for feline patients for vitamins E and A, the values measured in the serum were below expected values for patients being fed commercial vitamin E and A supplemented diets (recommendations are for serum vitamin E>2.0 μg/mL and vitamin A>200 ng/mL) (table 2).12 As this patient ate commercial diets prior to serum vitamin level measurement, EPI is considered the most likely aetiology of said deficiency.

**Learning points**

- Exocrine pancreatic insufficiency (EPI) in cats has the potential to lead to fat-soluble vitamin deficiency.
- Coagulopathic patients with EPI may need supplementation with vitamin K.
- Further investigation is needed into the necessity of long-term fat-soluble vitamin supplementation for cats with EPI.

**Contributors** AJB created the manuscript, which was edited by KG and JK.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, an indication of whether changes were made, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**REFERENCES**

1. Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clin Exp Gastroenterol* 2011;4:55–73.
2. Dodge JA, Turk D. Cystic fibrosis: nutritional consequences and management. *Best Pract Res Clin Gastroenterol* 2006;20:531–46.
3. Rashid M, Durie P, Andrew M, et al. Prevalence of vitamin K deficiency in cystic fibrosis. *Am J Clin Nutr* 1999;70:378–82.
4. Sikkens ECM, Cahen DL, Koch AD, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatologia* 2013;13:238–42.
5. Ruiz GM, Steiner JM, Bauer JE, et al. Effects of exchange of dietary medium chain triglycerides for long-chain triglycerides on serum biochemical variables and subjectively assessed well-being of dogs with exocrine pancreatic insufficiency. *Am J Vet Res* 2004;65:1293–302.
6. Adamamara-Moraitou KK, Rallis TS, Prassinos NN, et al. Serum vitamin A concentration in dogs with experimentally induced exocrine pancreatic insufficiency. *Int J Vitam Nutr Res* 2002;72:171–82.
7. Xenoulis PG, Zorin DI, Fosgate GT, et al. Feline exocrine pancreatic insufficiency: a retrospective study of 150 cases. *J Vet Intern Med* 2016;30:1790–79.
8. Steiner JM. Exocrine Pancreatic Insufficiency. In: Ettinger SJ, Feldman EC, Cote E, eds. *Textbook of veterinary internal medicine*. 8th edn. Elsevier Saunders, 2018: 4120–7.
9. Batchelor DJ, Noble P-JM, Taylor RH, et al. Prognostic factors in canine exocrine pancreatic insufficiency: prolonged survival is likely if clinical remission is achieved. *J Vet Intern Med* 2007;21:54–60.
10. Perry LA. Exocrine pancreatic insufficiency with associated coagulopathy in a cat. *J Anim Hosp Assoc* 1991;27:54–60.
11. Allenspach K, Steiner JM. Small animal gastroenterology. 1st edn. Hannover: Schultesche, 2008.
12. Ad Hoc Committee on Dog and Cat Nutrition. *Nutrient requirements of dogs and cats*. Washington, DC, 2001: 193–209.
