Journal of Feline Medicine and Surgery (2009) **11**, 935–940
doi:10.1016/j.jfms.2009.04.004

ELSEVIER

jfms

Feline exocrine pancreatic insufficiency: 16 cases (1992–2007)☆

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Medical records of 16 cats diagnosed with exocrine pancreatic insufficiency (EPI) were reviewed. The diagnosis was confirmed with either a serum feline trypsin-like immunoreactivity (fTLI) concentration ≤12 μg/l or a fecal proteolytic activity (FPA) <6 mm for three consecutive days. The majority of cats were castrated male domestic shorthairs. The median age of cats affected was 7 years. The most common clinical sign was weight loss followed by diarrhea, polyphagia and vomiting. Concurrent disease was present in 10/16 (63%) cats. The most common laboratory abnormalities were normocytic normochromic anemia, lymphopenia, neutrophilia, increased alanine transferase activity, hyperglycemia and increased bilirubin concentrations. All 10 cats that were tested for serum cobalamin levels were found to be deficient. All 10 cats that were tested for serum folate concentrations had normal or increased levels. Ten out of 11 cats had at least a partial response to treatment. All cats were discharged from the hospital alive. Results suggest that EPI should be considered a differential diagnosis in any cat with weight loss or poor growth after more common diseases have been ruled out. Concurrent disease is common in feline EPI. Cobalamin deficiency is common in cats with EPI and cats should receive cobalamin supplementation to improve response to treatment. Cats in this study had a good prognosis.

Date accepted: 22 April 2009

The exocrine pancreas has a large reserve capacity of digestive enzymes. In humans it is reported that 90% of the pancreatic acinar cells must be lost before clinical signs of exocrine pancreatic insufficiency (EPI) are seen. The exocrine pancreas secretes digestive enzymes via the pancreatic duct into the duodenum resulting in assimilation of nutrients. When there is an insufficiency of pancreatic digestive enzymes, macronutrients, including amino acids, triglycerides and carbohydrates are not broken down into smaller subunits and absorbed by the small intestine. These large molecules remain in the small intestine which creates an osmotic pull of water into the lumen that exceeds the threshold of water absorption. When the threshold is exceeded, loose, voluminous stools occur. Over time the lack of digestion of macronutrients creates a negative energy balance which results in weight loss, poor body condition and a compensatory polyphagia.[1–5]

Feline EPI is poorly described in the veterinary literature. To our knowledge, to date, there has only been one paper reviewing the diagnostic utility of feline trypsin-like immunoreactivity (fTLI) assay in the diagnosis of feline EPI,[1] as well as 11 single case reports that have been published to date.[5–13] Therefore, the purpose of this study was to describe clinical parameters in a population of cats with EPI.

Materials and methods

Case selection

The Veterinary Medical DataBases (VMDB; http://www.vmdb.org) were searched to identify cats which were diagnosed with EPI between January 1, 1985 and September 11, 2006. Medical records identified by this search from the veterinary teaching hospitals of Purdue University, Iowa State University and The University of Pennsylvania were available for review. The Animal Medical Center (AMC) database was searched independently between the dates of October 1, 2002 through October 1, 2007 to identify cats with EPI.

☆ Presented in part in abstract form at the 26th Annual American College of Veterinary Internal Medicine Forum, San Antonio, TX, June 2008.

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1098-612X/09/120935+06 $36.00/0

The medical record of an additional case of feline EPI was obtained from a private first opinion veterinary hospital in New York City. Cases were included in this study if the diagnosis had been confirmed with either a serum fTLI concentration $\leq$12 μg/l (Gastrointestinal Laboratory, Texas A&M, College Station, TX) or a fecal proteolytic activity (FPA) <6 mm for three consecutive days.[1] Furthermore all cases included had at least one clinical sign recorded in the medical record which was compatible with EPI. Cases were excluded if the records were incomplete or there was insufficient data to determine a diagnosis of EPI.

Review of medical records

Data obtained from the medical records of cats included in the study consisted of breed, age, gender, neuter status, body weight, and any changes in body weight if serial body weights were available. Cats were categorized as kitten (<1 year), adult (1−6 years), senior (7−12 years) or geriatric (>12 years) at the time of diagnosis. Further information extracted from the medical records included clinical signs, physical examination findings and concurrent disease. Results of initial laboratory tests performed were recorded and included clinicopathological data such as complete blood counts and serum biochemistries. Other results collected, if available, included serum thyroxine concentrations, diagnostic imaging, endoscopic and surgical procedures, as well as cytology and histopathology.

Initial type and dosage of treatment and treatment response were recorded. Cats were divided into groups based on treatment to evaluate if there were differences in response between groups. Group 1 were cats that received pancreatic supplementation alone, group 2 were cats that received pancreatic supplementation and cobalamin supplementation, group 3 were cats that received multiple treatments. All cats in group 3 received pancreatic supplementation. Three cats in group 3 received cobalamin supplementation. Other treatments administered to group 3 cats included antibiotics, prescription diets, anthelmintics, gastroprotectants and treatments for concurrent diseases. Treatment response was subjectively based on resolution of clinical signs typical of EPI including weight loss, diarrhea or polyphagia. Treatment response was defined as complete, partial or poor. For the purpose of this study complete treatment response was defined as resolution of all clinical signs, partial response was defined as resolution of at least one clinical sign, and poor response was defined as no resolution of clinical signs.[14]

Discharge status was recorded for all cats and was defined as alive, dead or euthanased when discharged from the hospital. Other survival data was not used due to the variability of length of follow-up time.

Statistical analysis

Statistical analyses were performed using a commercially available software program (STATA statistical software, version 9.2, Stata Corp, College Station). Summary measures were stated as median and range for non-parametric data. The prevalence of feline EPI at each institution was calculated in the following manner: for every year a cat was diagnosed with EPI at that institution the total number of cats seen during that year at that institution was determined. The prevalence was then calculated by dividing the total number of cats with EPI seen at each institution over the search period (defined above) by the total number of individual cats seen at that institution during those years.

Results

Sixteen records were evaluated. Five records were from the AMC, four each from Purdue University and The University of Pennsylvania, two from Iowa State University and one from a first opinion clinic in New York. Medical records obtained from the Veterinary Medical Databases from 1985 to 1991 were reviewed and excluded due to insufficient data available to determine a diagnosis of feline EPI. For example, a case was excluded if the diagnosis was made solely on microscopic examination of feces revealing undigested food products (ie, unsplit fat).

Population data was available from four of the institutions. The AMC had the lowest prevalence with five (0.013%) of 38,728 cats affected over a 5-year period. The prevalence of disease at the other institutions were 0.029% (4/13,674 cats) over a 3-year period at The University of Pennsylvania, 0.090% (4/4440 cats) over a 4-year period at Purdue University and 0.103% (2/1937 cats) at Iowa State University over a 2-year period.

The median age of cats included in the study was 7 years (range, 0.3−15 years). Cats in the senior age group were most commonly affected (11/16; 69%) followed by adult cats (three) and one each of cats in the geriatric or kitten age groups. There were nine castrated males, six spayed females and one intact male. Ten of 16 (63%) cats were domestic shorthair. Domestic longhair, Russian Blue, Siamese, Maine Coon, Persian and a Bengal mix breed cat were each represented by one cat.

Clinical signs were reported for all cats. Weight loss was the most common clinical manifestation, seen in 15 cats (94%). The only cat which did not exhibit weight loss was a 3-month-old kitten that exhibited poor growth and was noted to have a small stature for its age. Data regarding the amount of weight loss prior to diagnosis was available for 10 cats and ranged from 0.23 kg (0.50 lb) to 5.18 kg (11.4 lb) (median 2.09 kg (4.6 lb)). Median weight at time of diagnosis was 2.80 kg (6.15 lb) (range, 1.30−5.73 kg (2.86−12.6 lb)). While the majority of cats exhibited more than one clinical sign, weight loss was the only clinical sign in three cats (19%). Other clinical signs included diarrhea/loose stools (12), vomiting (five), polyphagia (five), anorexia (four), lethargy (four), and fecal incontinence (four), hair loss (three), polyuria and polydypsia (three), weakness (two), flatulence (two) and coprophagia (one).

Stool was described as normal in three cats (19%). Abnormal stools had one or more of the following characteristics: voluminous (seven), loose (seven), frequent (five), malodorous (five), discolored (five), hematochezia (four), steatorrhea (four) and containing mucous (one). Medical records of nine cats allowed characterization of the stool as mixed bowel (six), small bowel (two) or large bowel (one).

Physical examination findings were reported for 15 cats. The most common physical examination findings were thin/emaciated body condition in nine cats (56%). Other physical examination findings reported were muscle wasting (six), unthrifty hair coat (six), thickened intestinal loops (five) and diarrhea stained perineum (four).

Ten of the 16 cats had concurrent disease. Lymphoplasmacytic enteritis was found in three cats, two of which also had lymphoplasmacytic gastritis. Urinary tract disease was present in three cats and included chronic renal failure (two) and cystitis (one). Hepatic disease was diagnosed in one cat based on biopsy, which revealed cholangiohepatitis. An additional cat had hepatic failure and hepatic encephalopathy based on serum chemistry abnormalities (decreased blood urea nitrogen, elevated liver enzymes) and abnormal liver function tests (hyperammonemia, increased bile acid concentrations). A definitive cause of the hepatic disease was not determined. One cat had concurrent diabetes mellitus and one additional cat had transient hyperglycemia and glucosuria. Five of 16 cats had more than one concurrent disease.

Diagnosis of EPI was confirmed with FPA and compatible clinical signs in two cats and fTLI concentrations in 14 cats. The FPA results were 4 mm, 4 mm, 4 mm for three consecutive days for both cats. The median serum concentration for the fTLI was 6.4 µg/l (range, 1.8–9.6 µg/l; reference range, 12–82 µg/l). A serum feline pancreatic lipase immunoreactivity concentration was available for one cat and was within normal range (4.9 µg/l; reference range, 2–6.8 µg/l). Serum cobalamin concentrations were measured in 10/16 cats. All serum cobalamin concentrations were below the reference range. The median serum cobalamin concentration was 99 ng/l (range, <27–176 ng/l; reference range, 290–1499 ng/l) (Fig 1). Serum folate concentrations were also measured in 10 cats. The folate concentrations were increased in four cats. Median serum folate concentrations were 21.1 µg/l, (range, 12.2–42.5 µg/l; reference range, 9.7–21.6 µg/l). No cat evaluated had serum folate concentrations below the reference range (Fig 2).

Results of complete blood cell counts were available for 15 cats. Mild to moderate normocytic, normochromic anemia was identified in seven cats (median hematocrit 30%, range, 18.5–40.6%; reference range, 30–45%). Reticulocyte counts were performed in 3/7 anemic cats; the anemia was non-regenerative in all three cats tested. The mean corpuscular volume was within reference range in all cats but one. In that cat, which was not anemic, macrocytosis (59.5 fl, reference range, 41–58 fl) was observed. Lymphopenia was documented in seven cats, and a neutrophilic leukocytosis was detected in four cats. Lymphocytosis was not detected in any cats.

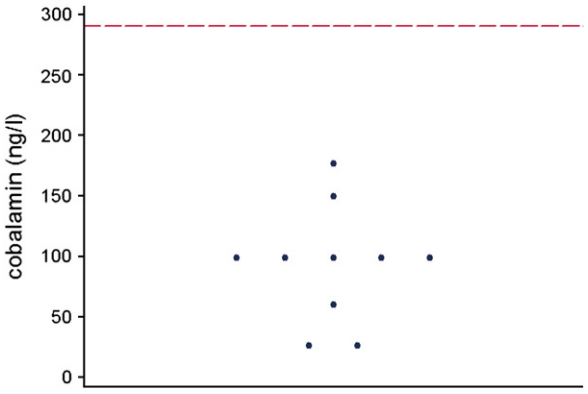

Fig 1. Results of serum cobalamin concentrations in 10 cats with EPI. Each dot represents the results for each individual cat. The dashed line represents the low end of the cobalamin concentration reference range.

Results of serum biochemical analysis were available for 14 cats. Moderate increases in alanine aminotransferase activity were identified in six cats (median 96.5 IU/l, range, 34–663 IU/l; reference range, 20–108 IU/l). Alkaline phosphatase activity was mild to moderately increased in three cats (median 51 U/l, range, 16–479 U/l; reference range, 20–108 U/l). Mild to moderate hyperglycemia was documented in five cats (median 120.5 mg/dl, range, 64–318 mg/dl; reference range, 75–134 mg/dl). Mild hypoglycemia was documented in two cats (64 and 68 mg/dl). Total bilirubin was mildly to moderately increased in four cats (median 0.2 mg/dl, range, 0.1–2.9 mg/dl; reference range, 0.1–0.4 mg/dl). Hypocholesterolemia (54 mg/dl) and hypercholesterolemia (265 mg/dl) were noted in one cat each (range, 54–265 mg/dl; reference range, 75–220 mg/dl). One cat was mildly hypoalbuminemic (2.6 g/dl; reference range, 2.7–3.9 g/dl). Triglyceride concentrations were not available for any

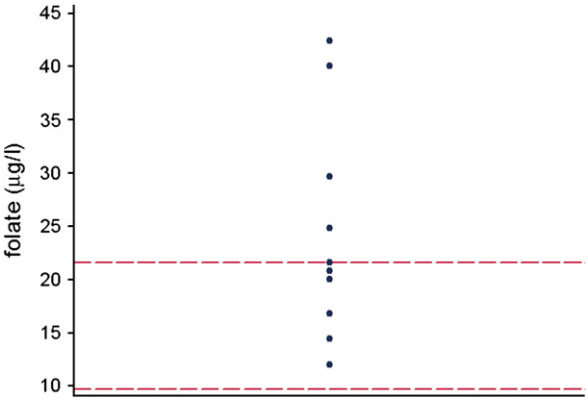

Fig 2. Results of serum folate concentrations in 10 cats with EPI. Each dot represents the results for each individual cat. The dashed lines represent the high and low end of the folate concentration reference range.

cats. Total serum thyroxine concentrations were normal or decreased in all 11 cats that were tested.

Abdominal ultrasound was performed in 10/16 cats. Nine of the 10 documented abnormal findings. Abnormal ultrasound findings included gastrointestinal (five), hepatic (five), and urinary tract (five) abnormalities. Peritoneal effusion was seen in two cats. The pancreas was described as normal in three cats and hyperechoic in one cat. No description was documented in the other six cats.

Histopathology was obtained via endoscopy in three cats and exploratory laparotomy in one cat. Results revealed lymphoplasmacytic enteritis (three), lymphoplasmacytic gastritis (two), pancreatic acinar atrophy (PAA) (one), cholangiohepatitis (one) and membranous glomerulonephritis (one). Necropsy results were available for one cat. This cat was euthanased 4 years after the diagnosis of EPI. Necropsy abnormalities included severe exocrine pancreatic atrophy and islet cell amyloidosis.

Thirteen cats were treated for EPI. All cats received pancreatic enzyme supplementation including Pancreazyme (eight), Viokase (four) and raw porcine pancreas (one). Other treatments included one or more of the following: cobalamin injections (seven), miscellaneous antibiotics (seven), a prescription diet (six), metronidazole (five), H_2-receptor antagonists (two), glucocorticoids (two), tylosin (one), and miscellaneous treatments (four). Sufficient information to determine response to treatment was available for 11/13 cats. Subjectively no differences in response to treatment (ie, poor response, partial response, complete response) were noted between groups (Table 1). The cats that responded to treatment exhibited weight gain (nine), resolution or improvement of diarrhea (eight), resolution of polyphagia (three) resolution of vomiting (one), and resolution of inappetence (one). Patient status at the time of discharge from the hospital was available for 15 cats. All cats were discharged from the hospital alive.

Table 1. Results of treatment response between three treatment groups

	Number of cats in group	Complete remission	Partial remission	No remission
Group 1	2	0	2	0
Group 2	4	2	2	0
Group 3	5	2	3	0

Cats in group 1 were treated with pancreatic supplementation only. Cats in group 2 were treated with pancreatic supplementation and cobalamin. Cats in group 3 received multiple treatments. All cats in group 3 received pancreatic supplementation and three cats received cobalamin supplementation in addition to various other treatments.

Discussion

Ten cats in our study had cobalamin concentrations measured and all of these cats exhibited hypocobalaminemia, eight of which were severely deficient (<100 ng/l). These findings are in accordance to previous studies, one of which showed that 10/11 cats with EPI had undetectable cobalamin concentrations and the remaining cat had subnormal concentrations.[1,15] Cobalamin deficiency secondary to feline EPI may occur due to insufficient production and secretion of intrinsic factor. Intrinsic factor is a cobalamin-binding protein that is only produced by the pancreas in cats, and is necessary for ileal absorption of cobalamin.[15–17] Cobalamin malabsorption may also result from failure of pancreatic enzymes to liberate cobalamin from binding by R protein in the duodenum, which results in failure to bind to intrinsic factor.[18] One final potential cause of cobalamin malabsorption in patients with EPI is secondary small intestinal bacterial overgrowth (SIBO). Loss of exocrine pancreatic function creates an optimal environment for bacterial growth due to the presence of undigested macronutrients, primarily carbohydrates, in the small intestine. Malabsorption and maldigestion leading to decreased intestinal motility, nutritional and immunologic alterations can further enable bacterial overgrowth. Abnormally high numbers of bacteria proximal to the ileum results in competition for cobalamin.[3] SIBO may be idiopathic primary SIBO (antibiotic responsive diarrhea) or secondary to an underlying cause such as EPI. In dogs, it is accepted that SIBO commonly occurs secondary to EPI. However, in dogs and cats the diagnosis and effects of SIBO are controversial.[19,20] One study concluded that SIBO is an uncommon clinical syndrome in cats. That study evaluated bacterial flora of the duodenum in healthy cats and cats with signs of gastrointestinal disease and found no significant difference in bacterial numbers between groups. However, none of the cats in that study were evaluated for EPI.[21] Increased duodenal bacteria has been reported in one cat with EPI.[5]

Cobalamin deficiency indirectly inhibits nucleic acid synthesis, therefore, rapidly dividing cells, such as the gastrointestinal epithelium, are most affected. With severe cobalamin deficiency intestinal crypts atrophy and malabsorption can result. Cats treated with pancreatic enzyme supplementation alone may have persistence of gastrointestinal signs and will be misinterpreted as failing treatment.[22] In addition multiple severe biochemical and metabolic abnormalities, such as altered amino acid metabolism, have been detected in cats with severe hypocobalaminemia.[23] Therefore, cobalamin levels should be routinely checked in any cat with EPI and lifelong cobalamin supplementation, at least intermittently will most likely be required.

Four (40%) of the 10 cats in our study in which folate was measured had increased folate concentrations and no cats had decreased folate concentrations. This is in contrast to previous feline EPI studies where folate concentrations have been reported as normal or decreased.[1,2] Folate absorption may be promoted in cats

with EPI due to decreased duodenal pH occurring as a result of reduced pancreatic bicarbonate secretion.[15] Increased folate concentrations have been reported in cats secondary to severe hypocobalaminemia (<100 ng/l).[16] Cobalamin is required for conversion of methylfolate to the active form tetrahydrofolate, which is required for DNA synthesis.[20,24] Therefore, severe hypocobalaminemia may result in decreased folate utilization. A recent study found that folate concentrations decreased significantly in cats with increased folate concentrations and severe hypocobalaminemia following cobalamin supplementation.[16] In our study 3/4 cats with increased folate concentrations had cobalamin concentrations <100 ng/l. The remaining cat had a cobalamin concentration of 149 ng/l. Follow-up folate concentrations were available for one of the cats with severe hypocobalaminemia, following cobalamin supplementation, revealing normalization of folate and cobalamin concentrations after 4 months of therapy. This may support cobalamin deficiency as the cause of the folate elevations; however, the cat also received pancreatic enzyme supplementation during this time. Increased folate concentrations may also be attributed to concurrent SIBO where small intestinal intraluminal bacteria synthesize and release folate, which occurs in dogs with EPI.[3] When evaluating the data from these cats it was noticed that unlike many of the other cases in the study they had clinical signs typical of EPI and only 1/4 cats had a concurrent disease. It is plausible that these cats had an underlying pathologic process similar to dogs with EPI, such as PAA, which resulted in SIBO and resultant increased folate concentrations.

The diagnosis of EPI was based on FPA results with concurrent clinical signs typical of EPI in two cats in this study. These cats were diagnosed in the early 1990s prior to the advent of the fTLI assay. At this time the FPA was the most reliable test available for the diagnosis of feline EPI.[4] False positive FPA test results can occur uncommonly in cats with small intestinal disease and in healthy cats due to daily variation of pancreatic enzyme secretion.[2] Neither of the cats with a positive FPA result had a diagnosis of small intestinal disease, and three consecutive day fecal samples were submitted for each cat to maximize the accuracy of the test. Treatment follow-up results were available for one of the cats and revealed resolution of diarrhea within 2 weeks of daily pancreatic enzyme and weekly cobalamin therapy. It also should be noted that this cat was previously treated with prednisone and metronidazole for potential small intestinal disease which did not result in resolution of signs. The second cat died 2 days after discharge and a necropsy was performed. Necropsy abnormalities included cholangiohepatitis, glomerular disease and PAA. No evidence of small intestinal disease was noted. The presence of PAA would support a diagnosis of EPI.

Seven of the cats in this study were anemic. Non-regenerative anemia has not been previously reported as a common finding in feline EPI.[1,5,8–10] Six of the seven cats with anemia had at least one concurrent disease. Concurrent diseases included renal failure, hepatopathy, inflammatory bowel disease and diabetes mellitus. It is most likely that the high prevalence of non-regenerative anemia was due to anemia of inflammatory disease rather than occurring as a direct result of EPI. In humans pernicious anemia (macrocytic, normochromic) has been associated with chronic cobalamin deficiency.[25] Only one cat in our study exhibited RBC macrocytosis. Interestingly, while this cat was not anemic (hematocrit 35.7%), it was hypocobalaminemic (149 ng/l).

The most common clinical signs of cats in our study were weight loss; the only cat that did not exhibit weight loss was a 3-month-old kitten that exhibited poor growth. In three cats weight loss occurred as the only clinical sign without diarrhea, polyphagia or vomiting, a phenomenon previously reported.[26] Due to these findings we recommend pancreatic function testing in cats with weight loss or poor growth after eliminating more common differential diagnoses regardless if other signs of EPI are present.

Ten of 16 (63%) cats in our study had at least one concurrent disease including lymphoplasmacytic enteritis in three cats, lymphocytic gastritis in two cats and cholangiohepatitis and diabetes mellitus in one cat each. Three out of the four cats that exhibited hyperbilirubinemia had concurrent disease including cholangiohepatitis in one cat and inflammatory bowel disease in two cats. Diabetes mellitus has been reported as a common concurrent disease in feline EPI, most likely secondary to end-stage chronic pancreatitis.[3] However, to our knowledge, there are only 4 documented cases of cats with EPI having concurrent diabetes mellitus including the 1 cat in this study.[1,5] In addition to the cat in this study with diabetes mellitus, four other cats in this study were hyperglycemic. Two of these cats were suspected of having hyperglycemia secondary to a stress response, evidenced by a lack of glucosuria. However, the other two cats had concurrent glucosuria. The first of these two cats had mild hyperglycemia with glucosuria and was lost to follow-up after discharge. The second cat, which had transient moderate hyperglycemia and glucosuria, developed insulin-dependent diabetes mellitus 3 years after being diagnosed with EPI. This is similar to humans who develop EPI secondary to chronic pancreatitis and suggests chronic pancreatitis as the cause of EPI in this cat. In these patients diabetes mellitus usually appears later than malassimilation in the disease.[6]

Feline EPI appears to be an uncommon disease in cats. The prevalence of this disease at four institutions ranged from 0.013 to 0.103% of all cats seen. The much lower prevalence of feline EPI cases (0.013%) seen at the AMC may have occurred for multiple reasons. Firstly, the AMC sees first opinion as well as a referral feline population; therefore, a larger portion of their feline patients is seen for preventative medicine, and less severe disease. Secondly, due to their urban location with a dense population of cats, the AMC sees a larger number of cats per year than the other collaborative

institutions in this study. Although the prevalence of feline EPI in this study was low, in cats with weight loss or poor growth, with or without other stereotypical signs, EPI should be considered as a differential diagnosis. The underlying cause of EPI is often unable to be determined once the clinical signs have occurred. With the advent of fTLI a diagnosis can be made easily.[3] Response to treatment appears to be rapid and results in resolution of at least one clinical sign. A poor response to treatment or unexpected clinicopathologic abnormalities should prompt an investigation for underlying concurrent disease which is common in this population of cats. Severe cobalamin deficiency is also common and testing is recommended to avoid misdiagnosing treatment failure. The prognosis for cats with EPI in our study was good, however, further prospective studies with long term follow-up are needed to evaluate treatment response and survival times.

Acknowledgements

The authors thank the Department of Veterinary Clinical Sciences at Iowa State University and Carnegie Hill Veterinarians for their case contributions.

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