Exocrine pancreatic insufficiency (EPI) is a syndrome caused by an insufficient amount of pancreatic digestive enzymes in the small intestine, which causes malassimilation of nutrients, leading to weight loss and diarrhea. For many years it was believed that EPI was extremely rare in cats. However, since the development of a reliable diagnostic test, it has been shown that EPI does occur in cats with considerable frequency, although it remains a disease that is much less common in cats than it is in dogs.

**Epidemiology**

EPI has traditionally been believed to be extremely rare in cats. For example, of 180,648 cats entered into the Veterinary Medical Data Base over a 10-year period (from the early 1980s to the early 1990s), only 11 cats were recorded to have EPI (0.006%). However, since the introduction of an assay for the measurement of serum feline trypsin-like immunoreactivity (fTLI) in cats in 1995, the diagnosis of EPI has been steadily increasing. For example, in 2002, 23 cats were diagnosed with EPI through submission of a serum sample for measurement of serum fTLI concentration to the Gastrointestinal Laboratory at Texas A&M University; in 2004 there were 225 cats, in 2006 there were 177 cats, in 2008 there were 476 cats, and in 2010 there were 775 cats (unpublished data, 2011). These data clearly show that EPI occurs with considerable frequency in cats and also point to the fact that the recognition of EPI is still increasing.

Traditionally, EPI has been thought of as a condition of older cats. However, the age distribution of 882 cats with a serum fTLI concentration ≤ 8.0 μg/L showed an even distribution of ages. Several cats were 6 months or younger and several more were 1 year of age or younger. Cats that were older than 12 years of age were less commonly represented, most likely because of a decreasing number of cats that are older than 12 years of age in the general feline population. A breed predilection has not been reported for feline EPI.

**Etiology and Pathogenesis**

The term "exocrine pancreatic insufficiency" suggests a disease that is due to insufficient synthesis and secretion of pancreatic digestive enzymes. However, there are a few additional conditions that lead to the same clinical signs and require the same treatment as a patient with a true insufficient synthesis and secretion of pancreatic digestive enzymes would require, namely an obstruction of the pancreatic duct by neoplasia, Eurytrema procyonis infestation (a pancreatic fluke that attaches itself to the wall of the pancreatic ducts; which may lead to mucosal proliferation, periductal fibrosis, and duct obstruction), or abdominal surgery or a lack of intestinal enteropeptidase leading to deficient activation of pancreatic zymogens. There are several potential causes for true EPI, including pancreatic destruction due to chronic pancreatic inflammation, pancreatic acinar atrophy, or pancreatic aplasia or hypoplasia. However, chronic pancreatitis is considered the most common cause of EPI in cats. Three cases of pancreatic acinar atrophy, a condition commonly seen in German Shepherd dogs, has been reported in 3 cats (Figs 1 and 2) and pancreatic hypoplasia has been observed in 1 cat (J. M. Steiner, unpublished data, 2009).

The clinical syndrome of EPI does not require deficiency of all pancreatic digestive enzymes. For example, isolated pancreatic lipase deficiency has been reported as a rare cause of EPI in people and a suspected case has also recently been reported in a single dog and a similar condition could occur in cats.

In humans it has been shown that about 90% of the functional reserve of the exocrine pancreas has to be lost before clinical signs of EPI develop. Digestive enzymes of pancreatic acinar origin play an integral role in assimilation of all major food components. Thus, a lack of pancreatic digestive enzymes will lead to malabsorption. The large amount of nutrients remaining in the intestinal lumen may lead to...
loose, voluminous stools and steatorrhea. At the same time, the lack of nutrient assimilation will cause weight loss and may lead to vitamin deficiencies in some patients. Serum cobalamin (vitamin B₁₂) concentrations are decreased in almost all cats with EPI. Serum folate concentrations in cats with EPI are usually either decreased, indicating concurrent small intestinal disease, or are within the reference interval. Also, a single cat with EPI and secondary vitamin K responsive coagulopathy has been reported in the literature.

In cases of EPI, which are caused by chronic pancreatitis, destruction of pancreatic tissue may not be limited to the acinar cells and concurrent diabetes mellitus is common in these patients. In fact, chronic pancreatitis has been recognized as an important cause of diabetes mellitus in humans and dogs. Thus, cats with diabetes mellitus and a history of chronically loose stools should be evaluated for concurrent exocrine pancreatic insufficiency. Also, because feline EPI is due to chronic pancreatitis in most cats, residual pancreatic inflammation may be present and may lead to additional clinical signs.

Clinical Picture and Diagnosis

Clinical signs most commonly reported in cats with EPI are weight loss, loose stools, and polyphagia. These clinical signs are nonspecific and are also seen in many cats with disorders more commonly seen in cats than EPI. Common differential diagnoses for cats with weight loss are hyperthyroidism, dental and periodontal disease, chronic renal disease (CKD), heart failure, neoplasia, and chronic intestinal disorders, such as inflammatory bowel disease, which are all common conditions, especially in middle-aged to older cats. The most common disorders causing diarrhea are primary chronic intestinal disease or a variety of secondary disorders such as hyperthyroidism, CKD, and liver failure, some of which also lead to weight loss as described earlier. Finally, common causes of polyphagia in cats are hyperthyroidism, corticosteroid treatment, or diabetes mellitus.

The diarrhea is characterized by loose or semi-formed voluminous stools, which may have a yellow- to clay-colored appearance, and may be quite malodorous. Some cats with EPI may develop watery diarrhea, but this is not common. The high fat content of the feces can lead to a greasy appearance of the hair coat of the cat, especially in the perianal and tail region. However, in a recent report of 20 cats with EPI, only 2 cats showed greasy soiling of the hair coat in the perianal region.

Recently, a cat with severe D-lactic acidosis with clinical signs of episodic generalized weakness, ataxia, and lethargy was shown to have underlying EPI. Because D-lactate is exclusively generated by bacteria, the authors speculated that the D-lactic acidosis was due to massive increased bacterial fermentation in the intestinal lumen because of small intestinal dysbiosis (formerly known as small intestinal bacterial overgrowth) secondary to EPI. Both the D-lactic acidosis and the clinical signs of the cat resolved after supportive care together with pancreatic enzyme supplementation.

As mentioned above, some cats with EPI may have concurrent diabetes mellitus and may thus be presented for polyuria/polydipsia or even with diabetic ketoacidosis. Also, because EPI is due to chronic pancreatitis in most cats, patients may show residual signs of pancreatic inflammation, such as anorexia or abdominal discomfort. It should also be noted that many cats with chronic pancreatitis have
concurrent inflammatory conditions of other abdominal organs, such as inflammatory bowel disease, cholangitis, or nephritis, which may all lead to additional clinical signs.

Results of routine blood tests are within the normal range in most cases. In a few cases, lymphopenia, lymphocytosis, neutrophilia, eosinophilia, and elevations of hepatic enzymes can be observed. However, it is unclear from the literature whether these changes are rare changes associated with EPI or, more likely, are associated with concurrent conditions, such as diabetes mellitus, inflammatory bowel disease, or cholangitis.

Abdominal radiographs or ultrasound also do not show any specific changes in cats with EPI. In one report, 2 cats with EPI showed an inhomogeneous pancreatic parenchyma and pancreatic nodules, but this has not been reported elsewhere. More common are radiographic and/or ultrasonographic changes that are due to concurrent conditions, such as cholangitis and/or inflammatory bowel disease.

As mentioned above, EPI is a functional disease and thus requires a functional diagnosis. Several tests have been recommended to estimate exocrine pancreatic function in cats. However, all of these tests, except the measurement of serum fTLI concentration, are unreliable and/or impractical in cats and are not recommended.

Immunosassays for the measurement of fTLI concentration have been developed and analytically validated. It should be noted that assays for the measurement of TLI are highly species-specific, and assays developed and validated for use in dogs or humans cannot be used to measure serum TLI concentrations in cats. Currently, there are only 2 assays for the measurement of serum fTLI available worldwide. The Gastrointestinal Laboratory at Texas A&M University offers a radioimmunoassay, an assay that has been fully validated analytically. The current reference range for serum fTLI measured at the Gastrointestinal Laboratory is 12.0 to 82.0 μg/L, with values of ≤ 8 μg/L being considered diagnostic for EPI. There is also an enzyme-linked immunosorbent assay for the measurement of fTLI that is exclusively available in Europe. To the author’s knowledge, the validation of this assay has not been reported.

The assay for fTLI quantifies the amount of trypsinogen, the inactive zymogen of trypsin, and related molecules (i.e., trypsin and some trypsin molecules bound to trypsin inhibitors). Pancreatic acinar cells synthesize a wide variety of digestive enzymes. Some of these enzymes are synthesized in an active form (e.g., lipase, amylase, and others), whereas others are synthesized aszymogens (e.g., trypsinogen, chymotrypsinogen, proelastase, and others). All of these products are packaged into the so-called zymogen granules that are released onto the luminal side of the acinar cells by way of exocytosis. However, a small number ofzymogen granules are also released into the bloodstream. The small amount of trypsinogen released into the bloodstream can then be measured by way of the fTLI assay. When the mass of acinar cells is severely decreased, the amount of trypsinogen released into the bloodstream is also decreased and serum fTLI concentrations are severely decreased.

The fTLI has been successfully used to diagnose feline EPI for more than 15 years. In one report, clinical data from the first 20 cats with serum fTLI concentrations ≤ 8 μg/L were evaluated; 17 of these 20 cats showed compelling evidence of EPI and the remaining 3 cats had supportive evidence of EPI. All 20 cats in that study showed clinical signs compatible with EPI and 17 cats showed a positive response to treatment. Two of the 3 cats that did not respond to therapy ultimately died, and a pancreatic biopsy strongly supported a diagnosis of EPI in both cases. The third cat that did not respond to therapy was vomiting and had decreased serum cobalamin (vitamin B12) and folate concentrations. Concurrent small intestinal disease or severe vitamin B12 deficiency may have impaired the therapeutic response to enzyme supplementation in this cat. On exploratory laparotomy, a small pancreas was noted by the surgeon, suggesting a diagnosis of EPI. However, a pancreatic biopsy was not collected. There were also 2 cats that were 6 months old at the time of diagnosis. One cat showed poor growth and hair loss and responded to enzyme replacement therapy with weight gain and hair growth. The second cat was very thin and had a greasy hair coat. It also responded to enzyme replacement with weight gain. However, the cat was found dead 3 weeks after diagnosis and start of therapy, and a necropsy was not performed. Both cats responded with weight gain, but both still were immature at the time of diagnosis. Remission of some undiagnosed gastrointestinal disorder other than EPI may have led to growth and weight gain. It was strongly suspected that these 3 last cats also had EPI, but evidence was not considered conclusive. Even if none of these 3 cats would have had EPI and should be considered false-positive results of the test, the specificity of serum fTLI concentration for EPI would still reach 85%, which would suggest that serum fTLI concentration is highly specific for feline EPI.

Recently, it was shown that decreased renal function has a significant effect on serum fTLI concentrations and serum fTLI concentrations may increase in cats with renal failure. Therefore, evaluation of serum fTLI concentrations in azotemic cats may obscure a diagnosis of feline EPI. However, no cases have been identified yet where a diagnosis of EPI was missed because of renal failure. Based on these results, the author would suggest reevaluation of serum fTLI concentrations in azotemic cats that have a borderline fTLI concentration and in which an alternative diagnosis for loose stools and weight loss cannot be identified.

Most cats with EPI have a severely decreased serum cobalamin concentration. In one recent study, serum cobalamin concentration was measured in 10 cats with EPI, and serum cobalamin concentration was decreased in all 10 of these cats. Because cobalamin deficiency can lead to various gastrointestinal (i.e., intestinal inflammation, villous atrophy, malabsorption of cobalamin and other nutrients, and others) and systemic complications (i.e., immunodeficiencies, central neuropathies, peripheral neuropathies, or others) and can also lead to treatment failure in cats with EPI, the author believes that serum cobalamin and folate concentrations should be measured in every cat suspected of having EPI and cobalamin deficiency should be managed by parenteral cobalamin supplementation.

Management

Most cats with EPI can be successfully managed by dietary supplementation with pancreatic enzymes. Dried extracts of porcine pancreas are available, but raw beef, pork, or game pancreas can also be used instead. If commercial products are used, powder is more effec-
tive than tablets or capsules, and enteric-coated products should be avoided. Initially, 1 teaspoon per meal should be given. Because cats often do not like the taste of the pancreatic powder, it is best to thoroughly mix the powder with some canned food. If the cat refuses to consume the food with the powder, it can also be mixed with fish oil and then mixed into the food. Pre-incubation of the food with pancreatic enzymes is not necessary. If raw pancreas is used, it should be finely minced, portioned, and frozen in packages for 1 meal each. Fresh-frozen pancreas can be kept frozen for several months without losing efficacy. One to two ounces (30-60 g) of raw, minced pancreas should be mixed in with each meal. Supplementation with bile salts is not necessary regardless of the source of pancreatic enzymes. Most cats respond quite rapidly to enzyme replacement therapy and show resolution of loose stools within 3 to 4 days. When clinical signs have resolved, the amount of pancreatic enzymes given with each meal can be gradually decreased to the lowest effective dose, which may vary from patient to patient, and may also vary between different batches of the pancreatic supplement.

Response to enzyme supplementation alone may not be satisfactory. This is not surprising if one considers that almost all cats with EPI have cobalamin deficiency. As mentioned above, cobalamin deficiency can lead to various gastrointestinal and systemic complications and it is thus crucial to measure serum cobalamin concentration in all cats suspected of having EPI and correcting cobalamin deficiency in all cats with a decreased serum cobalamin concentration. Because cobalamin deficiency causes cobalamin malabsorption, oral supplementation is not effective in patients with cobalamin deficiency. Recently, some empirical sources have suggested the use of sublingual formulations of methylcobalamin in cats, but there is no evidence that such formulations are effective. Multivitamin preparations do not contain sufficient amounts of cobalamin and thus cannot be used. Instead, pure cobalamin is needed for therapy, and 250 μg is administered subcutaneously once a week for 6 weeks, followed by an injection 1 month after that, and a recheck 1 month after the last dose. Some cats only need 1 treatment period with cobalamin supplementation, whereas others will need parenteral cobalamin supplementation for the rest of their lives. There have been anecdotal suggestions that supplementation with intrinsic factor may benefit cats with EPI and the author does not currently recommend such practice.

Vitamin status for other vitamins has not been systematically evaluated in cats with EPI and the author does not currently recommend supplementation of cats with EPI with either vitamin E or other fat-soluble vitamins. However, if the cat shows a bleeding tendency, a coagulation profile should be evaluated, and, if indicated, the cat should be treated with vitamin K. However, to date, only 1 cat with EPI and a vitamin K-responsive coagulopathy has been reported.

Because there are no studies available concerning the use of specific diets in cats with EPI, there are no specific dietary recommendations for these patients. However, the author believes that it is prudent to avoid low-fat diets, because fat digestibility does not normalize in EPI patients after enzyme supplementation and feeding a low-fat diet may lead to deficiencies of fat-soluble vitamins and essential fatty acids. Also, the author believes that diets that are high in nonfermentable fiber should be avoided because certain types of fiber may hinder the action of enzymes and thereby impede digestion of fat.

Cats that fail to respond to therapy may benefit from treatment with a proton pump inhibitor (e.g., omeprazole at 0.7 mg/kg every 12 hours). Such treatment may decrease the degree of irreversible inhibition of exogenous pancreatic lipase in the stomach. However, it should be noted that antacid therapy has a negative effect on gastric lipase, another important digestive lipase, so there may only be a minimal increase in fat absorption overall.

Some cats will not respond appropriately to enzyme and cobalamin supplementation. These cats may have concurrent small intestinal disease, such as inflammatory bowel disease. This hypothesis is supported by the decreased serum folate concentrations observed in many cats with EPI. In addition, some cats with EPI may have secondary small intestinal dysbiosis (formerly known as small intestinal bacterial overgrowth). Such patients may benefit from antibiotic therapy, such as tylosin at 25 mg/kg every 12 hours or metronidazole at 15 to 25 mg/kg every 12 hours. However, it should be noted that there is still a great deal of uncertainty about the normal intestinal microbiota and small intestinal dysbiosis in cats.

**Prognosis**

Most cats with EPI have an irreversible loss of pancreatic acinar tissue and recovery is extremely rare and poorly understood. However, with appropriate management and monitoring, these patients usually gain weight quickly, pass normal stools, and can go on to live a normal life for a normal lifespan.

**References**