In exocrine pancreatic insufficiency (EPI) there is insufficient production or secretion of digestive enzymes by the pancreas with associated maldigestion. Usually multiple enzymes need to be affected to show clinical disease, although there is one report of a patient with a lipase-only defect. Since lipase is the rate-limiting enzyme in pancreatic digestion, deficiency in just that single enzyme can also result in EPI.

Underlying Cause:
Potential underlying causes of EPI include:
- Pancreatic acinar atrophy (most common cause in dogs)
- Chronic pancreatitis (most common cause in cats and people)
- Pancreatic neoplasia
- Pancreatic flukes
- Pancreatic hypoplasia

In dogs, the most commonly affected breeds with pancreatic acinar atrophy are the German Shepherd dog, the rough-coated Collie, and the Eurasian dog. Pedigree analysis has suggested an autosomal recessive mode of inheritance, but more recent studies suggest a polygenic mode of inheritance.

In pancreatic acinar atrophy, an auto-immune-mediated atrophic lymphocytic pancreatitis gradually leads to destruction of the pancreatic acinar tissue. This is a progressive disease. Affected dogs are born with a normal pancreas. In the subclinical phase of the disease, there is marked t-lymphocyte infiltration of the pancreas. Grossly, there is still normal pancreatic mass with scattered areas of atrophied tissue. In the clinical phase of the disease there is end-stage acinar atrophy, with minimal-to-mild inflammation present. Grossly the entire pancreas is think and transparent. Typically, the endocrine pancreas is spared in dogs with pancreatic acinar atrophy.

Chronic pancreatitis is the most common cause of EPI in cats and the second most common cause of EPI in dogs. In the Cavalier King Charles Spaniel, chronic pancreatitis appears to be a more common cause of EPI as the age of onset of EPI in this breed is significantly older than in German Shepherds with pancreatic acinar atrophy. Chronic inflammation of the pancreas over time leads to atrophy and fibrosis. Ultimately enough exocrine tissue is destroyed to cause signs. Patients may also have concurrent diabetes mellitus.

Pathophysiology:
The pathophysiology of EPI is multifactorial. Patients with EPI are lacking more than just digestive enzymes. There are other components of pancreatic juice that are also important for intestinal health and digestion. Components include:
- Digestive enzymes: lack of these enzymes leads to maldigestion, osmotic diarrhea, and bacterial overgrowth
- Bicarbonate: lack of bicarbonate affects intraluminal pH of the intestine which affects to efficacy of brush border enzymes and can contribute to bacterial overgrowth
- Trophic factors for GI mucosa: lack of trophic factors contributes to malabsorption
- Intrinsive factor: lack of intrinsic factor leads to hypocobalaminemia as intrinsic factor is required for cobalamin transport in the ileum

**Clinical Signs:**
Clinical signs of EPI differ between dogs and cats. Dogs exhibit “classic” symptoms while cats symptoms tend to be more vague. In dogs, diarrhea and abnormal feces are present in as many as 95% of cases. Weight loss is a close second, present in 87% of cases. Other symptoms that may be seen in dogs include polyphagia, coprophagia, flatulence, polydipsia, and vomiting. In cats, weight loss is the primary clinical sign, present in 95% of cats. Remarkably, diarrhea or other fecal changes were present in only 50-75% of cats. Other symptoms may include polyphagia, vomiting and an unkempt haircoat.

**Diagnosis:**
Diagnosis of EPI is based on typical clinical findings and confirmed with abnormal pancreatic function testing. Routine bloodwork (CBC/chesmitry) often show unremarkable changes. Assessment of serum amylase and lipase activities are not useful in diagnosis. Fecal microscopy can be a useful adjunctive diagnostic. Stains such as Sudan or Iodine can stain for undigested fat and undigested starch respectively.

“The gold-standard for diagnosis of EPI in dogs and cats is measurement of trypsin-like immunoreactivity (TLI). Make sure the patient has been fasted for 12-14 hours prior to blood draw. Serum TLI measurement is species and pancreas specific. It will also not cross-react with pancreatic supplements. Pancreatic lipase immunoreactivity (PLI) is not recommended for the diagnosis of EPI. cPLI concentrations in dogs with EPI overlap with normal dogs.

<table>
<thead>
<tr>
<th>Species</th>
<th>EPI</th>
<th>Grey Zone</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>&lt; 2.5 μg/L</td>
<td>2.5 – 5 μg/L</td>
<td>5.7 – 45.2 μg/L</td>
</tr>
<tr>
<td>Cat</td>
<td>&lt; 8 μg/L</td>
<td>8 – 12 μg/L</td>
<td>12 – 82 μg/L</td>
</tr>
</tbody>
</table>

In a patient with a “grey zone” TLI measurement, this may either represent a patient in the subclinical phase or normal fluctuation of TLI. It is recommended to recheck the TLI in 1 month, then periodically thereafter depending on the patient’s clinical signs. The progression of subclinical disease is highly variable and may take years to progress to the clinical stage.

In Europe radioimmunoassays are difficult to obtain due to radiation regulations. Therefore an alternative test has been developed, the fecal pancreatic elastase concentration (cE1). It is sensitive, but not specific for EPI. There is a false positive rate of
25%. Elastase concentrations > 20 μg/g can help exclude EPI. Values < 10 μg/g may have EPI.

**Treatment**
While enzyme replacement therapy is the main treatment for EPI, successful management of the EPI patient requires the clinician balance multiple treatments, particularly in initial stabilization.

**Enzyme replacement therapy** is the mainstay of treatment for EPI. Not all enzyme replacements are equal in potency! Viokase-V and Pancreazyme are the recommended brands in the USA. Both of these powders are porcine in origin. The starting dose is 1 tsp extract per 10 kg body weight. Once a patient has responded completely, the dose of enzyme can be slowly tapered to the minimally effective dose. Pre-incubation of the food with the powder was found to now be necessary in one study, however anecdotally, many owners swear by pre-incubation.

Raw pancreas can also be used for enzyme replacement. Raw pancreas may be a more cost-effective option for some owners compared to Viokase or Pancreazyme. They are a better value as well since over-the-counter pancreatic enzyme powders have poor potency. Beef, pork, sheep or wild game pancreas have all been used in dogs. Roughly 1-3 oz of raw pancreas is equivalent to 1 tsp pancreatic power. Pancreas can be kept frozen for up to 3 months without loss of enzyme activity.

**Diet** A high-quality, easily-digestible maintenance diet is appropriate for more patients. Feeding a low fat diet has been recommended by some authors as fat digestibility does not return to normal in dogs treated with pancreatic supplements. However no benefit was found in restricting fat in one study. Fat restriction may even increase the risk if deficiencies of fat-soluble vitamins and fatty acids. However, a low fat diet may be used as a last resort for patients that due not respond to other therapies. Avoiding a high fiber diet has been recommended by others. High fiber diets are typically not calorie dense. Additionally, fiber may diminish the absorption of other nutrients and can inhibit the activity of pancreatic enzymes, particular lipase.

**Cobalamin** deficiency results from a lack of intrinsic factor and increased uptake by intestinal bacteria. Hypocobalaminemia may be responsible for poor response to enzyme treatment if it is not concurrent recognized and treated. The majority of dogs and cats with EPI are deficient, so all patients should be tested. Supplementation of cobalamin is recommended if serum cobalamin is in the low normal range (< 300 ng/L). Dogs are supplemented with 250-1500 μg SQ weekly for 6 weeks. Cats with 250 μg SQ weekly. After the 6 loading doses, subsequent doses are given every month.

**Antibiotics** Small intestinal bacterial overgrowth is a common problem in EPI patients. The undigested food in the intestine is a good substrate for bacterial growth. In addition, there are changes in intestinal motility and immune function in EPI patients that allow bacteria to overgrow. Antibiotics are recommended when diarrhea does not resolve with initial
treatment or when signs recur on long-term management. Tylosin (10-20 mg/kg PO q12hr) or metronidazole (7.5-10 mg/kg PO q12hr) are the main antibiotics used.

**Antacids** A large portion of orally administered lipase is destroyed by the low pH in the stomach. Antacids are recommended when diarrhea does not resolve after other modifications have been attempted. A human study showed that proton pump inhibitors were superior to histamine-2 blockers for EPI patients. In veterinary patients, drug options include famotidine (0.5-1 mg/kg PO q 12hr) or omeprazole (0.7 mg/kg PO q24hr).

**Prognosis**
By the time clinical signs of EPI appear, pancreatic destruction is almost total, therefore lifelong enzyme therapy is usually required. Response to treatment (weight gain, cessation of diarrhea and decrease in fecal volume) is typically seen within the first few weeks of treatment.

In one large review, 60% of dogs had a good response to initial therapy, 17% had a partial response and 23% had a poor response. There were no predictors of response found on multivariate analysis of the data. 30 dogs were known to have died within 1 year of diagnosis. Five were euthanized due to cost of treatment and ten were euthanized due to persistent clinical signs. The median survival time was over 5 years. Dogs with marked hypocobalaminemia had worse survival.