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# Canine Exocrine Pancreatic Insufficiency: A Review

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## Introduction

Pancreas is one of the vital viscera in the body, which has both Endocrine (Insulin, glucagon & somatostatin) and Exocrine (Pancreatic Juice) functions. Exocrine functions include digestion and breakdown of ingesta (by digestive pancreatic enzymes), absorption of cyanocobalamin/Vitamin B12 (intrinsic factor), regulation of intestinal bacteria homeostasis (Antimicrobial Peptides), Pancreas secretes antimicrobial proteins that consist about 10% of the proteins in the pancreatic juice (Medveczky P *et al*., 2009). Pancreatic juice contains Bicarbonate ions and water (buffers and maintain pH of gut). The pH of the pancreatic secretions is alkaline due to a very high concentration of NaHCO3 (up to 140 mM). At least one major function of the NaHCO3 is to neutralize the acidic pH of the gastric chyme delivered to the intestine from the stomach. A neutral pH in the intestinal lumen is necessary for optimal function of digestive enzymes as well as gastrointestinal surface epithelial function (Pandol SJ, 2010). Pancreas also secretes mucous (from goblet cells of pancreatic duct) and some trophic factors.

Canine Exocrine Pancreatic Insufficiency (EPI) is a serious condition where exocrine synthesis and secretions from pancreas is retarded leading to maldigestion syndrome, vitamin B12 deficiency and gut microbiota dysbiosis. Canine EPI is clinically characterised by progressive loss of body condition, polyphagia, voluminous faeces & flatulence, sometimes accompanied by vomiting & diarrhoea.

**Key Words:** Acinar cells, Steatorrhea, SIBO, PERT, cobalamin.

**Aetiology**: Insufficiency of the exocrine pancreas can be a consequence of various diseases, such as atrophy of pancreatic acinar cells, chronic pancreatitis, pancreatic cancer, cystic fibrosis, severe acute necrotizing pancreatitis or gastrointestinal and pancreatic surgical resections (Singh AK *et al*., 2018).

It can be also due to pancreatic hypoplasia (congenital), autoimmune pancreatitis & pancreatic duct obstruction. Sometimes dogs suffering with diabetes mellitus can also suffer with EPI and vice versa (depend upon the cause of pancreatic insult). Whatever the cause (inflammation or injury) there is gradual and progressive reduction of exocrine cells of pancreas leading to EPI.

**Prevalence:** mostly seen in middle aged dogs and also in slightly older ones, but can develop at any

age of life. No sex predisposition but female dogs are likely to develop the disease. Dogs fed with high fat diets, obesity has increased risk of EPI and other pancreatic diseases like pancreatitis.

The most well-documented breed predisposition is the German Shepherd Dog (GSD), and while any breed can be affected, Rough-coated Collies, Cavalier King Charles Spaniels, Cairn Terriers, Chows, Cocker Spaniels, Eurasier dogs, and West Highland White Terriers are reported to be at increased risk of EPI (Cridge, H *et al.*, 2024).

**Breed association with EPI**: Acc. to the study done by Daniel J Batchelor *et al*., 2007 using cTLI assays the results are as follows -

An association with EPI was found in Chows, Cavalier King Charles Spaniels (CKCS), Rough-Coated Collies (RCC), and German Shepherd Dogs (GSD) (all P < .001). Chows (median, 16 months) were younger at diagnosis than CKCS (median, 72 months, P < .001), but not significantly different from GSD (median, 36 months, P = .10) or RCC (median, 36 months, P = .16). GSD (P < .001) and RCC (P = .015) were younger at diagnosis than CKCS. Boxers (P < .001), Golden Retrievers (P < .001), Labrador Retrievers (P < .001), Rottweilers (P = .022), and Weimaraners (P = .002) were underrepresented in the population with EPI.

**Pathogenesis**

Proper functioning of pancreas is highly required for the digestion and absorption of nutrients from the ingesta, once the work of the exocrine part of pancreas is lacking, it leads to progressive changes in gut and then in the body;

1) Lack of pancreatic enzymes lead to mal-digestion of carbohydrates, fats, proteins and peptides etc. but the main changes occur in the fat digestion, as most of the lipase that are secreted in the gut are from pancreas (along with bile metabolises fats and aids in absorption). Once the lipase is lacking from pancreas there is no proper digestion and absorption of fats leading to steatorrhea. Presence of large undigested food in the gut changes change the gut osmosis making faces voluminous.
2) Lack of intrinsic factor from the pancreas lead to diminished cobalamin absorption and increase its breakdown due to bacterial overgrowth in gut causes Vitamin B12 deficiency.
3) Deficiency of fat-soluble vitamins (A, D, E, K) occur due malabsorption of fats (these vitamins absorption occurs along dietary fat).
4) lack of bicarbonate ions and buffering of chyme in small intestine, alters gut pH, increases the acidity and damages the intestinal tissue.
5) Change in the pH, more available undigested nutrients in gut and lack of pancreatic antimicrobial peptide (in pancreatic juice) there is severe faecal microbiota dysbiosis (restricted to Intestinal lumen [Anitha Isaiah et al., 2017]) and SIBO causing diarrhoea toxin build up in gut and also elevates serum folate levels.

**EPI and Immunity**: due to deficiency of vitamins and lack of enough nutrients to the dog, there is severe weakening of immune system.

*Phases of EPI in dogs***:** Subclinical phase (SEPI) and Clinical phase (EPI).

In Subclinical phase, there is progressive damage of pancreas and gradual loss of exocrine function



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occurs. Diagnosis of EPI is difficult in this phase as pancreas as clinical signs are not shown up till maximum damage happens to pancreas. The exocrine pancreas has incredible functional redundancy, and, regardless of its underlying pathogenesis, clinical signs of EPI emerge once > 90% of pancreatic acinar cell mass is lost (DiMagno EP *et al*., 1973). Clinical phase of EPI is where clinical cases are noticed.

**Microbiota Dysbiosis –** Acc. to the study done by Anitha Isaiah *et al*., 2017; They noticed there is significant changes in fecal microbial communities, the families Bifidobacteriaceae (P = 0.005), Enterococcaceae (P = 0.018), and Lactobacillaceae (P = 0.001) were significantly increased in the untreated and treated dogs with EPI when compared to healthy dogs. In contrast, Lachnospiraceae (P < 0.001), and Ruminococcaceae (P < 0.01) were significantly decreased in dogs with EPI.

**Clinical Signs**

Progressive weight loss and gradual loss of animal condition, animal becomes thin, changes in the appetite pattern shows polyphagia and sometimes coprophagia, (sometimes episodes of inappetance also can be noticed), changes in defecation pattern shows steatorrhea, amylorrhoea, voluminous foul-smelling faces, diarrhoea (due to SIBO), borborygmus and flatulence. Skin become rough and seborrhoea sets in. Sometimes animal may show vomiting, neurological signs (due to severe vitamin B12 deficiency), abdominal pain, coagulopathies (due to K deficiency) etc.

**Diagnosis**

Based on clinical signs tentative diagnosis can be made,but to confirm the case laboratory examination is needed.

**Levels estimation in serum and faecal testing;**

1) Measuring **Canine Serum Trypsin – like Immunoreactivity** (cTLI), Gold standard test for EPI. It is a radio-immunoassay.

   The fasting TLI concentration is an indirect measure of functional exocrine tissue mass. The reference range for canine TLI is >5 to 35 µg/l. In EPI, values are typically <2.5µg/l. Values between 2.5 to 5.0 µg/l are indicative of a dog developing EPI, or one that has subclinical EPI because of lymphocytic pancreatitis or chronic pancreatitis. It has been suggested that a TLI stimulation test, measuring cTLI after stimulation by eating, or injection of secretin or caeruletide (a cholecystokinin analogue) can be helpful in discriminating equivocal results (Edward J. Hall, 2003).

2) **Pancreas specific Elatase test:** Pancreas-specific elastase has been measured by fecal enzyme-linked immunosorbent assay as an indicator of exocrine pancreatic function in dogs. Fecal elastase <10µg/g is consistent with EPI and >20µg/g has good predictive value for ruling out EPI. This test is not widely available. (Robert G. Sherding *et al*., 2006).

3) **Film test** (Faecal Trypsin): Total 9 ml of 5% solution of sodium bicarbonate solution was taken in a cylinder and the solution was made 10 ml by adding 1 ml of faeces. A strip of exposed X- RAY film was submerged in it. The solution was incubated at 37°C for 1 hour. The strip was washed



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under gentle stream of tap water. Cleared area indicated presence of trypsin in faeces which is normally not present in the faeces of normal dogs. (Singh, A.K *et al*., 2018).

4) **Serum Pancreatic Lipase Immunoreactivity (cPLI),** Levels lower than 0.1 µg/L considered positive. Normal serum PLI concentration range, 0.1 to 1.4 µg/L (Steiner *et al*., 2006).
5) Other methods – faecal proteolytic activity, serum lipase activity (not specific to pancreatic problems and EPI), Faecal microscopy for Fat and Starch (stained faecal sample reveals undigested food particles). These tests are not specific for EPI, thus these can't solely use for diagnosing the EPI, but can be used for studies and research.
6) Serum Cobalamin & folate levels: low serum cobalamin (cobalamin<350ng/L) and high serum folate (folate>12µg/L) levels. (N Soetart *et al*., 2019).

**Diagnostic imaging** – MRI and ultrasonography are useful to study the topography of pancreas and surrounding structures and it should be supported with other diagnostic methods to conclude the case as EPI.

***Ultrasonography*** – highly inconsistent, most of the dogs shows thin pancreas and decrease in the thickness. The ultrasonography changes in EPI can be correlated to the cause of it (specific changes) Ex// Pancreatitis, Tumours etc.

**Histopathology** - In SEPI, Partial acinar atrophy, with diminished normal pancreatic tissue and scattered areas of partially destroyed and atrophied parenchyma and in clinical EPI reveals total destruction of acinar parenchyma (Wiberg ME et al., 1999).

**Differential Diagnosis**: Although the symptoms of EPI are typical, they are not pathognomonic. In dogs, the differential diagnosis includes the small intestinal disorders that cause malabsorption or maldigestion (intestinal parasites, inflammatory bowel disease, small intestinal villus atrophy, lymphangiectasia, diffuse small intestinal malignancies, short bowel syndrome, changes of the intestinal brush border enzyme activities). [Timoleon S. Rallis, 2004]

**Prognosis**: The prognosis for long-term management of dogs and cats with EPI with a high quality of life is generally good. A standard therapeutic strategy including PERT, cobalamin supplementation, and a high-quality diet is often all that is needed to restore normal body condition and fecal quality (Cridge, H *et al*., 2024). Serum folate and Cobalamin levels are prognostic indicators.

**Treatment**

1) Pancreatic enzyme supplementation/ Pancreatic Enzyme Replacement Therapy (**PERT**):

   **Commercial Preparations** – available as capsules/ tablets/ Powder form. These preparations should be given before every meal. Dosage should do as prescribed by company that's providing the product and alterations can be done later based on clinical improvement. Powders has activated whole raw porcine pancreas, it contains lipase, amylase, protease & also esterases, peptidases, nucleases and elastase. Ex// Pancrezyme™, Should be mixed in meal 15 to 20 minutes before feeding to dog. Capsules, Tablets (Ex// Pancresolve ™) contains lipase, amylase and protease.

   **Feeding Raw Pancreas** – bovine or porcine pancreas obtained from the slaughter house can be fed to animal about 100 to150 g (Edward J. Hall, 2003). Though costly (due to their pharmacological



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properties) but they are excellent source of enzymes. Feeding raw pancreas can transmit many pathogens like Coliforms etc.

2) **Antibiotics** – if animal is showing signs of SIBO, antibiotic therapy is needed to control their growth (Ex// Metronidazole), they can decrease the opportunistic pathogens count in gut. Once signs are alleviated antibiotics can be withdrawn.
3) **Antacids** – they decrease gastric acid secretion and prevent enzyme degradation in stomach. Ex// H2 blockers like Ranitidine, famotidine etc., Proton pump inhibitors like pantoprazole and omeprazole etc.
4) **Antiemetics** – if vomiting signs are noticed, antiemetics like ondansetron can be used.
5) **Probiotic Supplementation** – Oral supplementation of probiotics can aid in growth of beneficial bacteria in gut.
6) **Vitamin Supplementation** – if Coagulopathy noticed Vitamin K supplementation should be given. For cobalamin supplementation (can be given enteral/ parenteral), dosing based on body weight and current serum levels of B12. Initially give daily supplementation and later re-perform the Vitamin B12 estimation in serum and reduce the dose and frequency if improvement noticed in values.
7) **Other Therapies;** other lipase sources – fungal and bacterial

   **Fungal lipase;** derived from Aspergillus Sp.

   According to study by S M Griffin *et al*., 1989; Ten grams (60,000 U lipase) of pancreatin was compared with 400mg (4800 U lipase) of fungal lipase administered with each meal against a no treatment group. There was no significant difference in stool bulk and faecal fat excretion between pancreatin and lipase treated animals. Both groups showed a significant reduction in stool bulk and fat excretion when compared with the no treatment group (p less than 0.01). A markedly diminished treatment volume, in the form of fungal lipase, is as effective in controlling steatorrhoea as pancreatin and may prove to be a potentially valuable therapy for patients with pancreatic insufficiency.

   **Bacterial Lipase;** isolated from *Burkholderia plantarii.*

   According to the study by A Suzuki *et al*.,1997;

   With the standard meal, powder bacterial lipase reduced steatorrhea in a dose-dependent manner ($P = 0.03$), and 135,000 and 300,000 IU of the liquid form decreased steatorrhea more than powder bacterial lipase ($P = 0.017$ and 0.057, respectively). Coefficients of fat absorption with 300,000 IU of powder bacterial lipase correlated ($r2 = 0.79$; $P < 0.001$) with increasing proportions of fat calories in diets.
8) **Dietary management –** Providing animal with diet for pancreatic problems available commercially or feeding with Hydrolysed protein diet can improve the body condition. Low fat diets are recommended rather than high fat diets (as they will worsen the steatorrhea). Medium chain triglycerides are recommended, A high MCT content in the diet was associated with significantly higher serum vitamin E, cholesterol, triglyceride, retinyl stearate, retinyl palmitate, and total vitamin A concentrations in dogs with EPI (Gabriele M Rutz *et al*., 2004).



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**Key points -**

- Oral powder preparations can digest the oral mucous membrane (as they are mixed in meal in prior) causes bleeding. In such cases withdrawal of oral powders can alleviate the signs.
- Capsules are enteric coated can resist acid degradation show better recovery than tablets. Sometimes capsules maybe undissolved and excreted in faeces.
- Vitamin supplementation should be done only after estimation of current serum levels.
- Routine check-ups and follow-up is necessary to evaluate the health status of animal.
- Enteral nutrition is highly challenging in cases of Canine EPI.
- Use of corticosteroids are controversial, should be used only for treating the underlying cause.
- Veterinarians should advice the owner to use the supportive therapy recommended for lifelong and if owner want to have any changes in them should be informed to vet in prior. Un recommended alterations can again deteriorate the animal's health.
- Alternatives (that are proven successful) to Pancreatic extract can be followed if owners feel treatment is very costly, success rate depends on improvement in dog's symptoms.

**Conclusion:** Treatment protocol and supportive therapy should be followed for lifelong and dosage of medication should be altered based on health status and presence/alleviation of clinical signs. Usage of medication shows promising improvement.

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