Exocrine Pancreatic Insufficiency:

Current Perspectives and Research Priorities

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Outline

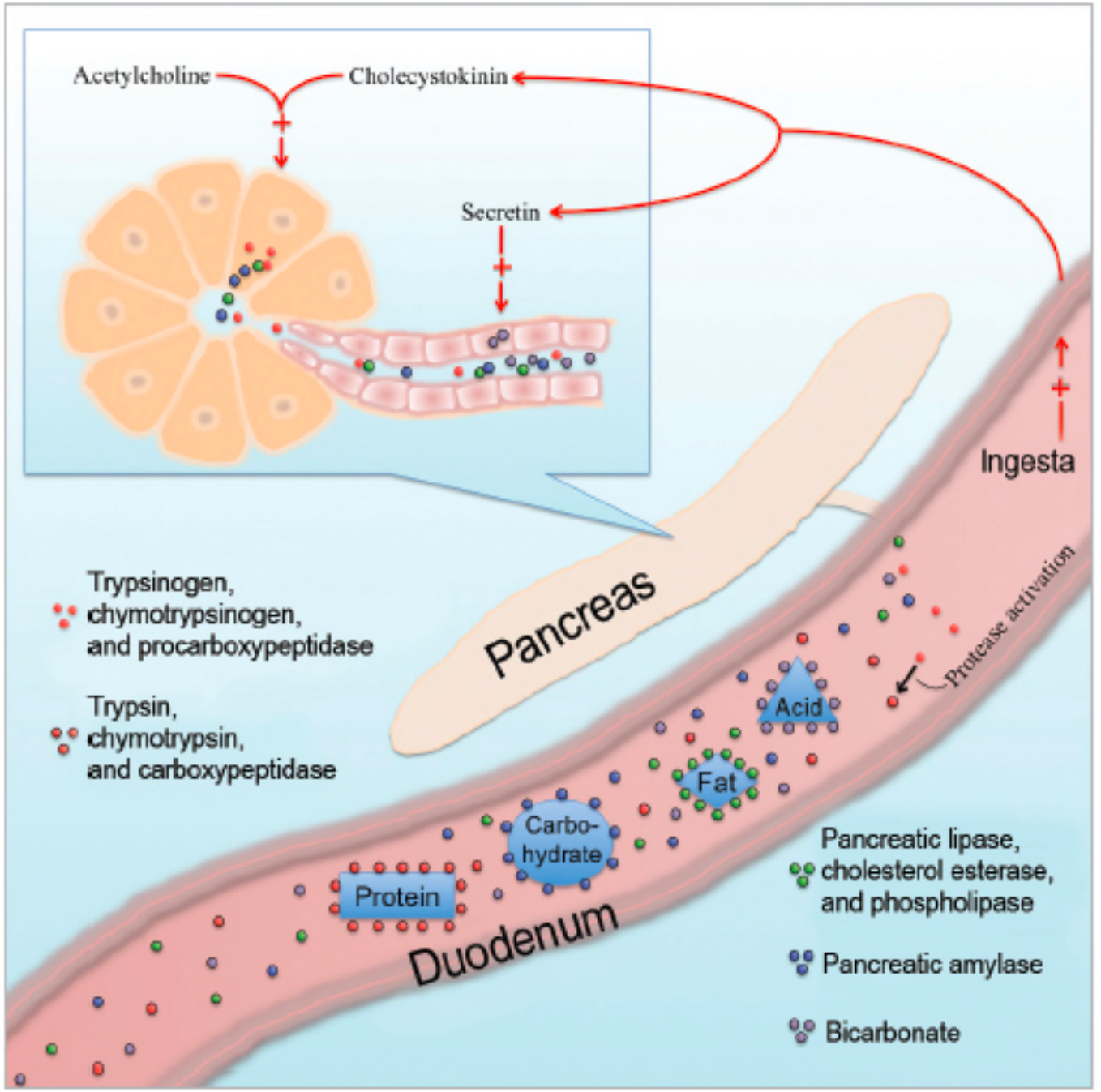
1) Introduction
    - Pathophysiology of EPI
    - Therapeutic response rate
    - Causes of a persistent clinical signs
2) Pancreatic enzyme supplementation
3) Small intestinal dysbiosis
    - Diagnosis and management
4) Dietary therapy
5) Cobalamin (vitamin B12) supplementation
    - Cause of B12 deficiency in EPI
    - Dosing strategies and monitoring
6) New research perspectives

Pathophysiology of EPI

- The pancreas has two functional cellular components:
  1. Endocrine – cells in the Islets of Langerhans regulate glucose homeostasis via secretion of insulin, glucagon, etc.
  2. Exocrine – pancreatic acinar cells secrete digestive enzymes (lipase, amylase, proteases)
- Exocrine pancreatic insufficiency – complete failure of pancreatic digestive enzyme secretion
- Causes of EPI:
  1. Pancreatic acinar atrophy (PAA)
  2. Pancreatic duct obstruction
  3. Severe, chronic pancreatitis
  4. Pancreatic neoplasia

Pathophysiology of EPI

- Insufficient digestive enzyme secretion → undigested lipids, proteins, and carbohydrates
- Maldigestion → Malabsorption
- Malabsorption causes…
  - Weight loss
  - Osmotic diarrhea
  - Small intestinal dysbiosis
  - Nutrient deficiencies



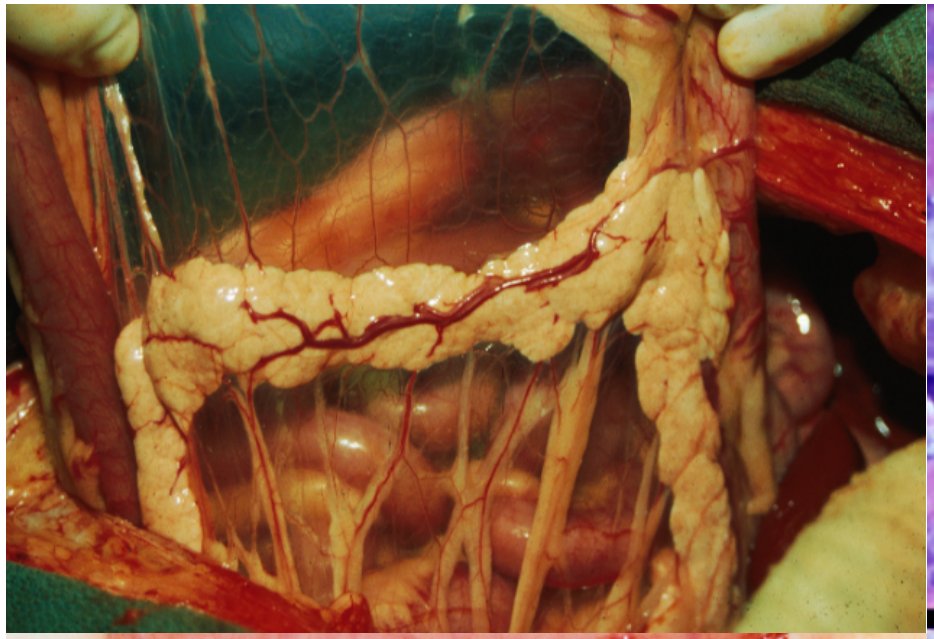
http://veterinarymedicine.dvm360.com/quick-review-canine-exocrine-pancreatic-insufficiency

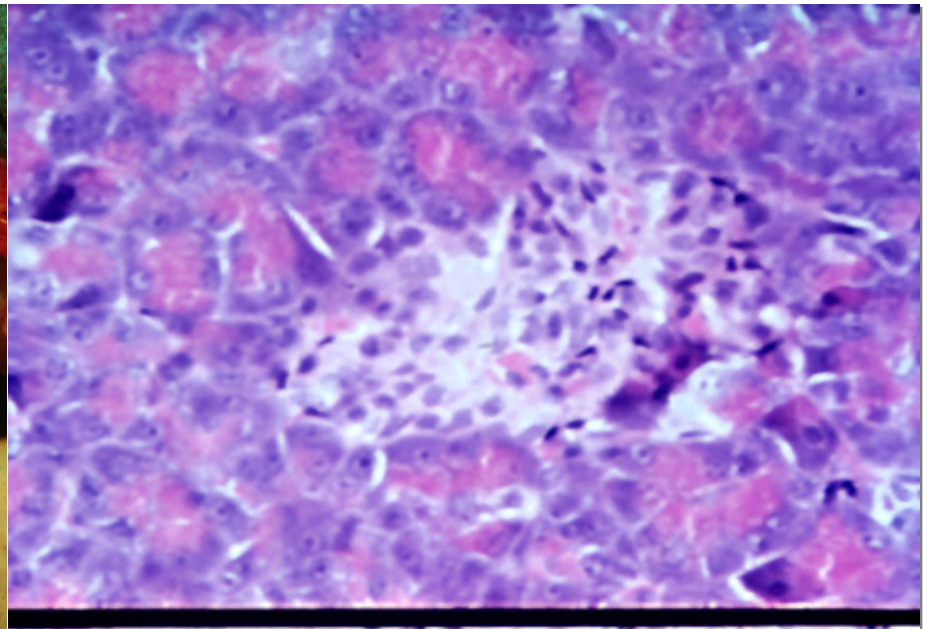
Pancreatic Acinar Atrophy

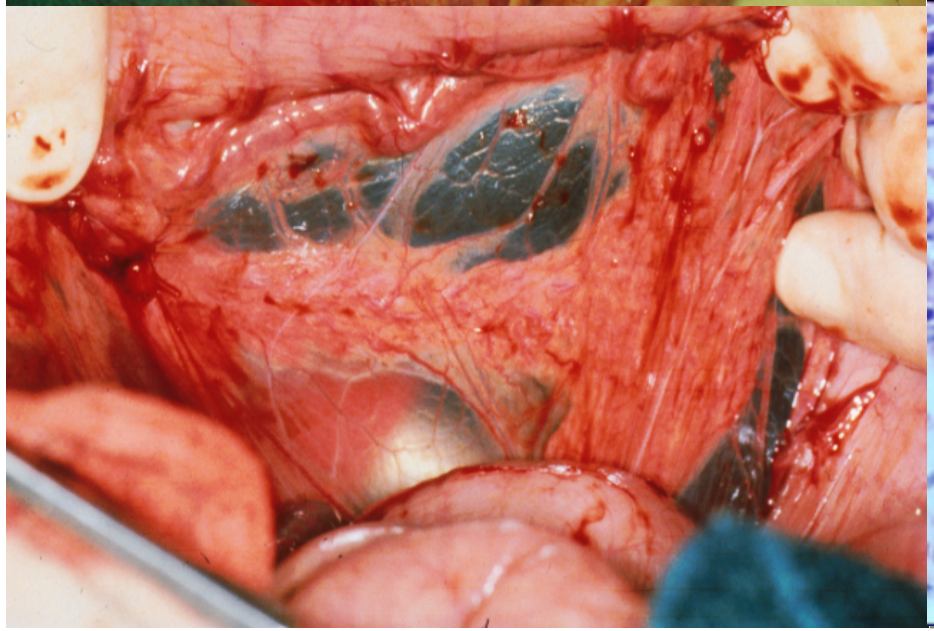
- PAA is the most common cause of EPI in dogs
- Progressive, irreversible loss of pancreatic acinar cells
- EPI is the clinical manifestation of end-stage of PAA
- ~90% of pancreatic function must be lost before secretory ability is reduced enough to cause clinical signs of EPI

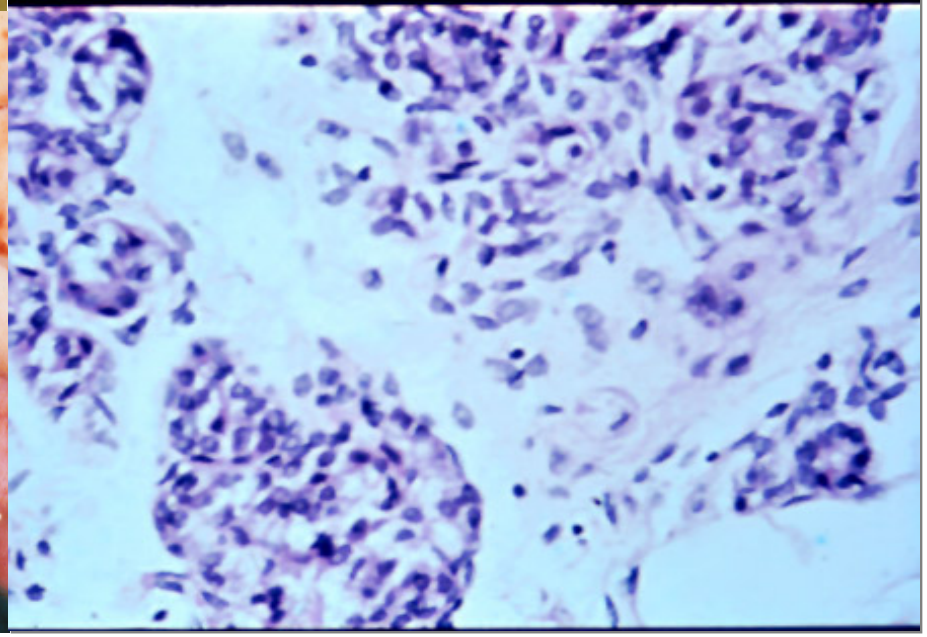
NORMAL

PAA









Images courtesy of DA Williams

Pancreatic Acinar Atrophy

- Traditionally considered to be a genetic, autoimmune disease, however…
  - Cross-breeding of affected dogs does not reveal a consistent inheritance pattern
  - Genetic studies have not identified a consistent genetic abnormality in dogs with EPI
- German shepherd dogs overrepresented, but dogs of **ANY BREED** can develop PAA/EPI

EPI Response to Therapy and Prognosis

- EPI is a an irreversible condition that will require **LIFE-LONG** management

- The prognosis for EPI can be excellent, provided that close attention is paid the patient's condition

  - At least 50% of dogs with EPI respond completely to enzyme supplementation with minimal need for other treatments
  - ~20% of dogs have a poor response to treatment initially

Timeframe for Recovery

- With diligent monitoring and logical therapeutic adjustments, even dogs that respond poorly to enzyme monotherapy can be managed successfully

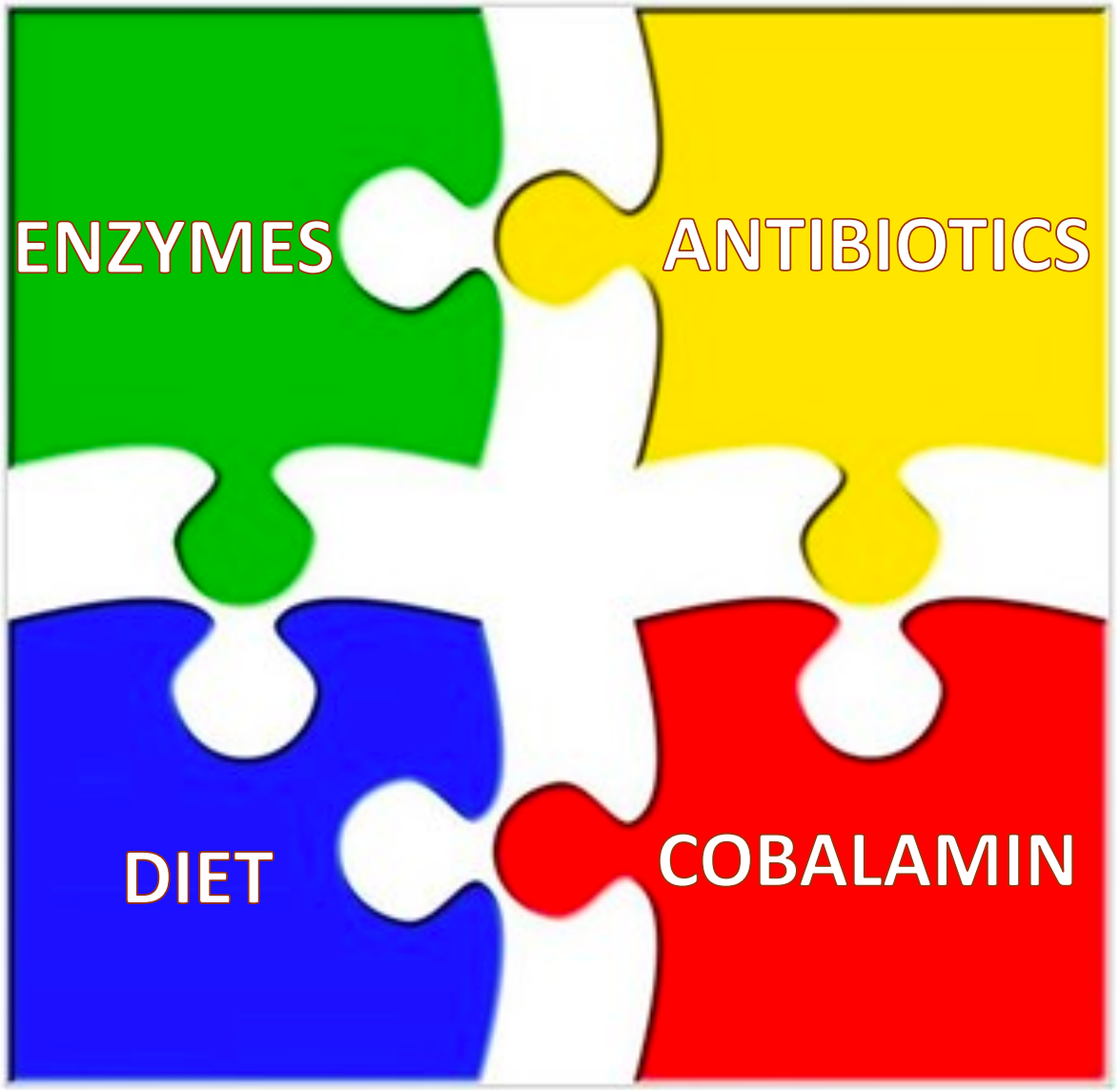
- Diarrhea – an effective therapy will typically resolve diarrhea in less than two weeks

- Weight
  - Significant weight gain within 30 days
  - Return to normal/ideal body weight in 3-6 months

Common Causes of Persistent Clinical Signs

1. Inadequate enzyme dose
2. Small intestinal dysbiosis (SID)
3. Hypocobalaminemia
4. Concurrent enteropathy
   - Folate deficiency
   - Diet-responsive diarrhea
   - Mucosal disease (e.g. IBD)

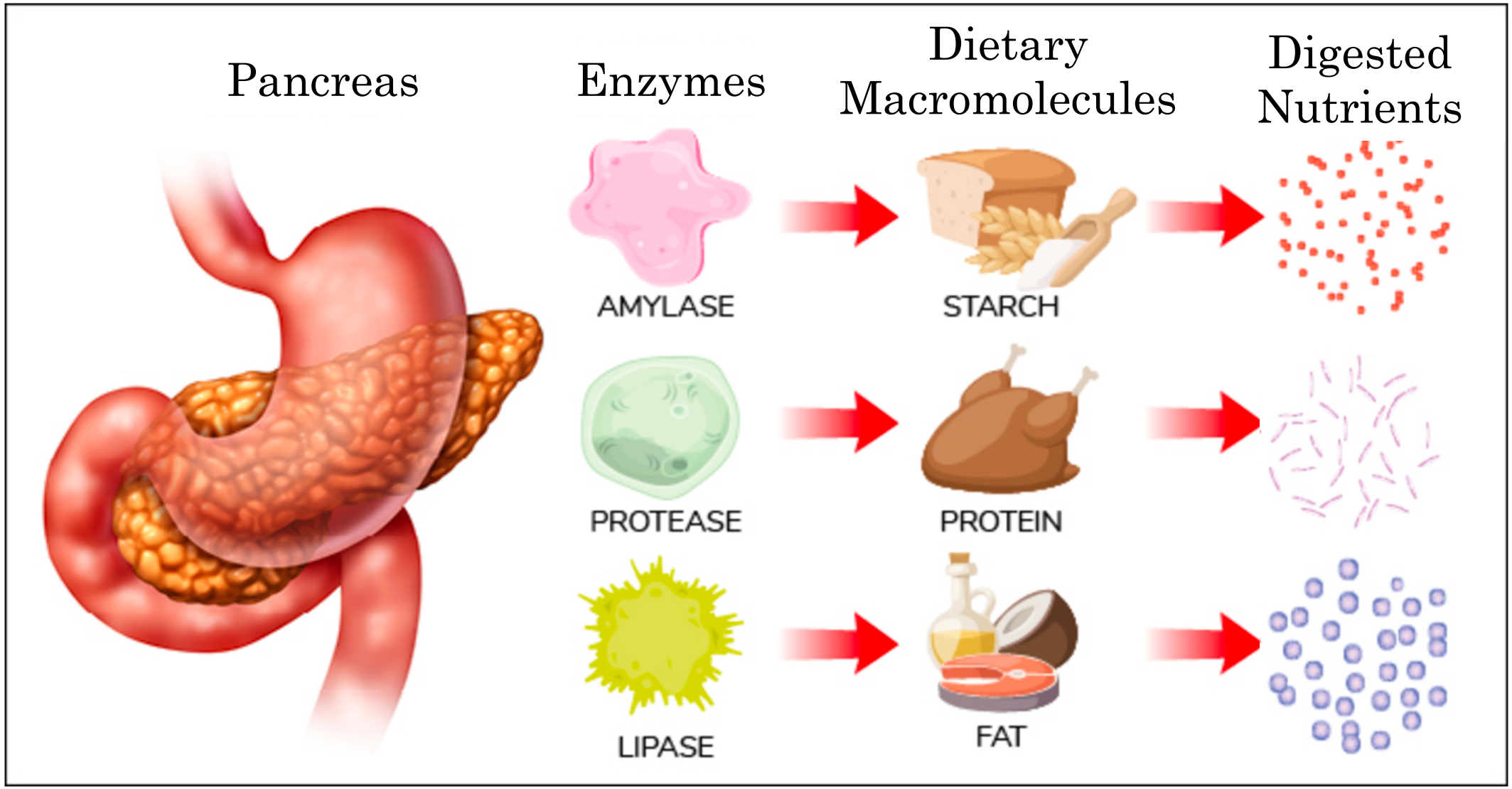
- Response to similar treatments is highly variable
- EPI management requires a personalized approach, no one-size-fits-all strategy
- Important to determine cause of treatment failure, rather than constantly changing treatment



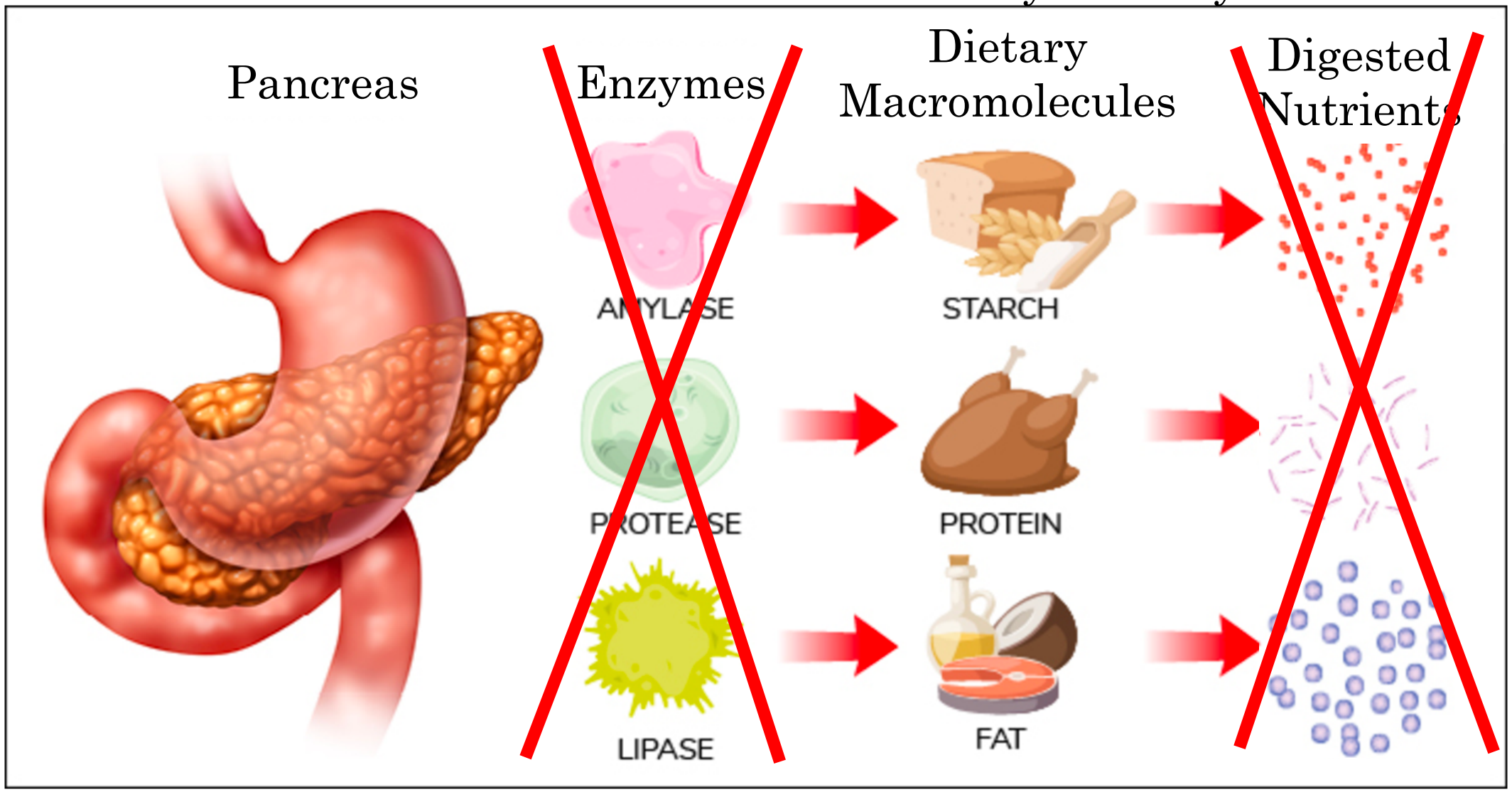
Pancreatic Enzyme Supplementation

Impact of enzyme deficiency, product selection, dosage, managing adverse effects

Normal Dog – Pancreatic enzymes digest polysaccharides, proteins, and lipids → absorption by enterocytes



Dog with EPI– Pancreatic enzyme deficiency → polysaccharides, proteins, lipids NOT digested → macromolecules **cannot** be absorbed by enterocytes



Enzyme deficiency → malabsorption → cachexia + dysbiosis

Pancreatic Enzyme Supplements

Raw Pancreas
- Beef and lamb preferred to reduce risk of trichinella, pseudorabies
- Variety of sources online
- Variable potency: 1-4 oz raw = 1 tsp powder

Powdered Enzymes (Pork)
- Preferred method of supplementation
- Widely available
- Easy to titrate dose (start at 1 tsp/cup of food)

Enzyme Tablets
- Crush prior to administration

Enteric-Coated Tablets
- EXPENSIVE

Pancreatic enzyme supplementation is the most important aspect of EPI management

A blinded randomised controlled trial to determine the effect of enteric coating on enzyme treatment for canine exocrine pancreatic efficiency

Aran Mas[1†], Peter-John M Noble[1†], Peter J Cripps[1], Daniel J Batchelor[1], Peter Graham[2] and Alexander J German[1*]

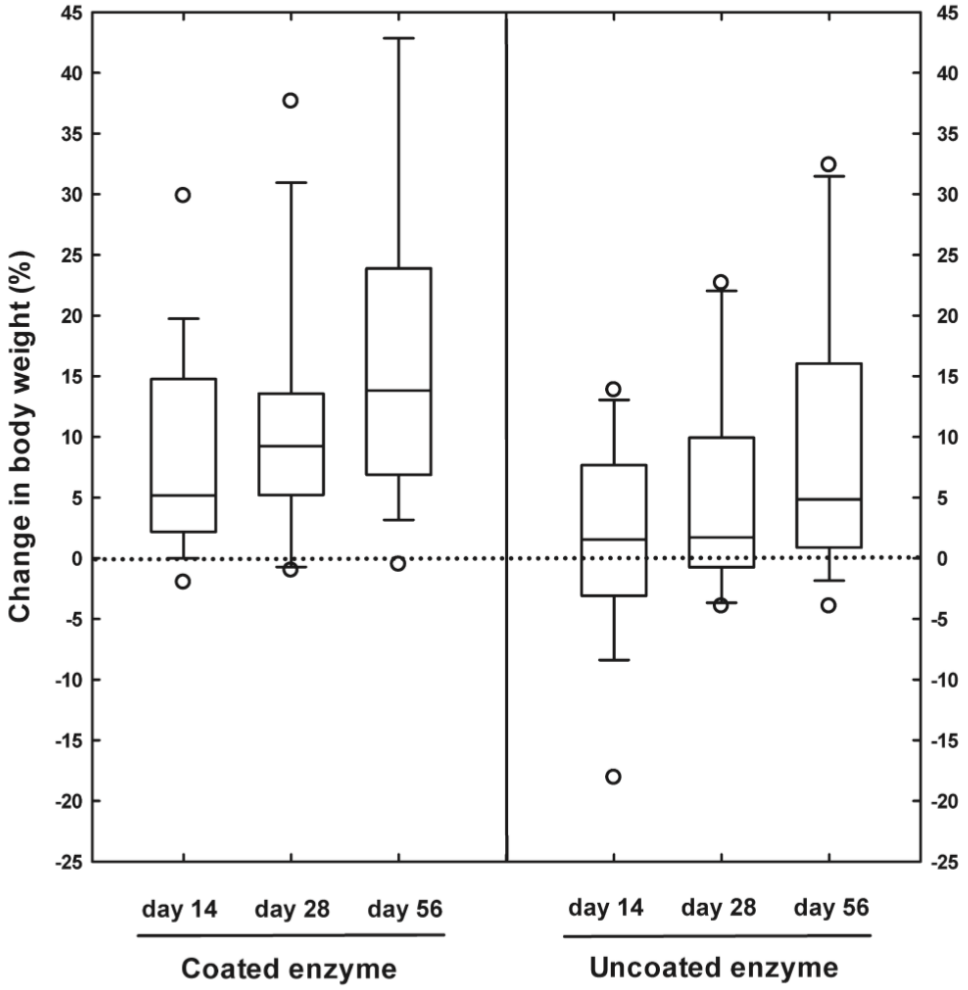
Abstract

Background: Enzyme treatment is the mainstay for management of exocrine pancreatic insufficiency (EPI) in dogs. 'Enteric-coated' preparations have been developed to protect the enzyme from degradation in the stomach, but their efficacy has not been critically evaluated. The hypothesis of the current study was that enteric coating would have no effect on the efficacy of pancreatic enzyme treatment for dogs with EPI.
Thirty-eight client-owned dogs with naturally occurring EPI were included in this multicentre, blinded, randomised controlled trial. Dogs received either an enteric-coated enzyme preparation (test treatment) or an identical preparation without the enteric coating (control treatment) over a period of 56 days.

Results: There were no significant differences in either signalment or cobalamin status (where cobalamin deficient or not) between the dogs on the test and control treatments. Body weight and body condition score increased in both groups during the trial ($P<0.001$) but the magnitude of increase was greater for the test treatment compared with the control treatment ($P<0.001$). By day 56, mean body weight increase was 17% (95% confidence interval 11-23%) in the test treatment group and 9% (95% confidence interval 4-15%) in the control treatment group. The dose of enzyme required increased over time ($P<0.001$) but there was no significant difference between treatments at any time point ($P=0.225$). Clinical disease severity score decreased over time for both groups ($P=0.011$) and no difference was noted between groups ($P=0.869$). No significant adverse effects were reported, for either treatment, for the duration of the trial.

Conclusions: Enteric coating a pancreatic enzyme treatment improves response in canine EPI.

Keywords: Dog, Pancreas, Malabsorption, Diarrhoea, Lipase, Trypsin



There are no veterinary preparations of enteric-coated enzymes in US – unpredictable effect in dogs

EXPENSIVE, may be more cost-effective to simply increase powdered enzyme dose

Antacid Therapy

- Lipase is inactivated by acid and dogs with EPI may have insufficient secretion of pancreatic bicarbonate → stomach acid may not be sufficiently neutralized in duodenum
- H2 antagonists (famotidine) and proton pump inhibitors (omeprazole) should ONLY be considered in patients that do not respond optimally to pancreatic enzyme supplementation
  - No evidence that antacid therapy improves efficacy of enzymes
  - Increase in enzyme dose will likely compensate for effect of gastric acid
- Before starting an antacid, consider other approaches first:
  - Increase enzyme dose (up to 2 tsp/cup of food)
  - Antibiotics for SID
  - Diet trial

Enzyme replacement therapy

- Porcine enzymes have highest lipase activity in dogs
- Powder enzymes are preferred as it is easy to titrate dose
- Dietary pork sensitivity is very rare, if no response to enzymes increase the dose before switching to beef enzymes

Tips and Tricks

- Oral bleeding is a rare complication, no evidence that pre-incubating enzymes with water prevents oral bleeding
- Enzymes MUST be given with EVERY meal – No treats!
- Some dogs will not eat food with enzymes – give enzymes in gel cap prior to feeding
- DO NOT need to pre-incubate enzymes with food, digestion occurs in the small intestine

Product	Lipase USP Units (Fat Splitting)	Protease USP Units (Protein Solubilizing)	Amylase USP Units (Starch Liquefying)	Other Ingredients	Cost
Viokase-V	71,400	388,000	460,000		12oz $140-$200
Bio Case V	56,840	434,000	495,000		12oz $80-105
PancreVed	71,400	388,000	460,000	Vitamins A D E	12oz $107
Pancrezyme	71,400	388,000	460,000		12oz $125.00
PancrePlus	71,400	388,000	460,000	Vitamins A D E	12 oz $96.00
PanaKare Plus	71,400	388,000	460,000	Vitamins A D E	12oz $115.00
Pancrea Powder Plus	71,400	388,000	460,000	Vitamins A D E	12oz $92.00
Pancrease-V	67,000	280,000	280,000		114g $85.00
Pancreatin 6x*per 2.8 grams	average 65,240	average 436,800	average 476,000		Shipping Included 250g $48, 500g $70, 1KG $140
Pancreatin 8x* per 2.8 grams	average 98,840	average 602,000	average 638,400		Shipping Included 8 oz $58 1KG $165

Enzyme Diane

Affordable and effective enzyme powder

enzymediane.com

Dietary Therapy

Dispelling the low-fat diet myth

Making appropriate dietary recommendations for patients with EPI

The Myth of the Low-Fat Diet

Early studies recommended long-term administration of a low-fat diet

(Pidgeon, 1982; Simpson, 1997)

Other studies refute this recommendation

- Westermarck, et al., 1995
  - No difference in treatment response to treatment in dogs fed low-fat, commercial, or home-cooked diets
- Suzuki, et al., 1999
  - High-fat, high-protein diets optimize fat absorption

Responses to diet trials are highly variable between individuals

- Diet is considered an **adjunct** therapy for EPI
- A therapeutic diet trial should be considered in a patient with persistent clinical signs, **AFTER** optimizing enzyme therapy and correcting B12 and/or folate deficiencies

Effects of diet on clinical signs of exocrine pancreatic insufficiency in dogs

Elias Westermarck, DVM, PhD, and Maria E. Wiberg, DVM, PhD

Objective—To assess the effects of dietary modification on clinical signs of exocrine pancreatic insufficiency (EPI) in dogs.

Design—Blinded randomized crossover study.

Animals—21 dogs with EPI.

Procedure—Dogs were fed the diet they received at home for 2 weeks. Thereafter, they received 3 special diets (a high-fat diet, a high-fiber diet, and a highly digestible low-residue diet) for 3 weeks each. Owners scored dogs daily for the last 2 weeks of each 3-week period for severity of 6 clinical signs including appetite, defecation frequency, consistency of feces, borborygmus, flatulence, and coprophagia. An EPI index was calculated for each dog by adding the daily scores for each clinical sign.

Results—Significant differences in daily EPI indices among diets were observed in 20 dogs. The original diet appeared to be the most suitable in 8 dogs, whereas the high-fat diet was most suitable in 5 dogs, the high-fiber diet was most suitable in 4 dogs, and the low-residue diet was most suitable in 2 dogs. In 1 dog, the lowest EPI index score was the same during the original diet and the high-fat diet feeding periods. One dog did not complete the feeding period for the high-fiber diet. Differences in mean EPI indices among diets were not significant.

Conclusions and Clinical Relevance—Results indicated that responses to different diets varied among individual dogs. Because responses to the feeding regimens were unpredictable, it is suggested that feeding regimens be individually formulated for dogs with EPI. (*J Am Vet Med Assoc* 2006;228:225–229)

So…What Diet Is Best for EPI?

- Response to diet is highly variable between individuals!
- Strongest evidence for a low residue diet (<2% crude fiber dry matter) with moderate fat content (10-20% dry matter)
  1. Purina EN
  2. Hills i/d
- If a patient does not respond to a low residue/moderate fat diets, try a hydrolyzed diet next
  - Purina HA
  - Royal Canin Ultamino
- If no response to a hydrolyzed diet, consider a limited ingredient diet.
  - Anecdotal success with fish-based diets

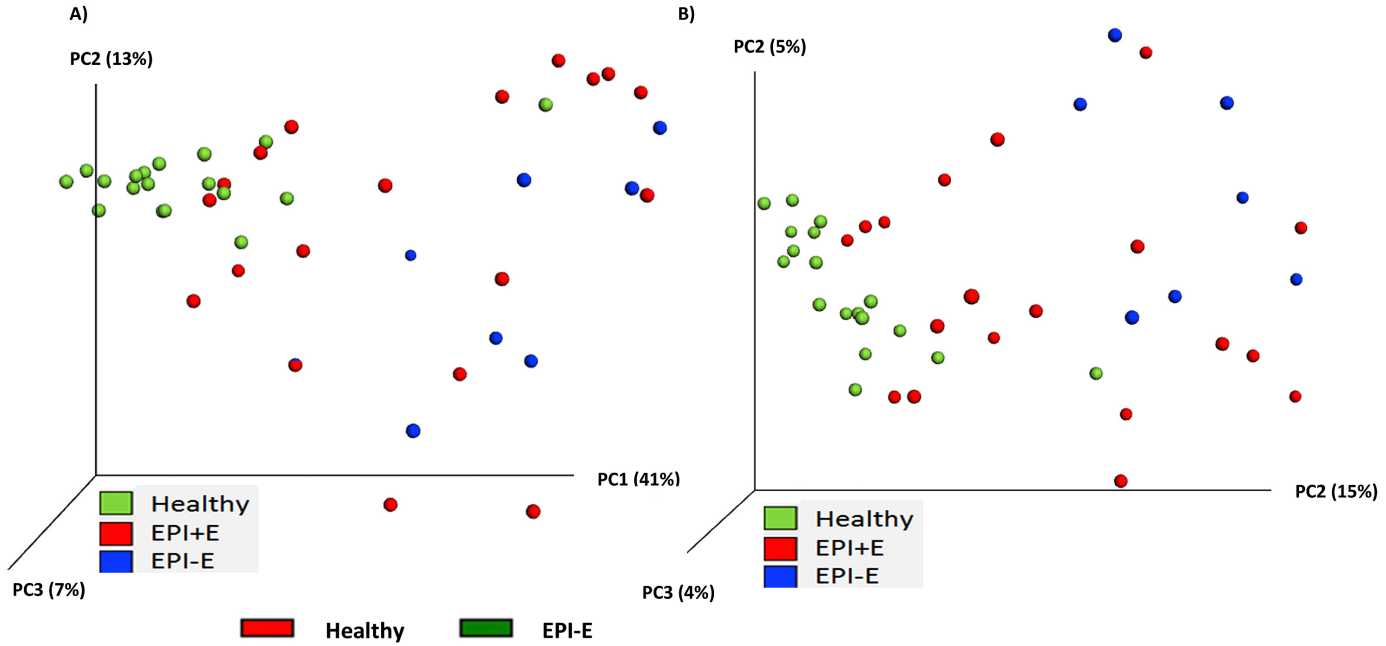
Managing Small Intestinal Dysbiosis

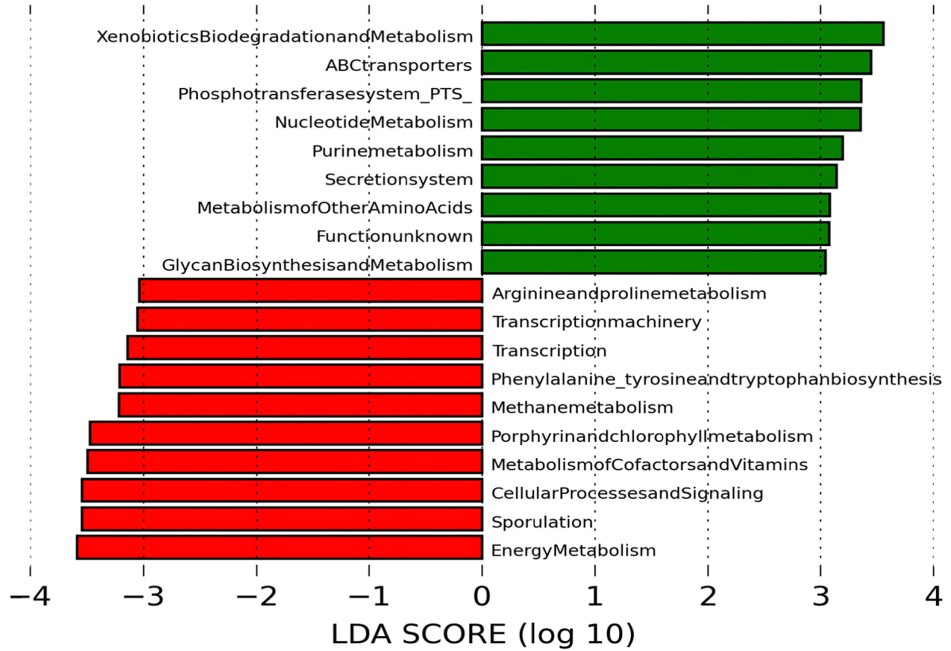
What is small intestinal dysbiosis?

Diagnostic evaluation, antibiotic therapy, probiotics, prebiotics

Small intestinal dysbiosis (SID) is common in dogs with EPI

- **Dysbiosis:** abnormal composition of the microbiome associated with disease
- SID formerly called small intestinal bacterial overgrowth (SIBO)
- **Significant cause of persistent diarrhea in dogs with EPI**





Diagnosis of SID

Clinical signs: Primarily persistent diarrhea

Serum [folate]:

- Folate *produced* by many instestinal microbes
- Serum [folate] > 24.4 µg/L consistent with SID
- Highly specific, not sensitive
- ~50% of dogs with SID have normal folate

Serum [cobalamin]:

- Cobalamin is *consumed* by intestinal bacteria
- Low cobalamin is NOT specific or sensitive for SID
- EPI and dz affecting the ileum → low B12

Canine Microbiota Dysbiosis Index:

- 1 gram feces sent frozen to TAMU GI Lab – PCR assay of 8 bacterial groups
- DI<0 is normal; DI>0 is consistent with SID

Treatment of SID

Tylosin (Tylan) Powder

- Optimal spectrum against bacteria associated with diarrhea
- Powder formulation facilitates dose titration
- Adverse effects are very rare, safe for long-term use
- Dose: 25 mg/kg PO every 12 hours for 4-6 weeks

Metronidazole

- Highly effective against anaerobic bacteria in the gut
- Neurologic toxicity possible at doses > 15 mg/kg
- Risk of toxicity increases with chronic administration
- Dose: 10 mg/kg PO every 12 hours

If diarrhea persists or returns after 4-6 weeks of antibiotics, consider a diet trial to avoid long-term antibiotic administration

Correction of Serum Cobalamin Deficiency

Pathophysiology of cobalamin deficiency in EPI, Approach to cobalamin supplementation

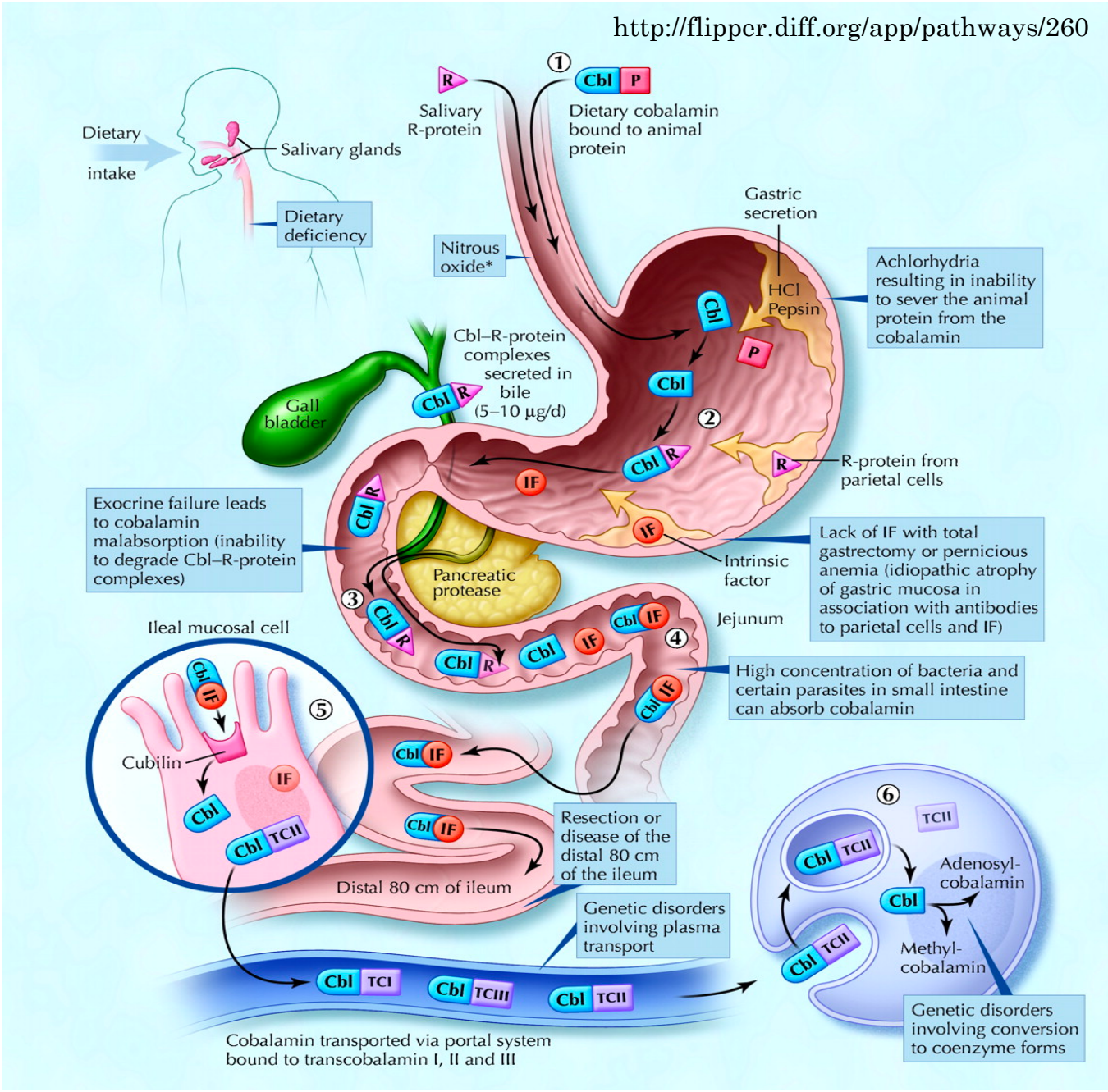
Cobalamin (B12) deficiency in EPI

Pancreatic enzyme insufficiency, decreased IF, and SID contribute to B12 deficiency

B12 is involved in numerous vital metabolic functions

80-90% of dogs with EPI are deficient in B12

Measure B12 in ALL dogs with EPI



Clinical signs of B12 Deficiency

- Most dogs with EPI will not respond optimally to enzyme therapy unless B12>300 µg/L
- Clinical impacts of deficiency:
  1. Weight loss
  2. Lethargy
  3. Poor appetite
  4. Diarrhea
  5. Immunodeficiency
  6. Villous atrophy in gut mucosa
  7. Neuropathies

Parenteral Cobalamin Supplementation

Use cyanocobalamin, NOT B-vitamin complex

Administer weekly for 4-6 weeks, then monthly

Retest 1 month after final weekly dose

- B12 >300-1000 µg/L continue monthly injections, retest every 6-12 months
- B12<300 µg/L, increase dose frequency (every 1-2 weeks) and retest in 30 days

Weight	<10 lbs	10-20 lbs	20-40 lbs	60-80 lbs	80-100 lbs	>100 lbs
Dose	250 µg	400 µg	600 µg	800 µg	1000 µg	1500 µg

Oral Cobalamin Supplementation

Oral Cobalamin Supplementation in Dogs with Exocrine Pancreatic Insufficiency

L. Toresson[1], J.M. Steiner[2], J.S. Suchodolski[3], T. Spillmann[4]

At inclusion, the median (range) serum CBL concentration was 204 ng/L (150–350 ng/L). It increased significantly to 1,113 ng/L (794–2,385 ng/L) after supplementation. This difference was statistically significant (P = 0.002; Wilcoxon matched-pairs signed rank test). Due to the retrospective nature of the study, metabolic markers of CBL deficiency could not be analyzed. Despite this limitation, our results suggest that oral CBL supplementation appears effective in treating dogs with EPI and subnormal or low-normal serum cobalamin concentrations. Since, according to the manufacturer, only traces of IF should be present in the PEz, this finding suggests that dogs, as has been demonstrated in humans, may have an IF-independent pathway for CBL absorption. Whether such an alternative pathway does exist in dogs requires further studies. Additionally, further studies comparing cellular cobalamin status after PO or PE supplementation in dogs with EPI are warranted.

Oral supplementation is effective at normalizing cobalamin in dogs w/EPI

Dosage:

- Small dog: 250 µg/day
- Medium dog: 500 µg/day
- Large dog: 1000 µg/day

Retest in 12 weeks

No indication/evidence for intrinsic factor supplementation

New Research Perspectives

What are we working on, and what have we learned?

The Maya Metabolomic Study

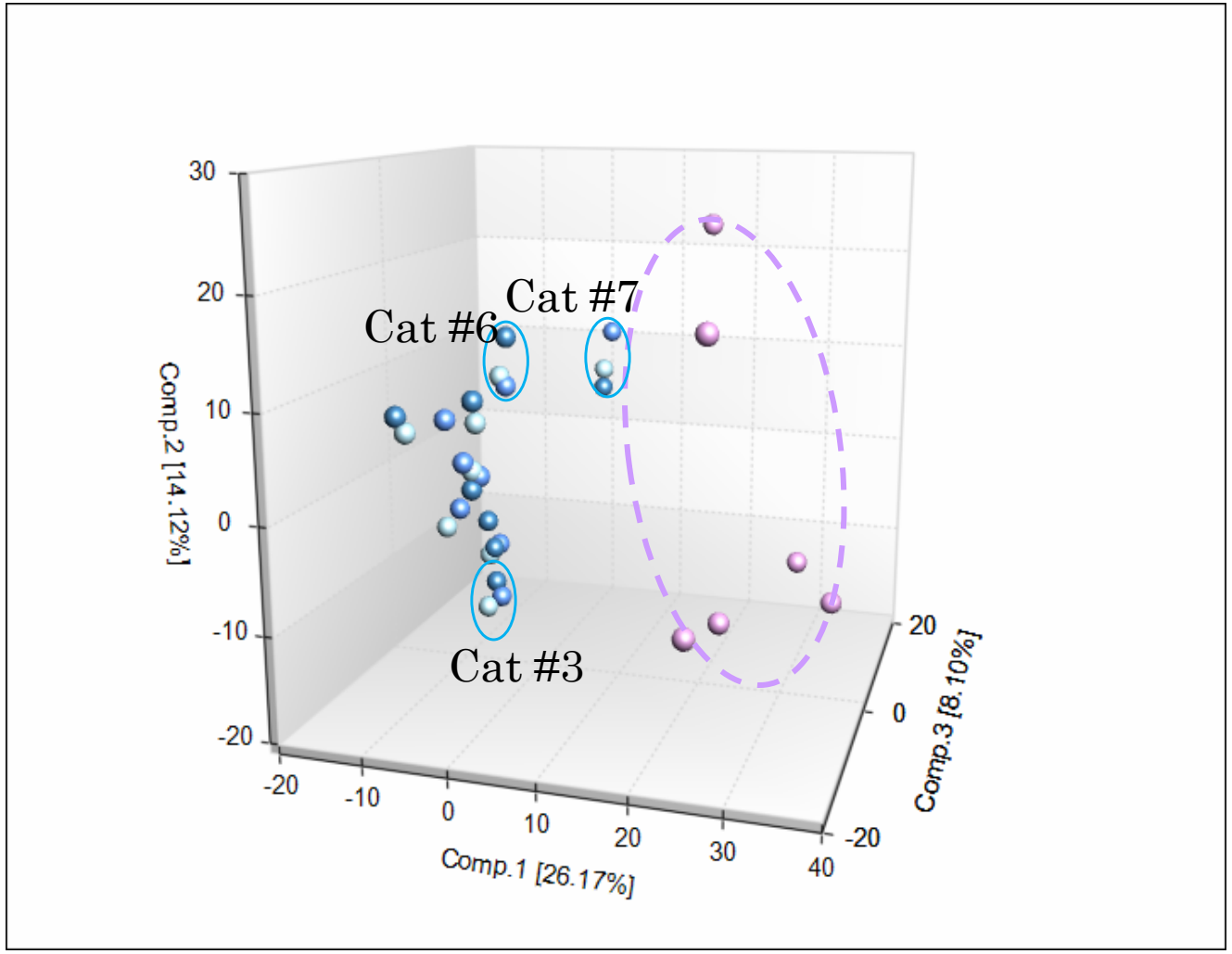
Hypothesis: EPI is caused by nutrient deficiencies that are caused/influenced by interactions between the diet and the intestinal microbiome

Most sophisticated study of EPI to date:

- We have recruited 30 dogs with EPI
- Serum metabolomics – analyze small molecules for evidence of nutrient deficiencies and/or metabolic disturbances in dogs with EPI
- Fecal microbiomics – look for associations between dysbiosis and systemic metabolism
- Study will be completed December, 2017

Cats get EPI too…

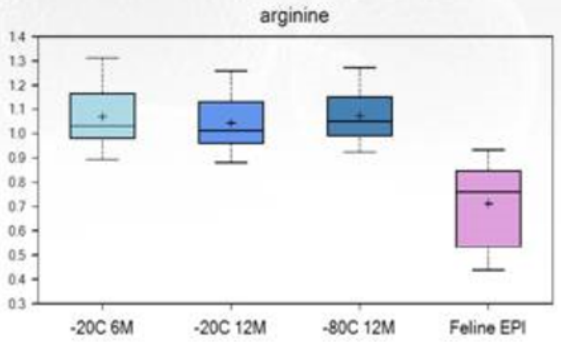
Cats with EPI have multiple metabolic disturbances

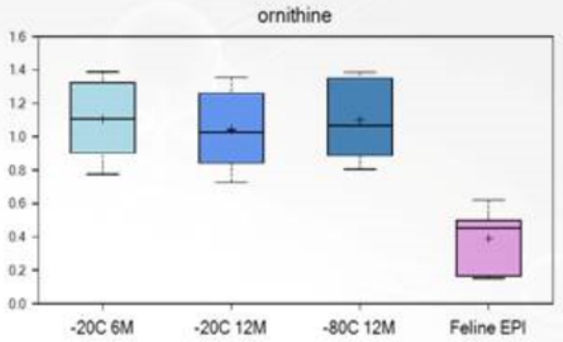


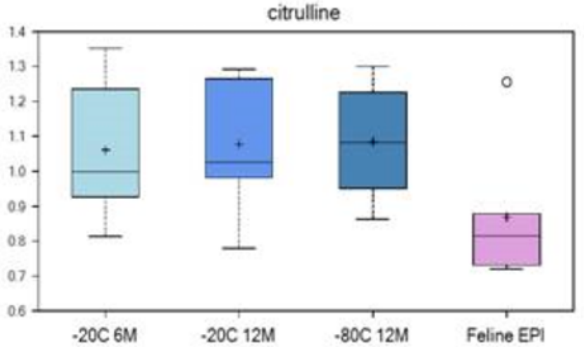
Feline EPI

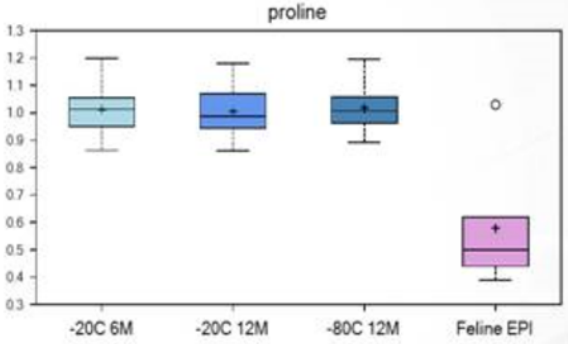
Lower amino acids and urea cycle metabolites in cats with EPI

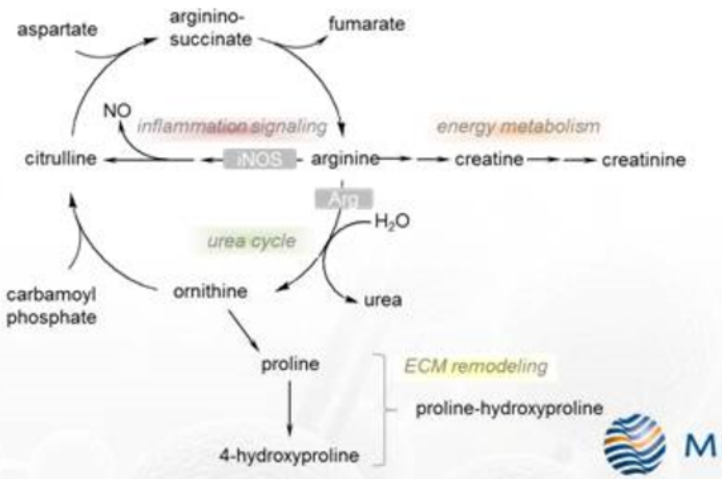
	Feline EPI -80C 12M
arginine	0.66
argininosuccinate	0.44
urea	0.88
ornithine	0.35
2-oxoarginine*	0.37
citrulline	0.80
homoarginine	1.63
homocitrulline	0.86
proline	0.57
dimethylarginine (SDMA + ADMA	0.74
N-acetylarginine	0.41
N-acetylproline	0.42
N-delta-acetylornithine	0.29
trans-4-hydroxyproline	0.43
pro-hydroxy-pro	0.88
N-methylproline	0.51
N-monomethylarginine	0.56





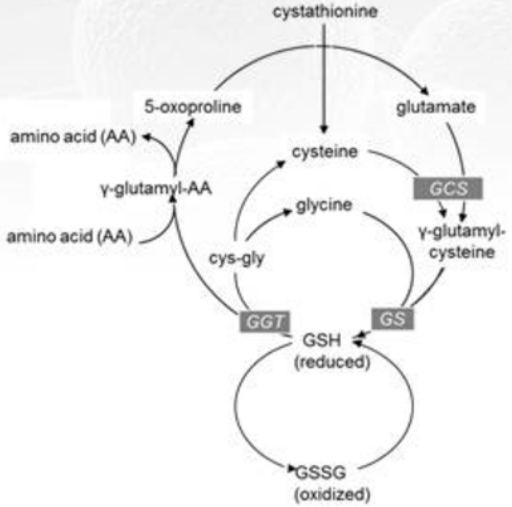


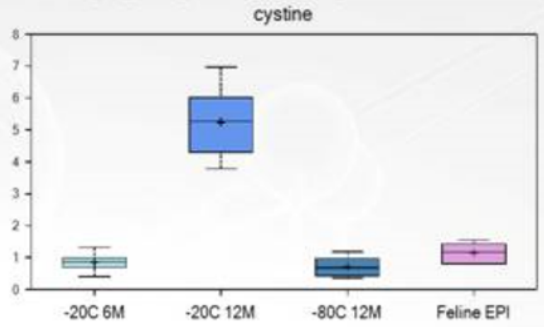


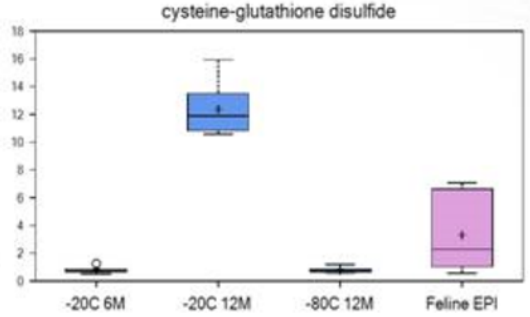


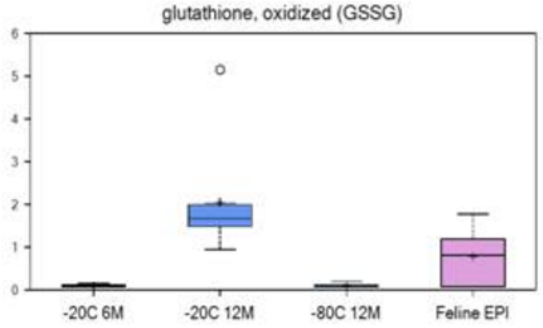
Markers of oxidative stress are higher in serum from EPI cats

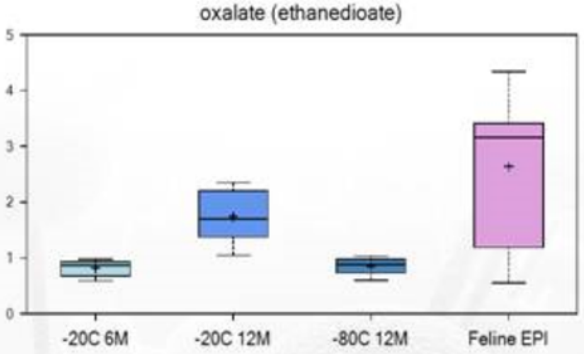
	Feline EPI -80C 12M
cysteine s-sulfate	6.19
cystine	1.62
glutathione, oxidized (GSSG)	7.81
cysteine-glutathione disulfide	4.21
S-methylglutathione	1.21
cysteinylglycine	0.62
5-oxoproline	0.70
2-aminobutyrate	1.18
2-hydroxybutyrate/2-hydroxyisobutyra	0.50
ophthalmate	0.32
gamma-glutamylalanine	0.68
gamma-glutamylglutamate	0.81
gamma-glutamylglutamine	1.04
gamma-glutamylglycine	0.40
gamma-glutamylhistidine	0.83
gamma-glutamylisoleucine*	0.89
gamma-glutamylleucine	1.00
gamma-glutamyl-alpha-lysine	0.48
gamma-glutamyl-epsilon-lysine	0.80
gamma-glutamylmethionine	0.97
gamma-glutamylphenylalanine	0.60
gamma-glutamylthreonine	0.71
gamma-glutamyltryptophan	0.60
gamma-glutamyltyrosine	0.49
gamma-glutamylvaline	0.80
gamma-glutamyl-2-aminobutyrate	1.19
gamma-glutamylserine	0.57

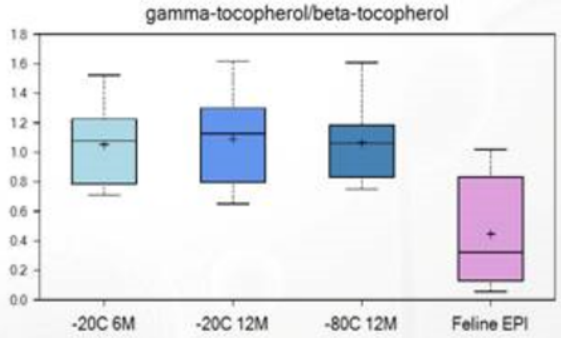






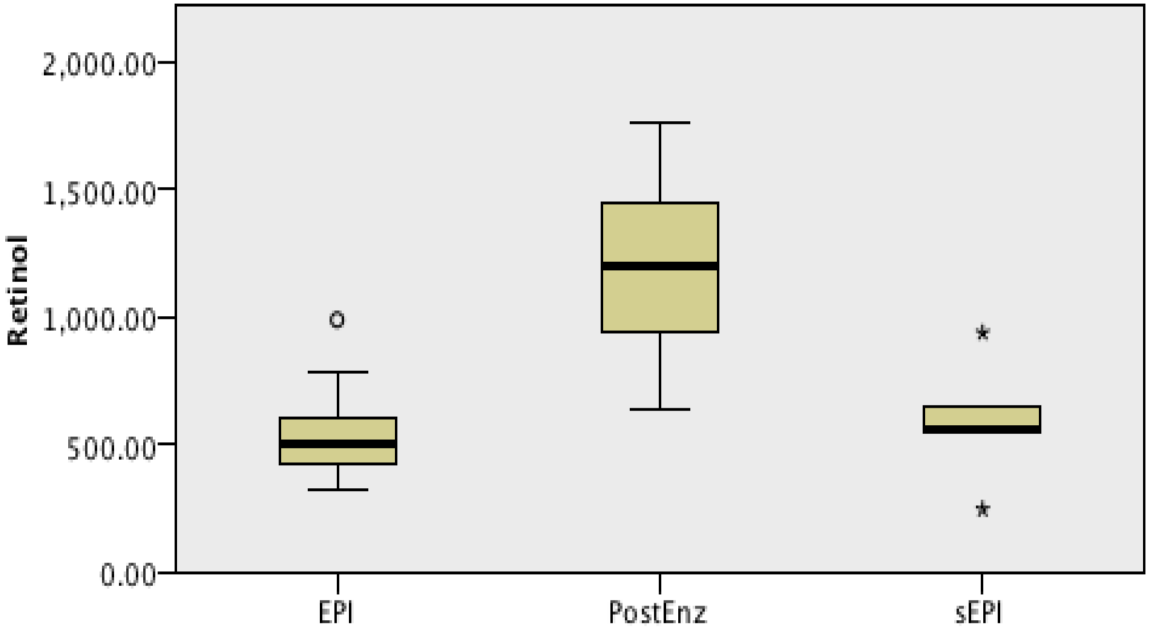




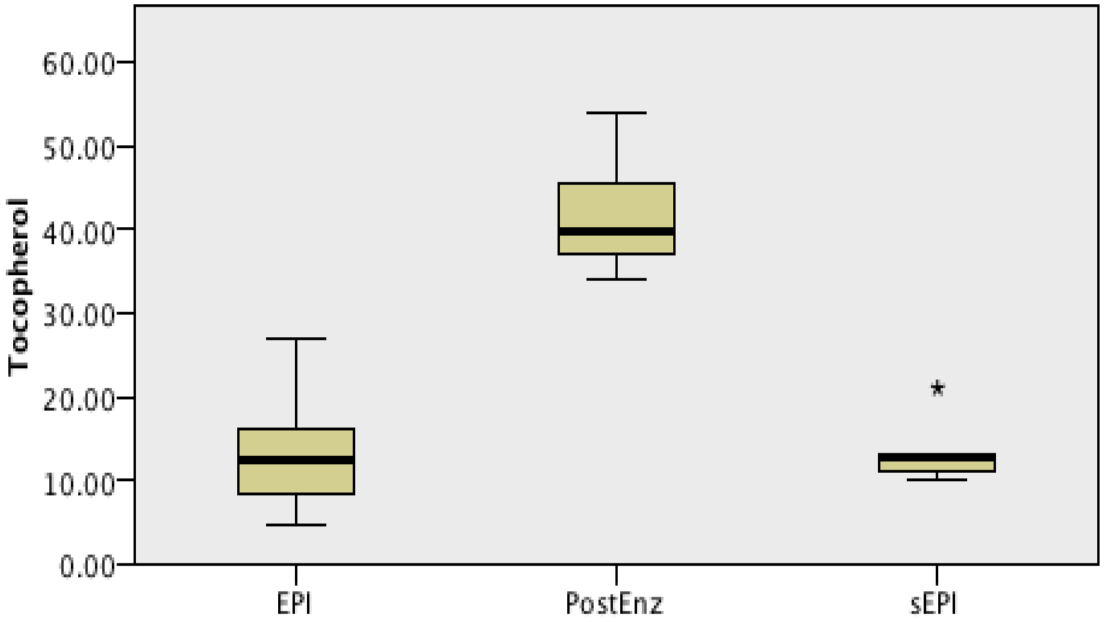


METABOLON®

Lipid-Soluble Vitamin Deficiency in Dogs with EPI



Vitamin A



Vitamin E

Altered Bile Acid Metabolism in Dogs with EPI

Dogs with Exocrine Pancreatic Insufficiency have Dysbiosis and Abnormal Fecal Lactate and Bile Acid Concentrations

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It has been reported that dogs with exocrine pancreatic insufficiency (EPI) commonly have intestinal dysbiosis. However, the effects of EPI on microbial metabolism are poorly understood. The aim of this study was to compare fecal dysbiosis as well as fecal lactate and bile acid concentrations between dogs with EPI and healthy control dogs.

Fecal samples were collected from eleven dogs with EPI that had not received antibiotics for at least 3 weeks and had been on enzyme supplementation for 0.5–10 years (median 5 years). Fecal samples from healthy dogs (n = 18), collected for three consecutive days and pooled, served as control samples. DNA was extracted and analyzed by qPCR for selected bacterial groups and data expressed as Dysbiosis Index (as previously reported). Fecal lactate was measured by enzymatic methods (D-/L-lactic acid kit, R-Biopharm) and bile acids were quantified with gas chromatography/mass spectrometry from lyophilized feces. The Mann-Whitney U test was used to compare the Dysbiosis Index and fecal lactate and bile acid concentrations between dogs with EPI and healthy control dogs. Correlations were assessed using Spearman's correlation coefficient and significance was set at $P < 0.05$.

Dogs with EPI had a higher Dysbiosis Index (median [min-max]: +3.08 [−7.29 to +7.62]) than healthy control dogs (−3.81 [−7.57 to +3.32]; P = 0.0232). Total fecal lactate concentrations were increased in dogs with EPI (3.44 mM [0.71–158.30 mM]) compared to healthy control dogs (1.14 mM [0.54–6.64 mM]; P = 0.0037). The proportion of secondary bile acid was lower in dogs with EPI (70% [6–96%]) compared to healthy control dogs (93% [12–97%]; P = 0.0431). There was no correlation between any measurements and duration of enzyme therapy.

In conclusion, this study identified differences in the fecal microbiota as well as fecal lactate and bile acid concentrations between dogs with EPI and healthy control dogs.

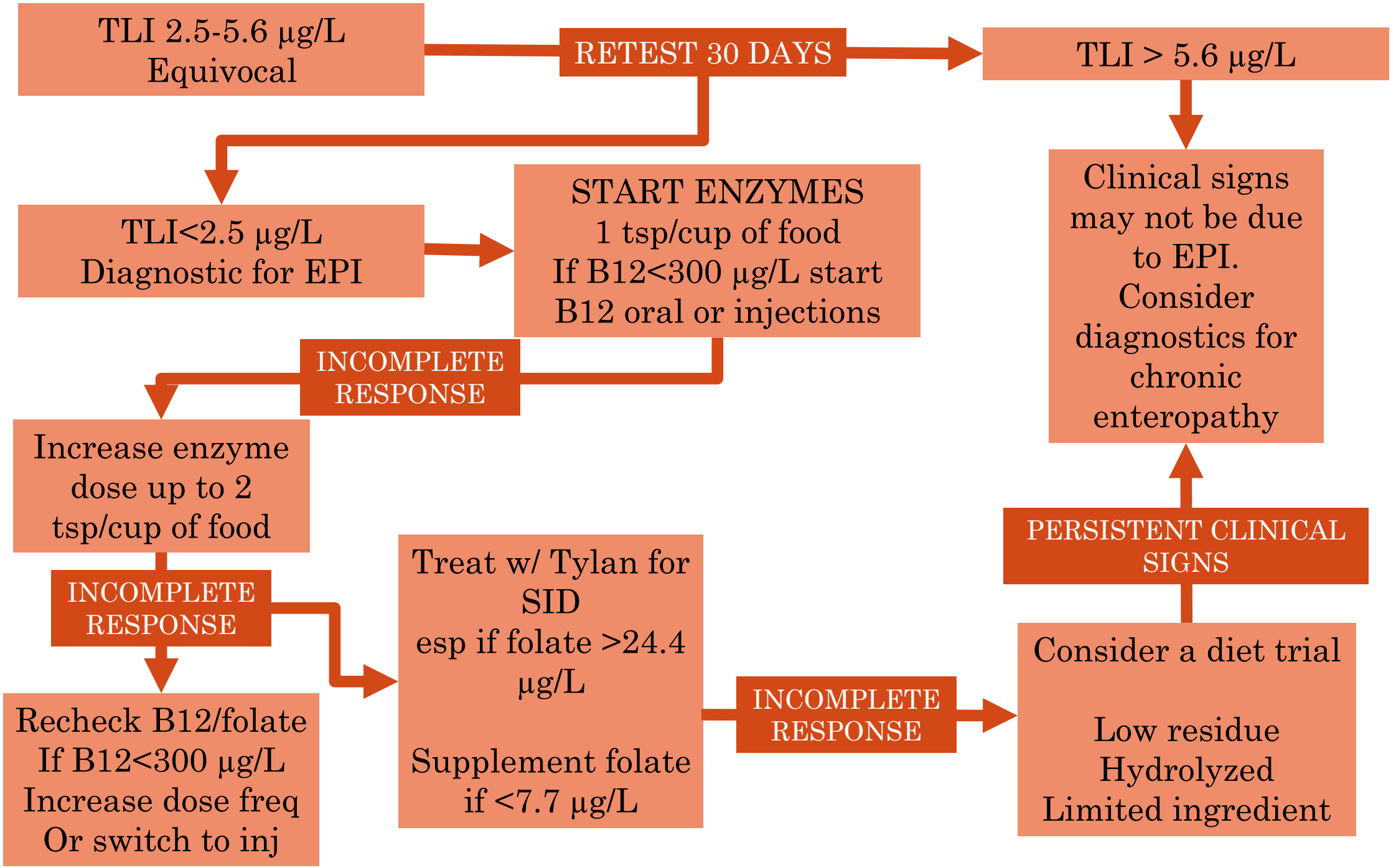
Future Directions

- Clinical study to assess the impact of bile acids sequestrants (e.g. cholestyramine) therapy
- Clinical study to determine the impact of high-dose vitamin E and A therapy
- Assess bile acid metabolism and lipid-soluble vitamin status in dogs with chronic enteropathies unrelated to EPI

Conclusions

- EPI is a differential diagnosis for a dog of any breed with weight loss, and diarrhea
- The prognosis for EPI can be excellent if the client and veterinarian are committed to long-term monitoring and rational therapeutic adjustments
- Common causes of treatment failure:
  1. Inadequate enzyme dose
  2. Small intestinal dysbiosis
  3. Nutrient deficiencies (cobalamin and folate)
  4. Diet-responsive diarrhea
  5. Concurrent mucosal disease (e.g. IBD)
- A patient's response to therapy is highly individualized
- CHANGE ONLY ONE THING AT A TIME!!

  …or you won't know what treatment is actually working!


TLI 2.5-5.6 µg/L
Equivocal
RETEST 30 DAYS
TLI > 5.6 µg/L
Clinical signs may not be due to EPI. Consider diagnostics for chronic enteropathy
TLI<2.5 µg/L
Diagnostic for EPI
START ENZYMES
1 tsp/cup of food
If B12<300 µg/L start B12 oral or injections
INCOMPLETE RESPONSE
Increase enzyme dose up to 2 tsp/cup of food
PERSISTENT CLINICAL SIGNS
INCOMPLETE RESPONSE
Treat w/ Tylan for SID
esp if folate >24.4 µg/L
Supplement folate if <7.7 µg/L
INCOMPLETE RESPONSE
Consider a diet trial
Low residue
Hydrolyzed
Limited ingredient
Recheck B12/folate
If B12<300 µg/L
Increase dose freq
Or switch to inj

Questions?

Thank You!

Special thanks to Olesia Kennedy and Epi4Dogs Inc. for organizing this seminar and for their tireless efforts to promote knowledge and provide support to the EPI community.