



1

GI DISEASE: WHAT'S THE SILVER BULLET



- Diet
 - Helpful for acute enteropathies
 - Curative for FRE
 - Helpful/necessary for IBD
 - Necessary for PLE



2



3

GI DISEASE: WHAT'S THE SILVER BULLET?

- Microbiome support/restoration
 - Acute enteropathies
 - Chronic enteropathies



4

CHRONIC INFLAMMATORY ENTEROPATHIES

- Food-responsive enteropathy
- Antibiotic-responsive enteropathy (dogs)
- Immunosuppressant-responsive enteropathy IRE/IBD/SRE
- Protein-losing enteropathy
- Refractory enteropathy

5

GI DISEASE: WHAT'S THE SILVER BULLET

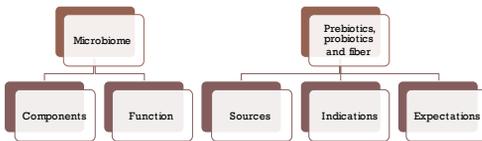
- Microbiome restoration
 - Antibiotic-associated diarrhea
 - Stress-associated diarrhea
 - Dysmotility
 - Bile acid diarrhea
 - Glucose regulation
 - Cardiovascular health
 - Dermatological health
 - Urinary health
 - Neurological health

6

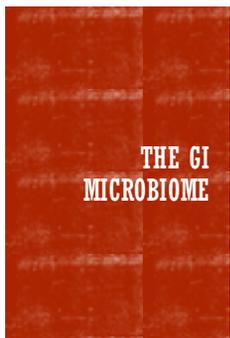


7

OVERVIEW



8



- Normal enteric flora of bacteria, yeast, fungi, viruses, protozoa that maintains GI health and function
- Trillions of bacteria
- Most are strict or facultative anaerobes

9

THE GI MICROBIOME

- The microbiome is a metabolic organ
- Fermentation of dietary molecules
 - CHO's (esp soluble fibers)
 - Proteins
 - Fats

POSTBIOTICS

- Production of substances beneficial to health of the the hosts
- Host and immune-system interaction

10

FUNCTIONS OF THE MICROBIOME

Modulation of immune system

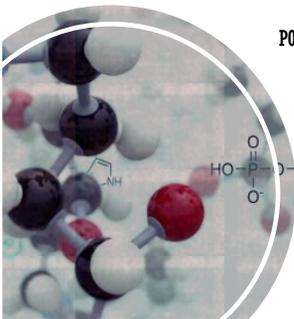
- Production of local immunomodulators
- Differentiation of precursors
- Epithelial barrier
- Development and maturation of GI immune system



GI Motility

Fermentation of substrates to produce beneficial **POSTBIOTICS**

11



POSTBIOTICS (THAT THE GUT LOVES)

- Part of the metabolome
- Produced by the fermentation of carbohydrates (esp. soluble fiber) protein, and fats
- Numerous benefits to the host
 - Immunomodulatory
 - Anti-inflammatory
 - Regulation of gut motility
 - Anti-diarrheic effects
 - Mucin secretion
 - Strengthen tight junctions

12



POSTBIOTICS THAT THE GUT LOVES

- Short-chain fatty acids (SCFA)
- Indole
- Secondary bile acids
- Neurotransmitters
 - GABA
 - Serotonin



13



SHORT-CHAIN FATTY ACIDS

- Acetate
- Propionate
- Butyrate
 - Major energy source of colonocytes



14

TABLE 1, VET CLIN PATH ANALYSIS OF THE GUT MICROBIOME IN DOGS AND CATS VET CLIN PATHOL 2022 FEB: 50



15



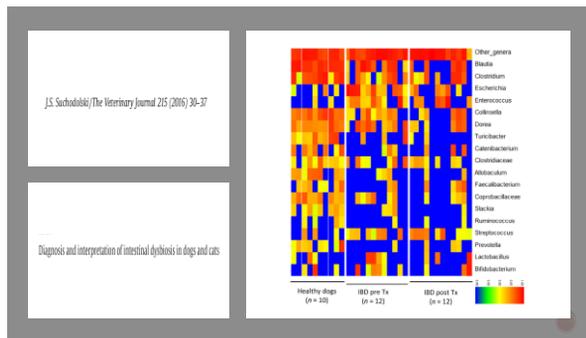
- Antibiotics
- Proton-pump inhibitors
- Chemotherapeutics
- Inflammation
- Structural changes
- Maldigestion
- Decreased perfusion
- Anorexia
- Hypomotility

19

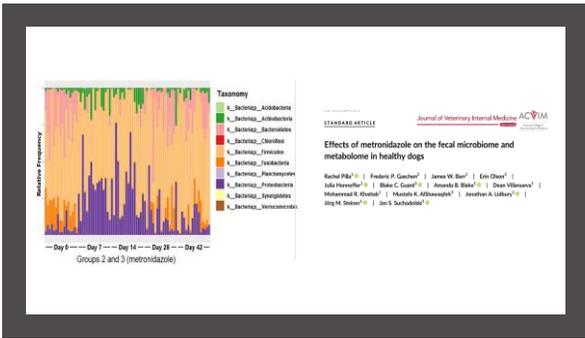
WHY DO WE CARE??

- Dysbiosis signals an unhealthy GI tract
 - Other organ systems are impacted
- We want to minimize GI inflammation and dysfunction
- Dysbiosis therapy may improve acute and chronic clinical disease
 - GI and beyond

20



21



22

HOW DO YOU PRACTICALLY ASSESS THE MICROBIOME?

- Fecal smear/cytology?
- Fecal culture?

23

COBALAMIN AND FOLATE

- Low normal cobalamin**
 - Malabsorption in the ileum
 - Dysbiosis
- Low folate**
 - Malabsorption in the duodenum
 - Dysbiosis
- Increased folate**
 - Dysbiosis

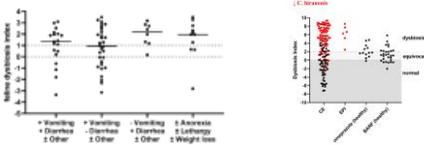
24



DYSBIOSIS INDEX

- qPCR approach offered by Texas AMGI Lab
- Mathematical algorithm that denotes the abundance of bacterial taxa and total bacteria
- A higher DI indicates lower microbial diversity
- DI > 2 = dysbiosis
- DI 0-2 = equivocal/ minor shifts
- DI < 0 = "normal" microbial diversity

25



CANINE AND FELINE DYSBIOSIS INDEX

• <https://vetmed.tamu.edu/glab/service/assays/canine-microbiota-dysbiosis-index/>

26

ARCHIE

- Chronic metronidazole for diarrhea
 - >1 year
- Prednisone trial
- Recent weight loss
- Endoscopy
 - Moderate IBD

27

Test	Reference Interval	Result
TUJ Fasting Interpretation: Result is within the reference interval.	10-50 µg/L	35.8 µg/L
Pancreatic Lipase Immunoreactivity Fasting Interpretation: Result within the reference interval. It is unlikely that this dog has clinically relevant pancreatitis. Investigate for other diseases that could cause the clinical signs observed.	≤200 µg/L	33 µg/L
Cobalamin Fasting Interpretation: Consistent with distal small intestinal disease, EPI or small intestinal bacterial overgrowth. Check canine TUJ to rule out EPI. Consider oral or parenteral cobalamin supplementation http://vetmed.tamu.edu/gi/lab/research/cobalamin-information	251-908 ng/L	200 ng/L
Folate Fasting Interpretation: Decreased serum folate	7.7-24.4 µg/L	6 µg/L

28

*Bifidobacterium Interpretation: Decreased abundance of Bifidobacterium is associated with intestinal dysbiosis. Changes in individual bacterial groups should be interpreted together with the Dysbiosis Index.	5.5-11 log DNA	8.6 log DNA
*Clostridium hiranonis Interpretation: Decreased abundance of C. hiranonis, consistent with reduced or absent conversion of primary to secondary bile acids in the intestine. Lack of C. hiranonis and secondary bile acids are an important contributor to intestinal dysbiosis.	5.1-7.1 log DNA	1.8 log DNA
*Dysbiosis Index Interpretation: The Dysbiosis Index (DI) is significantly increased, consistent with a major shift in the overall diversity of the intestinal microbiota. For more information on intestinal dysbiosis, visit https://rx.ag/DysbiosisDI	<0	6.7
*E. coli Interpretation: Increased abundance of E. coli is associated with intestinal dysbiosis. Changes in individual bacterial groups should be interpreted together with the Dysbiosis Index.	0.9-8 log DNA	8.1 log DNA
*Faecalibacterium Interpretation: Normal abundance of Faecalibacterium.	3.4-8 log DNA	4.6 log DNA
*Fusobacterium Interpretation: Normal abundance of Fusobacterium.	2-10.3 log DNA	8.6 log DNA
*Streptococcus Interpretation: Increased abundance of Streptococcus is associated with intestinal dysbiosis. Changes in individual bacterial groups should be interpreted together with the Dysbiosis Index.	1.9-8 log DNA	8.1 log DNA

29

REVISITING GI THERAPEUTICS



The microbiome influences/determines the health of the GI tract



The microbiome regulates the GI immune system



Treatment of dysbiosis is a strategy for GI disease

30



THERAPEUTIC STRATEGIES

- Diet
- Prebiotics
 - Soluble fiber
 - Fermentation → BENEFICIAL POSTBIOTICS
- Probiotics
- Fecal transplantation



31

PREBIOTICS

What are they?

- Non-digestible food substances, usually SOLUBLE fibers, that promote the growth and replication of existing beneficial microbiota
- Fermented by the host microbiota
- Yield short-chain fatty acids that nourish the GI tract

Why should I use them?

- Promotes growth and metabolic activity of healthy microbiome
- Long-lasting effect on the microbiome



32

PREBIOTICS

Sources

Pectin, FOS, MOS, GOS, fructans, inulin, chicory, lactosucrose, oligofructose, beet pulp, flaxseed, crushed pecan shells, pressed cranberries, citrus pulp

Diets

Synbiotics (Probiotic + Prebiotic)

Proviahle Forte®
FortiFlora SA®
ProPectalin®

OTC products

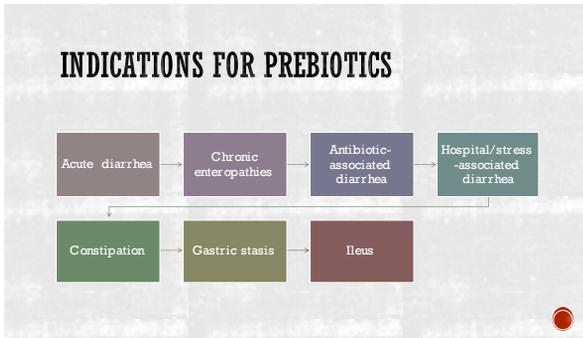


33



OTC OPTIONS??

34



35

PROBIOTICS

What are they?

- Live "good" bacteria (or yeast) that are supplemented or added to diets
- Colonizes the gut in 1-2 days
- Give bacterial probiotics 4 hours apart from antibiotics

Why should I use them?

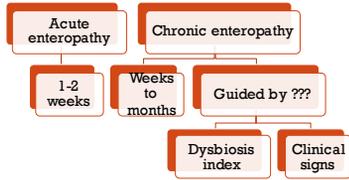
- Confers similar benefits as the healthy microbiota

How long should I give them?



36

DOSING



37

PROBIOTIC SOURCES



Veterinary Products

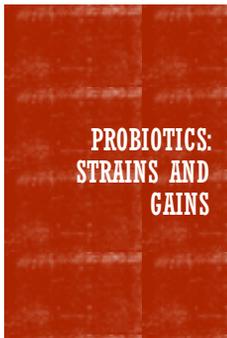


OTC



Diets

38



- Veterinary Products
 - FortiFlora SA*: *Enterococcus faecium*; 1×10^8 CFU/g
 - Provable Forte*: 7 strains; 10×10^9 CFU/capsul
 - Visbiome Vet: 8 strains; 112.5×10^9 CFU/capsul
 - Mycequin*: *Saccharomyces boulardii*; 5 billion CFU/capsule
 - Pro-Pectalin*: *Enterococcus faecium*; 6×10^9 CFU / tablet
- Diets

*Contains a prebiotic

39

Proviale®-Forte contains seven beneficial bacteria strains



40

Ingredients per Capsule:

Proviale®-Forte gum arabic, gelatin, maltodextrin, dried *Enterococcus faecium* fermentation product, dried *Bifidobacterium bifidum* fermentation product, dried *Streptococcus thermophilus* fermentation product, dried *Lactobacillus acidophilus* fermentation product, dried *Lactobacillus bulgaricus* fermentation product, dried *Lactobacillus casei* fermentation product, dried *Lactobacillus plantarum* fermentation product, magnesium stearate, titanium dioxide, and ascorbic acid.

Ingredients per Paste:

Boysen oil, lecithin, **Proviale®-Forte** gum arabic, dextrose, sucrose, silicon dioxide, maltodextrin, dried *Enterococcus faecium* fermentation product, dried *Bifidobacterium bifidum* fermentation product, dried *Streptococcus thermophilus* fermentation product, dried *Lactobacillus acidophilus* fermentation product, dried *Lactobacillus bulgaricus* fermentation product, dried *Lactobacillus casei* fermentation product, dried *Lactobacillus plantarum* fermentation product, artificial beef flavor, and ascorbic acid.

41



42

De Simone Formulation

Vision® Vet contains the De Simone Formulation, a high potency 8-strain probiotic blend, which has been one of the most widely studied probiotic formulations for humans on the market. New clinical evidence in canines and felines has established that this unique formula yields similar positive benefits in the microbiome of domestic pets.

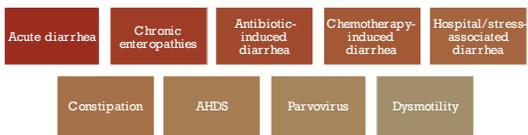
Genus	Species	Strain Reference Number
Lactobacillus	gasseri	DSM 24733 / SCS218
Lactobacillus	plantarum	DSM 24730 / SCS209
Lactobacillus	acidophilus	DSM 24732 / SCS210
Lactobacillus	delbrueckii subspecies bulgaricus	DSM 24734 / SCS216
Bifidobacterium	longum	DSM 24736 / SCS219
Bifidobacterium	infantis	DSM 24737 / SCS220
Bifidobacterium	breve	DSM 24732 / SCS206
Streptococcus	thermophilus	DSM 24739 / SCS221

43

MYCEQUIN: A DIFFERENT TAKE ON PROBIOTICS

- A yeast, *Saccharomyces bouardii*
- 5 billion CFU/capsule
- Contains beta-glucan polysaccharide, a soluble fiber
 - Improves gut immunity
- May be given concurrently with an antibiotic

44



INDICATIONS FOR PROBIOTICS

45



DO THESE PRODUCTS WORK??

- Research is increasing
- Controlled prospective trials are ongoing
- Products have improved
- Results are promising

46

Comparison of Microbiological, Histological, and Immunomodulatory Parameters in Response to Treatment with Either Combination Therapy with Prednisone and Metronidazole or Probiotic VSL#3 Strains in Dogs with Idiopathic Inflammatory Bowel Disease

Giacomo Rossi¹, Graziano Pengo², Marco Caldin³, Angela Palumbo Piccionello¹, Jörg M. Steiner⁴, Noah D. Cohen⁵, Albert E. Jergens⁶, Jan S. Suchodolski^{6*}

Conclusions: A protective effect of VSL#3 strains was observed in dogs with IBD, with a significant decrease in clinical and histological scores and a decrease in CD3+ T-cell infiltration. Protection was associated with an enhancement of regulatory T-cell markers (FoxP3+ and TGF-β+), specifically observed in the probiotic-treated group and not in animals receiving combination therapy. A normalization of dysbiosis after long-term therapy was observed in the probiotic group. Larger scale studies are warranted to evaluate the clinical efficacy of VSL#3 in canine IBD.

47

RESEARCH ARTICLE

Effect of probiotic treatment on the clinical course, intestinal microbiome, and toxigenic *Clostridium perfringens* in dogs with acute hemorrhagic diarrhea

Anna Lind Dimes^{1,2*}, Jan S. Suchodolski³, Kristin Hartmann⁴, Kathrin Buehler⁵, Alexander Androsch⁶, Fatima Sarver⁷, Natalie Strömmer³, Stefan Utzinger⁸

Conclusion

The probiotic treatment was associated with an accelerated normalization of the intestinal microbiome. Dogs with aseptic HDS showed a rapid decrease of *relF* toxin genes and fast clinical recovery in both groups under symptomatic treatment without antibiotics.

48

Effects of Synbiotics on the Fecal Microbiome and Metabolomic Profiles of Healthy Research Dogs Administered Antibiotics: A Randomized, Controlled Trial

Jacqueline C. Whittemore¹, Joshua M. Price¹, Tamberlyn Moyers¹ and John Schoenheit¹

CONCLUSIONS

Broad-spectrum antibiotic regimens in dogs are associated with a high incidence of AAGS. Adverse clinical effects are believed to be due to negative effects of antibiotics on the gastrointestinal microbiome, leading to alterations in the metabolome and opportunistic colonization by pathogenic bacteria. Based on results of this study, derangements in the fecal microbiome and metabolome secondary to combination enrofloxacin/metronidazole therapy are profound. Recovery of the fecal microbiome and metabolome composition overall after antibiotic discontinuation was greater for dogs administered synbiotics. Significant group-by-time interactions also were noted for numerous AAVs associated with eubiosis: SCFA, bile acid, tryptophan, and sphingolipid metabolites; antioxidants and antimicrobials; and bacterial energy substrates. Further study is warranted to determine the long-term clinical ramifications of

49

Randomized, controlled, crossover trial of prevention of antibiotic-induced gastrointestinal signs using a synbiotic mixture in healthy research dogs

Jacqueline C. Whittemore¹ | Tamberlyn D. Moyers¹ | Joshua M. Price²

Conclusions and Clinical Importance: Enrofloxacin/metronidazole administration is associated with a high frequency of AAGS. Synbiotic administration decreases food intake derangements. The presence of milder AAGS in period 2 suggests that clinical effects of synbiotics persist >9 weeks after discontinuation, mitigating AAGS in dogs being treated with antibiotics followed by placebo.

50

Effect of a Multistrain Probiotic on Feline Gut Health through the Fecal Microbiota and Its Metabolite SCFAs

Yiwei Li¹, Binyan Ali¹, Zhiqi Lei¹, Yanan Li¹, Min Yang¹, Caixia Yang¹ and Lian Li^{1*}

Abstract: With the increasing awareness of raising pets, following scientific methods, people are becoming increasingly more interested in the nutrition and health of pets, especially their intestinal health, which has become a research hotspot. Both *Lactobacillus* and *Pediococcus acidilactici* are probiotics with strong probiotic properties that can maintain the balance of intestinal flora. However, the role of *Lactobacillus* and *Pediococcus acidilactici* in felines has not been comprehensively studied to date. The aim of this study is to investigate the effect of multistrain probiotics consisting of *Lactobacillus* and *Pediococcus acidilactici* on the gut health of felines by modulating gut microbes and the production of metabolite SCFAs. The results show that the multistrain probiotic did not alter the intestinal microbial diversity and structure of short-haired domestic cats, promoted the colonization of beneficial bacteria, increased the levels of microbial-derived SCFAs and fecal antioxidants, and reduced the levels of fecal inflammatory markers. In conclusion, the use of a multistrain probiotic in healthy, short-haired domestic cats **can promote gut health by modulating gut microbes, increasing microbial-derived SCFA production, reducing inflammatory conditions, and improving antioxidant status.** These results provide new insights for further exploration of the role of probiotics in the gut microbiome of cats.

51

Advances in Small Animal Care 3 (2022) 95-107
ADVANCES IN SMALL ANIMAL CARE

Modifying the Gut Microbiota – An Update on the Evidence for Dietary Interventions, Probiotics, and Fecal Microbiota Transplantation in Chronic Gastrointestinal Diseases of Dogs and Cats

Silke Salavati Schmitz, Dr med vet, Dipl ECVIM-CA, FHEA, PhD, FRCVS
 Hospital for Small Animals, Royal (Dick) School of Veterinary Studies, College of Medicine and Veterinary Medicine, University of Edinburgh, Easter Bush, Midlothian EH25 9RG, United Kingdom

52

Saccharomyces boulardii	1 x 10 ¹⁰ cfu/day	6 treated, 7 placebo (all on other treatments) (D)	IRE with or without PLE	<ul style="list-style-type: none"> CCECAL improved significantly more in dogs receiving S boulardii compared with placebo on day 45 and day 60 Stool frequency was significantly reduced in the S boulardii group on days 30, 45, and 60 In the subgroup of PLE dogs, serum albumin was >2 g/dL in 3/3 dogs in the treatment and 2/3 dogs in the placebo group
LAB mixture "ce Simoes" formulation	110-225 x 10 ⁹ cfu/10 kg BW/day	14 treated, 12 placebo (all on standard treatment) (D)	IRE	<ul style="list-style-type: none"> Total number of mucosal bacteria increased in probiotic group Increased Lactobacillus spp., decreased Bifidobacteria spp. Intestinal tight junction proteins up-regulated

53

RETHINKING FIBER

Another way to modulate the microbiome

54

TYPES OF FIBER

Insoluble

- Non or poorly fermentable
- Little to no yield of postbiotics
- Promotes motility and bulkier stools

Soluble

- Usually fermentable
- Yield SCFA and other beneficial postbiotics
- Soluble fibers are PREBIOTICS

55

JAVMA



Dietary fiber aids in the management of canine and feline gastrointestinal disease

Adam A. Hirono, DVM¹; Valerie J. Parker, DVM, DACVP (SAH and Nutrition)²; Jessica A. Winters, DVM, PhD, DACVP (SAH)³; Adam J. Rubenstein, DVM, MS, DACVP (SAH)⁴

Dietary Fiber Sources		Solubility		
		High	Moderate	Low
Fermentability	High	Fructose, Galactans, Mannans, Mucilages, Apple pectin, Citrus pulp, Gum gum, Gum arabic, Soy fiber, Apple pomace, Carrot pomace, Citrus pectin		
	Moderate	Pectin, Flaxseed	Grape pomace, Tomato pomace, Pea hulls	Hemicelluloses, Beet pulp, Corn bran, Pea fiber, Rice bran, Soy hulls, Wheat bran, Wheat middings
	Low		Psyllio, Psyllium	Hemicelluloses, Cellulose, Soy hulls, Peanut hulls, Sunflower hulls

56



INTERPRETING FIBER CONTENT IN DIETS

- *Guaranteed Analysis* found on food labels is not helpful for determining how much soluble and insoluble fiber is in the diet
- *Crude fiber* only considers insoluble fiber
- *Total Dietary Fiber* provides both insoluble and soluble fiber content

57

FIBER TRIALS: RECOMMENDATIONS

- Keep it as a treatment option for GI disease
 - Especially large bowel
 - Especially prebiotic (soluble) fibers
- Consider fiber before trying a GI antibiotic
- Start with a mixture of insoluble and soluble fiber for colitis
- Add fiber slowly to limit diarrhea



58

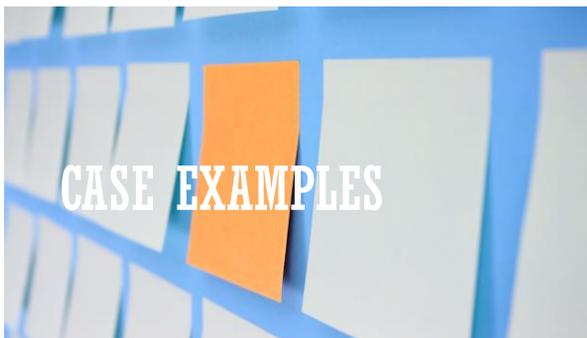
DOSING FIBER

Start low and increase dose every 1-2 weeks to avoid adverse side effects/assess response

$\frac{1}{4}$ teaspoon BID to 3 TBS BID, depending on size



59



60



CASE EXAMPLE

- Sadie, 5 year old female, spayed Shih Tzu
- Presented on ER over weekend for mild AHDS
- Treatment: IV fluids, maropitant, pantoprazole
- Loose stool continued on Day 4
 - Case rounds: "Add some metronidazole?"
 - "Nooooooooooooo"
 - FortiFlora added
 - Discharged Day 5 with improved fecal consistency



61



CASE EXAMPLE

- Leo, 8 year old MN DSH with IBD
 - Primarily small bowel diarrhea
- Treatments: prednisolone, cyclosporine, various hydrolyzed and novel protein diets
- Continued weight loss and progressive anorexia
 - Added Biome diet
- Obtained remission for years



62



CASE EXAMPLE

- Hartley, 2 year old FS GSD
- Intermittent small diarrhea since 8 months old



63



CASE EXAMPLE

- Initial remission with Biome® diet
- Flares controlled with Visbiome Vet®
- Later required endoscopy and was diagnosed with IRE
- Started on steroids and chlorambucil
- Flares controlled with fiber



64

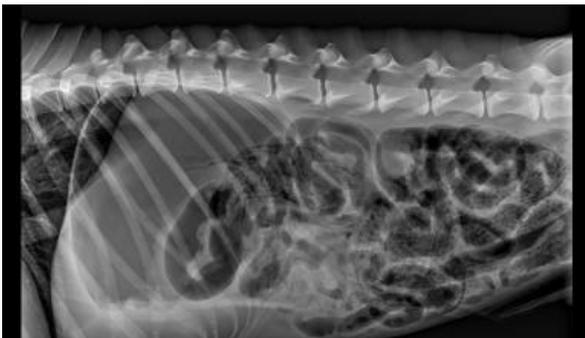
NORM

Norm is a 6 year old, male neutered, Standard Poodle that presented to MSU-CVM's Small Animal Emergency Service on 3/28/23 for chronic diarrhea and weight loss. According to weight tracking from Norm's owner, Norm has lost ~14lbs. He is currently being fed Purina HA Vegitarian (8 cups/day) and has been eating it for 2-4 weeks. He has also been receiving Tylenol powder (1/4 tsp BID) for 2-4 weeks. No response has been noted. Norm eats all the food offered to him but has historically been described as being a picky eater. Norm is not giving anything other than his prescribed diet. Prior to Norm's weight loss, he was being fed a Purina adult dog diet but at the onset of his GI problem, he was put on GI Biome with no improvement seen. He has also been given metoprolol and prednisone (10 mg tablet) with no response.

Mrs. Marks described Norm's diarrhea as initially being mucoid but then becoming bright yellow with soft service cream consistency. He has diarrhea 6-7 times per day with about 2-3 piles of diarrhea produced per incident. No blood in the diarrhea has been observed. Norm does drink large quantities of water and has started to develop hair loss. No incidents of vomiting have occurred. He has been tested for Addison's Disease and Hemiparasitosis with both found to be negative.



65



66

NORM

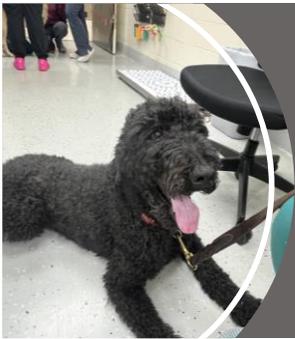
- Metronidazole and Clavamox x 4 weeks
- Concurrent Provable Forte
- Marked improvement in stool



67

NORM

- Fecal Transplant (1)
- Long-term Provable
- Currently normal!



68

SUMMARY

- Knowledge of the microbiome has changed GI medicine
- Microbiome support is a treatment strategy for acute and chronic GI disease

69

