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Gastrointestinal
Laboratory



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Management of intestinal dysbiosis - new treatment options beyond antibiotics

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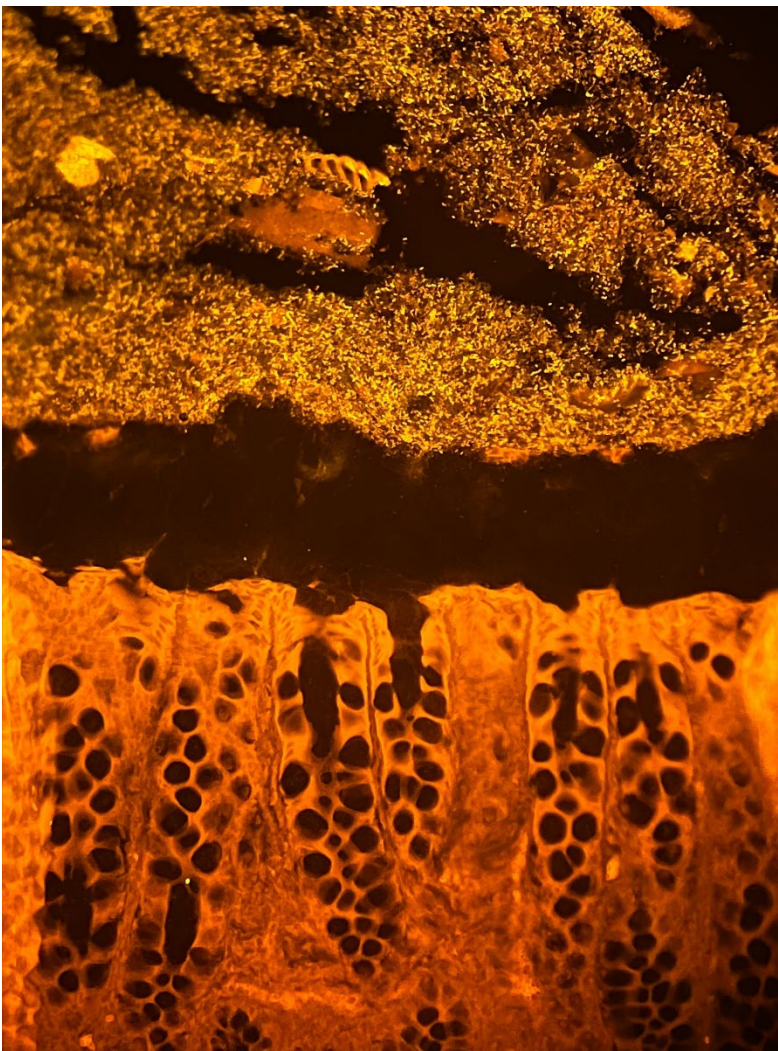
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Section through a
colon from a cat



Live bacteria (what we
see as feces)

Mucus layer

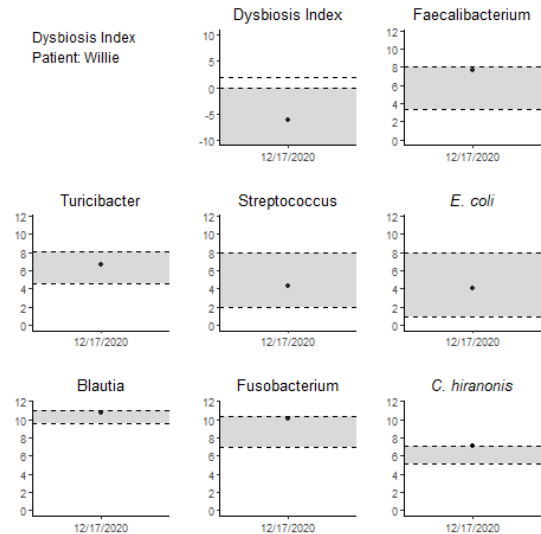
Epithelium

The gut contains approximately 100 trillion bacterial cells

- 1 Million seconds = 11 days

Blue – 10 month old Golden Retriever

- every 6-8 weeks episodes of watery diarrhea
- received metronidazole at 4 months of age
- testing because of repeated episodes of diarrhea
 - fecal parasites negative
 - enteropathogen panel - increase in *C. perfringens* toxin A
 - fecal dysbiosis index – all bacteria normal



CAUSES - ACUTE UNCOMPLICATED DIARRHEA

- very rarely bacterial infections
 - eg, *Campylobacter jejuni*
 - and even then in most cases self-limiting
- Clostridial overgrowth often consequence of underlying microbiota changes and unlikely causative
 - *netF toxin* associated with acute hemorrhagic diarrhea, but often also self-limiting
 - Ziese *et al*, *PLOS One* 2018
- parasites
- motility changes (stress) and dietary causes
 - undigested food can cause bacterial proliferation

TREATMENT - ACUTE UNCOMPLICATED DIARRHEA

- most cases are self limiting within 2-4 days
 - discuss with owner expectations and treatment options
 - risk and benefits of therapy
- gastrointestinal diet for 7 days
 - highly digestible, low to moderate fat, preferably wet
- antiemetic if needed – maropitant (1 mg/kg SQ)
- probiotic for 14-21 days
- kaolin-pectin q8 hours for the first 2-3 days may help improving fecal quality

Fecal consistency in acute diarrhea mean days until resolution

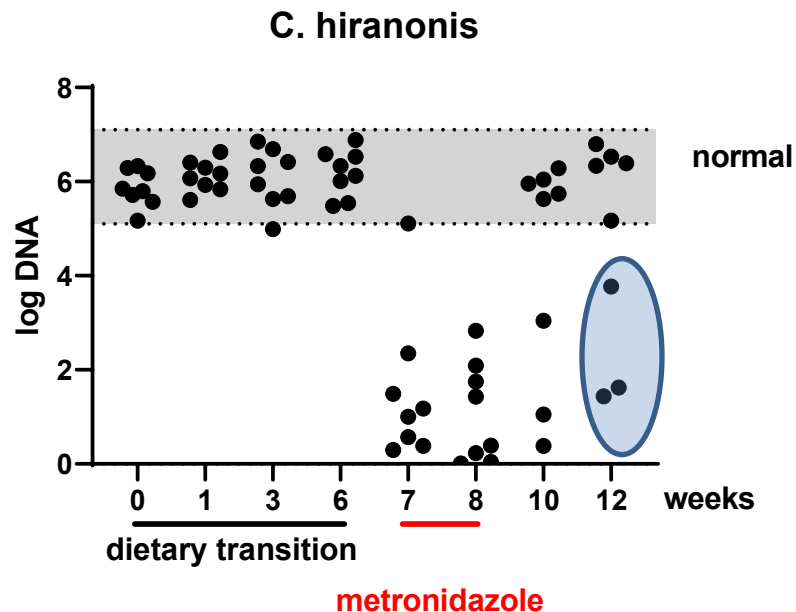
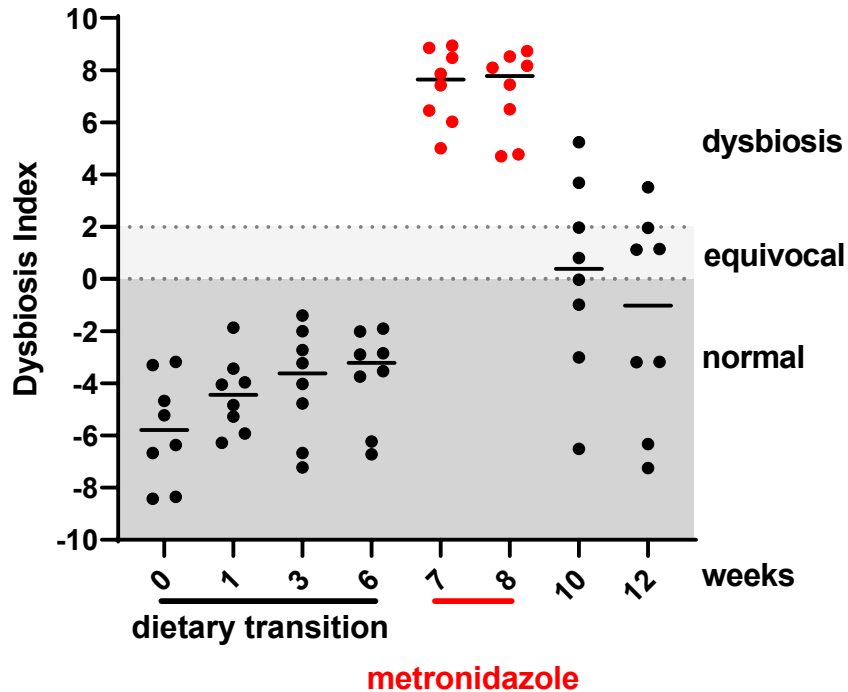
	placebo	probiotic	antibiotic		
ns	4.8	3.5	4.6	metronidazole	Shmalberg 2019
p<0.05	3.6	na	2.1	metronidazole	Langlois 2019
p<0.05	na	2.8 (plus metro)	4.4	metronidazole	Fenimore 2017
ns	1.8	na	1.7	amoxicillin clavulanate	Werner 2020
Average across studies		3.4	3.2		

ns - not significant



na - not applicable

Additional studies needed to assess benefits and risks of routine use of metronidazole because most dogs achieve resolution of diarrhea within several days regardless of treatment.
(Langlois et al, JVIM 2019)

Healthy dogs on various diets switched to hydrolyzed protein diet (Purina HA) and then administered metronidazole



Association of Infant Antibiotic Exposure With Childhood Health Outcomes

Zaira Aversa, MD, PhD • Elizabeth J. Atkinson, MS • Marissa J. Schafer, PhD • ... Walter A. Rocca, MD •
Martin J. Blaser, MD • Nathan K. LeBrasseur, PhD   • [Show all authors](#)

Published: November 15, 2020 • DOI: <https://doi.org/10.1016/j.mayocp.2020.07.019>

broad-spectrum antibiotics

- 14,572 children (7026 girls and 7546 boys)
 - 70% (10,220) received at least 1 antibiotic prescription during the first 2 years of life.
- Early antibiotic exposure associated with increased risk:
 - childhood-onset asthma
 - allergic rhinitis
 - atopic dermatitis
 - celiac disease
 - attention deficit hyperactivity disorder
 - hazard ratios ranging from 1.20 to 2.89; $P < .05$ for all

Probiotics

Probiotics have potential for GI health, but we need to understand the mechanisms

probiotic effect is strain specific

the administered dose is important

the quality of products is crucial for clinical success

PROBIOTICS

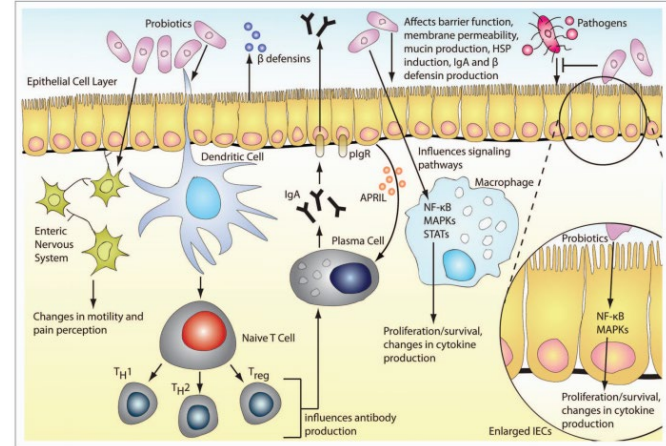
- Probiotics are defined as “live microorganisms, which when administered in adequate amounts confer a health benefit on the host”

PREBIOTICS AND SYNBIOTICS

- Prebiotics are non-digestible food ingredients
 - intended to stimulate growth of resident bacteria
 - typically carbohydrates
 - fructooligosaccharides (FOS), galactooligosaccharides (GOS)
 - beta-glucans
- Synbiotics are a combination of probiotics and prebiotics

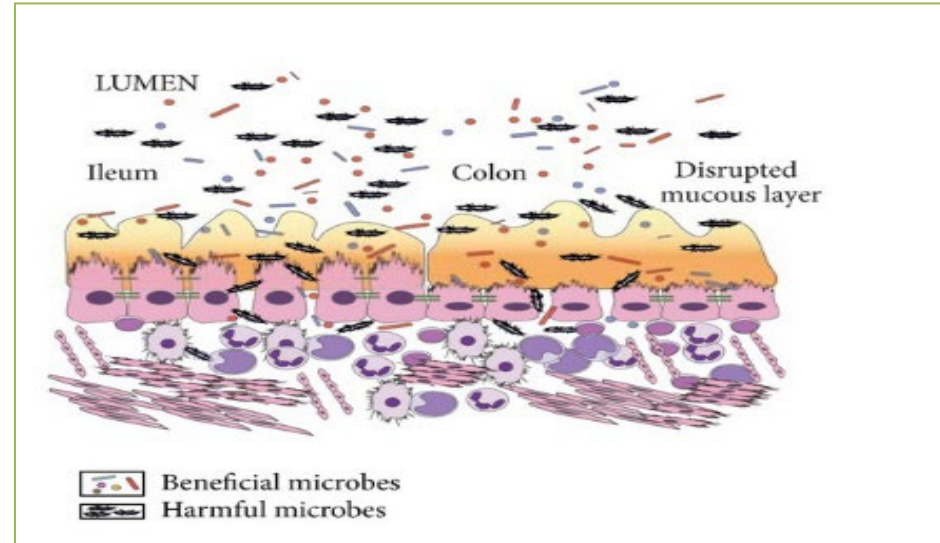
MECHANISMS OF PROBIOTICS

- exclusion of pathogens
- secretion of anti-microbial peptides
- anti-toxin effect on *C. difficile*
 - *Saccharomyces boulardii*
- immunomodulatory effects

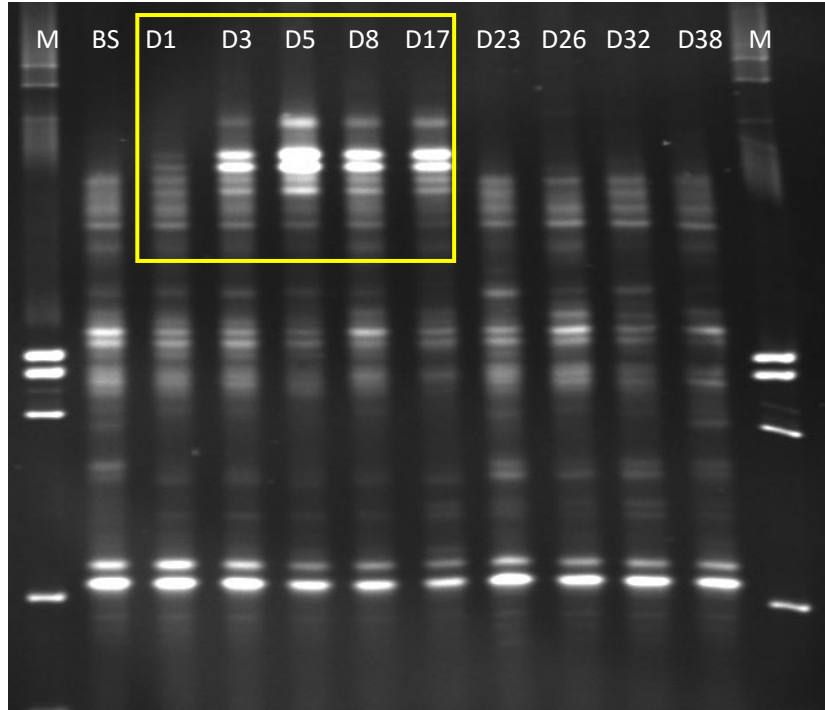


IMPROVEMENT INTESTINAL BARRIER

- upregulation of tight junction proteins
- increase mucin production – improve epithelial mucus layer
- long-term administration in dogs with CE useful as adjunct treatment



PROBIOTICS - FECAL COLONIZATION



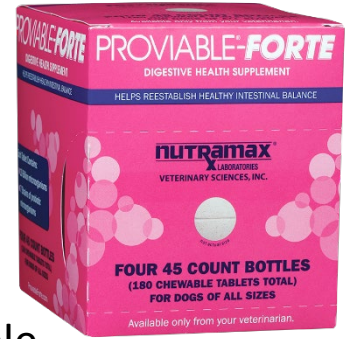
- rapid appearance (1-2 days) and disappearance (1-3 days) of probiotic species

INDICATIONS FOR PROBIOTICS

- stress-related diarrhea (prevention or treatment)
 - boarding, traveling, working dogs
- uncomplicated diarrhea (Fortiflora, Provable DC)
- prevention of antibiotic associated GI signs (Fortiflora, Provable DC)
- chronic enteropathies – improvement of intestinal barrier function
 - as adjunct therapy (Visbiome Vet)

DIARRHEA

- improvement in fecal consistency
 - improvement in fecal scores in cats with chronic diarrhea (Provable, Nutramax)
 - shortening of diarrhea by 1-2 days in dogs with uncomplicated diarrhea (Purina Fortiflora)
- more rapid normalization of intestinal microbiota (Visbiome Vet)
 - dogs with acute hemorrhagic diarrhea syndrome
 - improvement in intestinal barrier in dogs with CE



ANTIBIOTIC-ASSOCIATED GI SIGNS

- studies show that giving probiotics during periods of antibiotic administration ameliorate some of the clinical signs
 - bacterial probiotics should be given a few hours apart from antibiotics
 - but started on the same day or even before first dose of antibiotics

SACCHAROMYCES BOULARDII

- major clinical use in humans
- meta-analysis of 21 randomized controlled trials (4780 participants)
- *S. boulardii* is effective in reducing the risk of antibiotic-associated diarrhea in children and adults



Systematic Review with Meta-analysis | [Free Access](#)

Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea

H. Szajewska [✉](#), M. Kołodziej

First published: 27 July 2015 | <https://doi.org/10.1111/apt.13344> | Cited by: 32

SACCHAROMYCES BOULARDII

- yeast, 10x larger and different structured cell wall than bacterial cells
 - yeast cells recognized by different host receptors than bacterial cells causing different antigenic responses
- yeast cells are resistant
 - to low pH in the stomach, bile salts, intestinal enzymes
 - **resistant to common antibiotics**



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

Combination of metronidazole/enrofloxacin

Hyporexia (41%), vomiting (77%), and diarrhea (100%) of dogs

Synbiotic administration decreased food intake derangements



QUALITY OF PROBIOTIC PRODUCTS

- 25 probiotics were purchased, labels were scrutinized, and bacterial contents were enumerated
- only 4/15 (27%) products that had specific claims of viable organisms met or exceeded their label claim
- only 2 of these also had an acceptable label, which properly described the contents
- veterinarians and owners should scrutinize commercial probiotics

Fecal microbiota transplantation (FMT)



***C. DIFFICILE* IN HUMANS**

- important cause of hospital-associated and **antibiotic-associated diarrhea**
- estimated >250,000 cases in US occur in hospitals
 - many more develop in outpatient settings
- diarrhea, often with dysentery, pseudomembranous
- >20% of patients resistant to metronidazole or vancomycin

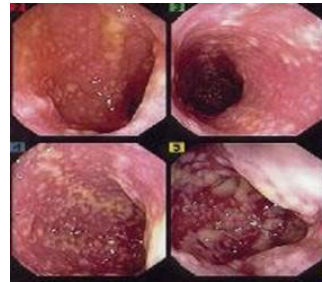


Table 4: Clinical burden of CDAD

Patient	Diarrhea duration (days)	Maximum stools per day (Avg Bristol Score)	Fever/Abdominal Pain
1	46	10 (7)	Yes/Yes
2	57	20 (7)	Yes/Yes
3	136	5 (6)	Yes/Yes
4	94	6 (7)	Yes/Yes
5	22	15 (7)	Yes/Yes
6	80	12 (7)	Yes/Yes
7	628	14 (7)	No/Yes
8	92	12 (7)	No/Yes
9	96	10 (7)	No/Yes
10	27	6 (7)	Yes/Yes
11	438	15 (6)	No/Yes
12	243	10 (7)	No/No
13	672	14 (7)	No/No
14	171	12 (7)	No/Yes

- Mean duration of 200.1 days of diarrhea
- Mean maximum of 11.5 stools/day

Fecal Transplantation via retention enema is effective for recurrent or refractory *C. difficile*-associated diarrhea

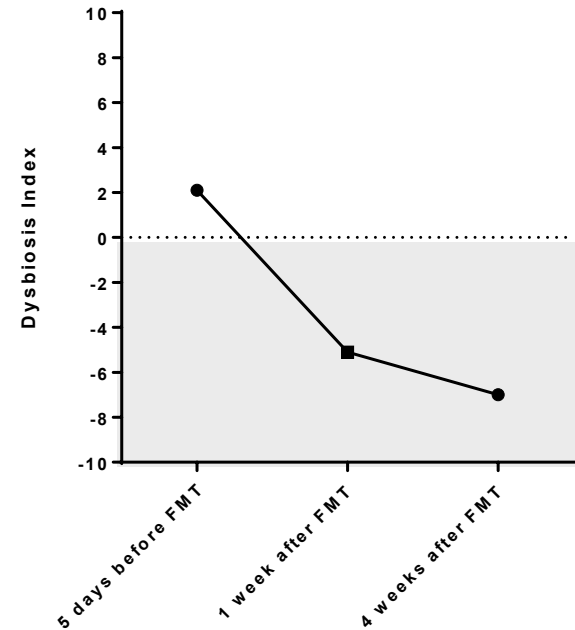
- 89% of patients experienced clinical resolution within 24 hours of FMT
 - some patients respond after 2nd FMT
- no documented relapses or adverse events with mean follow-up at 216 days post-FMT

INDICATIONS FOR FMT

- young animals with chronic diarrhea
 - after infections or antibiotic use

- in dogs with chronic CE, use FMT as adjunct treatment
 - dogs with CE require treatment for underlying GI inflammation
 - hypoallergenic diet as first step

- 9 month old puppy presented from the pet shop with a resistant giardia infection
- treated with panacur, metronidazole, sulfamethoxazole and trimethoprim over 3 months
- still soft stools – FMT performed
- clinical improvement



Fecal microbiota transplantation in puppies with canine parvovirus infection.

Pereira GQ¹, Gomes LA¹, Santos IS¹, Alfieri AF², Weese JS³, Costa MC⁴.

Protocol: 10 g of feces from a healthy dog diluted in 10 mL of saline given rectally 6-12 hours post-admission

ANIMALS:

66 puppies with parvovirus

METHODS:

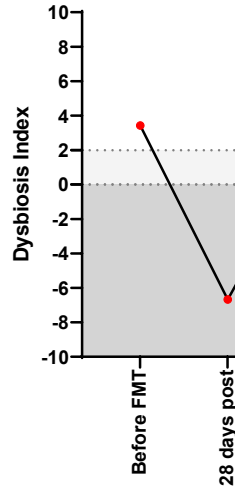
- group 1: standard treatment (STD) with antimicrobials (n=33)
- group 2: standard treatment plus FMT (n=33)

RESULTS:

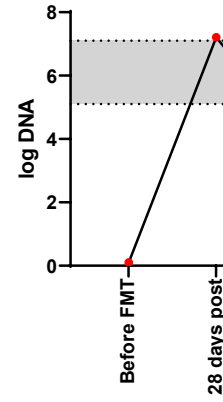
- FMT group quicker resolution of diarrhea and shorter hospitalization time (median 3 days vs. 6 days).
- mortality in STD was 36% vs. 21% in FMT, but not statistical significant (P = .174)



Dysbiosis Index



C. hiranonis



First Case Report of Fecal Microbiota Transplantation in a Cat in Israel

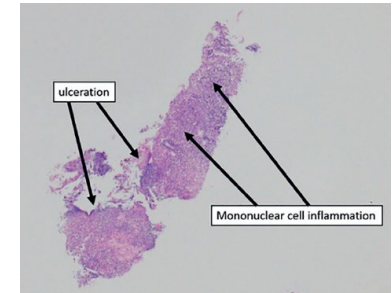
Furmanski, S.^{1,*} and Mor, T.²

¹ Medi-Vet Veterinary Hospital, 8 Einstein St., Haifa 3460506, Israel.

² Veterinary Endoscopic Services, 2 Reuven Ruben St., Tel Aviv 6941253, Israel.



- FMT (enema) as a last therapeutic option for cat before euthanasia
- immediate improvement in regards to fecal texture, odor and color
- due to relapse of diarrhea, a second FMT was performed 5 weeks later
- during a 3-month period the cat started passing gradually normal stools
- 11 months after FMT a prolonged clinical cure of the diarrhea was achieved with the cat passing normal feces



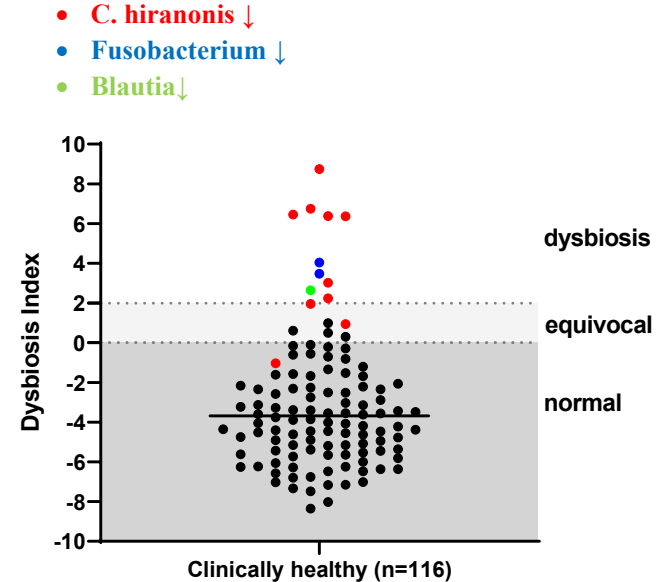
SUMMARY

- FMT improves at least temporarily clinical signs and microbiota in subset of dogs
 - correlates with secondary bile acid conversion
 - donor screening should include testing for normal BA metabolism

- FMT success may depend on underlying disease
 - if initial trigger gone (e.g., dysbiosis due to antibiotic use), then lasting improvement of microbiota
 - luminal dysbiosis
 - in chronic enteropathies possibly repeated FMTs necessary as adjunct to standard therapy

FMT DONOR SCREENING

- normal microbiota
 - Dysbiosis Index (IDEXX and TAMU GI Lab)
- normal *C. hiranonis*
 - indicates normal fecal bile acid conversion
 - 5-10% of healthy dogs do not have beneficial *C. hiranonis*
- screen for parasites
- screen for enteropathogens – PCR panel
 - *C. difficile*, *parvovirus*, *C. perfringens cpe* and *netF* genes, *C. jejuni*, *Salmonella*



FMT DONOR SCREENING

- microbiome generally stable, so no need for frequent screening
- alternatively select healthy dog
 - no signs of GI disease
 - no antibiotic administration for at least 6 months

FMT protocol via enema based on Chaitman *et al.*, ACVIM 2017



- Blend approx. 5 gram of donor stool per kg BW with enough 0.9% NaCl to achieve a mushy consistency

FMT protocol via enema based on Chaitman *et al.*, ACVIM 2017



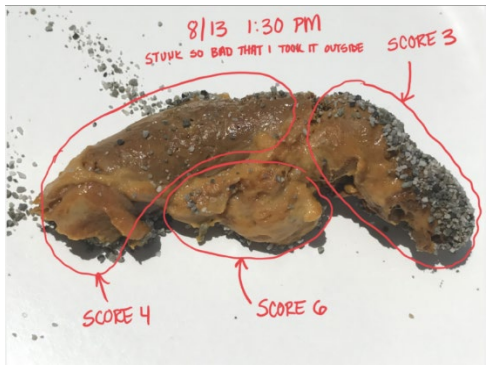
- Draw up in catheter tip syringe, attach 12 French red rubber catheter
- Push material into catheter until it comes out the tip to avoid air transplanted

STORAGE OF FECES

- stable at 4C for up to 1 week
- for longer storage in freezer, add glycerol
 - 50 ml aliquots contain 10g of Stool, 30-35 ml of saline, 5ml of glycerol
- storage up to 6 months at -20C

lyophilized fecal powder using a freeze-dryer for food





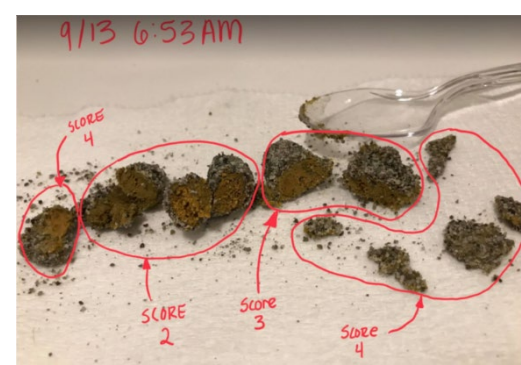
before FMT pills



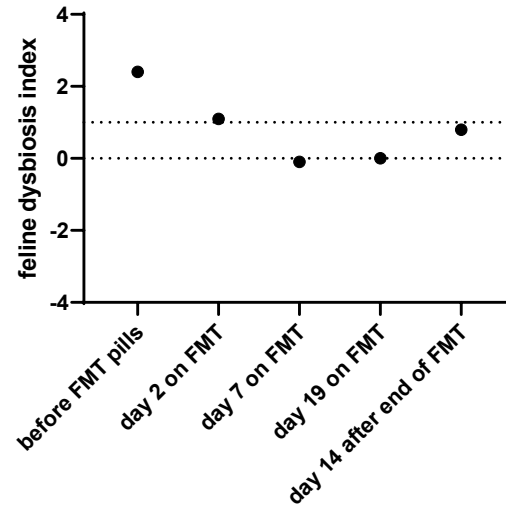
day 2 on FMT pills



day 19 on FMT pills



day 2 after end of FMT pills



CASE REPORT

- “Zorro”, 8 year old Rottweiler with CE
 - was stable on prednisolone for 4 years
 - 6 months ago, developed calcinosis cutis
- prednisolone stopped – dog developed watery diarrhea
- no success with treatment with cyclosporine, azathioprine, metronidazole, and fecal microbiota transplant
 - still watery diarrhea, weight loss of 3 kgs over 3 months

CASE REPORT

- dog received cholestyramine (Questran™)
- 2 grams BID – improvement of watery diarrhea
- dose increased to 3 grams morning + 2 grams evening
 - complete resolution of diarrhea with 10 days
 - dog vomited 3x in a week (side effect of cholestyramine)
 - dose reduced to 2 grams BID – diarrhea returned
 - dose again increased to 3 + 2 grams – complete resolution of diarrhea
- dog stable for 3 months, gained 3 kg



Toresson et al. *Canine Medicine and Genetics*
<https://doi.org/10.1186/s40575-021-00099-x>

(2021) 8:1

Canine Medicine and
Genetics

CASE REPORT

Open Access

Cholestyramine treatment in two dogs with presumptive bile acid diarrhoea: a case report

L. Toresson^{1,2*}, J. M. Steiner³ and J. S. Suchodolski³



BILE ACID DIARRHEA (BAD)

- under recognized in humans (limited diagnostic testing)
 - approx. 30% of patients with IBS
 - 40% of patients with Crohn's Disease
 - 1% of total population
- type 1: bile acid malabsorption, secondary to ileal inflammation
- type 2: idiopathic
- type 3: intestinal dysbiosis

TREATMENT OF BILE ACID MALABSORPTION

- cholestyramine (bile acid sequestrants)
 - 60 mg/kg q12h
 - can be increased if no response and no side effects
- corticosteroids
 - induce expression of bile acid transporters in ileum
 - helps with reabsorption of bile acids
 - should empirically try cholestyramine in dogs that have partial response to corticosteroids
 - or respond well to corticosteroids but not other immunosuppressive drugs when dogs don't tolerate steroids

OPEN ACCESS





Veterinary Clinics of North America: Small Animal
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Impact of Changes in Gastrointestinal Microbiota in Canine and Feline Digestive Diseases

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