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Fecal Transplantation: What's Coming Down the Pipeline

Learning Objectives

1. Understand the central role that the fecal microbiota plays in GI function and homeostasis.

2. Appreciate the uses and limitations of probiotics in GI disease, including Fecal Transplant.

3. Familiarize clinicians with the step-by-step logistics of Fecal Microbiota Transplantation.

Introduction

If our patients were cows instead of cats and dogs the use of Fecal Transplantation would be a no-brainer. Known as Rumen Transfaunation in bovine, the cud from a healthy donor cow is used to treat a sick cow, based on the assumption that changes in the intestinal microbial population could be associated with GI disease (indigestion), abnormal rumen function post-surgery (left-displaced abomasum), and manifestations of toxin exposure. Rumen Transfaunation is considered an effective, practical, and easy method to treat simple indigestion of ruminants. In humans Fecal Microbiota Transplantation (FMT) is the transfer of stool from a healthy donor into the GI tract of a patient whose disease is, again, presumed to either cause or result as the consequence of an altered microbiome. FMT is best studied and most frequently and effectively used for humans with recurrent *Clostricium difficile* (CDI) infection. The potential therapeutic benefit of FMT may extend beyond CDI in people, particularly in conditions of GI dysbiosis and immune dysfunction. As of April, 2018, searching PubMed for "fecal microbiota transplantation" AND "cat" or "feline" produced ONE publication on the Role of the GI Microbiota in Small Animal Health and Disease (Redfern et al. Vet Rec 2017). We have a lot to learn.

The Importance of an Altered Microbiota: Dysbiosis

The fecal Microbiota (actual organisms) and Microbiome (genetic material) are essential to the normal development and function of most every system in the body, although most often highlighted with regards to the gastrointestinal tract [these terms are often used interchangeably]. Although the microbiota includes all organisms (fungal, viral, protozoa, and bacteria) the bacterial population has dominated GI research and attempted therapies thus far. We (and cats and dogs) have 10 times more bacterial DNA than human genetic information inside us. The GI tract also houses the largest collection of immune cells anywhere in the body, so it is not surprising that the microbiota has a critical impact on immune function, and FMT might act as "immunotherapy".

Dysbiosis is a disruption or imbalance in the normal GI microbiota. Dysbiosis may result from an increase or decrease in some number of commensal bacteria, may involve the introduction of pathogenic organisms, or the proliferation of opportunistic bacteria. Because the microbiota is a metabolically active "organ", dysbiosis may also impact the production of beneficial nutrients or metabolites, such as short-chain fatty acids or secondary bile acids.

Significant dysbiosis is found in cases of acute diarrhea (infectious, non-infectious, and hemorrhagic), chronic diarrhea (food or antibiotic responsive and IBD), GI motility disorders, EPI, and the use of antibiotics and gastric acid reducers. Although the research is very limited, dysbiosis appears to be a

significant component of feline and canine diarrhea, both acute and chronic. Changes in GI bacterial groups results in changes in the microbiota metabolism of fatty acids, biotin, tryptophan, ascorbate, and glycosphingolipids.

FMT: The Ultimate Probiotic

Probiotics are given to patients with GI disease in an effort to correct dysbiosis (measured or assumed) and return the microbiota to a normal, healthy state. According to the World Health Organization, probiotics are living organisms (not just bacteria) that when administered in adequate amounts (the more the better) confer a health benefit on the host. Probiotics are available in droves OTC, and are not currently regulated by the FDA, so it is often, and unfortunately, a “crap shoot” as far as what is actually inside the bottle you are buying. In fact, several studies (Weese et al. 2011 & 2003) have demonstrated that the majority of OTC probiotics simply do not live up to label claims – including labels where the advertised components are misspelled! But there are a number of veterinary studies that, despite some challenges and faults, at least suggest that probiotic administration may be helpful in some number of cases of canine and feline, acute and chronic GI disease. Some of the likely limitations include our lack of understanding as to which “bugs” are best for which diseases, and the enormity in terms of numbers and diversity found in a healthy microbiota – that simply cannot be reconstituted in a commercial product. So how could a clinician replicate that complexity and those numbers? Of course, produce the product as it comes straight out of a healthy GI tract!

FMT: The Logistics

Screening a Donor: Patient Preparation

Even in our human counterparts, there is a lack of standardization when it comes to donor selection for FMT. Although it is unclear what makes for an optimal donor, common sense helps us with our exclusion criteria. Insufficient feces production, for instance; my long-haired Chihuahua has not entered the ranks of fecal donor at CSU. Poor doers, obese pets, unvaccinated animals, current clinical signs or history of relevant disease, recent (past 3 months) antibiotic use, or atopic or food allergic pets (Table). The patient (recipient) should be off antibiotics for at least 48-72 hours and off prebiotics, probiotics, and supplements, as is practical. The patient should undergo standard bowel preparation – so at a minimum a 12-hour fast and enemas, but more extensive if administering FMT by colonoscopy. In some human protocols the recipient is pre-treated with Imodium, but I am not aware of this being done in veterinary patients, and a number of post-procedure side-effects (constipation, bloat, flatulence) are likely due to the use of this drug.

Ideal Donor
No Hx GI disease or clinical signs
No systemic antibiotic use
Naturally born, fed by mother
No immune disorder
No immunosuppressive therapy
No cancer or allergic diseases
Matched diet (e.g. hypoallergenic)
Not obese, no behavioral issues
Diverse, species rich microbiome
Dysbiosis Index (Bile Acid Metabolism)

(Adapted from Ziga Gerbec Thesis)

Poop Preparation

And that's just the pet – now the poop. Obviously the goal is a clean, disease-free sample, where enteropathogens have been ruled out (Table). For both screening the donor and the feces the word "Ideal" is used as there is no agreed upon selection criteria, in either humans or veterinary patients, and these lists may well be longer or shorter in practice.

Ideal Fecal Screening
Screen for species specific parasites & pathogens
Fecal Floatation
Fecal Culture – *Salmonella* & *Campylobacter*
Giardia & *Cryptosporidium* IFA
Clostridium & *Yersinia enterocolitica*
Formed & Fresh (6-8 hours maximum)

Administration

There are many different protocols with varying amounts and dilutions; there is no evidence, as of yet, as to what constitutes an optimal FMT protocol. (the following was developed by Dr. Manchester, CSU Resident)

Fecal Preparation & Administration

Use approximately 2 gram feces/kg body weight
5-7 mL Ringer's solution:1 gram feces
Blend to a liquid slurry
Filter through a metal tea strainer
Load 50 mL syringes
10 mL Slurry/kg body weight
Given as a retention enema
Sedation as necessary
Pretreatment with maropitant (1 mg/kg SubQ)
Retention for 30 minutes if possible

Human patients are warned of potential side-effects that may occur in the first 24-48 hours following FMT: a low-grade fever, diarrhea, constipation, gas, bloating, and flatulence. Obviously these are possible in veterinary patients as well, although we find they are rarely reported by owners after FMT at CSU.

Summary

1. We have a lot to learn and a long way to go.

2. Screen the donor and their feces: At first do no harm.

3. To augment, not replace, appropriate work-up and targeted therapies.

Suggested Reading

Gerbec, Ziga. "Evaluation of Therapeutic Potential of Restoring Gastrointestinal Homeostasis by a Fecal Microbiota Transplant in Dogs." (n.d.): n. pag. 2016. Web. 23 Apr. 2017. http://www.ffa.uni-lj.si/fileadmin/datoteke/Knjiznica/magistrske/2016/Gerbec_Ziga_mag_nal_2016.pdf

Pereira GQ, Gomes LA, Santos IS, et al. Fecal microbiota transplantation in puppies with canine parvovirus infection. J Vet Intern Med 32:707-711, 2018.

Redfern A, Suchodolski J, Jergens A. Role of the gastrointestinal microbiota in small animal health and disease. Vet Rec 181:370-377, 2017.

Suchodolski JS. Diagnosis and interpretation of intestinal dysbiosis in dogs and cats. Vet J 215:30-7, 2016.

Suchodolski JS, Foster ML, Sohail MU, et al. The fecal microbiome in cats with diarrhea. PLoS One 10(5): e0127378, 2015.