NUTRITION NOTES

Microbiome-Targeted Therapies: Probiotics and Fecal Microbiota Transplants

Robin Saar, *RVT, VTS (Nutrition)*
AnimalBiome, Lethbridge, Alberta, Canada

Abstract

Microbiome-targeted therapies involve products that support the gut microbiome in patients experiencing dysbiosis. Choosing the best microbiome-targeted therapy is based on the type of dysbiosis. Probiotics, which work to support dogs and cats with gut dysbiosis, have taken on a large role in pet nutrition. In comparison, fecal microbiota transplantation is gaining attention because it more appropriately addresses all 3 types of gut dysbiosis. Familiarity with the differences in microbiome-targeted therapies can help veterinary nurses explain therapeutic options to clients.

Take-Home Points

- The gut microbiome plays a large role in overall animal health; gut dysbiosis is associated with systemic symptoms and disease.
- The 3 main types of gut dysbiosis in dogs and cats (type 1, missing common microbes; type 2, overgrowth of potentially pathogenic bacteria; or type 3, an imbalanced microbiome) are not mutually exclusive and can occur at the same time.
- Microbiome-targeted therapies (probiotic administration and fecal microbiota transplantation [FMT]) can support a patient with gut dysbiosis by removing potentially harmful microbes and supporting beneficial microbes.
- Both types of microbiome-targeted therapy often work by overwhelming the gut with beneficial microbes that outcompete undesirable microbes for space and nutrients.
- Probiotic administration is most effective for patients with types 2 and 3 dysbiosis; however, probiotics may need to be discontinued before their microbes outcompete the resident microbes and thereby become the overgrown and unfavorable strains.
- FMT is most effective for patients with all 3 types of gut dysbiosis and provides microbes at higher numbers and diversity than probiotics; however, because FMT material also contains other known and unknown substances, donor screening is recommended to reduce the risk of transferring disease to the recipient.

A new era of managing pet health is starting to affect specialty and general veterinary practices as the value of maintaining a balanced variety of microbes in the gut becomes better understood. Although microbiomes (the community of microbes in a particular environment, formerly called microflora) are ubiquitous, the gut microbiome has an all-encompassing effect on animal health. The functions of resident gut microbes influence many physiologic systems, and understanding their influence can be helpful when choosing a microbiome-targeted therapy.[1] For patients experiencing gut dysbiosis (changes in composition of the gut microbiota that affect their function), microbiome-targeted therapies can offer support, depending on the type of dysbiosis. Two microbiome-targeted therapies commonly used in veterinary practice are administration of probiotics and fecal microbiota transplantation (FMT) (**TABLE 1**). Although probiotic therapy has become more common in recent years, the ancient approach of FMT is gaining the attention of researchers and healthcare professionals.

WHY FOCUS ON THE GUT MICROBIOME?

Microbiomes comprise a variety of microbes that function together to support their microscopic environment. Microbiomes are found everywhere, including in and on animals. In ruminants, microbes function in the rumen and are crucial for proper digestion. In monogastric animals, the focus of this article, the largest microbial infrastructure is the gut microbiome in the large intestine.[2] The gut microbiome consists of approximately 100 trillion microbes (e.g., bacteria, fungi, protozoa, archaea, viruses) and their genetic components; although microscopic, their effect on physiologic functions is profound.[2] The ability of microbes to influence physiologic functions of the host results in part from microbial fermentation of gut ingesta or other energy sources. Much like chemical digestion in the upper gastrointestinal (GI) tract, microbes throughout the GI tract produce chemicals via the breakdown of food sources. Those chemicals are referred to as microbial metabolites, and the collection of all microbial metabolites fermenting a specific food source creates a functional metabolome. The various metabolite functions include influencing the immune system, providing energy, acting as neurotransmitters, assisting with nutrient digestion, reducing inflammation, and playing a role in bile acid recycling.[2,3] Some metabolites can cross into the bloodstream, travel to the liver, and then throughout the body via bile, blood, and lymph, completing chemical reactions in other organs, including the brain. That all-encompassing ability makes the gut microbiome a crucial aspect of animal health.

WHAT ARE THE MICROBIOME-TARGETED THERAPIES?

Probiotic Administration

The International Scientific Association for Probiotics

and Prebiotics (ISAPP, isappscience.org) defines probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[4] Probiotics supply the actual microorganisms, whereas prebiotics (not covered in this article) supply nutrients that promote the growth of beneficial microbes. According to the ISAPP 2013 consensus statement, probiotics provide a general benefit "on gut microbiota that derives from creating a more favorable gut environment, through mechanisms shared by most probiotics."[4] The general benefits conveyed by probiotics are improved GI signs/symptoms and immune function.[3] Probiotics can be given as supplements or may be incorporated into commercial diets. Probiotic supplements are commercially available in liquid, powder, capsule, and chewable forms. The microbes in probiotics are also present in fermented foods and may be sprayed onto or added to commercial diets. Formulations may include a single strain or a variety of strains. Commonly used bacterial probiotics are species of the lactic acid–producing bacterias *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Enterococcus*. A well-studied fungus (yeast) and commercially available probiotic is *Saccharomyces boulardii*.[5,6]

Fecal Microbiota Transplantation

FMT involves collecting feces from a healthy donor and transferring the fecal material to the large intestine of an ill recipient of the same species. Indications for using FMT to treat dysbiosis are based on the ancient theory that a healthy young donor animal would have a normally functioning gut microbiome.[7] The ideal donor would be a young adult (full grown but not yet a senior), in good body condition, eating a healthy diet, not taking any medication, and free of medical problems. The components of FMT material, in addition to beneficial bacteria, include organisms that digest food and produce enzymes, along with unabsorbed metabolites. The transfer of resident gut microbes that were completing normal physiologic functions in the healthy donor can decrease disease-associated symptoms and promote normal body functions in the recipient, thereby improving the recipient's health status. However, in addition to identifiable microbes, FMT material also includes unidentified microbes, metabolites, and other components, which could be harmful for the recipient. Thus, for the safety of recipient animals, each batch of FMT material should ideally undergo bacterial fecal microbiota identification and parasite testing.[8]

Microbiome testing tends to focus on bacteria. Common microbiome testing methods available include polymerase chain reaction and next-generation sequencing, which test for bacteria shed in a fresh fecal sample.[9] FMT material can be fresh, frozen, or commercially available lyophilized (freeze-dried), and it can be administered rectally (via retention enema) or orally (in enteric-coated capsules).[7,10]

WHAT AFFECTS THE GUT MICROBIOME?

Many factors influence the status of a gut microbiome. The largest shifts in the gut microbiome result from an animal's presentation at birth (vaginal or surgical delivery), age, sex, diet, environment, genetics, and receipt of antimicrobial drugs.[3,11] In addition, dysbiosis can result from repeated administration of antimicrobials to patients with chronic conditions.[12] The 3 most common types of dysbiosis in the gut microbiome are missing common microbes, overgrowth of potentially pathogenic bacteria, or an imbalance or loss in the density of common microbes. Types of dysbiosis are not mutually exclusive and can exist at the same time.[13]

MICROBIOME-TARGETED THERAPY EFFECTS ON DYSBIOSIS

Type 1: Missing Common Microbes

In patients with gut dysbiosis caused by missing microbes, the goal is to rebalance the microbiome by replacing the specific lost microbes in the gut. The species of missing bacteria need to be identified and their normal functions in the body understood. Knowledge of the species can be used to determine whether the missing bacteria are beneficial or potentially pathogenic. For example, *Clostridium hiranonis* is a key bacterium necessary for transforming primary bile acids into secondary bile acids. Bile acids are compounds made in the liver that, among other beneficial functions, block the growth of pathogens. Thus, loss of *Clostridium hiranonis* bacteria can result in bile acid–associated diarrhea.[3]

Probiotic therapy: Currently, probiotic administration is not effective for treating missing microbes because probiotics do not contain, or contain only a few, species-specific resident microbes common in animals. Probiotics are unable to replace all missing species of bacteria.[3]

Fecal microbiota transplantation: The current key to correcting missing microbes is FMT. A healthy donor animal should shed normally functioning species-specific microbes in its feces. FMT material contains the full collection of normal microbes; although fecal transplantation replaces the missing microbes, thereby correcting the dysbiosis, it also introduces other metabolites, waste, and toxins. Thus, to ensure that an animal is a viable donor candidate, its health status and ongoing history must be continually monitored.[7]

Type 2: Overgrowth of Pathogenic Bacteria

With regard to microbiome balance, not all bacteria are either strictly beneficial or harmful. The key to good health is a gut microbiome that contains a wide variety of many categories of microbes.[13] A higher concentration of beneficial bacteria does not necessarily result in a healthier animal; many bacteria have a beneficial effect when they are part of a balanced microbiome but can have a harmful effect when a select few outcompete and cause a microbiome imbalance. Outcompeting is the displacement of other species in competition for resources. Outcompeting can be used as a therapy to reduce the level of overgrown bacteria and help correct the gut microbiome imbalance.[14] It involves supplying a larger amount of 1 or more strains of beneficial bacteria that will compete for space and nutrients. The overgrown bacteria will not be able to sustain their level of growth as they lose nutrients and are unable to replicate.

Probiotic therapy: For patients experiencing overgrowth of pathogenic bacteria, probiotics work in an outcompete model in which the microbes (bacteria or fungi) in the probiotic help outcompete unfavorable overgrown microbes in the gut. The goal of administering a probiotic is to elicit a beneficial change in the patient's gut microbiome. After probiotic administration is discontinued, probiotics should leave (not colonize) the gut, enabling the beneficial resident microbes to flourish without further support from the probiotic. Another way probiotics outcompete is by changing the environment to be less favorable to undesirable microbes. For example, lactic acid bacteria can decrease the environmental pH of the microbiome. A more acidic environment decreases the ability of some resident microbes to function effectively, thereby enabling the lactic acid bacteria to thrive. Thus, administration of probiotics containing lactic acid bacteria may reduce the numbers of unfavorable overgrown bacteria.[15] However, to enable resident microbes to reestablish to normal levels, probiotic administration may need to be discontinued; otherwise, the probiotic microbes may continue to outcompete all the resident microbes in the gut, thereby becoming the overgrown strain and unfavorable bacteria. Further

TABLE 1 Comparison of Microbiome-Targeted Therapies

FEATURES	PROBIOTICS	FMT	ADDITIONAL INFORMATION
Contains bacteria and/or yeast	✓	✓	• Probiotics contain bacteria or yeast to complete specific functions. • FMT material contains multiple organisms that are expected to complete normal functions of a healthy pet.
Contains compounds other than bacteria and yeast	×	✓	• FMT material contains endogenous material, including some microbial metabolites.
Able to outcompete resident flora	✓	✓	• Large amounts of microbes outcompete current microbiota for space and nutrients. • More studies are needed to know if probiotics are outcompeting normal microbiota in pets.
Contains species-specific microbes	×	✓	• FMT microbes complete normal functions and may colonize to restore normal microbiota. • Probiotics should not colonize or remain after administration has stopped.
Can correct all 3 types of dysbiosis	×	✓	• Only FMT is able to replace missing species-specific bacteria at this time.
Requires strict screening	×	✓	• FMT donors should be frequently screened for microbial balance and pathogen levels. • Probiotics are not regulated. Ensure research is species-specific.

FMT = fecal microbiota transplantation

When considering probiotic use, identifying the species of bacteria is imperative to ensure that the patient experiences beneficial, not harmful, effects.

research is needed to determine the appropriate types of bacteria and duration of therapy needed to manage this type of dysbiosis with currently available probiotics.

Fecal microbiota transplantation: The goal of transplanting large doses of FMT material into patients with a microbiome experiencing an overgrowth of pathogenic bacteria is to directly rebalance the microbiome by introducing beneficial species-specific microbes that can outcompete the less desirable microbes. Similar to probiotics, outcompeting by the microbes in FMT material will reduce space and nutrients for the undesirable microbes, reducing their ability to continue to replicate. A main advantage of using FMT therapy over probiotic therapy is the higher density (total number) of species-specific microbes in FMT material. In addition, probiotics containing multiple microbes (usually 1 to 3 genera) do not contain the diversity of fecal microbiota (usually ≥25 genera) in FMT material.[10]

Type 3: Imbalanced Microbiome

Animals with an imbalanced microbiome dysbiosis have all the right microbes, but microbe density or concentration is not balanced. For patients with this type of dysbiosis, microbiome-targeted therapies can decrease associated signs/symptoms. Probiotics and FMT can each help rebalance the microbiome but can also support a patient with an imbalanced microbiome in other ways. Microbial metabolites can have both beneficial and harmful effects, which may change, depending on the level at which they are produced.[3] A collection of metabolites is called a metabolome. A patient with an imbalanced microbiome can experience imbalanced metabolite and metabolome production, and a shift in the volume of metabolites in a metabolome can affect a patient's health. Inflammatory, neurologic, and/or behavioral signs/symptoms may decrease the patient's health and/or quality of life.

Probiotic therapy: Some probiotic strains are administered to create a large beneficial metabolome. Through production of beneficial metabolites, such as short-chain fatty acids, probiotics can decrease signs/symptoms associated with an imbalanced microbiome, improve immune function, and decrease inflammation.[16] When considering probiotic use, identifying the species of bacteria is imperative to ensure that the patient experiences beneficial, not harmful, effects. Veterinary professionals should use products from reputable companies that have completed research on the strain(s) of microbes in their product and that follow strict production quality control guidelines.[17]

Fecal microbiota transplantation: FMT material contains residual metabolomes along with a variety of microbes able to create multiple metabolomes. Benefits of administering FMT material are that the metabolomes produced will contribute to normal function in a healthy gut and that the microbes will rebalance the state of the gut microbiome.[18]

SUMMARY

Before prescribing an antimicrobial drug for a patient with GI signs/symptoms, veterinary professionals should consider the functions of the gut microbiome. Identifying the type of dysbiosis a patient is experiencing will help indicate the best microbiome-targeted therapy to resolve the associated signs/symptoms and their cause. The type and severity of the dysbiosis indicate which product can best support the components of the gut microbiome, improve barrier function, increase production of beneficial metabolites, and correct the dysbiosis.

At this time, there are no probiotics to replace all common missing resident bacteria; rather, probiotics serve the purposes of outcompeting and producing beneficial metabolites. Recommended probiotics should have undergone species-specific studies, include species-level microbes, and should be prescribed according to the desired outcome. FMT material has the potential to better support microbiomes that are missing microbes and to correct microbial diversity that has become unbalanced, particularly after antimicrobial use. However, FMT material carries the risk of transferring unidentified components, which may or may not be harmful to the recipient, thereby emphasizing the value of completing the rigorous and sometimes difficult task of donor selection. The best

way to ensure safety and positive outcomes for FMT material recipients is to extensively and frequently screen potential donors. TVN

References

1. Jugan MC, KuKanich K, Freilich L. Clinical response in dogs with acute hemorrhagic diarrhea syndrome following randomized probiotic treatment or fecal microbiota transplant. *Front Vet Sci*. 2023;10:1050538. doi:10.3389/fvets.2023.1050538
2. Wernimont SM, Radosevich J, Jackson MI, et al. The effects of nutrition on the gastrointestinal microbiome of cats and dogs: impact on health and disease. *Front. Microbiol*. 2020;11:1266. doi:10.3389/fmicb.2020.01266
3. Pilla R, Suchodolski JS. The role of the canine gut microbiome and metabolome in health and gastrointestinal disease. *Front Vet Sci*. 2020;6:498 doi:10.3389/fvets.2019.00498
4. Hill C, Guarner F, Reid G, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11:506-514. https://doi.org/10.1038/nrgastro.2014.66
5. Suchodolski JS. Probiotics, prebiotics, synbiotics, and intestinal health of dogs and cats. *Todays Vet Pract*. 2020;10(4):24-27.
6. Lin CY, Alexander C, Steelman AJ, Warzecha CM, de Godoy MRC, Swanson KS. Effects of a *Saccharomyces cerevisiae* fermentation product on fecal characteristics, nutrient digestibility, fecal fermentative end-products, fecal microbial populations, immune function, and diet palatability in adult dogs. *J Anim Sci*. 2019;97(4):1586-1599. doi:10.1093/jas/skz064
7. Chaitman J, Jergens AE, Gaschen F, et al. Commentary on key aspects of fecal microbiota transplantation in small animal practice. *Vet Med (Auckl)*. 2016;7:71-74. doi:10.2147/VMRR.S105238
8. Niederwerder MC. Fecal microbiota transplantation as a tool to treat and reduce susceptibility to disease in animals. *Vet Immunol Immunopathol*. 2018;206:65-72. doi:10.1016/j.vetimm.2018.11.002
9. Saar R, Dodd S. Current methods for microbiome analysis. In: *Small Animal Microbiomes and Nutrition*. Wiley Blackwell; 2023:100-107.
10. Ganz HH, Jospin G, Rojas CA, et al. The kitty microbiome project: defining the healthy fecal "core microbiome" in pet domestic cats. *Vet Sci*. 2022;9(11):635. https://doi.org/10.3390/vetsci9110635
11. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. *Peer J*. 2019;7:e7502. doi:10.7717/peerj.7502
12. Queen J, Zhang J, Sears CL. Oral antibiotic use and chronic disease: long-term health impact beyond antimicrobial resistance and *Clostridioides difficile*. *Gut Microbes*. 2020;11(4):1092-1103. doi:10.1080/19490976.2019.1706425
13. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. *Cell Microbiol*. 2014;16(7):1024-1033. doi:10.1111/cmi.12308
14. Stubbendieck RM, Straight PD. Multifaceted interfaces of bacterial competition. *J Bacteriol*. 2016;198(16):2145-2155. doi:10.1128/JB.00275-16
15. Wang Y, Wu J, Lv M, et al. Metabolism characteristics of lactic acid bacteria and the expanding applications in food industry. *Front Bioeng Biotechnol*. 2021;9:612285. doi:10.3389/fbioe.2021.612285
16. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol*. 2013;6(1):39-51. doi:10.1177/1756283X12459294
17. Weese JS, Martin H. Assessment of commercial probiotic bacterial contents and label accuracy. *Can Vet J*. 2011;52(1):43-46.
18. Wu R, Xiong R, Li Y, Chen J, Yan R. Gut microbiome, metabolome, host immunity associated with inflammatory bowel disease and intervention of fecal microbiota transplantation. *J Autoimmun*. Published online May 27, 2023. doi:10.1016/j.jaut.2023.103062

Robin Saar

Robin is a registered veterinary technologist with a VTS certification in nutrition. Her professional experience includes working in small and mixed animal practices as an RVT and a practice manager and developing a nutrition program for a veterinary corporation. Robin has published peer-reviewed articles and recently coauthored a textbook dedicated to small animal microbiomes and nutrition. Robin is the customer services manager at AnimalBiome, education director for the Canadian Academy of Veterinary Nutrition, president-elect for the Academy of Veterinary Nutrition Technicians, and a member-at-large of the American Academy of Veterinary Nutrition. Robin is in the process of completing an MSc degree in animal nutrition at Glasgow University.