

PROBIOTICS: ENHANCING GASTROINTESTINAL HEALTH

A ROUNDTABLE DISCUSSION

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Dr. Arleigh Reynolds: Today we'll be discussing probiotics and guidelines for their use. To start I'll offer a working definition of the term *probiotic*: a viable organism that when ingested transiently becomes part of the gut microflora and exerts beneficial effects. These effects include the prevention and treatment of a number of gastrointestinal (GI) disorders, the stimulation of immunity, and inhibition of colonic carcinogens. Let's begin our discussion with a summary of the types of patients you each see, the most common causes of GI upset, and the role probiotics might play in these conditions.

CONSIDERATIONS IN SELECTING A PROBIOTIC

Dr. Kenneth Simpson: Inflammatory bowel disease (IBD) is the most common GI disorder I see in cats and dogs.

Dr. Susan Wynn: I see a mixture of primary and referral cases of GI parasitism, dietary indiscretion, exocrine pancreatic insufficiency, and IBD. A common GI problem I find is drug-induced diarrhea, especially associated with antibiotics. In those cases I use probiotics with great success. I also use probiotics for immune-mediated diseases, simple atopic disease, and food allergies.

Dr. Deb Zoran: At Texas A&M, I work entirely with cats—mostly referral cases. The most common GI cases I see are diarrhea in kittens and IBD in adult cats. Probiotics are useful in these conditions.

Dr. Stan Marks: I treat a number of patients with both acute gastroenteritis and chronic diarrhea. I think probiotics are most efficacious in dogs and cats that

PROBIOTICS

are relatively healthy, have not lost significant amounts of body weight, and do not have severe bowel disease characterized by anorexia, intractable vomiting, severe compromise of the intestinal mucosal barrier, and abdominal effusion. I believe probiotics will play an important role in managing patients with IBD as part of a multipronged approach. They are a newer therapeutic agent in our armamentarium that can be used along with dietary and pharmacologic therapy.

MODES OF ACTION

Reynolds: Before we delve into how probiotics can be used, let's first discuss how they work. Can you describe what probiotics do in the gut? What are the modes of action?

Zoran: Probiotics have a two-pronged effect. One is associated with the presence of a live microorganism in the intestinal tract that competes with, crowds out, and inhibits pathogens down there. Probiotics are also associated with immune modulation, which might be helpful in IBD.

Wynn: There is another effect, too. Probiotics have intraluminal effects on other bacterial populations and direct effects on the gut epithelial barrier.

CONSIDERATIONS IN SELECTING A PROBIOTIC

Reynolds: If you wanted to recommend a probiotic, what would you look for?

Simpson: The probiotic has to come from a reputable source. You want studies behind the product to show that it works—that it survives in the intestinal tract, modulates the immune response, and works effectively in well animals. Two products that have been shown to do this are *Lactobacillus acidophilus* strain DSM13241 and *Enterococcus faecium* strain SF68.

Wynn: I look for a probiotic product that gives a predictable daily dosage of at least 1×10^9 CFU/g. Pet foods that contain probiotics may lose stability if they sit on the shelf too long, and that can decrease the dosage the animal receives, so I use only capsules and sprinkles.

Zoran: The key point for me is the probiotic's track record. I want data to show that the organism

will survive, that it will not colonize for any length of time after the supplement is discontinued, and that it isn't antibiotic-resistant. *E. faecium* and the lactobacilli have that lengthy history.

Marks: The problem with most commercially available probiotics is that there is no federal regulation determining the quality of the product. A client could pick up a probiotic from a store with a different species of microorganism than what's listed on the label, the product could contain low numbers of the microorganism, or the product could contain species that are pathogenic. The most important characteristics of an effective probiotic are viability, the ability to survive the acidic milieu of the stomach, the ability to colonize the intestinal tract, safety, and the inability to transfer resistance genes. The benefits of utilizing a probiotic that has withstood the rigors of time and scrutiny by researchers in the field cannot be overemphasized.

USING PROBIOTICS PROPHYLACTICALLY AND THERAPEUTICALLY

Reynolds: What are your experiences with probiotics for prevention and treatment? What do you expect in terms of time frame and response?

Wynn: Prevention is an interesting subject. I have started recommending probiotics to puppy owners at weaning. When I see puppies at six to eight weeks, I tell their owners to give them a mixture of different probiotics.

Zoran: I am also a believer in the preventive side—for example, using probiotics in kittens to prevent giardiasis. However, I don't recommend them for the really sick guys—cases of hemorrhagic gastroenteritis, parvovirus, and severe dietary indiscretion. We don't have the data to support their use in those situations.

Simpson: Patient selection is important. I would choose to use probiotics in healthy animals with chronic gastrointestinal disease and modulate the diet if necessary.

Zoran: I have no problem whatsoever using probiotics in relatively healthy animals with chronic or acute diarrhea, or animals experiencing diarrhea while receiving an antibiotic. Maybe we should start giving probiotics before the antibiotic-associated

diarrhea begins, but we don't always see the patient at that point.

Marks: I have used the *E. faecium* product in a small number of dogs and *Lactobacillus* strain GG in a handful of patients as well. I think it is reasonable to use probiotics in relatively healthy animals with diarrhea, whether acute or chronic. Good examples of prophylactic and therapeutic applications include animals with stress-associated diarrhea, animals with antibiotic-associated diarrhea, and animals with IBD. For the latter, it seems prudent to include the probiotic as part of a multipronged therapeutic approach, which would include dietary intervention and immunomodulatory therapy if warranted.

Simpson: In dogs with chronic IBD, I tend to use dietary modulation and then antibiotics. But if a patient is healthy enough, I may start trying probiotics initially rather than antibiotics.

CONTRAINDICATIONS FOR PROBIOTIC USE

Reynolds: What are your recommendations in terms of safety?

Simpson: Severe cases with evidence of bacterial translocation from the gut are at risk for sepsis. I would be wary of using probiotics in these patients. Dogs with parvovirus infection and cats with panleukopenia are our poster children for GI translocation and sepsis risk. While the benefits of probiotics in these patients could be spectacular, the risks could also be severe.

Zoran: Another situation in which to avoid probiotics is aggressive large-cell lymphoma of the GI tract in which you are giving chemotherapy. *Salmonella* infection might also be a concern—you have to consider translocation issues.

Reynolds: Dr. Marks, you do a lot of work with chemotherapy patients. What is your opinion?

Marks: I have the same reservations that Dr. Zoran does. With chemotherapy, not only are we using drugs that alter the integrity of the mucosal barrier, we are significantly immunocompromising the patient as well. The same concerns apply to patients with a compromised intestinal mucosal barrier given a probiotic such as *S. boulardii*, which could result in systemic fungemia if the patient is severely immunocompromised. The bottom line is that I would be extremely reluctant to use probiotics in patients that are severely immunocompromised, are receiving enterotoxic chemotherapeutic agents, or that have parvovirus enteritis, intestinal salmonellosis, or infection with similar enteropathogens.

PROBIOTICS VS. YOGURT

Reynolds: Another question: What do you think of yogurt as an alternative to probiotics?

Wynn: I haven't seen dramatic effects. My clients can give yogurt if their pet doesn't need high probiotic doses, but for a therapeutic effect I recommend a product specifically for predictable numbers and viability of the probiotic organism.

Marks: All yogurt is not created equal. There's pasteurized yogurt with heat-killed bacteria and nonpasteurized yogurt with live cultures of bacteria such as *Streptococcus thermophilus* and *Lactobacillus delbrueckii* sp. *bulgaricus*. Most studies have shown better lactose digestion and absorption in subjects who consumed yogurt with live cultures, as well as reduction of gastrointestinal symptoms. We should note that there are more than 10 species of *Lactobacillus*, some of which can be pathogenic and some of which are nonpathogenic and are used as probiotics.

I want data to show that the probiotic will survive, that it will not colonize after the supplement is discontinued, and that it isn't antibiotic-resistant. *E. faecium* and the lactobacilli have that lengthy history.

—DEB ZORAN, DVM, PhD, DACVIM

Simpson: I don't typically recommend or use yogurt, and I haven't heard many success stories.

Wynn: However, it has been observed that populations that eat a lot of yogurt or other fermented foods have longer life spans. In my native Southeast we drink buttermilk, and sauerkraut is a fermented food. So I don't have a problem with fermented foods for prevention or giving low-dose yogurt on a daily basis to these pets. But that's different from a therapeutic use.

RECOMMENDING PROBIOTICS: PRACTICAL CONSIDERATIONS

Reynolds: Let's get as practical as we can. How would you position probiotics for clients or recommend them for practitioners?

Zoran: My current best recommendation is that probiotics are most helpful in young animals: puppies or kittens that are just starting new diets, that may have parasites, or that may have bacterial or viral disease. You may be able to improve their GI immune systems and their bacterial situation and help prevent or lessen the severity of disease. Also, probiotics might be useful in animals about to receive antibiotics that are known to affect GI flora and produce diarrhea. We are also starting to get some data showing that probiotics reduce clostridia numbers, so if an animal has a tendency to experience boarding- or stress-induced diarrhea, probiotics might be very useful. I would be more hesitant to suggest routine probiotics with severe diseases like IBD because we need to learn more, but I am excited about their potential use in this area.

Marks: I would tell practitioners that we want a viable microorganism present in sufficient quantities to survive the acidic environment of the stomach, survive transit to the small intestine, attach and colonize in the distal small bowel and colon, and exert a beneficial effect on the host. We want cats or dogs that are relatively healthy and stable and that have a relatively normal appetite. Kitten diarrhea is one area where we really could have a positive impact. In addition, probiotics could be used effectively for antibiotic-associated diarrhea, stress colitis, and perhaps patients with IBD. Based on the literature and the work that Nestlé Purina has done, I would give a

probiotic in the amount of 1×10^8 CFUs per gram once a day.

Simpson: In healthy pets, we can emphasize the safety of probiotics because a number of long-standing trials have shown no significant adverse effects.¹⁻³

Wynn: In my clinic I tend to think of two broad indications for probiotics: acute conditions such as stress- and antibiotic-associated diarrhea, dietary indiscretion, and diet changes; and conditions that may damage the gut. I know we are mostly discussing healthy animals, but animals that have been on long-term NSAIDs, prednisone, or other drugs that can damage the gut barrier may also benefit.

POTENTIAL INDICATIONS FOR PROBIOTIC USE

INFLAMMATORY BOWEL DISEASE

Reynolds: Dr. Simpson, can you comment further on using probiotics with IBD?

Simpson: With IBD the rationale is to modulate the local and systemic inflammatory response and modulate the flora that drive that inflammatory response in susceptible individuals. Probiotics haven't produced adverse effects in an 18-week trial of healthy dogs (unpublished data, Nestlé Purina, 2006). So I am ready to start probiotics with some of my relatively healthy IBD dogs to see if they will have an effect.

Reynolds: What species would you choose?

Simpson: *E. faecium* and *L. acidophilus* would be my choices because they have been studied.

Marks: I haven't seen a significant impact with probiotics, at least initially, in my IBD patients that are systemically ill, vomiting and having diarrhea. I have to modulate their regular diet, put them on immunosuppressive therapy, and add an antibiotic like tylosin or metronidazole. If those patients' clinical signs resolve, then I might introduce a probiotic and hope to maintain a more durable clinical remission.

Simpson: Maintaining remission of IBD might be a more achievable goal than treating with probiotics alone.

INFECTIOUS ENTERITIS

Reynolds: Our next topic is infectious enteritis. What is the rationale for using probiotics in these cases?

Marks: Caution should be heeded when giving probiotics to animals with infectious enteritis. As previously mentioned, I would be reluctant to use probiotics in animals with severe parvovirus enteritis; however, a probiotic might enhance recovery in an animal with a milder and less virulent disease caused by enteric coronavirus. This is different from using a probiotic in the management of IBD, where we might induce remission first and then introduce the probiotic to sustain the remission.

Zoran: Giving probiotics ahead of time in high-risk environments such as shelters and boarding situations probably has the greatest chance of making a difference with infectious enteritis—as opposed to using probiotics after diarrhea has already started.

Reynolds: Dr. Wynn, what would you recommend to clients regarding the type of probiotic bacteria to use, the timing of administration, and the duration of treatment?

Wynn: *E. faecium* is well-investigated and a good choice, especially with stress-related clostridial diarrhea. I tell clients to give it once or twice a day—and not just for three days. If we are trying to establish a better intestinal flora balance, we have to give it for two to four weeks. And to echo what has been said, I would not currently recommend probiotics for a very sick parvovirus case.

Reynolds: Would you consider using them in the resolution phase of parvovirus infection?

Wynn: Absolutely.

DRUG-ASSOCIATED DIARRHEA

Reynolds: How about using probiotics to manage medication-related intestinal issues, whether due to antimicrobials, chemotherapeutic agents, or NSAIDs? What is the rationale for treatment?

Wynn: For antibiotic-associated diarrhea, human products with *Lactobacillus* GG are effective. We also have evidence for the effectiveness of *E. faecium* SF68. I use these products for at least two weeks but longer in patients undergoing chemotherapy or other long-term immunosuppressive treatments. I also use probiotics in dogs receiving long-term drugs that will damage the mucosal barrier, such as NSAIDs.

Reynolds: Do you use probiotics at the onset of drug therapy?

Wynn: Generally patients come to me when they have been on these drugs for months to years. I can't describe it objectively—they

just don't look as good as they should. In these cases probiotics are part of the treatment. In my mind I'm helping maintain the mucosal barrier in the face of insult.

Marks: Antibiotics are among the most abused medications in veterinary medicine, and antibiotic-associated disorders are more common than one might think. But it's not always overt diarrhea that results. It may be a decrease in appetite, or the animal may feel blah or punkish while on the antibiotics. Secondary signs such as increased borborygmus and abdominal discomfort might also ensue.

Wynn: Many cases of antibiotic-associated diarrhea will resolve as the dog eats dirt and licks other dogs—I just wonder how fast they will respond on their own. At least one of my chronic

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—SUSAN G. WYNN, DVM

PROBIOTICS

diarrhea cases resolved with no other treatment besides probiotics. The dog had been receiving tylosin and metronidazole off and on for months, but it was not on an antibiotic when I saw it. It responded to probiotics within 24 hours—there was no doubt about it. So I do think it's important to try a probiotic by itself. I also believe that probiotics help some dogs who feel, as Dr. Marks says, punkish on antibiotics. With concurrent therapy, I tell clients to give the probiotic and antibiotic at different times of day and to use probiotics for at least two weeks after antibiotic therapy concludes.

Reynolds: Do you make a specific recommendation in terms of number of doses per day?

Wynn: Antibiotics are usually given twice or three times daily, so I feel lucky getting the probiotic in once a day during antibiotic therapy.

Zoran: Cats with toxoplasmosis have to be treated with high doses of clindamycin or another antibiotic that's rough on the GI tract. Those are automatic diarrhea cases. I have used probiotics at the start of antibiotic therapy to see if they would make a difference, but I don't have a strong sense yet because we haven't done it often enough. If you have to give a certain antibiotic and you want to ameliorate a problem you know is coming, probiotics may be helpful.

Marks: I don't think we are proactive enough in considering probiotics for patients receiving antimicrobial therapy. Why wait until the animal has a problem to give the probiotic?

WEANING

Reynolds: Any comments on using probiotics for weaning and soft stools in puppies and kittens?

Zoran: I can see using probiotics in young puppies and kittens being weaned onto solid food—the flora is being altered by the new diet.

It appears that kittens and puppies on *E. faecium* probiotics have less diarrhea during the stress of weaning and diet change.

Reynolds: Is there an age below which you don't feel comfortable using probiotics?

Simpson: I probably would not give them until the puppies or kittens were weaned.

Wynn: I see most patients for the first time at weaning, so I do recommend they start probiotics then. I might start sooner if I saw them earlier, but I am not brave enough to do it before three weeks. This is just a personal theory, but I'd like to see them develop some level of immunocompetence before supplementing with live organisms.

Also, in general practice we see patients that frequently change diets.

I know I buck the trend, but I

recommend that people not use one maintenance diet but offer a little variety over the life of a pet. In my discharge instructions I tell clients to use a probiotic for two weeks with every diet change and, if necessary, change foods gradually.

Zoran: Many diet changes trigger bacterial changes, which result in persistent diarrhea. Then we give antibiotics and alter the flora even more. That's an area where probiotics could be extremely useful.

STRESS-RELATED DIARRHEA

Reynolds: What are some of the etiologic factors that lead to stress-related diarrhea?

Simpson: German shepherds in the military experience stress-induced diarrhea, which is thought to be clostridial. It's a huge problem.

Reynolds: What application could probiotics have in those dogs?

Simpson: I would give the probiotics we know

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—STAN MARKS, BVSc, PhD, DACVIM, DACVN

about—*E. faecium* or *L. acidophilus*—for two to three weeks to see if there was an effect.

Wynn: Stress-related diarrhea is a huge problem in dogs that lose companions or whose owners travel. Some cats experience the same thing. And boarding is a factor. Those are the situations in which I see the most stress-related diarrhea. In my practice, probiotic therapy is a cornerstone for those patients, especially if the diarrhea is associated with clostridial overgrowth.

Reynolds: Do you use probiotics preventively if you know an animal will be boarding?

Wynn: Yes. And if they travel or the owners travel. This preventive approach has worked really well in my practice.

Simpson: Prophylactic probiotics in situations like high-stress kenneling might be a strategy for preventing stress-related clostridial colitis.

Marks: Stray cats and dogs are often stressed and malnourished, and when they are put into a crowded shelter they are likely to acquire an upper respiratory or intestinal infection. Perhaps those animals could receive a prophylactic course of probiotics for a period of time to minimize the likelihood of contracting an infection.

Simpson: Dr. Reynolds, we know that Alaskan sled dogs are massively predisposed to GI barrier damage. Have you used probiotics in those heavy-stress dogs?

Reynolds: In Alaska we have done a few pilot studies with client-owned sled dogs but haven't published anything yet. These dogs are stressed and exposed to pathogens from around the world—we have put them on probiotics for the entire racing season. We have seen significant positive effects prophylactically and therapeutically; probiotics have helped the diseases resolve. We are continuing to study this area and it looks promising.

Marks: I think stress diarrhea is a Pandora's box, and we have ignored it for too long. Probiotics have a potentially important role to play in this disorder. I would start giving them a

week before an animal was going to be kenneled or experience a change in environment, maintain the probiotic throughout boarding or during travel, and continue it for several more days after the animal has returned home from the kennel.

IMMUNOLOGIC DISEASE

Reynolds: Does anyone have any thoughts about the potential use of probiotics in immune-mediated diseases, particularly atopy?

Simpson: There are human studies that support their use in atopic dermatitis, but we have no good studies in veterinary medicine. It is an avenue that could be pursued. Most of those dogs are otherwise healthy. They don't have GI barrier damage, so they might be good candidates.

Wynn: I use probiotics in many patients with immune-mediated disease as part of a multimodal approach. I can't say that it's making a dramatic difference alone, but based on the human studies I have been using *Lactobacillus* GG, mostly for food allergies, atopy, and autoimmune diseases—although probiotics mixed with a carrier-containing protein should not be given to animals with allergies to those proteins. Regarding more serious immune-mediated disease, my own dog has pemphigus erythematosus, so I have been using probiotics along with her other treatments, and I believe I'm getting good results. She is safely maintained on a very low dose of an immunosuppressive drug.

Reynolds: Thank you all for your time and expertise. It is apparent from this discussion that probiotics have the potential to become an important modality in the prevention and treatment of many clinical conditions. It is also apparent that our application of this modality will continue to develop as our knowledge of its mechanisms of action grows in depth and scope.

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PROBIOTICS

POTENTIAL APPLICATIONS FOR PROBIOTIC THERAPY IN DOGS AND CATS

CONDITION	RATIONALE	CONSIDERATIONS	
Stress-related diarrhea	May be effective when dogs are boarding or traveling.	Probiotics can be used prophylactically in stressful situations.	
	May be used in working dogs, high-risk colony situations, and shelters to alleviate diarrhea.	May need to give for two to four weeks.	
Weaning and soft stools in puppies and kittens	Probiotics may enhance gut health in young puppies or kittens as they transition to solid-food diets.	Don't give probiotics before 3 weeks of age.	
Medication-related problems <ul style="list-style-type: none">• Antimicrobial therapy (short- and long-term)• Long-term NSAID or steroid therapy	Patients are prone to diarrhea caused by disruptions of flora; probiotics help restore natural gut flora.	Probiotics can be given prophylactically along with antibiotic therapy (administer at a different time of day than antibiotic).	
	May reduce the development of resistant bacteria if fewer antibiotics are used.	Besides diarrhea, signs of antibiotic-related problems may include poor coat condition and decreased appetite.	
	May prevent the need to change antibiotics or use other drugs to resolve diarrhea.		
Dietary change or indiscretion	Probiotics may decrease inflammation and reduce the need for some anti-ulcer and anti-inflammatory agents.		
	May help restore normal microbial balance in the small and large intestine, decreasing the incidence of diarrhea, vomiting, and lethargy.	Use probiotics prophylactically in conjunction with dietary changes.	
Food intolerance, maldigestion	Patients often have intestinal microflora imbalance due to food intolerance or maldigestion or malabsorption.	Use probiotics in conjunction with dietary changes.	
Inflammatory bowel disease (IBD)	IBD therapy includes steroids, immunosuppressive drugs, antibiotics, and diet changes—all of which may adversely affect normal gut health; modulation of intestinal microflora through probiotic supplementation may alleviate local and systemic inflammation.	Best candidates are animals that have no other problems besides IBD.	
	Evidence in human medicine suggests that IBD remission can be maintained with probiotics and that probiotics may reduce the need for immunosuppressants.		
Infectious enteritis <ul style="list-style-type: none">• Viral (coronavirus, parvovirus, panleukopenia virus)• Bacterial (<i>Clostridium</i> species)• Protozoal (<i>Giardia</i> species, <i>Cryptosporidium</i> species, <i>Trichostrongylus axei</i>)	May aid recovery.	Probiotics are contraindicated during acute stages of canine parvovirus infection and feline panleukopenia.	
	May prevent diarrhea resulting from chronic antibiotic therapy.		
	May be particularly effective for giardiasis in kittens.		
Immunologic disease	Studies in people support the use of probiotics in atopic dermatitis cases.		