

Rethinking our approach to diarrhea: when and why to consider prebiotics, probiotics and antibiotics

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Diarrhea is a common presenting complaint in small animal practice. Though acute diarrhea in many cats and dogs is self-limiting, the inconvenience caused by a pet's diarrhea often prompts veterinary visits. In one study diarrhea was the reason for 3% of all canine veterinary consultations and 2% of all feline veterinary consultations.¹ In the same study, 50% of patients presenting with diarrhea were prescribed metronidazole, 8% endoparasiticides, and 61% gastrointestinal nutraceuticals such as probiotics.¹ Despite the high rate of metronidazole prescribing, only diet modification and GI nutraceuticals were associated with resolution of diarrhea.¹ The usefulness of metronidazole for treatment of acute diarrhea has recently been called into question.² An increased understanding of the intestinal microbiota, the population of microorganisms in the gut, suggests that we should shift our focus from simply a return of stool quality towards a return of a healthy microbiota for dogs and cats with diarrhea.

Microbiome

Much of what is known about the intestinal microbiota is specifically focused on bacterial populations in the intestines. Molecular techniques allow investigation beyond those that are easily culturable, thus the focus on the microbiome, or the genomes of the microbes that inhabit the GI tract. Investigations of the human microbiome have shown that effects are far-reaching and include brain, kidney and immune health and metabolism and weight, to name a few. Within the gut, the microbiome is important for host defense and prevention of pathogen colonization, maintenance of gut function, antioxidant and anti-inflammatory activity and metabolism.

Colonization of the intestines with microorganisms begins during the birthing process when newborns interact with maternal microbes in the birth canal, the mother's skin and oral cavity and microbes in the environment. The microbiome becomes more diverse and stable with age. Though bacterial diversity is associated with a healthy microbiome, it is the function of the microbiome that is important for gut and overall health.

Bacterial metabolites and fermentation end products have various effects within and outside of the intestine. For example, short chain fatty acids (SCFAs) such as acetate, propionate and butyrate, the main metabolites of dietary fibers and resistant starch fermentation in the colon, function as trophic factors in the gut and maintain gut barrier function by supporting mucus production by Goblet cells.³ SCFAs also help to prevent pathogen engraftment and to increase regulatory T cells and tolerogenic dendritic cells within the lamina propria, thus serving to decrease intestinal inflammation.³ The microbiome also provides energy. SCFAs contribute up to 10% of resting energy requirements in the adult.

Colonic bacteria produce secondary bile acids, which prevent proliferation of pathogenic bacteria and aid in decreasing inflammation. In dogs, *Clostridium hiranosis* is important for formation of these secondary bile acids.⁴ Bile salts released into the duodenum are absorbed in the small intestine, but some traverse to the colon where they are first deconjugated to primary bile acids and then dehydroxylated to secondary bile acids (deoxycholic acid and lithocholic acid).

Dysbiosis

Aberrant alterations to the gut microbiome, or dysbiosis, can have impacts within and beyond the GI tract. There are many potential causes of dysbiosis, including infection, inflammatory diseases, dietary indiscretion and antimicrobials. Whether dysbiosis is transient or persistent depends upon the age of the animal, the degree of dysbiosis and the chronicity of the disturbance.⁵ Dysbiosis commonly is associated with decreased bacterial diversity, including a decrease in beneficial bacteria such as Fusobacteria, Bacteroidetes, and some Firmicutes. Additionally, pathogenic bacteria, such as *E. coli* in inflammatory bowel disease or *C. perfringens* in acute diarrhea, may increase.^{6,7}

A measure of dysbiosis has been established by the Gastroenterology Laboratory at Texas A&M University. This measure, called the dysbiosis index, includes a synthesis of measurements of many bacterial groups that are altered in patients with gastrointestinal disease.⁸ These include decreases in Fusobacterium and *Clostridium hiranosis*, among others, and increase in *E. coli* and *Streptococcus*. Dysbiosis index values greater than 2 indicate dysbiosis, while those less than 0 reflect a normal microbiome.⁹

Use of Antibiotics

A recent study in dogs with acute diarrhea showed that there was no significant difference in time to clinical resolution of acute diarrhea between dogs treated with metronidazole and those treated with a placebo.¹⁰ This finding was supported in another study comparing metronidazole to probiotics and placebo in treatment of acute diarrhea in dogs.² Thus the use of metronidazole in the treatment of acute diarrhea is not supported, as it does not hasten recovery compared to probiotics or no treatment.

Metronidazole has been recently shown to cause dysbiosis in healthy dogs.¹¹ Dogs were given metronidazole for 2 weeks and changes to the microbiome and its metabolome were evaluated during treatment and for 4 weeks after cessation of metronidazole. Metronidazole resulted in decreases in microbiome richness and diversity and secondary bile acids and an increase in dysbiosis index, disturbances that lasted at least 4 weeks after discontinuation of antibiotic in some dogs.¹¹

Even in cases of acute hemorrhagic diarrheal syndrome (AHDS, formerly known as hemorrhagic gastroenteritis), antibiotics are seldom needed. In a prospective, placebo-controlled study of dogs with AHDS, treatment with amoxicillin-clavulanic acid did not alter the course of disease or recovery compared to placebo.¹² In a separate study, even dogs with a neutrophilic left shift recovered despite a lack of antibiotic treatment.¹³ Thus antibiotic treatment for AHDS should likely be reserved for those patients with a degenerative left shift or evidence of sepsis.

In very young animals whose microbiome is not fully established, disruption can lead to persistent dysbiosis. Unfortunately, it is often these same young animals that are prone to infectious insults as well as dietary indiscretion. Treatment of diarrhea in young cats and dogs should aim to re-establish and mature their microbiomes. Use of antibiotics in otherwise healthy patients with diarrhea may further exacerbate dysbiosis.

Use of Probiotics and Prebiotics

If a goal of diarrhea management is restoration of a normal healthy microbiome, what interventions are available? In otherwise healthy patients, probiotics were as good or better than metronidazole in the treatment of acute diarrhea in dogs.² Probiotics provide populations of beneficial bacteria to the gut. Metabolites (so called post-biotics) of such bacteria, such as SCFAs may aid in resolution of inflammation and clinical signs. Probiotics are beneficial in chronic enteropathies as well. A probiotic, VSL#3 (now marketed as Visbiome), was as effective in improving clinical disease activity and histology scores as prednisone and metronidazole in

dogs with inflammatory bowel disease.¹⁴ More T regulatory cells, which help to maintain homeostasis and prevent autoimmunity, were present in biopsies of the probiotic-treated dogs compared to the steroid/metronidazole treatment group.¹⁴ Thus probiotics may have additional beneficial effects in the gut over traditional therapy.

Probiotic effects are generally short-lived after treatment is stopped, likely because engraftment does not occur. Prebiotics, typically dietary fibers, have the potential for more long-lasting effects in the gut because they help to foster populations of microbes present already.

Prebiotics provide bacteria the substrates needed to thrive. Psyllium is a commonly used prebiotic. Psyllium in addition to a highly digestible diet was effective in dogs with chronic large bowel diarrhea.¹⁵ Hill's Gastrointestinal Biome diet is optimized to provide prebiotics for beneficial post-biotic effects. Psyllium and fiber diets can be used as short-term treatments, which is particularly helpful for patients who need to be on other therapeutic diets long-term. Hydrolyzed diets are beneficial as well. In dogs with chronic enteropathies fed a hydrolyzed diet, clinical remission was accompanied by an increase in *C. hiranosis* and secondary bile acids and a decrease in *E. coli* and *C. perfringens*.

Probiotics and prebiotics can be used together to optimize therapy and restore the function of the microbiome in dogs and cats with diarrhea.

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