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KEY POINTS

- ▶ Dysbiosis occurs in patients with acute and chronic enteropathies, exocrine pancreatic insufficiency, and secondary to pharmacologic interventions.
- ▶ Dysbiosis can contribute directly to clinical disease, even when it occurs secondary to other processes. Antibiotic-associated dysbiosis is associated with increased risk of asthma, obesity, and IBD in people.³⁻⁵
- ▶ Antibiotic-associated gastrointestinal side effects (AAGS), including food aversion and hyporexia, are common secondary occurrences in cats after antibiotic administration.⁶
- ▶ Administration of Provable[®]-DC 1 hour after each antibiotic dose in a recent study significantly reduced the severity of AAGS (particularly vomiting) and increased food intake as well as the likelihood that cats would complete the antibiotic course.⁷

The Role of Probiotics in the Management of Intestinal Dysbiosis

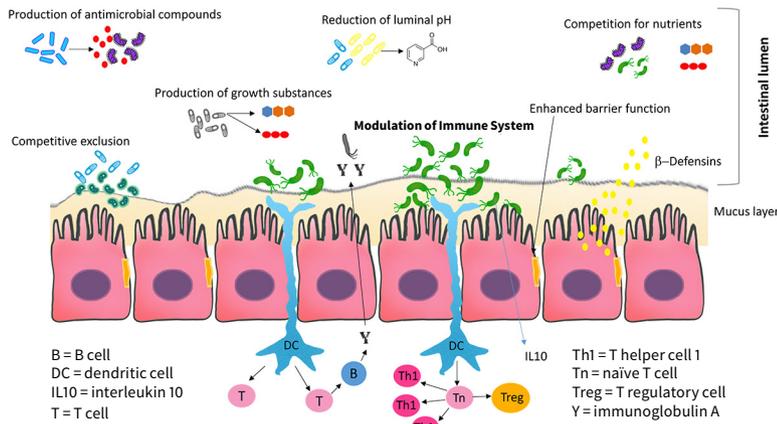
Clear evidence indicates that the intestinal microbiota plays an important role in gastrointestinal health. An alteration of the intestinal microbiota composition, termed *dysbiosis*, can contribute to gastrointestinal (GI) diseases such as chronic enteropathies.¹ Modulation of the intestinal ecosystem by oral administration of beneficial bacteria (probiotics) has gained wide popularity. Many studies in the human and veterinary literature have demonstrated that the administration of probiotic bacteria can aid in the prevention and treatment of disease.²

Importance of the Intestinal Microbiota

The intestinal microbiota consists of viruses, bacteria, fungi, and protozoa. An estimated 100 trillion microbial cells are present in the GI tract—approximately 10 times more than the number of host cells.⁸ This complex ecosystem has a tremendous influence on host health. A balanced microbiota regulates the immune system, helps in the defense against enteropathogens, and provides nutritional benefits.

Interactions between intestinal bacteria and the host immune system are mediated through direct contact between microbes and the immune system (eg, dendritic cells, Toll-like receptors), and through microbiota-derived metabolites. The gut is home to mostly anaerobic bacteria, such as *Ruminococcus* and *Faecalibacterium*. All these bacteria produce metabolites that have direct beneficial effects on the host. For example, nutrient sources such as complex carbohydrates (eg, starch, cellulose, pectin) are fermented by bacteria, resulting in the production of short chain fatty acids (SCFAs). These act as energy sources for the host, regulate intestinal motility, and are important growth factors for epithelial cells. SCFAs also have direct anti-inflammatory properties through expansion of immunoregulatory lymphocytes.

Other bacterially derived metabolites such as indole, a by-product of tryptophan degradation, and secondary bile acids are also immunomodulatory, maintaining immune homeostasis and strengthening intestinal barrier function. Beneficial



▲ **Important Microbiota-Mediated Pathways**

The commensal intestinal microbiota exerts health benefits through various pathways. In intestinal dysbiosis, the changes in bacterial populations lead to altered physiological pathways. Dysbiosis is therefore an important component of many intestinal but also extra-intestinal disorders.

Probiotics are defined as live microorganisms that, when administered in sufficient quantities, confer a health benefit to the host.

effects of the gut microbiota reach beyond the GI tract, as alterations in gut microbes play a role in the pathogenesis of diabetes mellitus and obesity.³

Dysbiosis

Intestinal dysbiosis is associated with acute and chronic GI disorders. Dysbiosis can be deleterious due to the production of bacterial toxins or reductions in anti-inflammatory metabolites derived from bacteria. Dysbiosis could also serve as a risk factor for the development of chronic GI disease in susceptible individuals. For example, antibiotic-induced dysbiosis in early childhood is one of the most important risk factors for the development of allergies, obesity, and IBD in adult humans.³⁻⁵

Changes in the microbiota result in functional and immunological consequences for the host. For example, mucosa-adherent bacteria in the small intestine are important stimulators of mucosal immunity, and changes in microbial composition can have significant effects on the host immune response. Dysbiosis can also lead to destruction of brush-border enzymes, damage of carrier proteins, and competition for nutrients (eg,

vitamin B₁₂). Also, bacterial enterotoxins stimulate mucosal fluid secretions, resulting in diarrhea. Dysfunction of the mucosal barrier can lead to altered intestinal permeability and bacterial translocation. Depletion of commensal groups (**Figure**) in the large intestine and their respective immunoregulatory metabolites (eg, SCFAs, indoles, and secondary bile acids) can impair the host's ability to down-regulate the aberrant intestinal immune response, making dysbiosis an integral part of the pathogenesis of chronic GI disease.

Dysbiosis can be primary (idiopathic), but it often occurs secondary to other disease processes or environmental factors (**Table**). Even when dysbiosis is secondary, it can exacerbate or maintain disease. Therefore, recognition of dysbiosis (eg, via molecular tools such as the Dysbiosis Index) and therapeutic intervention to correct it are critical to optimize the patient's clinical outcome.⁸

Correction of Dysbiosis

Strategies to correct dysbiosis include administration of prebiotics and probiotics. Prebiotics include carbohydrates and fermentable fibers. After ingestion, they are fermented by intestinal bacteria to produce SCFAs, resulting in numerous positive benefits as described above. Probiotics are defined as live microorganisms that, when administered in sufficient quantities, confer a health benefit to the host. Probiotics are not regulated as drugs in the United States and, thus, undergo minimal regulatory scrutiny.

Objective evaluations have shown that all probiotics are not created equal. In one study, no evaluated food contained all the bacterial strains listed on the label, and 26% of tested foods did not contain live bacteria.⁹ Additionally, up to two thirds of probiotics labeled for animal use have failed quality testing.¹⁰ Thus, we recommend that only probiotics that undergo regular evaluations for content and viability by their manufacturers be prescribed. Other major considerations include the number of species and colony forming units (*cfu*) of bacteria, presence of prebiotics (such combination products are referred to as synbiotics), and use of flavoring agents. The ideal number of

bacterial strains and *cfu* likely varies by indication, but higher doses are currently used for correction of active disease.¹¹ Products with flavorings should probably be avoided when managing patients with food-responsive disease or inflammatory bowel disease (IBD).

Probiotics have been used in dogs and cats to correct dysbiosis associated with acute and chronic enteropathies. In placebo-controlled trials, administration of probiotics significantly shortened diarrhea secondary to acute gastroenteritis in dogs.¹²⁻¹³ Probiotic administration was also shown to significantly decrease the duration of diarrhea in cats in a shelter environment.¹⁴ In one open-label trial of cats with idiopathic chronic enteropathy, owners reported their cats had significantly improved fecal scores after synbiotic (Provable®-DC) administration.¹⁵

One randomized controlled trial evaluated clinical and histologic response rates in dogs with moderate to severe IBD treated with either probiotics (11-22 billion *cfu/kg/d*) or combination prednisone (1 mg/kg/d) and metronidazole (20 mg/kg q12h) therapy.¹¹ Although median time to remission was about 6 days longer in dogs receiving probiotics, the two groups had equivalent remission rates and histologic improvement. Excitingly, enhanced T regulatory cell function and normalization of dysbiosis 30 days after discontinuation of treatment were found only in dogs treated with probiotics.

One additional major indication for probiotics is prevention of antibiotic-associated gastrointestinal side effects (AAGS), which occur in 5% to 39% of people, with incidences as high as 70% in children.¹⁶ In people, even a 7-day course of antibiotics can alter the fecal microbiome and increase the presence of bacterial resistance for at least 4 years.¹⁷ Administration of probiotics is associated with ≤ 3 -fold decrease in AAGS in people.¹⁶ Although the incidence of AAGS in dogs and cats is largely unknown, prolonged derangements in the microbiome have been demonstrated in animals receiving antibiotics.¹⁸ In the authors' experience, AAGS are an important cause of non-compliance with treatment recommendations. Cats seem particularly sensitive to AAGS such as hyporexia, food aversion,

DISORDERS ASSOCIATED WITH INTESTINAL DYSBIOSIS

- ▶ Chronic enteropathies (food-responsive, antibiotic-responsive, and inflammatory bowel disease)
- ▶ Acute diarrhea (eg, stress-related, infectious, or secondary to dietary indiscretion)
- ▶ Abnormal intestinal motility (eg, blind loops, diverticula, strictures, obstruction of the intestine)
- ▶ Exocrine pancreatic insufficiency
- ▶ Pharmacologic interventions (eg, antibiotics, NSAIDs, acid-suppressing drugs)

PROVIABLE-FORTE AND ORIGINAL PROVIABLE-DC FOR DOGS & CATS

Total bacteria: Minimum of 10 billion *cfu* per Provable-Forte capsule; minimum of 5 billion *cfu* per Provable-DC capsule, including the following bacteria:

- ▶ *Enterococcus faecium* NCIMB 30183
- ▶ *Bifidobacterium bifidum* NCIMB 30179
- ▶ *Enterococcus thermophilus* NCIMB 30189
- ▶ *Lactobacillus acidophilus* NCIMB 30184
- ▶ *Lactobacillus bulgaricus* NCIMB 30186
- ▶ *Lactobacillus casei* NCIMB 30188
- ▶ *Lactobacillus plantarum* NCIMB 30187

Administration:

- ▶ Give with Provable-KP paste for short-term use during times of intestinal imbalance
- ▶ Use alone for long-term intestinal health support and balance
- ▶ Single-size sprinkle capsule for easy administration



vomiting, and degradation of the human-animal bond due to owner avoidance.

In recent work, we compared food intake, vomiting, and diarrhea in 16 healthy cats receiving 75 mg clindamycin once daily followed 1 hour later by either placebo or 2 capsules of a synbiotic (Provable®-DC) using a randomized, double-blinded, cross-over design with a 6-week washout period.⁷ Cats receiving the synbiotic were significantly more likely to complete treatment in period 1 (100% vs 50%) due to decreased vomiting. Cats also had significantly higher food intake while receiving the synbiotic. Interestingly, cats that received the synbiotic first had significantly less vomiting when receiving the placebo compared to cats that received the placebo first, in spite of the prolonged washout period. This finding suggests that clinical benefits of

synbiotic administration persisted longer than 6 weeks after discontinuation, partially protecting cats from AAGS when they received clindamycin with placebo. Fecal microbiome analysis is underway to determine whether these effects are due to correction of dysbiosis.

Although data are lacking on efficacy of synbiotics for prevention of AAGS secondary to use of antibiotics other than clindamycin, it is unlikely that they would confer a negative effect. Therefore, pending further study, we recommend the use of synbiotics (or probiotics) in dogs and cats receiving antibiotics to help decrease AAGS and potentially dysbiosis. To avoid inactivation due to direct antibiotic effects, we recommend administering the synbiotic 1 to 2 hours after each dose of antibiotics.

Pending further study, we recommend the use of synbiotics (or probiotics) in dogs and cats receiving antibiotics to help decrease AAGS and potentially dysbiosis.

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