The use of probiotics in small animal medicine

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Introduction

In recent years, through the advance of molecular tools, we have been able to better characterize the bacteria present in the canine and feline gastrointestinal (GI) tract (i.e., the intestinal microbiota) [1]. This has led to a completely new understanding of the importance of the intestinal microbiota for the wellbeing of the host. A balanced intestinal ecosystem provides nutritional benefits to the host, primes the immune system, and protects the host from pathogens. There is evidence that alterations in the intestinal microbial ecosystem contribute to gastrointestinal disorders such as inflammatory bowel disease and small intestinal dysbiosis or antibiotic-responsive diarrhea [1]. The modulation of the intestinal ecosystem by oral administration of beneficial bacteria (probiotics) has gained wide popularity in human and veterinary medicine. Clinical studies in the human literature have demonstrated that the administration of specific probiotic bacterial strains can be useful in the prevention and/or treatment in a subset of patients with specific GI disorders [2]. While the efficacy of probiotics is not yet well elucidated in veterinary medicine, mostly due to an absence of well-designed placebo controlled studies, initial results suggest that probiotics can be a useful treatment adjunct for veterinary patients.

To proper select probiotic products for use in small animals, it is important to understand their mechanisms. Health effects of probiotics are strain specific, and not every bacterial strain will have the same biological characteristics. Therefore, it is crucial to know which bacterial strain is contained in a product, and if there is evidence in literature that this bacterial strain has been evaluated for the targeted disorder (e.g., acute stress diarrhea, inflammatory bowel disease).

Definition

The World Health Organization currently defines probiotics as "live microorganisms, which when administered in adequate amounts confer a health benefit on the host". This definition stresses that health benefits need to be demonstrated before a bacterial strain can be designated as a probiotic. In the United States, probiotics are classified as nutritional supplements (beneficial claims relate to the consumption of the product to normal functioning of the body rather than health claims that relate to disease treatment and/or prevention) and therefore undergo little regulatory scrutiny.

In contrast, in the EU the beneficial claims of probiotic products have been under strict regulatory scrutiny for health benefits and since 2007 most probiotic product have not been approved because of insufficient prove of their health claims. Furthermore, because according to the EU, the term “probiotic” carries an unsubstantiated “implied health claim”, since December 2012 the EU has banned the use of the general term “probiotic” on packaging and marketing materials.

Strains of lactic acid bacteria (i.e., *Lactobacillus, Enterococcus, Streptococcus,* and *Bifidobacterium* spp.) are commonly included in probiotic products, as these have traditionally been associated with health benefits. However, other microorganisms have also demonstrated health benefits, and are therefore used as probiotics (e.g., *Escherichia coli* strain Nissle 1917, *Saccharomyces boulardii*). Many probiotic products are offered in combination with prebiotics (non-digestible food ingredients that are added to diets to stimulate the growth of resident bacteria). Such products are called synbiotics (Table 1).

Intestinal microbiota in health and disease

The important role that intestinal bacteria play in health and disease of animals is well recognized. New improved molecular characterization methods have revealed that the gastrointestinal tract harbors a very complex ecosystem, including bacteria, archaea, fungal organisms, viruses, and protozoa. The total microbial load in the intestine is estimated to consist of 10^{12}-10^{14} microbial cells, representing approximately 100 times as many genes as the host genome. It is estimated that the canine intestine harbors more than 1,000 different bacterial phylotypes [3]. Each animal possess are very unique and distinct microbiota [4]. The resident microbiota provides various metabolites to the host (e.g., butyrate, acetate, indoles, etc), which stimulate mucosal growth and have shown to have direct immunomodulatory properties. Furthermore, the resident intestinal microbiota protects from the invasion by potentially pathogenic organisms.

New evidence suggests that abnormal shifts in populations of intestinal bacteria (termed dysbiosis) cause a disturbance in the intestinal homeostasis, which may have a negative impact on the host. For example, there is strong evidence linking dysbiosis to inflammatory bowel disease (IBD) in several species including humans, dogs, and cats [1]. Therefore, treatment strategies geared towards modulating microbial populations (i.e., nutritional intervention or probiotics) may be of therapeutic benefit in such patients.

Mechanisms of probiotics

Early studies about the mechanisms of probiotics have involved studies of entire bacterial genera, most commonly *Bifidobacterium, Lactobacillus, Enterococcus* spp., as it was believed that all species within these genera have beneficial properties. Today it is recognized that every bacterial strain has unique functional and immunological properties. Therefore, not all bacterial

species or strains within a genus will have the same effects, and only specific bacterial strains may have probiotic functions. This is the reason why probiotic product labels should specify which strain is present in the product (e.g., *Enterococcus faecium* strain NCIMB 10415; *Lactobacillus rhamnosus GG*, etc.). In fact, different strains of the same bacterial species can have quite opposite effects. For example, *Bifidobacterium animalis* strain AHC7 was shown to be useful in shortening the duration of acute stress diarrhea in dogs [5], while another strain of the same species, *Bifidobacterium animalis* strain ATCC 25527(T) was associated with duodenal inflammation in immunodeficient mice [6].

Due to strain specificity, the mechanisms of actions will differ for various probiotic strains, and therefore specific strains may need to be chosen for a specific clinical application. However, this is currently an area in veterinary medicine where only limited data is available, as only few clinical studies have evaluated specific probiotic strains in specific clinical scenarios.

The specific mechanisms of action of probiotic strains are poorly understood. For example, some probiotic strains act immunomodulatory and stimulate the release of various anti-inflammatory cytokines or enhance IgA production. Other strains affect the intestinal mucosal barrier and reduce abnormal intestinal permeability. The exact mechanisms how these effects are induced *in-vivo* remain unclear. New research suggests that the beneficial effects may be in part due to secretion of various metabolites by probiotic strains, which evoke the specific beneficial responses in the host. For example, probiotic strains contained in the probiotic product VSL#3 secrete alkaline sphingomyelinase, an enzyme that has demonstrated an anti-inflammatory property in inflammatory bowel disease [7]. Another example is the production of the short-chain fatty acid acetate by some *Bifidobacterium* strains (e.g., *Bifidobacterium longum* JCM 1217T), which also improve intestinal barrier function [8]. There is still much research needed to

understand the exact mechanisms of various bacterial strains and how their properties can be used for clinical application in specific diseases.

Recommendations for probiotic selection

To be able to exert a health benefit, a probiotic strain should be safe, should survive the passage through the GI tract, and it should be able to at least temporarily colonize the GI tract. Furthermore, it should be stable during storage. Based on recommendations from human medicine, a probiotic strain should be used that has shown beneficial effects in clinical studies, and the product should be administered at the dose as published. Due the individuality of the resident intestinal microbiota of patients, it is likely that different probiotic strains will have differing levels of efficacy in individual patients. Therefore, the success or failure of one probiotic strain in a particular patient does not predict its efficacy in other patients.

Safety

Side effects of probiotics are rarely reported, as the strains commonly used are part of the normal commensal flora. A relative small number of case reports in human medicine have shown that probiotics can cause septicemia in hospitalized patients. Therefore, probiotics should be used cautiously in severely immunocompromised patients.

Dosage

A substantial percentage of orally administered probiotic bacteria will be lost through competitive exclusion by the highly complex resident microbiota. Therefore, probiotics need to be administered at very high doses. Even then, probiotics will represent only a minor fraction of the total microbiota. For dogs and cats, it is difficult to provide a proper dosage for probiotics as

no dose-response studies have been performed in clinical patients. Currently, we are extrapolating information from human studies to dogs and cats. Based on the review of veterinary literature, doses between 1×10^8 and 4.5×10^{11} colony forming units (cfu) of bacteria have demonstrated clinical benefits.

Concurrent antibiotic administration

For the prevention of antibiotic-associated diarrhea, antibiotics and probiotics are often prescribed concurrently. Probiotic strains can be either susceptible or resistant to the administered antibiotics. The manufacturer should be able to provide information regarding the susceptibility patterns of their products. Generally, *Enterococcus* spp. and *Bifidobacterium* spp. are typically resistant to commonly used antibiotics such as tylosin and metronidazole. Therefore, in most cases no interaction between concurrent use of probiotics and antibiotics is to be expected.

Multi-strain vs. single-strain probiotics

Products are available on the market that contain either one single probiotic strain or they contain a mixture of several probiotic strains. The reasoning behind multi-strain products versus single-strain probiotics is the potentially higher chance that at least one of the strains will colonize the gut, and multiple strains can also have synergistic probiotic properties. However, there is no clear guideline which product will be superior for a specific disease.

Species specificity of probiotics

It has been suggested that a probiotic strain should be isolated from the same animal species that it will be used in. The theory is that a host specific probiotic may be better adapted to its target organism (e.g., stomach pH, bile acid composition, adherence to epithelial cells). However, several *in vivo* (based on animal models) and *in vitro* (based on the adherence to epithelial cells) studies have shown that human or diary derived probiotic strains are capable of conferring a health benefit to other animal species. At this point there is no proven benefit of using an animal specific strain.

Use of probiotics in clinical disorders of dogs and cats

In human medicine, strong data is available for the treatment and prevention of infectious diarrhea in children and adults, in the prevention of antibiotic-associated diarrhea, and in induction and maintenance of remission of ulcerative colitis [2]. In veterinary medicine, promising applications of probiotics are the prevention and treatment of acute or stress-related diarrhea (during periods of weaning, boarding, traveling, or in working dogs). The most commonly observed effect is a shortening in the duration of diarrhea. A prophylactic administration a few weeks ahead of the event may be useful in such instances.

Several studies have been performed that have shown benefits of administering probiotics in cases of acute or stress related diarrhea in cats and dogs. In a large double-blinded placebo controlled study, shelter cats received a dose of 2.1 x 10^9 cfu/day of *Enterococcus faecium* SF68® NCIMB 10415 (Purina Fortiflora, Feline Nutritional Supplement) or a placebo. Fewer cats on the probiotic developed diarrhea for more than 2 days duration, when compared to cats that received placebo (7.4% vs. 20.7% in the placebo group) [9]. The strain *Enterococcus*

faecium NCIMB 10415 has also shown clinical benefits in other studies. For example, it has shown to reduce the incidence of diarrhea in dogs that came through a canine re-homing center (*Enterococcus faecium* (NCIMB 10415) E1707; Protexin Synbiotic, Probiotics International Ltd; at a dose of $5x10^9$ cfu daily).

A multi-species probiotic product (ZooLac Propaste; Chem Vet A/S Denmark) containing *Lactobacillus acidophilus* MA 64/4E, *Lactobacillus farciminis*, *Bacillus subtilis*, *Bacillus licheniformis*, and *Pediococcus acidilactici* significantly shortened the duration of acute diarrhea in dogs from 48 to 24 hours when given at a dose of 4.2×10^9 cfu/10 kg three times daily [10]. Administration of *Bifidobacterium animalis* strain AHC7 (Prostora™ Max/Canine, IAMS Veterinary) at a dose of 2×10^{10} cfu per day to dogs with acute idiopathic diarrhea significantly reduced the time to resolution by 2.5 days and decreased the percentage of dogs that required adjunctive use of metronidazole (38.5% vs. 50.0% in the placebo group) [5].

Recent studies have also shown promising results for the treatment of chronic enteropathies in cats and dogs. In an open-label study of a multi-strain product, 70% of cat owners reported an improvement in their pets clinical condition with supplementation of a multi-species synbiotic (Proviable-DC, Nutramax Laboratories) at a dose of 5×10^9 cfu/day for 21 days [11]. A high dose multi-strain probiotic (VSL#3, VSL Pharmaceuticals, Inc.; containing 4 strains of *Lactobacillus* spp., 3 strains of *Bifidobacterium* spp., and 1 strain of *Streptococcus*) was successfully used as monotherapy in a pilot study with dogs with inflammatory bowel disease. Enrolled dogs received on average 450 billion lyophilized bacteria daily for 60 days (4.5×10^{11} cfu per day). Dogs responded within 10 days of administration and showed no relapse while on the product [12]. While not many studies have been performed in animals with chronic enteropathies, based on human studies it is likely that these probiotic products may be useful as

an adjunct to standard therapy until remission of the disease. It is possible that in such chronic enteropathies long-term administration may beneficially influence the immune system.

Probiotic applications for extra-gastrointestinal disorders

Several studies have evaluated the effects of probiotics for non-specific immune stimulation (e.g., improving vaccine responses and increase of immunoglobulin production in young animals) and also for the prevention of atopic dermatitis. While some of these results are promising, more studies are needed to evaluate which probiotic strains are most useful, the required dosage, and also the time of administration (i.e., during pregnancy, before or after weaning). More studies are therefore needed before useful recommendations can be provided.

Key points

- Probiotics are commonly recommended, but clinical data is scarce in veterinary medicine.
- The beneficial effect of a probiotic dependent on the bacterial strain.
- A probiotic health benefit should be demonstrated in well-conducted controlled study. Examples of a health benefit are the prevention, shortening, or treatment of a disease. Ideally, veterinarians should select a product containing a probiotic strain that has demonstrated a beneficial effect for the targeted disorder.
- The probiotic strain should be administered in the same dose as shown in the clinical study.
- Probiotic strains are quickly eliminated from the intestine after end of administration. For chronic diseases, long-term administration of probiotics is required.
- It is crucial to select a product from a reputable manufacturer who has extensive data to show that the product contains a sufficient amount of viable organisms during shipping, storage, and at the end of the recommended shelve life.

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Table 1. Definitions of Probiotics, Prebiotics, and Synbiotics

Probiotics are defined as live microorganisms, which when administered in adequate amounts confer a health benefit on the host.

Prebiotics are non-digestible food ingredients that are added to diets to stimulate the growth of native probiotic bacteria. These are usually carbohydrates such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS). The theoretical advantage of prebiotics is that they promote the growth of the already present beneficial bacteria in the gut. However, some of the resident bacteria that drive on prebiotics might not have the efficacy of exogenous probiotics.

Synbiotics are a combination of probiotics and prebiotics. They are often administered together to add a growth substrate for the administered probiotic.

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