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PROBIOTICS, PREBIOTICS, AND SYNBiotics. WHAT ARE THEY AND WHEN SHOULD THEY BE IMPLEMENTED?
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The mammalian intestinal tract contains a complex, dynamic, and diverse population of non-pathogenic bacteria. Researchers have estimated that the human body contains $10^{14}$ cells, only 10% of which are not bacteria, and belong to the human body proper. There has been a plethora of research focusing on the mechanisms by which pathogenic bacteria influence intestinal function and induce disease; however, recent attention has focused on the indigenous non-pathogenic microorganisms and the ways in which they may benefit the host. Initial colonization of the sterile newborn intestine occurs with maternal vaginal and fecal bacterial flora. The first colonizers have a high reduction potential and include species such as enterobacter, streptococcus, and staphylococcus. These bacteria metabolize oxygen, favouring the growth of anaerobic bacteria, including lactobacilli and bifidobacteria. Colonization with these bacteria is significantly delayed in caesarean deliveries, leading to delayed activation of the efferent limb of the mucosal immune response. Additional beneficial effects of developing a normal bacterial flora is seen in germ free mice that have small intestines that weigh less than their healthy counterparts. This effect occurs partly due to underdevelopment of lymphoid constituents, with a lack of plasma cells in the lamina propria and Peyer’s patches, and subsequent reduction in IgA production. Exposure to bacteria results in a reversal of this phenomenon within 28 days of exposure.

PROBIOTICS:
Probiotics refer to live microorganisms which when administered in adequate amounts confer a health benefit on the host. The term probiotic was derived from the Greek, meaning “for life.” The Food and Agricultural Organization of the United States (FAO) and the World Health Organization (WHO) have stated that there is adequate scientific evidence to indicate that there is potential for probiotic foods to provide health benefits and that specific strains are safe for human use. There has been a literal explosion of interest and research on the subject during the past 8 years. A PubMed search of the term “probiotics” for peer-reviewed publications published from the year 2000 revealed over 4,400 publications, in contrast to 300 publications over the previous 55 years. Despite this activity, much still remains to be done to standardize the meaning of the term probiotic and to determine which strains fulfil the criteria of true probiotic microorganisms. There has been tremendous interest among veterinary pet food companies and manufacturers of animal health and wellness products to market probiotic formulations that are safe, pure, stable, and confer a beneficial effect in dogs and cats. Two recently launched products (Proviable-KP and Proviable-DC, Nutramax Laboratories, Edgewood, MD) contain a source of viable beneficial microorganisms and fructooligosaccharide, a nondigestible food ingredient (prebiotic) which beneficially affects the host by selectively stimulating the growth of and/or activating the metabolism of one or a limited number of health promoting bacteria in the intestinal tract. Proviable-KP is a paste, which also contains kaolin and pectin. Both probiotic formulations as well as those marketed by the major pet food companies are only available from veterinarians.

Caution should be heeded in utilizing over-the-counter probiotics marketed for veterinary use, as many of these products have not been properly identified, manufactured under appropriate practices, or proven clinically. A recent study by Weese et al. highlighted the deficiencies pertaining to the labelling of commercial veterinary and human probiotics. A number of criteria are essential for efficacy and safety of probiotics. These include resistance to gastric acid and bile, ability to colonize the gastrointestinal tract, efficacy against pathogenic microorganisms and modulation of the immune system. Several potential mechanisms have been proposed for how probiotics reduce the severity or...
duration of diarrhea: competition with pathogenic bacteria or viruses for nutrients, competition for receptor sites, modification of the metabolic activity of the intestinal microflora, and the direct antagonism through the action of antimicrobial metabolites.8,9

Role of Probiotics in the Management of Diarrhea

A number of clinical trials involving probiotics demonstrating reduction of duration of diarrhea in children have been published. Intestinal infections in newborn children are common, and in developing countries diarrhea is a prime cause of morbidity and mortality. Necrotizing enterocolitis is a devastating intestinal disorder seen more commonly in preterm infants. The syndrome is characterized by abdominal distention, bilious vomiting, bloody stools, lethargy, apnea, and bradycardia.10 Progressive intestinal necrosis leads to an inflammatory cascade with septic shock and possibly death. The mortality rate ranges from 20 to 30%, and of those who survive, 25% experience long-term sequelae, such as short bowel syndrome and intestinal obstruction.10 The benefits of administration of the probiotics, Lactobacillus acidophilus and Bifidobacterium infantis were readily appreciated when the incidence of necrotizing enterocolitis and overall mortality were reduced by 60% in an intensive care unit.11 Evidence is also accumulating for the benefits of probiotics in preventing Clostridium difficile associated diarrhea (CDAD) in hospitalized human patients receiving antibiotics. A meta-analysis to evaluate the efficacy of probiotics in prevention and treatment of diarrhea associated with the use of antibiotics recently showed an odds ratio of 0.39 (95% confidence interval, 0.25 to 0.62; P < 0.001) in favor of active treatment over placebo with Saccharomyces boulardii and 0.34 (0.19 to 0.61; P < 0.01) for lactobacilli.12 It should be noted that cases of fungal infection have been reported in rare cases, usually associated with immunocompromised catheterized patients.13 Administration of Enterococcus faecium SF68 to dogs was recently shown to enhance production of secretory IgA in the intestine.14

Encouraging studies have been published evaluating the role of probiotics for managing human patients with IBD. Beneficial responses have also been documented in atopic infants fed with the probiotics, L. rhamnosus GG and Bifidobacterium Bb12.15 Atopic infants fed with these probiotics had less allergic reaction to cow’s milk proteins and a lower incidence of atopic dermatitis. Administration of probiotics to dogs and cats with IBD represents a novel alternative therapeutic modality that warrants further investigation. It has been demonstrated that colitis in both humans and mice is associated with increased levels of cytokines such as TNF-α, IL-6, IL-12p70 and IL-23.16,17 Thus, a proper selection of probiotic strains for the treatment of IBD is crucial and should be based on the estimation of their capacity to induce anti-inflammatory pattern of cytokines (IL-10high, TGF-βhigh, IL-12p70low, IL-23low, TNF-αlow). Apart from immunomodulatory effects, probiotics have a protective effect on the normal microflora of the human gut by their antimicrobial activities directed toward intestinal pathogens.18

Probiotics have also been utilized to facilitate eradication of intestinal parasites. A recent study documented the ability of the probiotic organism Enterococcus faecium SF68 (FortiFlora, Nestle-Purina, St. Louis, MO) to antagonize Giardia intestinalis infection in mice.19 Oral feeding of E. faecium strain SF68 starting 7 d before inoculation with Giardia trophozoites significantly increased the production of specific anti-Giardia intestinal IgA and blood IgG. This humoral response was mirrored at the cellular level by an increased percentage of CD4(+) T cells in the Peyer’s patches and in the spleens of SF68-fed mice. The improvement of specific immune responses in probiotic-fed mice was associated with a diminution in the number of active trophozoites in the small intestine as well as decreased shedding of fecal Giardia antigens (GSA65 protein).

Enterococcus faecium strain SF68 was supplemented to kittens in an effort to enhance immune function following administration of a multivalent vaccine. Enterococcus faecium was detected in the feces of seven of the nine treated cats, and supplementation was associated with a significant increase
in CD4\(^+\) lymphocytes, although the probiotic did not alter most of the immune parameters measured.\(^{20}\)

**PREBIOTICS:**
A prebiotic is defined as a “nondigestible food ingredient which beneficially affects the host by selectively stimulating the growth of and/or activates the metabolism of one or a limited number of health promoting bacteria in the intestinal tract.”\(^{21}\) The most common prebiotics studied are fructans, although other prebiotics such as mannans, lactosucrose, and lactulose are also being evaluated. A relatively large body of information is present in the human literature evaluating the effects of prebiotics on human health; however, little information exists regarding the canine. Unfortunately, there is a dearth of information evaluating the clinical benefits of prebiotics in dogs with intestinal disease. Instead, most of the outcomes published in the literature are limited to nutrient digestibility, microbial concentrations in feces, and fecal protein catabolites which may not necessarily denote a health benefit in the patient. The effects of short chain fructooligosaccharides (scFOS) were evaluated in a group of German Shepherd dogs suspected to have IgA deficiency.\(^{22}\) Although the scFOS supplemented dogs had decreased aerobic and anaerobic bacteria in intestinal biopsies, the findings of the study were clouded in light of the fact that anaerobic bacterial counts did not decrease in the intestinal fluid samples of the dogs supplemented with scFOS. The effects of various oligosaccharides have been tested in adult ileal cannulated dogs to evaluate the effects on ilial and total tract nutrient digestibilities, microbial populations, ileal pH, ammonia, blood glucose, fecal consistency, and SCFA concentrations. Oligosaccharides (oligofructose, mannanoligossacharides, and xylooligosaccharides were each given at 0.5% of the diet in a Latin square design. The only significant finding was a decrease in fecal *Clostridium perfringens* populations in dogs fed MOS.

**SYNBIOTICS:**
Synbiotics are nutritional supplements containing combinations of pre- and probiotics. An example of a commercial synbiotic marketed for veterinary use is Proviable-KP, manufactured by Nutramax Laboratories, Inc.

**Conclusions and Future Directions:**
Specific clinical conditions that warrant further evaluation for implementation of probiotics include stress-related diarrhea (boarding dogs, travelling animals, shelter environments); prevention and management of antibiotic-associated diarrhea; management of diarrhea associated with dietary indiscretion, and management of atopy. Most of the studies published to date have focused almost exclusively on healthy dogs and cats, and there is clearly a need to optimize probiotics for clinical use. In addition, probiotics have different mechanisms, including protection against pathogenic bacteria adherence (reduction of intestinal pH, production of short-chain fatty acids, production of antimicrobials), facilitation of competitive exclusion of pathogens, and immunomodulatory effects. The optimal combination and spectrum of beneficial microorganisms needs to be determined, and the type of probiotic should be tailored to the specific needs of the patient that is being managed.

**References:**

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