Probiotics and their validity in small animal patient therapy

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Probiotics supplementation is gaining popularity – for example, as promoted in advertisements for people as "good bacteria". A website shows more than 20 different products available for humans, but often with vague and sometimes unsubstantiated claims – for example, "benefits digestive function" and "strengthens the body's natural defences".

In humans, evidence exists for effectiveness of probiotics in treating acute infectious diarrhoea, preventing or treating antibiotic-associated diarrhoea and maintaining remission of ulcerative colitis. Evidence also exists of probiotic usefulness in treating "traveller's diarrhoea", preventing bacterial translocation and sepsis secondary to severe acute pancreatitis.

One study has shown a worse prognosis with use in acute pancreatitis, therefore caution is advised (Besselink et al, 2008) with regards to this disorder.

What are probiotics?

Figure 1. Probiotic bacteria.

Probiotics contain living microorganisms that, when ingested in adequate numbers, confer health benefits. The microbes are usually defined as live, non-pathogenic organisms such as various *Bifidobacterium* or *Lactobacillus* species, *Enterococcus faecium* or non-bacterial organisms including as the non-pathogenic yeast *Saccharomyces boulardii* (**Figure 1**).

A product may also contain several probiotic organisms. Criteria for these include resistance to low gastric pH, adherence to intestinal mucosa, ability to proliferate and colonise the colon, activity against pathogenic microorganisms and modulation of the immune system. They must also have no pathogenic, toxic, mutagenic or carcinogenic effects (Wynn, 2009). Some evidence exists that isolated probiotic DNA has immune stimulatory properties, so some of the effects may not require live organisms.

Prebiotics are non-digestible food ingredients such as oligosaccharides and some fibre sources, which promote the growth of the beneficial bacteria. When prebiotics and probiotics are combined for a proposed synergistic effect, the product is called a synbiotic.

Gastrointestinal tract and gut microorganisms

The gastrointestinal (GI) tract contains a huge population of microbes. The interacting system of host mammalian cells and the resident microbial community is called the intestinal microbiome. The microbiome can cause, contribute to and modulate health and disease. It has been referred to as the "second genome" due to its effects on the body.

The intestinal microbiome has implications for various disorders (Grice and Segre, 2012). These include the more obvious, such as acute and chronic diarrhoea, to more far-reaching, such as periodontal disease, obesity, chronic kidney disease, oxalate urolithiasis, atopy, cardiorespiratory disease and cancer.

Understanding the body's normal bacteria populations aids in understanding the potential uses of probiotics. The complexity of the microbiome is a major limiting factor in the development, assessment and use of probiotics. Only recently have techniques and bioinformatics methods developed to where they appear to provide a good representation of the intestinal microbiome. Individuals also vary in the make-up of their microbiome.

Many investigations of the GI microbiome are under way, including studies of companion animals, although there is a vast amount yet to learn. Additionally, the use of faecal samples, which is a practical necessity, has limitations since the intestinal microbiome varies throughout the intestinal length and faeces provide only some indication of the state of more distal areas (Weese, 2012).

In the GI tract, proposed benefits of probiotics include blocking intestinal pathogenic bacterial effects, regulation of intestinal epithelial cell functions, regulation of mucosal immune responses and effects on general immune function.

Lactobacilli species also synthesise B vitamins (niacin, pantothenic acid, pyridoxine, biotic and folic acid) and some of the lipolytic and proteolytic digestive enzymes. The actual mechanisms of action are complex and multifactorial (Wynn, 2009).

Probiotic use in dogs and cats

Studies in GI disease

A study evaluated whether a “cocktail” combination of probiotic supplementation in 21 dogs with food-responsive diarrhoea had beneficial effects on intestinal cytokines and microbiota and on clinical signs. All dogs clinically improved after dietary treatment. While intestinal cytokine patterns changed (in vitro) in response to probiotic treatment, the changes were not significantly associated with any clinical response to the probiotic supplementation (Sauter et al, 2005).

Dogs with inflammatory bowel disease (IBD) generally show less intestinal microbial diversity than normal dogs. Dogs with IBD supplemented with *E faecium* showed a significantly increased richness of the faecal bacterial microbiome, more similar to that of healthy dogs (Schmitz et al, 2014).

A combination probiotic, VSL#3, has been shown to restore the expression tight junction components (claudin-2, occludin and adherens junction proteins) of the intestine in dogs with IBD (Rossi et al, 2013). Restoring the tight junctions decreases the “leakiness” of the inflamed intestines. Further trials with a similar probiotic combination on canine IBD and other disorders are under way.

In a study in cats and dogs housed in a rescue shelter, the addition of the probiotic *E faecium* SF68 resulted in significantly lower incidence of diarrhoea in the cats, although the results in the dogs did not reach statistical significance (Bybee et al, 2011).

In a study of dogs with acute gastroenteritis, a probiotic cocktail shortened time to production of a normal stool from 2.2 days to 1.3 days compared to a placebo control group (Herstad, 2010).

Figure 2. Probiotics are often tried in the treatment of diarrhoea.

Another study, using canine-derived *Bifidobacterium animalis* strain AHC7 in dogs with acute idiopathic diarrhoea, also showed a shortened time to resolution of signs from a mean of 3.9 days in the treated group compared to 6.6 days for the placebo control group (Kelley et al, 2009; **Figure 2**).

The mean faecal score for cats completing a probiotic study decreased from 6.0 to 4.4, representing a significantly firmer stool character. A total of 72% of owners perceived an improvement in their cat's diarrhoea following a 21-day course of synbiotic supplementation (Hart et al, 2012).

Studies of *Lactobacillus acidophilus* in dogs and cats have shown a decrease in clostridial species.

One study evaluating the effect of dietary supplementation with the probiotic strain of *L acidophilus* DSM 13241 administered to 15 healthy adult cats demonstrated a significant reduction in *Clostridium* species and *Enterococcus faecalis* (Baillon and Butterwick, 2003).

Administration of a species-specific probiotic containing *Lactobacillus* group two and *E faecium* to 27 juvenile cheetahs was associated with a significantly increased bodyweight in the treatment group, with no increase in the control group. In addition, administration of the probiotic was associated with improved faecal quality (Koeppel et al, 2006).

Short-term treatment (six weeks) with the probiotic *E faecium* SF68 to 20 dogs with chronic, naturally acquired subclinical giardiasis failed to affect giardial cyst shedding or faecal giardial antigen and did not alter innate or adaptive immune responses at multiple time points (Simpson et al, 2009).

The effects of probiotic supplementation are temporary as the intestinal microbiome generally reverts to the population present prior to probiotic supplementation shortly after the probiotic is stopped. Overall, studies of the use of probiotics in GI disease have shown some positive results, although the results are not consistent.

Probiotics and immune system

Several canine and feline studies have looked at the effects of probiotics on white blood cells (for example, lymphocytes and eosinophils) and on serum and faecal immunoglobulins in response to vaccines (Lappin et al, 2009; Marshall-Jones et al, 2006; Benyacoub et al, 2003). These studies have shown various increases in these measurements of immune response.

Overall, the clinical relevance of these changes is hard to determine. Simply finding changes, while indicating something is probably happening with the immune system, does not necessarily indicate whether those changes are beneficial, detrimental or neither, and how they may be related to the potential for clinical efficacy. Nonetheless, they indicate the potential for probiotics to have at least some effect on the immune system.

Other potential uses of probiotics

Chronic kidney disease

In rats and pigs, a combination probiotic has shown a decrease in uraemia. In a small case study of azotaemic big cats, the serum urea nitrogen and creatinine concentrations decreased after 60 days of probiotic administration, although the concurrent treatments varied and the relationship to the quality of life of survival time was not clear (McCain et al, 2011).

In another study in cats with naturally occurring azotaemia, supplementation with a synbiotic had no effect on the level of azotaemia (Rishniw and Wynn, 2011).

Oxalate urolithiasis

Studies in humans have also shown some probiotics containing *Lactobacillus* can degrade oxalate in the intestine, resulting in decreased absorption and decreased urinary excretion (Lieske et al, 2005).

A study of the lactic acid bacteria in dog and cat faeces suggests manipulation of GI bacterial components may decrease intestinal oxalate, similarly potentially decreasing intestinal oxalate absorption and renal excretion (Murphy et al, 2009; Weese et al, 2004).

Obviously, further studies are required, but this shows potential for reducing the chances of stone formation in animals at risk.

Obesity and weight management

The causes of obesity are complex and include genetic, endocrine, neural, sociocultural and behavioural factors. There are also differences in the gut microbiota between obese versus lean rodents and people.

Figure 3. Probiotics may, in future, have a role in the treatment of overweight dogs and cats.

Animal studies have established the gut microbiota can contribute to obesity by improving the animal's ability to ferment indigestible dietary polysaccharides into short-chain fatty acids, which can provide up to 10% of the daily energy supply.

On the other hand, there are potential uses for probiotics in weight loss. Theories about the anti-obesity effects of some probiotics include an increase in conjugated linoleic acid, an increase in brown tissue thermogenesis, a decreased absorption of lipids, an altered activity in the brain's appetite centre and an increase in the fasting-induced adipose factor (Million et al, 2013).

No studies on probiotic effects on weight have been performed in small animals, but there could be potential uses in the future (**Figure 3**).

Safety of probiotics

Only a few safety studies have been performed with probiotics in dogs and cats. One study showed increased intestinal adhesion of *Campylobacter jejuni* in an in vitro model of canine intestinal mucus following incubation with *E faecium* (Vahjen and Männer, 2003). It should be noted this *E faecium* strain is different from the *E faecium* SF68 strain available commercially. Moreover, there has been no clinical or anecdotal evidence of Campylobacter-associated diarrhoea in dogs associated with *E faecium* administration.

The safety and palatability of a three-week course VSL#3 has been examined in cats in an uncontrolled study; other than a few vomiting episodes and changes in stool quality and appetite, it appeared to be safe (Waugh et al, 2013). The probiotic *Bifidobacterium animalis* AHC7 administered orally to dogs once per day at a dose of up to 5 × 1010 colony-forming units for at least 12 consecutive weeks was well tolerated with no safety concerns (Kelley et al, 2010).

It has been recommended probiotics should not be used in puppies and kittens under three weeks of age, or in animals that are markedly debilitated, immunosuppressed or affected with severe clinical signs of intestinal infections such as parvovirus or panleukopenia (Bowles, 2010).

Probiotic products are not all the same

The effects of probiotics are often extrapolated from one product to another and it is not uncommon to hear "I tried probiotics and they didn't (or did) help". Like antibiotics, we should not generalise from one product or one condition to another. Products differ widely in the types and amounts of microorganisms, and we don't yet fully understand which type and amounts may be effective in different disorders.

Summary

Evidence exists that the probiotic bacteria supplements are beneficial in dogs and cats for some GI diseases and there is increasing interest in their use for other diseases such as oxalate urolithiasis and renal disease. While few safety issues have been identified in dogs and cats, care should probably be used in immunocompromised or neonatal patients.

As the strains of bacteria have different effects, and combinations sometimes appear to be more efficacious, the results of studies should not be extrapolated to those using different probiotics.

The amount of microbes present in a product also probably affects the response. As always, well designed studies using larger numbers of cats and dogs are needed to more fully understand the benefits of these products.

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