Probiotics: the new treatment for acute diarrhoea in cats and dogs?

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Karin Allenspach, Silke Schmitz examine the use of this treatment in felines and canines, focusing on its effects, and discuss if and how probiotics might be used in the future

Summary

Probiotics are defined by the World Health Organisation to be “live microbes that, when administered in adequate amounts, confer a health benefit to the host”. They are frequently, though not necessarily, commensal bacteria. Probiotics are believed to interact with different parts of the innate immune system, thereby modulating the body’s inflammatory responses in health and disease. They have been used successfully in clinical trials in humans diagnosed with chronic inflammatory and/or autoimmune processes, such as atopic dermatitis, rheumatoid arthritis and IBD, as well as in acute infectious diseases (such as acute diarrhoea in paediatric patients).

Probiotics have the potential to skew the immune responses in the gut towards an antiinflammatory state. The probiotics in use in the UK for dogs and cats belong to the *Lactobacillus* and *Enterococcus* species. In cases of acute diarrhoea in dogs and cats, evidence is emerging that they have a beneficial effect on the severity and duration of clinical signs, as well as the frequency and amount of supportive treatments needed.

The use of probiotics in selected cases of acute diarrhoea may, in future, allow us to reduce the frequency and duration of antibiotic treatment in these situations.

Further studies investigating the exact immunologic actions and treatment benefits of probiotics in dogs and cats in chronic inflammatory conditions are long overdue. We are conducting a clinical

trial at the RVC investigating the efficacy of probiotics in dogs with confirmed inflammatory bowel disease. If you are interested in referring a case to the RVC, contact the clinical investigation centre cic@rvc.ac.uk

Key words

dog, cat, inflammatory bowel disease, innate immunity, probiotics, bacterial-host interactions

THE World health Organisation defines probiotics as “live microbes that, when administered in adequate amounts, confer a health benefit on the host”.

They are frequently, though not necessarily, commensal bacteria. To qualify as a probiotic, microorganisms should fulfil certain criteria: they should be identifiable at the genus, species and strain level; they should be safe for food and clinical use; able to survive intestinal transit in the target species; able to adhere to and colonise the mucosal surfaces; and possess clinically documented and validated health effects.

Development

As probiotics are usually derived from the commensal intestinal flora, they are species-specific, have co-evolved with their host and are essential for developing a healthy gut. Not only do they facilitate diverse processes, such as digestion, absorption and storage of nutrients, they are essential for the gut’s tolerogenic micro-environment.

The human gut harbours 100 trillion organisms and more than 500 species, and there is data emerging that a similar level of complexity exists in the intestinal microbiome of cats and dogs. Since most of these species are not culturable, the methods to try to elucidate the composition of the microbiome have dramatically changed.

It has become commonplace to sequence bacterial DNA obtained from intestinal biopsies or faecal samples and relate the sequences to published taxonomy data. The data obtained using such techniques show that most commensal bacteria colonise the gut of mammals within hours after vaginal birth. Bifidobacteria are the predominant species in the gut at the stage of colonisation, and the change to a more complex diet after weaning then allows the microbial population to diversify to a predominant population of Firmicutes (such as Clostridia and Bacilli) and Bacteroidetes (*Bacteroides*).

After weaning, the composition of the microbiome is specific to the individual animal and very stable over time[1]. This stability of the microbiome is, in most cases, maintained after acute injuries, such as infections or toxic insults to the intestinal mucosa and, although it can temporarily be

altered, will switch back to its normal composition after the mucosa has healed. The microbiome as a whole has many essential functions in the host, such as the production of essential nutrients, (glutamine and butyrate), which are especially important for intestinal epithelial cells.

In addition, the microbiome is critical for the normal development of the intestinal immune system. It has been shown that in mice, adequate production of mucosal antigen-specific immunoglobulin A (IgA) depends on normal homeostasis of the microbiome[2]. This has been shown in studies of mice raised in a germ-free environment, as such mice do not develop their gut-associated mucosal lymphoid tissue (GALT) appropriately, and, specifically, lack any Peyer's patches. They also do not develop appropriate antigen-specific IgA responses.

Furthermore, the specific role of the microbiome in intestinal inflammation has been studied in immunodeficient interleukin – 10-/- knockout mice, which do not develop intestinal inflammation as long as they are kept in a germ-free environment. However, they develop severe intestinal inflammation resembling human inflammatory bowel disease (IBD) as soon as their gut is colonised by commensal flora. This provides some evidence that the microbiome can be implicated in the development and maintenance of chronic inflammation in the intestine. Several studies in humans and dogs have replicated these findings in clinical disease situations[3], [4].

In people with inflammatory bowel disease, such as Crohn's disease and ulcerative colitis, the microbiome is enriched in *Enterobacteriaceae* species and, specifically, some species of *Escherichia coli*[5]. Similar findings have been published for boxer dogs with ulcerative colitis, where adherent-invasive *E coli* bacteria can be found in the lower areas of the inflamed mucosa6. Furthermore, certain species conventionally considered as beneficial for intestinal health, such as sequences belonging to the phylum Bacteroidetes, are consistently depleted in the intestines of human beings with IBD.

Similarly, intestinal biopsy samples from dogs diagnosed with IBD were significantly enriched in sequences of the *Enterobacteriaceae* family, and showed a markedly reduced diversity compared to samples from healthy dogs. Taken together, these data indicate that the microbiome is significantly changed in chronic intestinal inflammation, and it probably contributes to the ongoing inflammation in a way that prevents the flora from "switching back" to a normal composition. The result can be that the intestinal immune system is constantly mounting a reaction against bacterial components of the microbiome, especially if there is a imbalance in the microbiome, as described in cases of IBD.

Immune response

Probiotics may be one way to help switch back the microbiome to a more normal homeostasis, and they could also modulate and direct the host's immune response towards an antiinflammatory profile. Probiotics could do this by being recognised by specific receptors of the innate immune system and could, therefore, alter the adaptive immune response towards tolerance of the specific

antigen or microbe. Specific conserved molecules on the surface of microorganisms (for example, lipopolysaccharides, lipopeptides and flagellin), called microbeassociated molecular patterns (MAMPs), bind to the patternrecognition receptors (PRRs).

The most well-documented PRRs are toll-like receptors (TLRs) and nucleotide-oligomerisation domain-like receptors (NODs). Binding of a MAMP to a PRR triggers a signalling cascade within the cell that either results in a tolerogenic response of the adaptive immune system (dendritic cells and regulatory T-helper cells) or, when encountering pathogens, in an inflammatory response, with the recruitment of numerous T-helper cells of different cell lineages depending on the encountered pathogen (Th1, Th2 or Th17 response).

As shown in several studies in humans and experimental animals, probiotics have the potential to skew a chronic proinflammatory state, as encountered in allergies, atopy, IBD or rheumatoid arthritis, back towards a more tolerogenic state. This reduces the production of inflammatory cytokines in the gut and the periphery and, therefore, alleviates clinical signs.

However, there are some important caveats to this principle. Experiments in mouse models of IBD have shown that the minimum amount of probiotics per dose is 109 colony forming units or CFU/gram; any less and there will be no beneficial effect. These experiments have also shown that the probiotics must be live bacteria for them to have the desired effect, and that heat, or acid-inactivated bacteria, will not work. This obviously means that the bacteria should also be able to survive in the gastrointestinal tract, which ideally should have been tested in the species that the probiotics are used in. In addition, repeated dosing once a day over several weeks is important to induce an antigen-specific IgA response[7].

Use and effects of probiotics

There are only two probiotic bacterial strains licensed in the UK for use in small animals: *Enterococcus faecium*, available for cats and dogs, and *Lactobacillus acidophilus*, available only for dogs. Both have been assessed by the European Food Safety Authority and were declared safe to use in 2004.

Several studies have investigated effects of different probiotics in healthy animals. L *fermentum* caused significant increases in serum total protein and lipid concentrations and decreases in blood glucose levels in healthy dogs. Another study assessed the survival of probiotic *Lactobacillus* strains when administered via jejunal fistulas. It found that although the probiotic strains disappeared within seven days of discontinuation of administration, there was a permanent change in the jejunal microflora with native *Lacidophilus* predominating. The ability of lactic-acid producing bacteria to interfere with adhesion by enteropathogens was also evaluated by using dogs with jejunal fistulas.

Different strains of *Lactobacillus, Bifidobacterium* and *Enterococcus* were tested, and all of them

reduced adhesion of *Clostridium perfringens*, but not that of *Salmonella typhimurium* or *Staphylococcus intermedius*. Two strains increased adhesion of *Campylobacter jejuni*. One study indicated that only with very high numbers of administered *lactobacilli* (5 × 1,011 CFU/day) could maximal colonisation and faecal recovery be achieved in healthy beagle dogs[8].

There is only one study to date assessing the effects of probiotics in healthy cats[9]. Cats were fed *Lacidophilus* and several haematological (decrease in lymphocyte numbers, increased eosinophils, increased granulocyte phagocytic activity, decreased erythrocyte fragility and reduced plasma endotoxin concentrations) and faecal changes (decreased pH, decreased Bifidobacteria, Clostridia and *Enterococcus faecalis* numbers) were observed.

The use of probiotics in disease has most extensively been studied in canine acute diarrhoea. In a study of 36 dogs with acute diarrhoea, a probiotic cocktail, including strains of *Pediococcus acidilactici, Bacillus subtilis, Bacillus licheniformis* and *Lactobacillus farciminis* was evaluated in a randomised, double blind and single centre study[10]. The results of that study showed that the time from initiation of treatment to the last abnormal stools was significantly shorter (P = 0.04) in the probiotic group compared to the placebo group (mean time was 1.3 days and 2.2 days). In a study of an acute outbreak of *Giardia* in dogs, treatment with *E faecium* did not show any effect compared to placebo treatment[11].

To the contrary, one study in cats included 33 kittens with acute diarrhoea in a naturally occurring outbreak of *Giardia* infection. Half the cats were treated with *E faecium* and half with a placebo. There were significantly fewer kittens that needed additional supportive treatment in the probiotic treatment group (9.5 per cent of the kittens administered the probiotic, compared with 60 per cent of the placebo group). In another study, 50 kittens with acute diarrhoea from a *Campylobacter* outbreak were first treated with 10 days of cephalosporin, and then with either *L acidophilus* versus placebo for three weeks. The results showed there was significantly less shedding of *Campylobacter* in the group treated with probiotics as compared to the placebo.

In chronic diarrhoea, there is less evidence that probiotics could have beneficial effects in dogs and cats. One study included 30 adult cats with chronic diarrhoea that had been ongoing for more than a year. Clinical signs improved in 30 per cent of cats treated with *E faecium* for three weeks versus none of the placebo-treated cats.

In dogs with chronic diarrhoea, only one study has been published to date. A probiotic cocktail of three different *Lactobacillus* strains given to 22 dogs with food-responsive diarrhoea was given for four weeks. No additional beneficial effect was seen either on clinical signs or the level of intestinal cytokine expression profiles when compared to the placebo treatment group[12].

Conclusion and outlook

Probiotics have shown the potential to influence the immune response of the body and,

subsequently, be useful in treating several immune-mediated conditions in humans and animal models. They specifically have an effect on the intestinal microbiome, and there is proven efficacy in both species, especially in cases with acute diarrhoea.

However, in more complex diseases, such as IBD in cats and dogs, where genetic and environmental factors seem to be interacting and are equally responsible for the clinical picture, probiotics may not be the solution for sole treatment of the disease. We believe, however, that they may represent an important adjunctive treatment or may be useful in a subgroup of cases. The characteristics of the individual animals that may benefit from this treatment still need to be determined further. The evidence for using probiotics points towards good efficacy in acute diarrhoea cases in dogs and cats, which may mean the amount and duration of antibiotic treatments could be reduced in many cases seen on a daily basis in clinical practice.

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