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PURINA® SYMPOSIUM 2024

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PURINA® PRO PLAN® Symposium 2024

Rosa Carbonell i Ferré
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Nestlé Purina PetCare & FEDIAF President

Gastrointestinal health plays a crucial role in the overall well-being of our canine and feline companions. As we gather for this symposium on New Advances in Canine & Feline Gastroenterology, we aim to explore the latest breakthroughs in understanding and managing gastrointestinal conditions in our beloved pets.

Throughout this symposium, we had the privilege of bringing together esteemed specialists in the field of veterinary medicine and research. Their expertise and dedication allowed us to delve into the fascinating world of gastroenterology, uncovering innovative approaches to diagnosis, treatment, and nutritional management.

At PURINA®, we are committed to advancing the field of gastroenterology and improving the lives of our furry friends. Through ongoing research and collaboration with leading experts, we strive to develop innovative solutions that address the unique needs of dogs and cats with gastrointestinal conditions.

We firmly believe that through global collaboration and knowledge exchange of evidence-based science, we can all ensure the long and healthy lives of pets.

I hope you enjoy the PURINA® PRO PLAN Symposium on New Advances in Canine & Feline Gastroenterology!

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Canine chronic enteropathies: classification (facts & controversies) and nutritional management

Dr Valérie Freiche Hospital Practitioner, Head of GI diseases consultation at École nationale vétérinaire d'Alfort

Biography

Valérie Freiche graduated from Alfort National Veterinary School near Paris, France.
After her graduation, she completed an internship and French internal medicine specialisation at the Department of Internal Medicine in the same Vet School.

She defended her PhD project on the Comparative Oncogenesis of Indolent T-cell Lymphoproliferative Intestinal Disorders in cats and humans. This study involved both human and vet researchers and this collaboration is still ongoing.

Nowadays Valerie is a member of the Internal Medicine Department of Alfort Vet School, and she is involved in clinical teaching and research. She is the head of the gastroenterology consultation.
She is currently the vice-president of the ECVIM-European Society of Comparative Gastroenterology (ESCG).

Her main interest is gastroenterology, particularly digestive oncology and interventional endoscopy. Her publication list consists of journal articles, research abstracts and book chapters. Valérie is strongly involved in veterinary continuing education.

CANINE CHRONIC ENTEROPATHIES: CLASSIFICATION (FACTS & CONTROVERSIES) AND NUTRITIONAL MANAGEMENT

Dr Valérie Freiche Hospital Practitioner, Head of GI diseases consultation at École nationale vétérinaire d'Alfort

Canine chronic enteropathies (c-CE) also referred to as Canine Chronic inflammatory enteropathies are a heterogeneous group of disorders that are defined by persistent or recurrent clinical signs of gastrointestinal disease without a primary neoplastic, metabolic, parasitic, or other infectious cause. Their diagnosis is established after a thorough assessment. Clinical expression includes diarrhea, vomiting, and/or tenesmus, mucoid stools, hematochezia, weight loss, abdominal pain, and potentially anorexia for a period of >3 weeks. CE are considered as debilitating diseases in dogs.

This presentation will aim to:

1. Depict the interest and limits of the current classification

2. Describe an overview of the therapeutic approaches of c-CE and their limitations, highlighting nutrition. **The medical treatment of c-CE will not be extensively developed during this session**

3. Focus on FRE management according to the author's own experience

4. Challenge preconceived ideas & outline potential prospects

1. Depict the interest and limits of the current classification: although the etiology of c-CE is unknown, it is thought to be the result of complex interactions between host genetics, its immune system and microbiota.

Over the past decade, to standardize the clinical management of the cases, canine CE have been sub-categorized according to therapeutic response, with food-responsive enteropathy (FRE), antibiotic-responsive enteropathy (ARE), immunosuppression-responsive enteropathy (IRE) described, with the latter including protein-losing enteropathies, and finally non-responsive enteropathies (NRE).

A recent paper has recently called the c-CE classification into question, evoking:

a. The scientific data published concerning gut microbiota over the past years,
b. The deleterious effects of antibiotics administration in C-CE,
c. A proportion of dogs classified as NRE ultimately responding to additional diet trials.

2. Describe an overview of the therapeutic approaches of c-CE and their limitations, highlighting nutrition: the therapeutic approach of c-CE includes, according to the subtype classification of the canine patient:

a. Diet
b. Microbiota modulation
c. Antibiotics (?)
d. Immunosuppressive drugs

a. Diet: nutrition management is a cornerstone of CE treatment. Nutrition is known to influence the immune system, enhancing epithelial barrier function, modulating the microbiota, and even regulating gene epigenetics expression. The paradox is that nutrition is known to be both a triggering factor and a therapeutic weapon. Any type of diet should meet the World Small Animal Veterinary Association (WSAVA) Global Nutrition Committee (GNC) recommendations. The acceptance of the diet will be a crucial requirement in dogs suffering from c-CE.
According to established guidelines, dietary trials are required both for diagnosis and as first-line therapy, and most dogs respond without the need for immunomodulating drugs. They most usually involve:

a. Hyperdigestible diet ("gastrointestinal diet")
b. Limited ingredient / novel protein diets (home-cooked diet is possible too).
c. Hydrolyzed diet

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Hyperdigestible diet is a first step in the nutritional management of c-CE. Some studies showed that an extruded animal protein-free was able to enhance the fecal microbiota richness. Given that both the size and structure of dietary proteins influence its ability to induce an antibody-mediated hypersensitivity response, there is a biological rationale for hydrolysis of dietary proteins to create oligopeptides that are of a smaller molecular weight and are less likely to be immunogenic.

Several therapeutic diets with a hydrolyzed protein source are now commercially available to assist with management of CE, with these differing in the nature and extent of hydrolysis that has taken place.
A hydrolyzed diet formula contains soy and omega-3 fatty acids which are known to be immunomodulatory, and a lower fat percentage which has been proven to be effective.

That said, in daily practice, no attempt is performed to characterize the food antigens responsible in each case, and no rechallenging with the original diet is accepted by the owners.
Essential nutrients are crucial in the treatment of c-CE:

-Fiber cannot be digested by mammalian enzymes (plant-based carbohydrates). Their fermentation by intestinal microbiota produces short chain fatty acid (SCFA) and plays an essential role in the integrity of the intestinal barrier function. Fiber adjunction may resolve chronic colitis in dogs. Furthermore, dietary fibers promote the expansion of an optimal intestinal microbiota.
-Fat digestion or absorption can be defective in many Gi diseases in dogs. Dietary fat composition is a real concern in dogs suffering from protein losing enteropathy (PLE), particularly those showing a lymphangiectasia.
-Vitamins and minerals deficiencies: hypocobalaminemia is a real concern in c-CE. Low serum Vitamin D concentration is a negative prognosis factor in PLE in dogs. Magnesium deficiency is established as well in those dogs.

c. Microbiota modulation

Gut dysbiosis is constant in c-CE and is characterized by a decrease in diversity and richness of the microbiota. The dysbiosis in affected dogs is defined by an increase of Actinomycetota and Pseudomonadota phyla and by a decrease of Fusobacteria, Bacteroidota and Bacillota. The microbiota alteration leads to important metabolic mensformation and proteolytic activities, short-chain fatty acids synthesis alterations...

A dysbiosis index has been established according to a mathematical algorithm and allows a rapid assessment and follow up in dogs suffering from CE.
Restoring intestinal microbiota implies different prescriptions but further studies are needed to validate their clear indications.

-Fecal Microbiota transplantation (FMT).
-Prebiotics administration/diet adjunction.
-Probiotics prescription.
-Symbiotics.
-Bile acid sequestrants.

d. Antibiotics:

When the response to dietary trial is poor, antibacterials are supposed to be trialed, even this subtype is called into question according to the recent microbiota studies. ARE represent 15 to 25% of the cases. Young, large-breed dogs are overrepresented, particularly German Shepherds in which genetic predispositions have been confirmed. Tylosin and metronidazole are the most frequently prescribed drugs. That said, relapses are very frequent, and no guidelines have been established concerning the duration and the repeatability of the treatment.

Over the past years, a gradual decrease of the prescription has been validated by specialists, but unfortunately, like in other specialties, antibiotics are still over-prescribed in gastroenterology. In the One Health era, the inappropriate prescription of antibiotics enhances antimicrobial resistance.

e. Immunosuppressant drugs:

IRE probably represent a minority of c-CE. Due to the potential harmful effects of immunosuppressant, the need for prescription must be formally confirmed.

4. Focus on FRE management according to the author's own experience: The FRE form is the predominant type of CE, being more likely to affect younger dogs and with less severe clinical signs than for IRE. They represent more than 60% of the cases.
Furthermore, in the author's experience, it is quite difficult to assess the nature and the different subtypes of treats administered to the dog.

As previously mentioned, this classification is currently reconsidered on some issues.
Immune dysregulation has been implicated in the pathogenesis of CE, including FRE where immune dysregulation to dietary protein -or any other food component- is suggested.

Hypersensitivity to proteins involves the binding of antigens to antigen specific IgE on the surface of mast cells, causing degranulation and the release of heparin and histamine.

No clear limit defines the different subtypes of c-CE. According to the current guidelines, one-to-three diet trials should be performed prior to performing more invasive investigations, and obtain endoscopic gastrointestinal biopsies submitted to histopathologic analysis.

These recommendations (2-3 diet trials) may lead to inappropriate investigations, incorrect classification of the dog in the IRE group and generate the prescription of complex and potentially ineffective medical treatments.

According to the author's clinical experience, some dogs may benefit from more diet trials than expected to show clinical improvement: thus, in any dog under 6 y.o. in good clinical condition, if the thorough investigations including abdominal ultrasound examination are nonspecific, the probability to diagnose FRE is high.

We recently performed a descriptive retrospective study in our Institution over the last 24 months. A part of the results will be presented.

5. *Challenge preconceived ideas & outline potential prospects.*

The results of our descriptive study confirm the need of multiple diet trials and highlight the risk of assigning the dog to a wrong CE subtype (i.e. IRE or NRE instead of FRE).

A more accurate understanding of the underlying mechanisms of pathophysiology of c-CE is needed.

-Prospects will probably define more accurately the indications and limits of fecal microbiota transplantation and microbiota modulation and further studies are needed to establish standardized protocols.

-New studies will focus on reliable biomarkers already suggested by the literature data. The availability of the dosages is currently a limit to their daily application.

-In vitro cell culture systems are unable to give the same results as in vivo due to the interplay between the intestinal epithelium and the gut microbiome. As in human patients, a strong variability exists between the responders and an individual approach will probably be needed. Patient-derived organoids have provided substantial advancement in personalized medicine. Intestinal organoids can provide important findings on dysregulation of epithelial permeability. Furthermore, candidates-drugs or nutritional elements may confirm their usefulness thanks to this innovative process.

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Omics Technologies in Veterinary gastroenterology: Review and New Perspectives

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Biography

Jan S. Suchodolski is a professor, Purina PetCare Endowed Chair for Microbiome Research, associate director and head of microbiome sciences at the Gastrointestinal Laboratory at Texas A&M University.

He received his DrVetMed from the University Vienna, Austria and his PhD in veterinary microbiology from Texas A&M University. He is board certified in immunology by the American College of Veterinary Microbiologists (ACVM).

His research is focused on developing biomarkers for gastrointestinal disease and therapeutic approaches for the modulation of the intestinal microbiota.

He has authored or co-authored more than 360 peer-reviewed articles in the area of veterinary gastroenterology and microbiome research.

OMICS TECHNOLOGIES IN VETERINARY GASTROENTEROLOGY: REVIEW AND NEW PERSPECTIVES

Dr Jan S. Suchodolski Professor, Small Animal Internal Medicine, Purina PetCare Endowed Chair for Microbiome Research, Associate Director for Research, Head Microbiome Sciences, Gastrointestinal Laboratory Texas A&M University

Overview

Recent studies have utilized various -omics platforms to better characterize the intestinal environment in dogs and cats. These techniques encompass evaluation of the intestinal microbiome using next-generation sequencing, serum and fecal metabolomics to evaluate host- and microbial derived metabolites, and proteomics. These results demonstrate that acute and chronic enteropathies encompass various abnormalities in the function of the gastrointestinal tract, with severity and duration of the dysfunction depending on the underlying cause.

In chronic enteropathies (CE), chronicity is associated with chronic mucosal remodeling with subsequent loss of function and malabsorption that is associated with inflammation and persistent dysbiosis in a subset of patients. However, the extent of these changes varies tremendously between individual patients, and this is likely the reason why the response to therapy varies between animals. Will allow us to better tailor multi-modal approaches to the subsets of disease, which in turn may allow for better long-term management of intestinal disease.

Finally, earlier detection of intestinal changes before clinical signs manifest also may improve the long-term outcome of patients. Therefore, assessing changes in the intestinal tract on both the host and microbiota side using multiomics approaches will be helpful.

Background

The gastrointestinal tract (GIT) encompasses various functions by the host and also the resident microbiota, which is part of the host physiology. Within the GIT, dietary compounds are digested into smaller micronutrients. These are subsequently absorbed by active or passive transport in the brush border of the small intestine. Therefore, proper and balanced host and microbiota functions are required (figure 1). The intestinal microbiome itself consists of various microorganisms such as bacteria, viruses, fungi, and protozoa within the gastrointestinal tract (GIT). The intestinal microbes provide important immunological and metabolic functions.[1] Intestinal bacteria interact with the immune system through microbial surface molecules on bacterial and through microbiota-derived metabolites. Bacteria also metabolize dietary substrates (eg, fiber, protein, and fat) or host molecules (e.g., primary bile acids). These provide energy, can be immune-modulatory, regulate motility, and/or improve gut barrier. Bacteria, such as Faecalibacterium ferment dietary carbohydrates to SCFAs. Indole compounds are metabolized from dietary tryptophan. Intestinal bile acid metabolism and conversion by bacteria is important in maintaining normal microbiota.[2] Briefly, primary BAs are released into the small intestine and a small percentage will be converted by intestinal microbes to secondary BA in the large intestine. In physiological amounts, they act as signaling molecules, have glucose-lowering effects, and are anti-inflammatory.[2] A lower abundance of

Clostridium (Peptacetobacter) hiranonis and decreased conversion of primary to secondary BAs is associated with intestinal dysbiosis due to antibiotics or chronic enteropathy in a subset of dogs and cats.[3]

The intestinal microbiota is in contact with the intestinal epithelium, mucus layer, the immune system, and the luminal environment. Depending on the extent of changes within the intestinal environment, these can affect the microbiota composition, and severe dysbiosis is a biomarker of an abnormal gut environment in disease. In addition, the altered microbiota can contribute to clinical signs in a subset of patients. Broad-spectrum antibiotics like metronidazole or tylosin have major effects on the microbiome, which persist for at least several weeks in some animals.[4]

Microbial metabolites that are associated with intestinal health (eg, SCFA, fecal bile acids) are negatively impacted by these antimicrobials and correlate with the changes in the microbiota composition.

Changes in intestinal disease

Intestinal inflammation and structural changes lead to changes in intestinal function (eg, absorption). The pattern differs between acute and chronic diseases.

In acute hemorrhagic diarrhea (AHD), changes in microbiome are associated with increased net-F toxin encoding C. perfringens that is self-limiting.

However, independent of treatment (antibiotics vs probiotics) the abundance decreases within a few days. The core bacterium and bile acid converting organism C. hiranonis remains typically with the reference interval in acute diarrhea, and the dysbiosis index is either not or only mildly increased.[5,6] Metabolic analysis indicates that in AHD, variousmarkers of intestinal damage (fecal long-chain fatty acids, fecal cholesterol, nervonic acid)[7] are increased at the time of presentation, but these markers normalize very quickly within a few days, and their normalization correlates with normalization of the microbiome and clinical recovery with a few days.[8]

In animals with chronic enteropathies (CE) non-invasive markers like calprotectin or C-reactive protein often decrease with successful therapy and correlate with clinical remission.[9]

However, mucosal infiltrates remain typically abnormal for a prolonged time. Furthermore, structural changes in the architecture of the intestine indicate chronic mucosal remodeling (eg, shortened and blunted villi) which is associated with damage of the mucus layer and changes in function (ie, changes in the expression of transporters)
malabsorption and altered oxygen levels at the mucosal surface and often leads to increases in aerobic bacteria and decreases in anaerobic bacteria, which correlate with intestinal inflammation.[11] C. hiranonis is decreased in 50-70% of dogs with CE, reflecting a dysbiosis pattern associated with chronic intestinal disease. Of note is that these microbiota and metabolomic changes typically persist for at least several months (if not years) and only moderately correlate with clinical remission.[7,12]

This is likely due to persistent changes in intestinal function due to chronic mucosal remodeling and fibrosis.[7,13] Another important new finding is that only a subset of animals with chronic enteropathy has detectable intestinal dysbiosis and/or these metabolic changes, as demonstrated by next-generation sequencing, quantitative PCR (Dysbiosis Index) and metabolic profiling.[3,7,12,14] This suggests that the extent of chronic intestinal inflammation and mucosal remodeling varies between individual animals. Therefore, there is a need to develop a staging system of intestinal damage and dysfunction, to better characterize the extent of changes in individual animals. This will allow for a more accurate

prognosis and recognition of which animals need long-term management of the underlying intestinal disease. This will also allow better individualized multi-modal treatment approaches, consisting of dietary modulation, immune-modulation, combined with microbiota based therapies (probiotics or fecal microbiota transplantation).

The intestine in health and disease

A healthy intestine is characterized by a balanced microbiome, an established mucus layer separating luminal bacteria from the epithelial cells, a normal epithelial cell barrier, and a regulated immune system.

In chronic inflammatory enteropathy, various changes may occur, with all of them potentially contributing to clinical signs. Loss of mucus allows luminal bacteria to attach to epithelial cells, stimulating pro-inflammatory cytokines. A broken barrier leads to translocation of food and bacterial antigen, which also activates the immune system. Loss of transporters in the brush border leads to malabsorption of dietary compounds, which can lead to bacterial overgrowth.

The inflammation (changes in pH and oxygen on mucosal surface) and the low-grade malabsorption of nutrients (provides substrate for bacterial overgrowth) both can contribute to intestinal dysbiosis. Therefore, assessment by multiple -omics tools can be helpful to describe the various parts of the intestinal tract.

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Fecal Microbiota Transplantation: Recent Advances & protocols

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Biography
DVM, Dr. med. vet.
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Kathrin Busch completed her doctoral thesis about "Acute hemorrhagic diarrhea syndrome" at the Small Animal Clinic of the Ludwig Maximilians university in Munich, Germany.

After an internship, she remained loyal to the small animal clinic and internal medicine and completed her residency in 2018. Since then, she has been working there as a senior physician and has rediscovered her love for gastroenterology.

Her research focuses on the intestinal microbiome, its influence on other organ systems and fecal microbiota transplantation.

FECAL MICROBIOTA TRANSPLANTATION RECENT ADVANCES & PROTOCOLS

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Introduction

The term fecal microbiota transplantation (FMT) describes the transfer of feces from a healthy donor into the gastrointestinal tract of a diseased recipient aiming to improve the recipient's health. As our understanding of the profound influence of the intestinal microbiome on overall health grows, the significance of modulating this community becomes increasingly apparent.

Mechanisms

While the precise mechanisms of action remain somewhat elusive, the growing success of FMT in both human and veterinary medicine has spurred its popularity. FMT goes beyond simply introducing a high quantity of beneficial bacteria. The transferred microorganisms function as a symbiotic community, capable of temporarily colonizing the recipient's colon and reshaping the composition of their microbiome. The precise mechanisms enabling the donor microbiome to do so, despite the stability and defense mechanisms of the resident microbiota remain inadequately understood. [1].

History

The concept of FMT was firstly described in the fourth century by Ge Hong, a Chinese physician,orally administered feces to patients suffering from severe diarrhea [2]. Centuries later, Andrea Acquapendente (1537 – 1619), an Italian surgeon, transferred gastrointestinal content from healthy to sick animals and German physician Franz Paullini described in his book "Die Heilsame Dreckapotheke" (1697) the benefits of feces for numerous diseases. During World War II, German soldiers stationed in Africa, consumed fresh camel feces as a treatment for bacterial dysentery. Though the benefits of bacteria were described in 1907 by Metchnikoff, it wasn't until Dr. Eiseman's publication in 1954, that FMT was formally introduced as a treatment for patients with pseudomembranous enterocolitis [3].

Possible indications

In human medicine, Clostridoides (C.) difficile infection is the most common indication for FMT, with high resolution rates (up to 90%) [4]. Moreover, FMT serves as a supportive therapy for chronic gastrointestinal disorders like Crohn's disease or ulcerative colitis [5, 6]. While studies on FMT in dogs and cats remain limited, some have shown promising results. For instance, a study in puppies with parvovirus infection for example, demonstrated faster resolution of diarrhea ($p < 0.001$) and shorter hospitalization times (median 3 days vs 6 days), if the dogs received a FMT in addition to standard treatment [7]. Another study found that 31/41 dogs with chronic enteropathy and inadequate response to standard therapy showed less severe clinical signs post FMT [8]. Initial indications also suggest that FMT may positively impact extra-gastrointestinal diseases such as immunological, neurological, or dermatological diseases [9-11].

Donor selection

Selecting a good donor is important and demands strong criteria. Beyond having good clinical health and a responsible owner, donors should be tested for possible enteropathogens and possess a healthy intestinal microbiome. Whether donor-recipient matching is necessary and if a "Super-Donor" exists remains uncertain [12].

Preparation

The feces are usually processed into a homogeneous slurry by adding saline solution, using aids such as blenders or stomacher bags. Coarse components are filtered out by using a sieve. Rapid processing and administration are advantageous to minimize microbiome composition changes. Glycerol may be added to preserve the FMT slurry, which is then portioned and frozen at -20°C or -80°C. Another method that has been established in recent years is the freeze-drying of feces and then orally administering them in capsule form.

Administration

FMT can be administered orally, endoscopically, or rectally. While rectal administration is common in veterinary medicine, no method has demonstrated superiority to date. Oral administration has shown a positive effect in some studies as well.

Risks

FMT is considered a safe treatment method in human medicine with less than 1% of serious side effects [13]. Although there are currently no large studies on the safety of FMT in dogs and cats, this therapy is also considered to be quite safe.

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The science behind probiotics & postbiotics

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& Purina's Director of Program Management

Biography

Dr. Jason Gagné is a Board-Certified Veterinary Nutritionist® and is Purina's Director of Program Management where he develops strategies to cascade research across Purina's portfolio of Brands. He also works with innovation and renovation of dietary formulations, developing clinical trials, and Sales and Marketing.

Prior to, and throughout his residency at Cornell, he served as an Associate Veterinarian in a small animal practice in Syracuse, New York.

Jason has authored several publications in veterinary journals and textbooks, given scientific presentations at the regional and national level, and serves as a scientific reviewer for leading journals.

THE SCIENCE BEHIND PROBIOTICS & POSTBIOTICS

Dr Jason Gagné Board-Certified Veterinary Nutritionist®
& Purina's Director of Program Management

The Science Behind Probiotics & Postbiotics

The gastrointestinal tract contains thousands of species of bacteria, some of which are beneficial and some of which are potentially pathogenic. The gut microbiome contains an entire ecosystem of microorganisms – called microbiota – that includes these bacteria, as well as viruses and fungi. It is a complex ecosystem in which the resident microbiota and the host interact in numerous ways to establish and maintain a functional barrier that protects the host from attack and infection by pathogens and ingested substances to which the host is continually exposed.

The majority of microbiota are in the large intestine, with bacteria from genera including Bifidobacterium, Lactobacillus, and Enterococcus, as well as some potentially pathogenic bacteria from genera such as Clostridium and Staphylococcus.[1-4] The predominant phyla present in the gut microbiome of healthy dogs and cats include Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria.[5-7] Despite phyla similarities, the microbiome is unique for each dog. In one study analyzing the fecal microbiota in 76 healthy dogs by qPCR and shotgun sequencing, only a small number of bacterial species (17/1190) were consistently present in the microbiomes of these dogs.[8]

A growing body of evidence has shown that the resident microbiota also play a number of active, beneficial roles in host health. Some of the known functions of the gut microbiome include:[9,10]

- Providing nutrients for the host via fermentative and metabolic activities
- Breaking down dietary fibers
- Helping develop the immune system and maintaining homeostasis
- Defending against intestinal pathogens
- Aiding nutrient digestion and absorption in the gastrointestinal tract
- Supporting gastrointestinal health

Many of these functions result in improved stool quality, enhanced immune function, decreased stress-related GI signs, and reduced anxious behaviors. In addition to directly impacting GI health, the gut microbiome may affect other organs and systems, such as the brain. Maintaining microbial balance in the gastrointestinal tract can help ensure optimal gastrointestinal and immune function and influences the overall health of the animal.

The gut composition of the microbiota can be affected by the pet's environment, genetics, diet, stress, medications, host health, and other factors. Microbiota imbalance, or changes in the composition of the gut microbiome that impact microbiome function, is called dysbiosis and can significantly impact the health of the GI tract and other systems.

gut microbiome is crucial to maintaining health and to helping manage GI disease. Potential stressors to the gut microbiome that may contribute to development of a dysbiosis include environmental changes, dietary modification, administration of antibiotics, stress, or dietary indiscretion. Animals with GI diseases such as

diseases such as chronic enteropathies may have a greater degree of dysbiosis versus healthy dogs and cats.[11]
Diet has a profound impact on health, including gut health and the health and resilience of the microbiome. Nutritional interventions with "biotics" such as prebiotics, probiotics, postbiotics, and tribiotics (combinations of prebiotics, probiotics, and postbiotics) may be beneficial in cases where intestinal dysbiosis is present and offer numerous opportunities to positively impact host health.

Probiotics
A probiotic is defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host."[13,14] Probiotics have the potential to provide many benefits to pets. These benefits include promoting digestive health, supporting immunity, and many other benefits outside the gastrointestinal tract in systems affected by the gut microbiome, such as the brain.

Probiotics are referred to by their genus, species, and strain. Probiotics are strain-specific and dose-dependent, meaning different strains have different effects, and a specific amount must be provided to deliver benefits to the pet. When recommending probiotic supplements, veterinarians should research the probiotic in the supplement to ensure it has demonstrated efficacy in the target species.

Probiotics are one way to influence gut health and other aspects of pet health. Probiotic supplementation or providing a probiotic in a pet food may aid in maintaining or improving digestive health by:

- Competition with potentially pathogenic bacteria in the GI tract
- Production of antibacterial substances
- Creation of an environment that is unfavorable for pathogens
- Production of metabolites that can be beneficial to the host and other microbiota (such as SCFAs)

To be effective, a probiotic must be stable throughout its shelf-life to be present in sufficient numbers or colony forming units (CFU). This means the probiotic must remain stable during manufacturing, shipping, and typical storage conditions. A study of 25 commercial veterinary probiotic products showed only 2/25 of the products had a label that accurately described the content, including the specific strains and the CFUs.[15] Therefore, it is important to investigate a probiotic's efficacy in the target species and to use products from trusted manufacturers, so an appropriate, safe, and reliable product can be selected.

Probiotics can help veterinarians manage several different health issues in dogs and cats. These include reducing GI signs such as diarrhea associated with stress, dietary change, dietary indiscretion, or antibiotic usage.[16-18] Some probiotics are also safe for these uses in puppies and kittens over eight weeks of age. They may also reduce anxious behavior and increase social interactions by impacting the gut – brain axis.[19-21] Additionally, probiotics can also be immunomodulatory; supplementation or feeding of certain probiotics has been shown to support immune function.[22]

To influence health, a probiotic provided as a supplement or in food should meet some or all of the characteristics of an effective probiotic for pets, which include the following:

- Be resistant to digestion by gastric acid or intestinal enzymes
- Reduce or prevent the adherence of pathogenic bacteria in the gut
- Produce products unfavorable to pathogen growth (example: short chain fatty acids that lower intestinal pH)

· Remain viable until consumption by the pet
· Promote a normal and balanced microbiome
· Provide a health benefit to the dog or cat
· Be safe for the pet, noninvasive, and nonpathogenic

There are multiple probiotics that meet these characteristics and requirements, such as Enterococcus faecium SF68, Bifidobacterium longum BL999, and others. Results of clinical studies using these probiotics are applicable only to the specific strains in the probiotic supplement or pet food and cannot be assumed to be effective for all strains of the bacterial species.
Extensive research has led to the development of probiotics that are both effective and safe for dogs and cats.

SF68
Enterococcus faecium SF68, or E. faecium SF68, has a long history of safe use in both animals and humans. It is nonpathogenic and nontoxic and does not have abnormal resistance to antibiotics. Importantly, it survives the conditions of the gastrointestinal tract since it is microencapsulated increasing the stability and viability. It then reaches the intestines but does not colonize the GI tract permanently.[23]

An extensive number of publications show E. faecium SF68 supplementation results in an improvement of diarrhea associated with multiple causes, and that it supports a strong immune system.[16-18,20,22,24-28]
One example is E. faecium SF68 improving diarrhea resulting from stress and antibiotic usage.[17,18,26] E. faecium SF68 can be safely fed to puppies and kittens 8 weeks and older, in addition to adult and senior dogs and cats.

BL999
Bifidobacterium species have a wide variety of effects on host health including inhibition of adhesion of pathogenic bacteria, stimulation of immune function, and reducing anxious behaviors.[19,21,29]
Studies evaluating the effects of Bifidobacterium longum BL999 NCC 3001 have shown benefits on psychological stress in humans.[30] B. longum BL999 NCC 3001 has also been shown to reduce the expression of anxious behaviors in dogs and in cats.

Dogs fed B. longum BL999 for 6 weeks had improved behavioral evaluations versus dogs receiving a placebo. Improvements such as reduced barking, reduced pacing, and increased exploratory behavior were noted.[21] Dogs supplemented with B. longum BL999 had a decreased heart rate and increased heart rate variability, suggesting improved adaptation to stimuli of potential anxious behaviors. The researchers also noted decreased salivary cortisol in response to stimuli.[21]

Anxious behaviors can be reduced in cats supplemented with B. longum BL999 as well. Cats given B. longum BL999 for 12 weeks showed reduced signs of stress and more social behavior versus cats given a placebo.[19] The cats fed B. longum BL999 were less likely to have abnormal serum cortisol concentrations.[19]

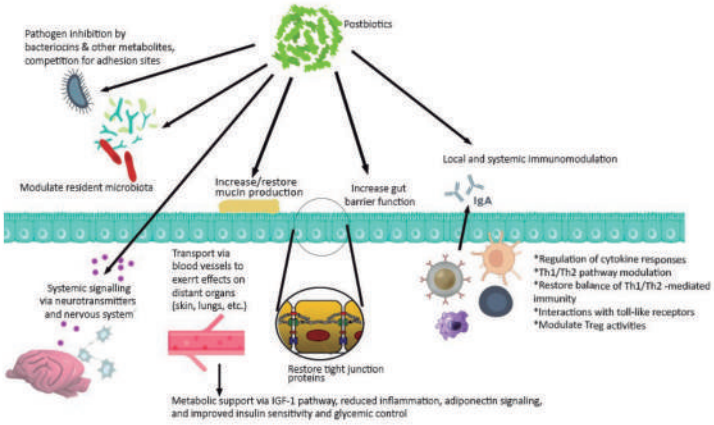
Postbiotics
The term "postbiotic" is derived from the Greek language, with "post" indicating "after" and "biotic" meaning "living thing;" therefore, a postbiotic is something that was alive but is now in its "after life" phase and inanimate.[31] In contrast to probiotics, bacterial viability is not an essential requirement for the health benefits of postbiotics. Beneficial effects of probiotics with viable microorganisms may also be observed when administering the same microorganisms after they have been killed/inactivated and can serve as biological response modifiers.[32-37]

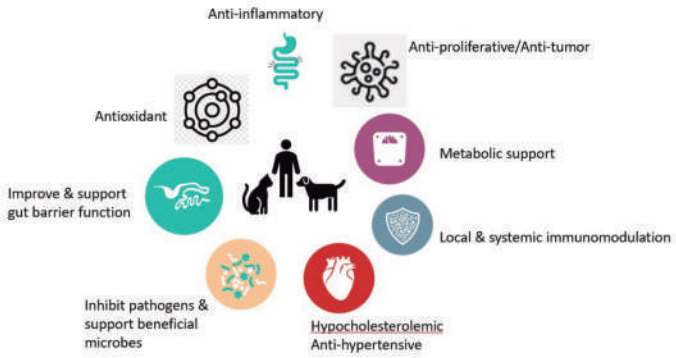
The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines a postbiotic as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host," indicating two primary parts: 1) inanimate cells and/or cell components; 2) with or without metabolites.[31,37] Most currently available postbiotics are derived from probiotic strains, but this is not a requirement.[37-39]

The efficacy of the postbiotic may differ from that of its parent source,[40] and a postbiotic cannot be presumed safe and effective because the microorganism from which it is sourced has been demonstrated safe and effective; the postbiotic's beneficial effects and safety must be demonstrated in the target host.[37,41] Similarly, the effects of a postbiotic cannot be fully predicted by the effects of its source.[42]

Postbiotic effects can arise from the dead cells, the cell walls and cell fractions, pili, and the metabolites in the extracellular medium.[32,33,37,42] Postbiotics may be derived from bacteria, yeast, or fungi. Their production involves rendering the cells of the microorganism inanimate by physical (e.g., heat, irradiation, pressure, etc.) or chemical means (e.g., acid deactivation).[33] The production process can have a notable influence on the composition of the postbiotic as well as its nutritional value, sensory characteristics, and flavor.[37]

The mechanisms of action of postbiotics have not been fully elucidated.[33,34] Postbiotics can affect physiological, immunological, neuro-hormonal, regulatory, and metabolic reactions via metabolic and signaling pathways.[33,35,43-45] They can also directly and indirectly induce alterations of the gut microbiome.
effects depends on their composition, with some postbiotics having more profound clinical effects in one or more of these categories compared to other postbiotics.





The effects of postbiotics are not limited to the gut; they can be as far-reaching as the effects of the microbiome itself.[37] In addition to GI and immunomodulatory benefits, postbiotics and microbial metabolites have shown some beneficial effects for atopic dermatitis,[47,48] respiratory tract immunity,[49,50] allergic rhinitis,[51] gingivitis,
diabetic retinopathy,[55] and muscle strength and athletic endurance.[56]

Unlike probiotics, postbiotics are not comprised of live microorganisms and therefore they do not face some of the same challenges, such as surviving the environmental conditions within the GI tract or surviving the processes of manufacturing, packaging, transporting and storing the products.[32,33,36,41,46,51,57]
Because postbiotic function does not rely on live microorganisms, a great benefit of postbiotic administration is there is no need to worry whether live microorganisms will survive the pet food manufacturing process.

Many pet food ingredients that may be classified as postbiotics are already recognized as safe. However, regulatory frameworks regarding postbiotics are limited to date from a global perspective.[39]

Postbiotics may offer opportunities to reduce, or even replace, antimicrobial use in a number of situations.
Although antimicrobials can provide life-saving treatment of infection, they are not without potentially significant negative impact on microbiome and host health: antimicrobials alter gut microbial diversity and population, with some effects being transient while others are long-lasting.[58] An imbalanced, or dysbiotic, microbiome may induce metabolic and immunological disorders.[58]

Antimicrobial administration can select for antimicrobial-resistant microorganisms that may transfer resistance genes, further propagating antimicrobial resistance.[58,59]
In contrast, postbiotics may offer comparable benefits without the adverse effects of antimicrobial medications.

Postbiotics have been investigated in a number of species, and research is ongoing to determine optimal use of postbiotics for a range of uses.

- In livestock and poultry species, postbiotics have been shown to increase feed efficiency, growth performance, and quality of the products (e.g., eggs, meat) derived from animals as well as exert immunomodulatory effects.[60-68]

- Human studies have shown beneficial postbiotic effects for chronic diarrhea,[69,70] pediatric diarrhea,[71-73] respiratory infection,[49] and irritable bowel syndrome [74,75]

- Industrial uses include biopreservatives, stabilizers, emulsifiers, palatability enhancers, bacterial biofilm removers and inhibitors, and antimicrobial packaging methods.[33,45]

To date, the published research on postbiotics for companion animals is focused on postbiotics' effects in healthy animals. Observations in healthy pets include the following, depending on the postbiotic evaluated in the study:

- Immunomodulation, including stimulation of non-specific immune responses as well as cell-mediate immune responses; increased IgA production and interferon-γ secretion; and reduced TNF-α secretion[44,76-79]
- Reductions of inflammatory cytokines (e.g., IL-18)[42]
- Improved response to mild stress[42]
- Increased microbiome diversity and resilience[42]
- Improved stool quality in dogs exposed to mild transport stress[44,80,81]
- Increased antioxidant capacity[44,79,80]
- Increased skin sebum production and variable effects on skin barrier integrity[79]

In conclusion, postbiotic research is still in its early stages and much remains to be learned about their composition, effects, and appropriate clinical uses.

Postbiotics present a number of potential opportunities for improving health through functional benefits such as immunomodulation, metabolic support, improved gut barrier function, and anti-inflammatory and antioxidant effects. Postbiotics also offer advantages such as safety, stability, and long shelf-life as well as the potential to reduce antimicrobial use for certain conditions.

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