SYMPOSIUM PROCEEDINGS

Critical Updates on Canine & Feline Health

From 2011 NAVC and WVC Conferences

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From 2011 NAVC/WVC Conferences
Dogs with chronic intestinal disease typically present for investigation of diarrhea, weight loss, or vomiting. Diarrhea lasting 3 weeks or longer is usually considered chronic. The initial approach to treating chronic diarrhea is based on determining its nature and severity, along with specific or localized clinical findings. The onset of additional clinical signs often points to the underlying cause, such as:

- Tenesmus and dyschezia — large bowel disease
- Melena — upper gastrointestinal (GI) bleeding or ulceration
- Abdominal pain — structural disorders, perforation, thrombosis
- Abdominal distention, difficulty breathing, or peripheral edema — enteric protein loss.

This information is integrated to determine whether the diarrhea is attributable to large bowel disease, as characterized by dyschezia, tenesmus, increased frequency of defecation, and small volume of feces with mucus and blood, or is a consequence of small intestinal disease or exocrine pancreatic insufficiency, as characterized by a large volume of diarrhea, weight loss, and...
possible vomiting. In patients with abdominal pain, dehydration, frequent vomiting, or localized findings (eg, abdominal mass), these problems are pursued ahead of an in-depth workup for chronic diarrhea.

In patients with chronic diarrhea and no obvious cause, it is best to adopt a systematic approach as determined by the localization of diarrhea to the small or large bowel. Patients with signs of large and small bowel involvement are usually evaluated for diffuse GI disease.

This presentation reviews the diagnosis and management of dogs with chronic enteropathies predominantly associated with small bowel diarrhea.

**Investigation of Chronic Small Bowel Diarrhea**

The initial diagnostic approach to patients with chronic small bowel diarrhea is summarized in Table 1.

After exclusion of infectious and parasitic agents, non-GI disorders, exocrine pancreatic insufficiency, and intestinal structural abnormalities requiring surgery, the most common groups of intestinal diseases associated with chronic small bowel diarrhea are idiopathic inflammatory bowel disease (IBD), diet-responsive enteropathy, antibiotic-responsive enteropathy, and lymphangiectasia.

The approach to these patients is usually determined by the severity of clinical signs (ie, frequent severe diarrhea, excessive weight loss, decreased activity or appetite), along with the presence of hypoalbuminemia or hypocobalamimia and intestinal thickening or mesenteric lymphadenopathy. In patients with these abnormalities, intestinal biopsy is required to define the cause (eg, lymphangiectasia, lymphoma) and to optimize therapy.

The clinical severity of intestinal disease can be quantified by determining the clinical disease activity index (eg, attitude, activity, appetite, vomiting, stool consistency, stool frequency, weight loss). Measurement of serum C-reactive protein (CRP) has been shown to correlate with clinical disease activity (canine IBD activity index [CIBDAI]) and implies that severe clinical disease is accompanied by a systemic inflammatory response. Measurement of clinical disease activity or CRP can also serve as a baseline for determining response to treatment.

Controlled studies have shown that hypoalbuminemia is associated with a poor outcome in dogs with chronic enteropathy. Serum concentrations of cobalamin and folate can be measured to determine whether supplementation is required and low serum cobalamin concentration (< 200 ng/L) is associated with a negative prognosis. Evaluation of hemostatic function is recommended to ascertain if hypo- or hypercoagulability has developed as a consequence of enteric protein loss.

In stable patients with chronic diarrhea (ie, good attitude, appetite, mild weight loss, normal serum proteins, no intestinal thickening or lymphadenopathy), measurement of serum cobalamin and folate concentrations can help determine the need for intestinal biopsy, localize the site of intestinal disease (eg, cobalamin absorbed in the ileum), determine the need for vitamin B12 supplementation, and establish a prognosis. In stable patients with chronic diarrhea and normal cobalamin concentrations, the client can be given the option of empirical treatment trials with diet, followed by antibiotics if there is no response to diet (see section on Minimal change enteropathy). Failure to respond to empirical therapy or a worsening of disease is indication for endoscopy and intestinal biopsy. In stable patients with chronic diarrhea and subnormal serum cobalamin, I pursue endoscopic evaluation and intestinal biopsy rather than empirical treatment trials.

**Intestinal biopsy**

Intestinal biopsy samples can be acquired endoscopically or surgically. In patients without an indication for surgery (eg, intesti-

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**Table 1**

<table>
<thead>
<tr>
<th>Action</th>
<th>Steps to Take</th>
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<tr>
<td>Integrate signalment, history, and physical</td>
<td>Note breed predisposition, environment, diet, other clinical signs; localize</td>
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<tr>
<td>examination</td>
<td>findings</td>
</tr>
<tr>
<td>Detect endoparasites and enteric pathogens</td>
<td>Conduct CBC, profile, UA, ±TLI, ACTH stimulation, free T4/TSH, bile acids</td>
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<tr>
<td>by conducting clinicopathologic testing</td>
<td></td>
</tr>
<tr>
<td>• Detect non-GI disease</td>
<td></td>
</tr>
<tr>
<td>• Detect/characterize intestinal disease</td>
<td>Rule out hypoproteinemia, hypocalcemia, hypocholesterolemia, leukopenia, leukocytosis; check for low serum cobalamin and/or folate</td>
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<tr>
<td>Conduct diagnostic imaging</td>
<td>Radiography, ultrasound (liver, spleen, pancreas, lymph nodes, masses, effusions)</td>
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<tr>
<td>• Detect non-GI disease</td>
<td></td>
</tr>
<tr>
<td>• Detect/characterize intestinal disease</td>
<td>Radiography, ultrasound (obstruction, intussusception, focal masses, thickening, loss of layering, hypeerechoic striation)</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; CBC = complete blood count; GI = gastrointestinal; T4 = thyroxine; TLI = trypsin-like immunoreactivity; TSH = thyroid-stimulating hormone; UA = urinalysis.

**Hypoalbuminemia is associated with a poor outcome in dogs with chronic enteropathy, and low serum cobalamin concentration is associated with a negative prognosis.**
tinal masses, anatomic or structural disease, perforation), I prefer to perform diagnostic endoscopy to visually inspect the esophageal, gastric, and intestinal mucosa and to procure endoscopic biopsy samples. It is noteworthy that the endoscopic appearance of the small intestine correlates better with outcome than histopathologic appearance does. If there is a suspicion of ileal involvement (eg, low cobalamin, ultrasonographic evidence of disease), I perform a transcolonic ileoscopy in addition to the standard endoscopic examination.

Guidelines for biopsy acquisition have recently been published. Operator experience and biopsy sample quality and number are of key importance in facilitating histopathologic evaluation. Surgical biopsy is usually performed if involvement of the submucosa or muscularis is suspected or when endoscopic biopsy findings do not adequately explain the clinical picture.

Histopathologic evaluation
The most common histopathologic diagnoses in dogs with chronic diarrhea are IBD, lymphangiectasia, and lymphoma. The most common histopathologic lesion found in the intestines of dogs involves increased cellularity of the lamina propria and is usually referred to as IBD. The extent of inflammation varies and ranges from focal to diffuse involvement of the small and large intestine. The degree of cellular accumulation is also variable and is subjectively categorized as normal, mild, moderate, or severe.

Increased numbers of lymphocytes and plasma cells, so-called lymphoplasmacytic enteritis, is the most frequently reported form of IBD.

Unfortunately, the interpretation of GI histopathology varies considerably among pathologists. To address this problem, a working group established by the World Small Animal Veterinary Association (WSAVA) formulated a scheme to standardize the evaluation of intestinal histopathology. However, this scheme has poor agreement among pathologists, and clinical relevance of the pathologic criteria evaluated remains to be established.

Intestinal infiltration with macrophages or neutrophils raises the possibility of an infectious process, and culture, special staining, and fluorescence in situ hybridization (FISH) are indicated.

The presence of moderate-to-large numbers of eosinophils in intestinal biopsy samples, often accompanied by circulating eosinophilia, suggests possible parasitic infestation or dietary intolerance.

Increased numbers of lymphocytes and plasma cells, so-called lymphoplasmacytic enteritis, is the most frequently reported form of IBD. Moderate-to-severe lymphoplasmacytic enteritis is often described in association with a protein-losing enteropathy. Predisposed breeds include the basenji, Lundehund, and shar-pei. However, whether the term lymphoplasmacytic enteritis is appropriate or has clinical relevance is a contentious issue. Dogs have similar numbers of CD3-positive T cells before and after clinical remission, and cats with and without signs of intestinal disease have similar numbers of lymphocytes and plasma cells.

Recent studies indicate that changes in mucosal architectures, such as villous morphology and goblet cell mucus content, are related to the presence and severity of GI disease. These studies have used quantitative observer-independent variables (eg, inflammatory cytokines, intestinal mucus) to identify histopathologic correlates of disease. In cats with signs of GI disease, villus atrophy and fusion correlated with the severity of clinical signs and degree of proinflammatory cytokine upregulation in the duodenal mucosa. Architectural changes in the gastric mucosa also correlated with cytokine upregulation in dogs with lymphocytic gastritis.

In the colon, loss of mucus and goblet cells correlates with the severity of disease in dogs with lymphoplasmacytic and granulomatous colitis and is inexplicably discounted as a criterion in the WSAVA scheme on the basis of possible changes related to sample collection.

Dilation of lymphatics and the presence of crypt abscesses and cysts are most frequently encountered in dogs with protein-losing enteropathies and often are accompanied by lymphoplasmacytic inflammation of varying severity.

Treatment Considerations
Treatment is guided by the clinical severity of disease, presence or absence of hypoalbuminemia or hypocobalaminemia, and nature and severity of endoscopic and histopathologic lesions.

Minimal change enteropathy
Minimal change enteropathy is characterized by low clinical disease activity, serum albumin > 2 g/L, normal cobalamin, and normal intestinal histopathology. Empirical treatment. Empirical treatment for Giardia and endoparasitic infection involves fenbendazole at 50 mg/kg PO for 5 days.

Dietary trial. Options for dietary trials are outlined in Table 2. A positive response suggests diet-responsive enteropathy, a term that includes both dietary allergy and intolerance. In dogs with GI signs related to diet, a clinical response is usually observed within 1 to 2 weeks after the diet was changed. If the response is good, the diet should be continued. Rechallenge with the original diet is required.
to confirm that clinical signs are related to the diet. Challenge with single dietary ingredients is necessary to define the specific components that are eliciting an adverse response. If dietary trials are unsuccessful, the next step is usually an antibiotic trial.

Antibiotic trial. The antibiotic trial can include tylosin at 10 to 15 mg/kg PO Q 8 H, oxytetracycline at 20 mg/kg PO Q 8 H, or metronidazole at 10 mg/kg PO Q 12 H. A positive response suggests antibiotic-responsive enteropathy. The patient should be maintained on antibiotics for 28 days, after which they should be discontinued. If the response is good, the veterinarian should consider transition to probiotics. If the response is poor, the veterinarian should reappraise the patient record and findings before considering other treatment options. Chronic therapy with tylosin at a dose of 5 mg/kg PO Q 24 H can be used to maintain dogs that are tylosin responsive (Westermack E. Personal communication, March 2010).

Inflammatory bowel disease

Treatment of any disease is ideally directed at the underlying cause, which is problematic for IBD because its pathogenesis is unclear.

IBD in humans and animals is increasingly considered a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric luminal constituents (principally microbial and dietary), and immunoregulatory factors in genetically susceptible individuals.

Genetic susceptibility. In humans, genetic susceptibility is linked increasingly to defects in innate immunity exemplified by mutations in the innate immune receptor NOD2/CARD15, which in the presence of enteric microflora may lead to upregulated mucosal cytokine production, delayed bacterial clearance or killing, and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation.

The predisposition of certain breeds (eg, boxer, German shepherd), along with clinical response to such antibiotics as enrofloxacin in boxers and tylosin or oxytetracycline in German shepherds, points to a similar interaction of host susceptibility and microflora in dogs. In boxers with granulomatous colitis, lasting remission correlates with eradication of mucosally invasive bacteria. Genome-wide analysis of boxers has identified disease-associated single nucleotide polymorphisms (SNPs) in a gene (NCF2) that is involved with killing intracellular bacteria. Recent studies in German shepherds have identified polymorphisms in innate immunity factors TLR5 and NOD2 that segregate with disease and have shown that German shepherds have increased TLR2 and decreased TLR5 expression relative to healthy greyhounds. These results suggest that genetic abnormalities in sensing the enteric microbiome underlie the antibiotic responsiveness of German shepherds. An interaction of genetics and diet is supported by the finding that gluten-sensitive enteropathy in Irish setters is an autosomal recessive trait.

The intestinal microenvironment. While intestinal bacteria are implicated frequently as a pivotal factor in the development of IBD in humans and animals, the specific bacterial characteristics that drive the inflammatory response have remained elusive. Advances in molecular microbiology have enabled the analysis of complex bacterial communities without bacterial culture. Culture-independent analyses of bacterial 16S rDNA libraries in humans reveal that only 30% of fecal flora appears cultivable, and there is significant variation in the flora in different GI segments and luminal contents versus the mucosa of healthy individuals.

Application of these techniques to boxers with granulomatous colitis led to identification of invasive Escherichia coli that are similar in pathotype to adherent and invasive E coli (AIEC) associated with intestinal inflammation in humans. Application of these culture-independent techniques to humans, dogs, and cats has revealed that intestinal inflammation is associated with a floral shift from gram-positive Firmicutes (eg, Clostridiales) to gram-negative bacteria, predominantly proteobacteria, including Enterobacteriaceae.

Interestingly, increased numbers of Entobacteriaceae have been found to correlate with mucosal inflammation and clinical signs in cats with signs of GI disease. Studies in German shepherds with antibiotic-responsive enteropathy indicated increased prevalence of Lactobacillales relative to greyhound controls and a complex and variable dysbiosis in dogs with tylosin-responsive enteropathy. It remains to be determined whether alterations in luminal bacteria of dogs with lympho-

### TABLE 2
Options for Dietary Trials

<table>
<thead>
<tr>
<th>Type of Modification</th>
<th>Options</th>
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<tbody>
<tr>
<td>Global modification</td>
<td>• Switch to a different diet or different manufacturer</td>
</tr>
<tr>
<td>Optimize assimilation</td>
<td>• Highly digestible (usually rice based)</td>
</tr>
<tr>
<td></td>
<td>• Fat restricted (&lt; 15% DM)</td>
</tr>
<tr>
<td></td>
<td>• Easy-to-digest fats (eg, MCT oil)</td>
</tr>
<tr>
<td></td>
<td>• Restricted fiber</td>
</tr>
<tr>
<td>Antigenic modification</td>
<td>• Novel protein source</td>
</tr>
<tr>
<td></td>
<td>• Protein hydrolysate</td>
</tr>
<tr>
<td>Immunomodulation</td>
<td>• Altered fat composition (eg, omega-3 or 6, fish oil)</td>
</tr>
<tr>
<td></td>
<td>• Prebiotics (eg, inulin)</td>
</tr>
</tbody>
</table>

DM = dry matter; MCT = medium-chain triglyceride.
plasmacytic IBD are a cause or a consequence of the inflammation, but their discovery has provided new opportunities for therapeutic intervention.

**Dietary constituents.** Growing evidence also supports diet as an important role in the development of canine IBD. Irish setters develop an enteropathy that is related to ingestion of gluten, and soft-coated wheaten terriers have dietary responses and positive protoplasm-staining antineutrophil cytoplasmic antibodies (pANCA). In controlled studies of 65 dogs with diarrhea of at least 6 weeks’ duration, 39 of 65 responded to an antigen-restricted diet of salmon and rice (10 days of Purina Veterinary Diets LA Limited Antigen Canine Formulaa). A positive response to hydrolyzed soy diet (Purina Veterinary Diets HA Hypoallergenic Canine Formula Dry) has also been observed in 59% of 27 dogs with IBD. In this study, marked perturbation of the duodenal microbiome "dysbiosis" was detected in a majority of dogs with IBD, including those with a response to diet, and was likely a dietary consequence of inflammation.

**Therapeutic Approaches for Inflammatory Bowel Disease**

The overall therapeutic approach for IBD is influenced by suspicion of a breed-related problem; severity of disease as characterized by clinical signs, albumin and cobalamin concentrations, and endoscopic appearance; type of cellular infiltrate; and presence of architectural changes, such as lymphangiectasia/crypt cysts.

**Granulomatous or neutrophilic**

Enteropathies characterized by neutrophilic or granulomatous inflammation are described infrequently in dogs. Some may be associated with bacterial infections, such as from *E coli* (granulomatous colitis in boxers), *Streptococcus*, *Campylobacter*, *Yersinia*, and *Mycobacteria*, or with fungal or algal (eg, *Prototheca*) infections. Special stains (eg, Gomori-Grocott methenamine-silver, periodic acid-Schiff, Gram’s, modified Steiner) are traditional cytochemical methods used to search for infectious agents in fixed tissues. FISH with probes directed against eubacterial 16S rRNA is a more contemporary method of detecting bacteria within tissues. It is imperative not to immuno-suppress patients with granulomatous or neutrophilic infiltrates until infectious agents have been excluded.

Eradication of mucosally invasive *E coli* in boxers with granulomatous colitis is associated with clinical cure, but treatment failure associated with antibiotic resistance is increasing. The prognosis for idiopathic granulomatous or neutrophilic enteropathies is often guarded to poor if an underlying cause is not identified.

**Lymphocyte and plasma cell predominant**

Studies in dogs with chronic diarrhea diagnosed as lymphoplasmacytic enteritis provide reasonable evidence that various subsets of dogs will respond to treatment with diet, antibiotics, or immunosuppressive therapy (Figure 1). At present, there is no reliable means for predicting which dogs will respond to which treatment, treatment consists of a series of therapeutic trials.

**Response to standardized therapy.** As mentioned earlier, in controlled studies of 65 dogs with diarrhea of at least 6 weeks’ duration, 39 of 65 responded to dietary modification, and the remaining dogs were treated with corticosteroids (2 mg/kg Q 24 H for 10 days, followed by a tapering dose over 10 weeks). The CIBDAI and histopathologic scores were similar (> 70% moderate to severe in each group) in dogs that did and did not respond to diet. Dogs that responded to diet tended to be younger and have higher serum albumin than did dogs that failed to respond to diet. Dogs that did not respond to diet were treated with steroids. Interestingly, intestinal histopathology did not differ in either diet-responsive or steroid-responsive dogs before and after treatment.

**Prospective therapeutic protocol.** The approach outlined in Prospective Protocol for Dogs with Lymphoplasmacytic Inflammatory Bowel Disease has been evaluated in 27 dogs with a histopathologic diagnosis of IBD. In this ongoing research, 26 of 27 (96%) dogs responded to standardized treatment as follows:

- Sixteen dogs were diet responsive.
- Three dogs were steroid responsive.
- Three dogs were partially responsive to a combination of food and antibiotics.
- Three dogs were responsive to a combination of food, steroids, and antibiotics.
- One dog was responsive to antibiotics alone.

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*aThe name of this diet has been changed to Purina Veterinary Diets DRM Dermatologic Management Canine Formula.*
The positive response to dietary modification alone in 59% of patients with IBD suggests that dietary change is a good therapeutic starting point. The response to diet was 67% in 21 dogs with normal serum proteins compared with 33% in 6 dogs with low serum proteins. It is noteworthy that clinical remission in response to dietary manipulation alone was observed in 2 of 6 dogs with IBD accompanied by hypoproteinemia. An unexpected positive finding was how few dogs required treatment with corticosteroids.

Eosinophil predominant

Eosinophilic enteritis is characterized by excessive accumulation of eosinophils in the lamina propria. It is speculated that it may result from an immunologic reaction to parasites or diet. The disease may also involve other areas of the GI tract.

Clinical findings. The principal clinical signs are chronic small bowel diarrhea accompanied by vomiting or weight loss. Large bowel signs or vomiting predominate in some cases. Physical findings range from normal to focally or diffusely thickened intestines and marked weight loss.

Diagnosis. A diagnosis of eosinophilic enteritis is achieved by adopting a similar approach to that described for lymphoplasmacytic enteritis. Clinicopathologic abnormalities may include peripheral eosinophilia. Mast cell neoplasms, hypoadrenocorticism, and endoparasites can produce a similar spectrum of clinical signs and should be ruled out.

The degree of eosinophilia can be extreme in cats and may be associated with eosinophilic infiltrates in the spleen, liver, lymph nodes, and bone marrow. Intestinal protein loss may be encountered.

Histopathology is characterized by accumulation of large numbers of eosinophils in the intestinal mucosa.

Treatment. Prophylactic administration of an anthelmintic, such as fenbendazole at a dose of 50 mg/kg PO Q 24 H for 3 days, is warranted to treat potential visceral larval migrans, which has been associated with eosinophilic gastroenteritis. Some patients may respond to antigen-restricted or protein hydrolysate diets, and patients failing dietary therapy are usually started on prednisolone at a dose of 2 mg/kg PO Q 24 H, tapered over an 8-week period.

Cats with hypereosinophilic syndrome often respond very poorly to treatment with immunosuppressive agents, diet, and anthelmintics. Relapse is likely unless the underlying cause is found and removed. The prognosis in cats with hypereosinophilic syndrome is poor.

Lymphangiectasia/crypt cysts

Intestinal lymphangiectasia is characterized by abnormal distention of lymphatic vessels within the mucosa. Lymphangiectasia is a consequence of a localized or generalized lymphatic abnormality or increased portal pressure (eg, right-sided heart failure, caval obstruction, hepatic disease). Lymphatic abnormalities are often associated with lipogranulomatous inflammation that is visible as small white granules on the intestinal mesentery. Tumor infiltration of lymphatics or lymph nodes can also cause lymphangiectasia. In some cases lymphangiography reveals a generalized lymphatic abnormality. Dilatation of lymphatics is associated with exudation of protein-rich lymph into the intestine and severe malabsorption of long-chain fats. Crypt cysts and abscesses may also be observed in intestinal biopsies.
Clinical findings are essentially a consequence of the intestinal loss of protein and range from weight loss to chronic diarrhea, ascites, edema, and chylothorax. Diagnosis. Lymphangiectasia usually presents as a protein-losing enteropathy, with endoscopic appearance of white blebs on the mucosa (dilated lymphatics). Endoscopic biopsies are often adequate. Surgical biopsy should be undertaken carefully, with appropriate precautionary measures to avoid dehiscence.

Treatment. The cause of lymphangiectasia is usually not determined. Treatment is supportive and symptomatic. Dietary recommendations are similar to those for other causes of small bowel diarrhea, but fat restriction may have to be more severe. Medium-chain triglyceride (MCT) oil, usually in the form of coconut oil at 0.5 to 2 mL/kg body weight per day, can be added to the diet, or a diet already containing MCT can be fed to provide a source of calories that is, in theory, easy to assimilate. Prednisolone is often necessary at a dose of 1 to 2 mg/kg PO Q 12 H and may work by decreasing lipogranulomatous inflammation or concurrent mucosal inflammation. Prednisolone is tapered to the lowest effective dose once remission has been achieved.

In patients with severe malabsorption, parenteral glucocorticoids may be required, and a switch to dexamethasone may be made in patients with ascites or edema. Escalation of immunosuppression (eg, by administration of 5 mg/kg cyclosporine PO Q 24 H) may be tried if the patient is unresponsive. However, patients with lymphangiectasia appear more prone to sepsis than do patients with other forms of IBD, so it is imperative not to over-immunosuppress these patients; concurrent therapy with metronidazole or tylosin is often initiated to decrease the risk for bacterial translocation through the markedly impaired gut. Aspirin at 0.5 mg/kg PO Q 24 H is frequently given to dogs with low ATIII if they are considered at risk for thromboembolism. Diuretics are used if ascites is problematic (IBD with albumin < 2 g/L).

Response to therapy is variable, with some dogs staying in remission for several years and others pursuing a path toward fulminant hypoproteinemia or thromboembolic disease. The prognosis is always guarded.

Acknowledgments
The support of The Morris Animal Foundation and Nestlé Purina in ongoing studies of inflammatory bowel disease in dogs is greatly appreciated.

Disclosure: Dr. Simpson is a member of the Nestlé Purina Advisory Council.

References


Food allergy is a common term used to describe the myriad of adverse reactions dogs may experience after exposure to certain food items. Gastrointestinal (GI) abnormalities, including vomiting, diarrhea, change in frequency of bowel movements, and pica, are only a few of the clinical signs that may occur independently or concurrently with cutaneous reactions, including pruritus, urticaria, otitis, and skin infections.

This presentation reviews and evaluates current concepts regarding the pathogenesis, diagnosis, and management of dogs with suspected cutaneous adverse reactions to food (CARF).

**Pathogenesis**

The pathogenesis of the development of CARF is poorly defined. True food allergic causes, however, may exist and can be represented by three of the four hypersensitivity reaction types (Table 1): I, III, or IV.
Oral allergy syndrome, which is a localized immunoglobulin E (IgE)-mediated type I reaction, has been reported in dogs. Mixed IgE-mediated, non-IgE-mediated, and late-phase reactions may also be implicated. Immunoglobulin E-mediated reactions

Oral allergy syndrome was described in a dog with Japanese cedar allergy characterized by cross-reactivity between tomato allergens and Japanese cedar. When fresh tomato was offered to the dog, it exhibited clinical signs consisting of salivation, swelling of the lips, and quivering of the tongue. However, the signs were not seen when the tomato was cooked before being fed to the dog. Therefore, this study demonstrated both cross-reactivity between allergens and oral allergy syndrome, which might partially explain why some dogs with CARF develop acute muzzle pruritus after eating. Because many cross-reactions between food allergens and environmental allergens have been implicated in humans with oral allergy syndrome, one could postulate that dogs with atopy could be exacerbated by oral challenge with these cross-reacting antigens.

Furthermore, the role of type I hypersensitivity as a cause of canine food allergy has been investigated with the use of an atopic dog model. Dogs were selected as being high IgE producers and were purposely bred accordingly. The puppies were administered whole-food allergens subcutaneously soon after birth. A modified-live virus vaccine was used as an immune stimulant to encourage production of IgE antibodies to the food allergens. Early findings demonstrated that these dogs could be used to investigate the role of IgE in canine food allergy as a subset of CARF. These studies also demonstrated the genetic predisposition for the development of high levels of IgE antibody. This canine model, however, had limitations in allowing extrapolation of data to the canine population at large.

Further investigations with this model led to contradictory data. Some reports indicated that oral challenges led to clinical signs, including GI changes and pruritus. However, using the same model, it was shown that oral challenge with soy- or corn-based diets did not produce cutaneous or GI changes even though dogs were sensitized to these foods. It appeared that the timing of the subcutaneous food allergen “booster” as these dogs matured may have played a greater role in maintaining high IgE levels than oral exposure through feeding. Further investigations using this model are warranted, with consideration given to a mechanism that can help induce the breakdown of oral tolerance.

A spontaneous dog model of IgE-mediated food hypersensitivity may prove to be superior to the atopic dog model for investigating type I food hypersensitivity reactions.

Immunologic and nonimmunologic reactivity

In the intestinal tract, a single epithelial layer separates innate and adaptive immune-effector cells from a vast amount of antigens. Immune tolerance is maintained by an intact barrier and a complex interaction of immune responses. Oral tolerance is a state of immunologic unresponsiveness. Therefore, a breakdown of tolerance can lead to the development of immunologic reactivity with localized and systemic clinical signs.

A full review of the immunologic processes is beyond the scope of this review. However, human and murine research has led to some interesting findings regarding the roles of TCR-alpha-beta CD8-positive and TCR-gamma-delta intraepithelial lymphocytes and unconventional T-cell subsets (ie, regulatory T cells [Tregs]) in the pathogenesis of common human GI diseases.

A spontaneous dog model of IgE-mediated food hypersensitivity may prove to be superior to the atopic dog model for investigating type I food hypersensitivity reactions.

**TABLE 1**

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<tr>
<td><strong>Type I</strong></td>
<td>Immediate hypersensitivity; mediated by immunoglobulin E (IgE) attached to mast cells</td>
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<tr>
<td><strong>Type II</strong></td>
<td>Cytotoxic hypersensitivity; immune response destroys normal cells</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>Immune complex hypersensitivity; antigens and antibodies form and cause inflammation when deposited in large amounts in tissue</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>Delayed hypersensitivity; antigens in skin cause slowly developing inflammatory response mediated by T cells and natural killer cells</td>
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Nonimmunologic CARF can also occur in dogs with similar clinical signs. Food intolerance is an abnormal physiologic re-
response to an ingested food item or additive. GI changes are likely seen. Toxic reactions from the ingestion of bacterial- or fungal-contaminated food may also occur.

It is evident that the pathogenesis of the development of CARF is not linear and that many factors, including genetics, diet, concurrent health status, and immune status, may all play a role. Human and murine research provides interesting portals for investigation, but data from these studies may not be applicable to canine patients because of differences in the human, murine, and canine immune systems. Further studies are, therefore, warranted using dogs.

**Diagnostic options**

In human medicine, the gold standard for the diagnosis of food allergy is the double-blind placebo-controlled food challenge (DBPCFC). Individual food items are administered orally in a blinded manner, and the patient is evaluated on clinical signs. Patients with oral allergy syndrome may experience a tingling sensation in the mouth or on the tongue. Sometimes tinnitus is present. Skin prick testing of whole-food extracts has been used as a screening tool for IgE-mediated food allergy.\(^\text{14}\) It appears to have good negative predictive value but is only useful in patients experiencing type I hypersensitivity.\(^\text{15,16}\)

In canine medicine, the elimination test diet is considered to be the diagnostic tool of choice. Skin prick testing and intradermal skin testing using whole-food items has been shown to be of little diagnostic value. Intradermal testing in dogs has shown low sensitivity and high specificity (few false-positive results) similar to skin prick testing in humans.\(^\text{17}\)

Endoscopic-guided injections of food allergens into the mucosa of the stomach have been investigated as a diagnostic tool.\(^\text{18}\) Time, the repeatability of the procedure, and the expertise needed to conduct such a test demonstrate its limitations. In addition, this procedure is only useful in evaluating type I hypersensitivity reactions. One can argue that the stomach is not necessarily an important organ of immunity in a dog exhibiting food allergy or CARF. It is assumed that a type I hypersensitivity reaction is the most common cause of CARF in dogs and humans. There is recent evidence that when human patients are challenged with offending allergens in a blinded manner, changes in serum IgE levels are not significantly different than what occurs in control patients. The IgE reactions occurred locally in the GI tract.\(^\text{19}\)

Such evidence may partially explain why skin testing and serum testing for food allergy are inaccurate in dogs.\(^\text{20}\) In one study, 13 dogs with food allergy were evaluated with an elimination test diet, ELISA testing, and intradermal testing of food allergens. Skin and serum tests were unable to adequately predict positive or negative reactions compared with the results of an elimination test diet.\(^\text{21}\) Serum evaluation for IgE levels to food items by conducting a radioallergosorbent test
Elimination test diet

Selection of an elimination test diet is based on dietary history (see Elimination Test Diets: Key Points to Remember). It is generally recommended to feed the test diet for a minimum of 8 weeks. Some cases may respond to the dietary test in fewer than 8 weeks, whereas others may require longer for clinical signs to abate. Once the patient has clinically improved, the original diet may be fed to demonstrate induction of clinical signs. Reactions may occur very quickly on challenge, especially if there is a type I hypersensitivity component to the CARF. Most adverse signs occur in fewer than 14 days on challenge. Once CARF has been “proven,” the owner may elect to introduce individual food items as a challenge to attempt to identify the source of the reaction. It has been shown that most dogs with CARF have reactions to one or two individual food items.

Although the product selection is based on dietary history, the best approach to elimination test diets remains controversial, as there are advantages and disadvantages associated with home-prepared or commercial diets containing limited antigens and with hydrolyzed protein-source diets. The ideal test diet should be free of preservatives and additives, although documented adverse reactions to these items in dogs are rare. A home-prepared diet consisting of a single protein source and a single carbohydrate has been recommended, whereas commercial limited-antigen diets containing novel protein sources are an alternative. It has been suggested that the preparation of commercial diets may have an impact on allergenicity, and other studies have suggested that commercially prepared diets are not as accurate in diagnosing food allergy as home-prepared diets.

Of importance to note, commercial diets are usually complete and balanced. In contrast, home-prepared diets may not be balanced and may lack minerals, especially calcium. Balanced home-prepared menus, however, are available through several resources.

Hydrolyzed diets provide an alternative to novel protein elimination test diets. It has been shown that hydrolyzed diets are beneficial in humans with known allergic reactions. These diets have also been demonstrated as useful for investigating dogs suspected of having food allergy. In one study, 34 of 36 dogs improved when fed a soy hydrolysate diet and relapsed on challenge. Some of the limitations of hydrolyzed diets include cost and palatability, but these are subjective, depending on the client and patient.

Recently, an extensive review investigated the use of hydrolyzed diets and CARF in dogs. It was suggested that these diets are best used in dogs suspected not to be hypersensitive to the individual components. I have documented a sole case in which a 10-year-old, spayed golden retriever suspected of having CARF improved when fed a hydrolyzed soy diet (Purina Veterinary Diets HA Hypoallergenic brand Canine Formula) and relapsed when orally challenged with fresh tofu.

Owner compliance can be a challenge. In a recent study of 28 dogs started on a home-cooked elimination diet, 10 dogs did not complete the diet as prescribed. There are many possible reasons for poor compliance, including but not limited to:

- Time of preparation
- Limitation of treat items
- Reduced appetite or adverse reactions to the test diet
- Cost
- Poor communication between the owner and the veterinarian
- Clients stopping the test diet prematurely because of a disbelief that their dog may have CARF.

Closing Remarks

The diagnosis of food allergy as a component of canine CARF continues to be a challenge. It has become increasingly difficult to find novel protein and carbohydrate sources because of the plethora of commercial diets available. Hydrolyzed protein diets provide an alternative but are not without their own limitations.

Simple diagnostic tools, such as intradermal or skin prick testing and serum ELISA testing alone, have not been shown to be useful. Novel diagnostic procedures, such as gastroscopic-assisted injections into the gastric mucosa and/or colon, are unlikely to be of clinical importance.

The future of realizing a more definitive diagnosis and treatment may lie in investigating the relationship between canine atopic dermatitis and CARF as hypothesized by some investigators. The evaluation of cross-reactivity between food aller-

**Elimination Test Diets: Key Points to Remember**

- The test diet should be fed a minimum of 8 weeks.
- Reactions may occur swiftly on challenge, especially with type I hypersensitivity; most reactions occur in fewer than 14 days.
- Hydrolyzed diets are an alternative to novel protein elimination test diets.
- Owner compliance can be challenging and may prevent successful completion of a test diet and challenge.
- Some dogs may require more than one food trial with different diets to confirm CARF.
15. Intradermal skin tests in the diagnostic evaluation of food allergy. Sampson HA.


10. Food allergy: when mucosal immunity goes wrong. Sampson HA.


15. Intradermal skin tests in the diagnostic evaluation of food allergy. Sampson HA.


Probiotics are live microorganisms that, when administered in adequate amounts, can confer health effects on the host.\(^1\) Many studies of the effects of probiotics on the health of humans have been conducted, but very few have involved small animals.

This presentation examines research findings on the role of probiotics in human medicine in general and, specifically, the beneficial effects of one probiotic as investigated in three recent studies of *Enterococcus faecium* strain SF68 (also known as *E. faecium* NCIMB 10415) in cats. Notably, a recent review of human studies on probiotics\(^2\) described the “well-established probiotic effects” as follows:

- “Prevention and/or reduction in the duration and complaints of rotavirus-induced or antibiotic-associated diarrhea and alleviation of complaints attributed to lactose intolerance
- Reduction of the concentration of cancer-promoting enzymes and/or putrefactive (bacterial) metabolites in the gut

Clinical and Research Experiences with Probiotics in Cats

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- Reduction of the concentration of cancer-promoting enzymes and/or putrefactive (bacterial) metabolites in the gut
The biologic effects of individual probiotics can vary, and each probiotic introduced should be rigorously evaluated in a controlled fashion to define its potential for clinical value.

- Prevention and alleviation of nonspecific and irregular complaints of the gastrointestinal tracts in healthy human adults
- Notable beneficial effects on microbial aberrancies, along with complaints about inflammation and other complaints in connection with inflammatory diseases of the gastrointestinal tract, Helicobacter pylori infection, or bacterial overgrowth
- Normalization of passing stool and stool consistency in subjects suffering from obstipation or an irritable colon
- Prevention or alleviation of allergies and atopic diseases in infants
- Prevention of respiratory tract infections (eg, common cold, influenza) and other infectious diseases as well as treatment of urogenital infections.

Because infectious diseases are common in small animals, the potential beneficial effects of probiotics could significantly impact the practice of veterinary medicine. All mechanisms of immunomodulation have not been characterized, and it is likely that these effects vary by the probiotic. However, it is known that many probiotics in the lactic acid bacteria group help balance endogenous microbiota and some can inhibit replication of pathogenic bacteria. The proposed mechanisms of action include competition for essential nutrients or receptor sites, binding with pathogenic bacteria, and production of inhibitory substances. In addition, it is now known that some probiotics can beneficially influence innate and acquired immunity systematically by a variety of proposed mechanisms, including inducing cytokine production, natural killer cell activity, and both specific and nonspecific immunoglobulin (Ig) production.

**Effects of Individual Probiotics**

Several considerations should be evaluated when selecting individual probiotics, including the role of biologic effects as evidenced by human research findings. In addition, the source of probiotic should be considered, as evidenced in a recent canine study conducted in Canada in which a majority of diets claiming to contain probiotics generally did not meet the label claims when evaluated.

**Human study findings**

Based on several recent review articles in human medicine, the biologic effects of individual probiotics can vary and each probiotic introduced should be rigorously evaluated in a controlled fashion to define its potential for clinical value. These articles also suggested that evidence for the beneficial effects of individual probiotics on various conditions affecting humans, such as Clostridium difficile diarrhea and hospital-acquired pneumonia, is minimal, thereby indicating that larger, more rigorously controlled multicenter studies should be conducted.

**Puppy study findings**

*E. faecium* strain SF68 was originally isolated from the feces of a healthy baby and initially shown to inhibit the growth of a number of enteropathogens.

In one canine study, *E. faecium* strain SF68 was fed to a group of puppies vaccinated with canine distemper virus (CDV) and compared over time with a control group that was similarly vaccinated but was not fed the probiotic. A number of findings suggested an immunomodulating effect of the probiotic. The puppies supplemented with SF68 had increased serum and fecal total IgA concentrations, increased CDV-specific IgG and IgA serum concentrations, and an increased percentage of circulating B lymphocytes compared with control puppies. The effect on CDV-specific IgG and IgA antibodies in serum materialized only after the puppies had been supplemented for 31 and 44 weeks, and it was believed that SF68 prevented the decline in antibody titers observed in the control group by maintaining high levels of antibodies in the supplemented puppies.

**Collaborative Study: Role of SF68 in Healthy Kittens**

**Methodology and evidence collection**

After the puppy study was published, our research group at Colorado State University collaborated with Nestlé Purina PetCare on a similar study conducted in healthy kittens. Of note, *E. faecium* strain SF68 is the probiotic of choice in the company’s FortiFlora veterinary product (purinaveterinarydiets.com).

In this study, we hypothesized that feeding *E. faecium* SF68 to kittens would enhance their nonspecific immune responses; humoral immune responses to feline herpesvirus-1 (FHV-1), feline calicivirus (FCV), and feline panleukopenia virus (FPV); and FHV-1-specific cell-mediated immune responses. Twenty, 6-week-old specific pathogen-free (SPF) kittens were purchased from a commercial vendor and divided into two groups: One group was fed SF68 daily, and the other was fed the palatability enhancer starting at 7 weeks of age. At 9 and 12 weeks of age, a commercially available FVRCP modified-live vaccine was admin-

**Hypothesis: Feeding E. faecium SF68 to kittens would enhance nonspecific, humoral, and cell-mediated immune responses.**
istered subcutaneously, and the kittens were followed until 27 weeks of age. The attitudes and behavior of the kittens were monitored daily throughout the study, and body weight was measured weekly. Blood, saliva, and feces were collected from all cats before probiotic or palatability enhancer supplementation was initiated at 7 weeks of age, followed by collections at 9, 15, 21, and 27 weeks of age. In addition, feces were collected from kittens in the treatment group at 28 weeks of age.

For each group of kittens, five fecal samples per day were randomly selected from the shared litter box and scored using a standardized graphic scoring card; fecal extracts taken at 9 and 27 weeks of age were analyzed for total IgA and IgG levels. Other parameters monitored included randomly amplified polymorphic DNA (RAPD)-PCR on feces to determine if viable E faecium SF68 was in the stools of treated cats and to assess whether the probiotic was accidentally transmitted from the treated kittens to the control kittens. Commercially available ELISAs were used to determine whether Clostridium perfringens enterotoxins or C difficile toxins A/B were present in the feces of the kittens. Routine aerobic fecal cultures for Salmonella and Campylobacter were also conducted. Complete blood counts, serum biochemical panels, and urinalyses were done to assess whether any adverse events were induced by the probiotic.

Antigen-specific humoral immune responses were estimated by measuring serum FHV-1-specific IgG, FHV-1-specific IgA, FCV-specific IgG, and FPV-specific IgG in sera, as well as FHV-1-specific IgG and IgA levels in saliva using adaptations of previously published ELISAs. Total IgG and IgA concentrations in sera, fecal extracts, and saliva were estimated using commercial ELISAs or radial immunodiffusion (RID) assays. Cellular immune responses were assessed via flow cytometry and whole blood proliferation assays. Lymphocytes were stained for expression of CD4, CD8, CD44, MHC Class II, and B cells. In addition, lymphocyte proliferation in response to concanavalin A and FHV-1 antigens was assessed.

The results of a collaborative study in healthy kittens suggested that SF68 was safe for long-term use in cats.

Interpretation of findings

The cats readily ingested the probiotic or palatability enhancer. Body weight and fecal scores were not statistically different between the two groups over time or at any individual time points. Complete blood counts and biochemical profiles were within normal limits for the age group for all cats at all time points. The results suggested that SF68 was safe for long-term use in cats. Feces from seven of nine treatment kittens were positive for SF68 on at least one time point during the study, whereas feces from all control kittens were negative for SF68 at all time points, suggesting there was no cross-over of SF68 into the control group cats. SF68 DNA was not amplified from feces of any treated kitten one week after supplementation was stopped (week 28), thereby showing that the probiotic did not colonize the kittens. All samples from placebo kittens were negative for SF68 by RAPD-PCR. Neither Salmonella nor Campylobacter organisms were grown from feces. The number of positive samples for C difficile toxins A/B or C perfringens enterotoxins was not significantly different between the groups over the course of the study.

At 21 and 27 weeks of age, the mean levels of FHV-1-specific IgA in serum and saliva were numerically greater in the treatment group compared with the placebo group. Furthermore, the mean FHV-1-specific serum IgG levels were numerically greater in the treatment group compared with those in the placebo group at 15, 21, and 27 weeks of age. However, these differences in FHV-1 antibody levels did not reach statistical significance. No FHV-1-specific IgG was detected in saliva.

FCV-specific IgG levels in serum were similar for both groups. At 15 weeks of age, the mean FPV-specific IgG serum levels in the treatment group kittens were numerically greater.
than levels in the placebo group kittens, but the differences were not statistically significant. Concentrations of total IgG and IgA in serum also were similar for both groups. Total IgG was not detected in saliva, and total IgA concentrations in saliva were similar between groups. Total IgA and IgG concentrations in fecal extracts also were similar between groups.

Proliferation assays using either concanavalin A or FHV-1 antigen preparation did not produce significantly different mean maximum counts between groups at any time points. There were no statistical differences between the groups for any cell surface markers at the first four time points. However, at 27 weeks of age (Figure 1), the treatment group had a significantly higher percentage of gated lymphocytes positive for CD4 (mean, 13.87%) than did the placebo group (mean, 10.61%; P = .0220).

In this study, we concluded that SF68 was safe to administer to cats and the increase in CD4+ cell counts in the treatment group compared with the placebo group without a concurrent increase in CD8+ counts at 27 weeks of age demonstrated a systemic immunomodulating effect by the probiotic. Because we did not show a significant increase in lymphocyte stimulation by FHV-1 or an increase in the expression of the memory cell marker CD44 on the CD4+ lymphocytes in the treatment group, the increase in CD4+ T lymphocytes may have been nonspecific, as the cells appeared to be unprimed.

However, because the CD4+ T lymphocytes of kittens in this study were not additionally characterized via cytokine production profiles or additional cell surface marker characterization, it could not be determined whether a Th1 or Th2 (helper T cells) response predominated. We believed that sample size or the duration of the study may have precluded detection of statistical differences between the groups in regards to FPV, FCV, and FHV-1 antibody titers. In the puppies, those effects were noted at 31 weeks and 44 weeks. In addition, inclusion of greater numbers of cats may have led to detection of additional statistical differences between groups for those parameters with numeric trends.

Follow-up Studies
Effects of SF68 on FHV-1 in cats
The results of the first study prompted a follow-up study on FHV-1. This virus is extremely common in cats and is frequently associated with morbidity because of recurrent ocular and respiratory clinical signs of disease (Figure 2). In addition, there is no known drug therapy that consistently eliminates the carrier state and vaccination does not provide sterilizing immunity.

We hypothesized that feeding SF68 would decrease clinical disease, episodes of FHV-1 shedding, and numbers of FHV-1 DNA copies shed over time in cats with chronic FHV-1 infection. In this study, 12 cats with chronic FHV-1 infection were administered either SF68 or the palatability enhancer as a placebo, monitored for clinical signs of disease, episodes of FHV-1 shedding, and evaluated for FHV-1-specific humoral and cell-mediated immune responses and fecal microbiome stability. After an equilibration period, mild stress was induced over time by changing the housing of the cats from cages to gang housing repeatedly over a 5-month period.

Hypothesis: Feeding SF68 would decrease clinical disease, episodes of FHV-1 shedding, and numbers of FHV-1 DNA copies in cats with chronic FHV-1 infection.
SF68 supplementation was well tolerated by all study cats. Fecal microbial diversity was maintained throughout the study in cats supplemented with SF68 but decreased in cats fed the placebo, indicating a more stable microbiome in cats fed SF68. Upper respiratory signs of disease were not exacerbated in this model of stress, so the use of a glucocorticoid stress model in future studies should be considered.

Although the study results varied among cats, those receiving SF68 had fewer episodes of conjunctivitis than did cats in the placebo group during the supplementation period, suggesting that administration of the probiotic lessened morbidity associated with chronic FHV-1 infection (Figure 3). The results of this study also suggested that the immunomodulated effects of SF68 demonstrated in the healthy cat study may induce clinically beneficial results for this viral infection. Additional data should be collected from cats in the field to further substantiate these findings.

**SF68 effects on nonspecific diarrhea in an animal shelter**

In previous work, mice administered SF68 and then infected with *Giardia intestinalis* shed fewer trophozoites and less *Giardia* antigen than did the placebo group. In addition, supplemented mice had increased CD4+ cells in Peyer’s patches and the spleen as well as increased anti-*Giardia* intestinal IgA and serum IgG when compared with untreated mice. This work prompted our next study on the SF68 effects on nonspecific diarrhea in cats and dogs housed in an animal shelter.

**Hypothesis:** Cats and dogs housed in an animal shelter and fed SF68 would have decreased episodes of diarrhea and improved fecal scores compared with untreated dogs and cats when housed in the same environment.

We hypothesized that cats and dogs housed in an animal shelter and fed SF68 would have decreased episodes of diarrhea and improved fecal scores compared with untreated cats and dogs in the same environment. In a northern Colorado animal shelter, cats were housed in two different rooms and dogs were housed in two different rooms. All study cats and dogs were fed the same species-specific standardized diet. In the animals in one room, the diet was supplemented daily with FortiFlora, whereas the animals in the alternate room received daily supplementation of a FortiFlora carrier without SF68. Otherwise, the management of animals in both rooms was identical for the duration of the study.

However, to minimize any risk that room selection could influence the study results, the rooms were switched after one month (ie, cats and dogs supplemented with FortiFlora and those receiving the carrier without SF68 switched rooms). During the study, routine shelter cleaning and disinfectant protocols were followed. At the time of the room switch, the study was discontinued for one week to lessen the possibility that SF68 surviving in the environment could influence study results.

Before the rooms were cleaned each morning, feces in the cage of each animal were scored by one of the investigators (see Purina Fecal Scoring System). This person was blinded to the treatment groups. At the conclusion of scoring, feces from dogs or cats with a score of 4 to 7 were collected and transported to Colorado State University for infectious disease testing, which

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**Purina Fecal Scoring System**

Fecal consistency is primarily a function of the amount of moisture in the stool and can be used to identify changes in colonic health and other problems. Ideally, in a healthy animal, stools should be firm but not hard, pliable and segmented, and easy to pick up (Score 2).

**Score 1**
- Stool very hard and dry
- Much effort required to expel feces from body
- No residue left on the ground when feces picked up
- Often expelled as individual pellets

**Score 2**
- Stool firm but not hard
- Pliable and segmented in appearance
- Little or no residue left on the ground when picked up

**Score 3**
- Stool log-like
- No segmentation visible
- Moist surface
- Leaves residue but remains firm when picked up

**Score 4**
- Feces very moist (soggy)
- Distinct log shape
- Leaves residue and loses form when picked up

**Score 5**
- Feces very moist
- Distinct shape (piles rather than log shape)
- Leaves residue and loses form when picked up

**Score 6**
- Feces watery, flat, with no texture
- Occurs in piles or looks like spots
- Leaves residue when picked up

**Score 7**
- Feces watery, flat, with no texture
- Occurs as puddles
- Leaves residue when picked up
included microscopic examination for parasite eggs, cysts, and oocysts after zinc sulfate centrifugation flotation and immunofluorescent antibody (IFA) testing for *Cryptosporidium* oocysts and *Giardia* cysts (Merifluor *Cryptosporidium/Giardia*, www.meridianbioscience.com).

The percentages of dogs or cats with diarrhea of greater than 2 days’ duration were calculated over the course of the study. A generalized linear mixed model using a binomial distribution with treatment being a fixed effect and the room being a random effect was used to assess for statistical differences between treatment groups. The presence of parasites was included as a covariate, and significance was defined as $P < .05$.

Because diarrhea prevalence rates were low for all dogs in the study, statistical differences were not detected. However, the percentage of cats with diarrhea lasting longer than 2 days was 7.7% for the probiotic group and 20.7% for the placebo group (Figure 4). This result was significantly different ($P = .0297$).

The results suggest that administration of SF68 to cats housed in shelters may lessen the numbers of days with diarrhea. However, because this was a short-term study, the effect was likely from probiotic influences on intestinal flora rather than systemic immune-enhancing effects.

**Closing Remarks**

In a recent study, administration of SF68 alone to dogs shedding *Giardia* cysts had no measurable effect on cyst shedding.$^{13}$ In a previous study of nutritional supplementation in dogs with giardiasis, however, those treated with silymarin and an anti-*Giardia* drug had improved clinical outcomes in some categories compared with those in other treatment groups.$^{14}$ Therefore, in our current work, we are evaluating the effect of SF68 on the outcome of shelter animals with diarrhea and concurrently being treated with metronidazole.

### References


Obesity is a common problem in dogs in the United States, and the incidence in other countries is reported to be as high as 41%.1,2 Approximately 20% of adult dogs suffer from osteoarthritis (OA) in one or more diarthrodial joints,3 including the shoulder, elbow, carpus, hip, stifle, tarsus, and spinal articulations. Unfortunately, progression of this disease can only be slowed but never completely stopped. Of importance in managing OA in obese dogs is restriction of caloric intake, which necessarily requires strict adherence and compliance by owners. The role of nutrition and rehabilitation in obese dogs that also suffer from OA is the focus of this presentation.

Nutrition, Obesity, and Osteoarthritis

The incidence of knee and hand OA is increased in obese people,4,5 with most researchers...
The hip joints 50% less often than their free-fed littermates. However, obesity may play an important role in progression of OA of joints in the hands of people, where excessive weight-bearing does not play a role in the development of OA. Adipose tissue produces adipokines that affect many tissues, including endocrine and immune tissue. Two of these adipokines have been identified as mediators of inflammation in the joint: leptin and adiponectin. Leptin induces proinflammatory cytokine expression (interleukin-1, matrix metalloproteinase-13 and 9) and inhibits the growth of chondrocytes. Adiponectin induces chondrocytes to produce interleukin-6, matrix metalloproteinases-3 and 9, and nitric oxide, resulting in cartilage degradation. What the association of these cytokines is to the disease in dogs is unknown at this point. However, research is continuing to progress in this field, and the relationship of obesity to OA in dogs is developing as outlined here.

**Increased Adipokine Levels Linked to Osteoarthritis in Humans**

Evidence now suggests that obesity in humans may be a direct cause of OA due to fat cell release of the adipokines leptin and adiponectin. These hormones have receptors on chondrocytes and may stimulate OA in the hands of people, where excessive weight-bearing does not play a role in the development of OA. Adipose tissue produces adipokines that affect many tissues, including endocrine and immune tissue. Two of these adipokines have been identified as mediators of inflammation in the joint: leptin and adiponectin. Leptin induces proinflammatory cytokine expression (interleukin-1, matrix metalloproteinase-13 and 9) and inhibits the growth of chondrocytes. Adiponectin induces chondrocytes to produce interleukin-6, matrix metalloproteinases-3 and 9, and nitric oxide, resulting in cartilage degradation. What the association of these cytokines is to the disease in dogs is unknown at this point. However, research is continuing to progress in this field, and the relationship of obesity to OA in dogs is developing as outlined here.

**Hip OA in dogs has been most commonly linked to hip dysplasia.** However, obesity may play an important role in progression of this disease. Genetically predisposed Labrador retriever littermates that were fed 25% less than ad libitum developed OA of the hip joints 50% less often than their free-fed littermates did. These same dogs had a decrease in the severity of shoulder OA and a decrease in the severity, but not incidence, of elbow OA over their lifetime. The dogs fed ad lib developed radiographic signs of hip OA at 6 years of age versus the restricted-fed dogs, which developed radiographic signs at 12 years of age.

Clearly, preventing obesity can have a significant effect on the progression of OA in dogs, but what about dogs that develop the disease and are already overweight? Can weight loss help by improving their lameness and slowing the progression of deterioration in their joints?

**Safe weight reduction**

Researchers have found that overweight dogs with hip OA and pain have a significant decrease in lameness following weight reduction. Many believe that keeping affected dogs slightly underweight can help slow progression and severity of the disease. The problem with getting affected dogs to lose weight is in keeping clients motivated. That is not an easy task. First, owners have to recognize that the dog is overweight, as defined by acceptable body condition scoring (see Nestlé Purina Body Condition System chart), after which they need to appreciate how weight can affect joint pathology. One approach is assuring owners that weight loss will improve their dog’s mobility and then keeping owners motivated as they see their dog lose weight.

Of importance is ensuring that the dog does not lose weight too fast, which can result in loss of lean tissue and an unhealthy nutritional state. A rate of weight loss greater than 2% of body weight per week is considered too fast. To maintain owner interest and compliance in continuing the dog’s weight loss and exercise program, some researchers recommend adhering to a weekly weight loss rate of at least 0.5%.

In most dogs, improvement in lameness will be noticeable after a 6% to 9% loss in body weight. Achieving this noticeable loss safely without changing the dog’s exercise level takes 6 to 18 weeks.

More profound improvement in lameness and gait may be seen in dogs with forelimb lameness than in dogs with bilateral hip OA, possibly due to the symmetry of lameness that occurs in dogs with bilateral hip OA and the fact that dogs carry more body weight on the forelimbs than the hindlimbs, resulting in more obvious changes in gait patterns with weight loss. Regardless, improvement in lameness is seen in dogs with both hindlimb and forelimb OA when an ideal body weight is reached, which may take some time to achieve in obese dogs that are 20% to 30% above their ideal weight.

**Caloric intake and resting energy requirement**

A realistic goal for owners and their dogs is to reduce the current caloric intake to achieve a loss of 0.5% to 1% of body weight per week. Diets vary widely in caloric density, even when they are labeled for weight management, weight loss, overweight, or calorie restriction. Caloric density for these diets can range from 217 to 440 kcal per cup of dry food and 189 to 398 kcal per can of wet food.

In addition, the amount of food to be fed varies greatly as specified on the dog food packages, with the recommended caloric intake for weight loss in dogs ranging from 0.73 to 1.47 times the resting energy requirement. The resting energy requirement is calculated as:

$$70 \times [\text{kg of lean body mass}] \times 0.75 = \text{kcal/day}$$

A 6% to 9% loss of body weight in obese dogs will have a noticeable improvement in lameness that most owners can appreciate.
**Nestlé PURINA**

**Body Condition System**

1. **Too Thin**
   - Ribs, lumbar vertebrae, pelvic bones and all bony prominences evident from a distance. No discernible body fat. Obvious loss of muscle mass.

2. **Too Thin**
   - Ribs, lumbar vertebrae and pelvic bones easily visible. No palpable fat. Some evidence of other bony prominence. Minimal loss of muscle mass.

3. **Too Thin**
   - Ribs easily palpated and may be visible with no palpable fat. Tops of lumbar vertebrae visible. Pelvic bones becoming prominent. Obvious waist and abdominal tuck.

4. **Ideal**
   - Ribs easily palpable, with minimal fat covering. Waist easily noted, viewed from above. Abdominal tuck evident.

5. **Ideal**
   - Ribs palpable without excess fat covering. Waist observed behind ribs when viewed from above. Abdomen tucked up when viewed from side.

6. **Too Heavy**
   - Ribs palpable with slight excess fat covering. Waist is discernible viewed from above but is not prominent. Abdominal tuck apparent.

7. **Too Heavy**
   - Ribs palpable with difficulty; heavy fat cover. Noticeable fat deposits over lumbar area and base of tail. Waist absent or barely visible. Abdominal tuck may be present.

8. **Too Heavy**
   - Ribs not palpable under very heavy fat cover, or palpable only with significant pressure. Heavy fat deposits over lumbar area and base of tail. Waist absent. No abdominal tuck. Obvious abdominal distention may be present.

9. **Too Heavy**

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The **Body Condition System** was developed at the Nestlé Purina Pet Care Center and has been validated as documented in the following publications:

- Laflamme DP. *Development and Validation of a Body Condition Score System for Dogs.* Canine Practice July/August 1997; 22:10-15
- Kealy, et al. *Effects of Diet Restriction on Life Span and Age-Related Changes in Dogs.* JAVMA 2002; 220:1315-1320

Call 1-800-222-VETS (8387), weekdays, 8:00 a.m. to 4:30 p.m. CT
To lose weight, most pets require a daily caloric intake less than the calculated resting energy requirement at the current body weight, with some researchers suggesting feeding 40% to 60% the maintenance energy requirement, that is, 1.2–1.88 × resting energy requirement.23,24 Another approach is to reduce the amount of caloric intake by 40%, which in overweight to obese dogs can result in a reduction of 11% to 18% in body weight over approximately 4 to 5 months.14

When calculating the exact amount that owners should feed their dog, veterinarians must take into account all foods ingested, including treats and table scraps, to ensure success with the weight loss plan. One computerized feeding program allows veterinarians to calculate the dog’s food intake required to lose a certain percentage of body weight per week. The weight loss is based on the dog’s current body weight, and at the recheck examination, the software program determines a new weight loss recommendation based on the dog’s current weight and the time since the last examination.25

**Diet, Nutraceuticals, and Osteoarthritis**

The number of nutraceuticals on the market today are too numerous to discuss in their entirety. Therefore, only the agents most commonly used for the treatment of OA in dogs are addressed here.

**Eicosapentaenoic acid and omega-3 fatty acids**

Matrix metalloproteinases are enzymes with increased levels in joints affected by OA, and their inhibition, at least experimentally in dogs, may slow the progression of degenerative joint disease.26-28 The production of arachidonic acid generates precursors to inflammatory mediators, including prostaglandin E2, which increases in joints with OA, resulting in joint pain and inflammation in dogs.29,30

Both arachidonic acid and prostaglandin E2 levels decrease in normal joints after oral administration of fish oil, specifically eicosapentaenoic acid found in omega-3 fatty acids.31 Several canine diets (eg, Purina Veterinary Diet JM Joint Mobility Canine Formula, Hill’s Prescription Diet j/d Canine, Eukanuba Senior Plus) include eicosapentaenoic acid. Unfortunately, according to one study in dogs,31 eicosapentaenoic acid does not decrease metalloproteinases or arachidonic acid levels in injured cranial cruciate ligament joints following surgical treatment.

However, supplements, including capsules and diets containing omega-3 fatty acids, are capable of reducing lameness and improving clinical signs in dogs with OA.32-33 A recent evaluation of omega-3 fatty acids fed to dogs with OA found improvement in their ability to rise from rest and to play.34 In addition, switching dogs to these diets following cruciate ligament injury to one stifle may be able to prevent rupture in the contralateral stifle.34

Although these diets may not prevent increased degenerative proteins in the joints of dogs following surgery, they can improve weight bearing and limb use in dogs with naturally occurring OA.32,33 When a diet high in omega-3 fatty acids is fed to dogs before and after experimental cranial cruciate ligament transection and repair, affected dogs have not only better ground reaction forces but also fewer radiographic changes in their stifles following surgery.16

**Antioxidants**

Antioxidants such as vitamin E, vitamin C, and selenium have not been definitively proven to be beneficial to humans or dogs with OA, but many conflicting reports exist.35-39 Therefore, they are not recommended at this time. Methyl-sulfonyl-methane (MSM) may improve function and decrease pain in humans, but no clinical trials have been conducted in dogs.16

**Glucosamine–chondroitin sulfate**

Glucosamine and chondroitin sulfate are components of normal joint cartilage that may be capable of rebuilding damaged cartilage.40 A prospective double-blind study of the effects of carprofen, meloxicam, and glucosamine–chondroitin sulfate (Cosequin DS, www.nutramaxlabs.com) on ground reaction forces of dogs with established OA found that Cosequin had no effect and only carprofen and meloxicam improved lameness in the study dogs.31 Dasuquin, one of the new formulations of Cosequin, may have a more profound effect on lameness because it contains unsaponifiables of avocado and soybeans, which have been shown, at least experimentally in humans with OA, to reduce inflammation and promote cartilage aggrecan synthesis.42,43

While these nutraceuticals may not lessen pain associated with canine OA, they can decrease matrix metalloproteinases (believed to degrade cartilage in arthritis) and synovial membrane fibrosis, which could slow progression of the disease.44,45 In combination, glucosamine and chondroitin may restore a more normal synovial fluid environment, thereby helping slow OA progression.46 Different formulations of these nutraceuticals have different bioavailability, which must be considered when recommending these supplements.

As little as 50% of nutraceutical products on the market today meet their label claims.46 A recent review of OA treatments found a moderate level of comfort for the effectiveness of glucosamine and chondroitin.47-48
Polysulfated glycosaminoglycan
Polysulfated glycosaminoglycan (PSGAG; Adequan, Novartis; www.adequancanineus.com) can protect articular cartilage from degradative enzymes as well as stimulate chondrocytes to produce normal components of articular cartilage and thus prevent OA.49-52 Puppies from dysplastic parents were given 5 mg/kg IM twice a week from 6 weeks to 8 months of age and had a reduction in coxofemoral subluxation and improved Norberg angles (measure of hip joint congruity).53

The drug inhibits the intrinsic clotting system and can increase coagulation and buccal mucosal bleeding times. Conflicting reports exist as to whether PSGAG is beneficial in slowing OA progression, but the drug does appear to have a greater beneficial effect the earlier it is administered and, therefore, may be best as a preventative.40,54

A recent review of OA treatments found a moderate level of comfort for the effectiveness of PSGAG.47,48,55

Pentosan sulfate
Pentosan sulfate, a derivative of PSGAG, is used similarly. It can be given intraarticularly, intramuscularly, or subcutaneously and can decrease the amount of degradative products present in osteoarthritic cartilage.40

Given once weekly at 3 mg/kg SC for 4 weeks following extraarticular repair of a ruptured cranial cruciate ligament, pentosan caused faster recovery of breaking ground reaction forces and decreased collagen degradation products if a partial meniscectomy was performed.56 General observation of the dogs’ gaits following surgery was not different from dogs receiving placebo injections and, therefore, owners may not see the benefit of using this drug postoperatively.56

Other research has shown no effect with pentosan sulfate administration, while one study showed improvement.57,58 Further studies are needed to determine whether administration of pentosan sulfate can slow long-term progression of OA in dogs.

Hyaluronan
Hyaluronan is produced by chondrocytes and fibroblasts in articular cartilage and synovial fluid to act as a shock absorber and lubricant in the joint. Hyaluronan is given intraarticularly but lasts only a short time in synovial fluid. Its effects are believed to last longer than its actual presence in the joint.59 Therefore, hyaluronan injection does not restore the normal concentration of hyaluronan in the joint or reduce the volume of synovial fluid.59 Hyaluronan may decrease metalloproteinases, stimulate chondrocyte proliferation, and decrease degenerative cytokines, such as tumor necrosis factor-alpha and interleukin-1.60

There are conflicting reports about the effectiveness of hyaluronan in preventing or slowing the progression of OA.57,61,62 Therefore, its use cannot be definitively recommended at this time. High molecular weight with cross-linking of hyaluronan may be a formulation with better efficacy, but further study is needed.60

Additional nutraceuticals
Green-lipped mussel (GLM) has PSGAGs and acts as an anti-inflammatory through tetraenoic acid. Stabilized lipid preparations may decrease joint swelling and lameness, but there are no definitive studies of its effects.47,63 As part of a formulated diet, GLM has been found to be somewhat beneficial for dogs with OA; however, further studies are needed.55,63

P54FP, an extract of curcuma (a turmeric), has been shown to decrease lameness but not peak vertical force on a force plate system.64 Rarely this nutraceutical can cause a malodor of the skin, urine, and feces.65 Again, further studies are warranted, but its use may help OA patients clinically.54,64

Elk velvet antler has been shown in one objective placebo-controlled study to improve weight bearing in the arthritic limbs of dogs.66 Two of 38 dogs developed Addison’s disease; however, no other dogs were affected, and it was unlikely related to elk velvet antler.66 There is moderately strong evidence that elk velvet antler is effective in treating OA.55

Exercise
The type of exercise activities that dogs are engaged in can also affect the progression of OA. For example, strength training
can reduce progression of the disease in human knees compared with passive range-of-motion exercises.57

The appropriate exercise can decrease pain associated with mild-to-moderate OA as well.68,69 The exercise, however, must be controlled and continued indefinitely or the beneficial effects will not be long-lasting. By controlling exercise, excessive force on the joint and articular cartilage is avoided while building muscle strength. Examples of controlled exercises include swimming, jogging, or walking on non-slick surfaces (eg, grass lawns) and treadmill activities.

I recommend that dogs with an increased risk for developing OA avoid activities that place undue stress on joints, such as high-impact activities on hard or slick surfaces. For example, dogs that fetch a ball can still do so after a joint injury, but the ball should be rolling slowly on the ground or stopped by the time the dog retrieves it. The dog should not retrieve the ball on asphalt, and if there are predominantly hardwood, tile, or linoleum floors in the home, area rugs need to be placed where the dog walks.

Rehabilitation

Increased muscle strength can result in increased stability to joints, thereby reducing pain and slowing the progression of OA.18 Participation in regular exercise, along with weight loss, results in improved function and quality of movement.18

In one study, twice-weekly physiotherapy sessions in a veterinary clinic coupled with weight loss and exercises performed at home reduced lameness in obese dogs with OA within 30 days of treatment.18 Dogs participating in the study were treated with transcutaneous electrical nerve stimulation (TENS), using skin electrodes that send an electrical current to the underlying and intervening muscles, stimulating them to contract. The intensity can be modified to maintain comfort for the patient while increasing the strength of muscle contractions.

Rehabilitation and physical therapy exercises may also prevent further injury to joints by building muscle strength and stimulating conscious proprioception in the injured limb. Proprioception is often lost following injury to a limb, which can result not only in muscle atrophy but also to further injury from stumbling, twisting, and abnormal use of the limb. There are several ways to increase proprioception in dogs; one of the easiest is engaging in water activity to increase resistance, thereby allowing the dog to feel where its leg is in relation to the rest of its body. Underwater treadmills stimulate proprioception, build muscle, and encourage limb use while reducing the body weight load on the osteoarthritic joint. If the dog and owner cannot participate in underwater treadmill therapy, other modalities include resistance bands, cavaletti, and balance boards.70

Passive range-of-motion can help maintain joint mobility but is not a substitute for strength training in dogs with OA. Development of muscle in the entire body helps the overweight dog by minimizing the stress and strain on arthritic joints and reducing the overall body fat content.

When instituting an exercise/rehabilitation program for an overweight osteoarthritic patient, realistic goals must be set and accepted by the owner (see Points to Discuss with Owners). A therapy program that is too intense can result not only in progression of OA in the primarily affected joint but also in trauma to other joints, including rupture of the cranial cruciate ligament, collateral ligament instability, biceps tendonitis, and others.71

Continued maintenance of the exercise program is also imperative to the long-term outcome of these patients. I usually recommend recheck examinations every 6 months to promote ongoing progress and think it is important for the owner to understand that although OA is a disease without a cure, proper management allows affected dogs to live a full and productive life, especially if an ideal body weight is maintained.

References

4. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study


