

## **RECOGNITION AND TREATMENT OF FELINE ENTEROPATHY - 2017 CENTRAL FLORIDA ACADEMY OF VETERINARY MEDICINE**

**Katie Tolbert, DVM, PhD, DACVIM  
Assistant Professor, Sm Animal Clinical Sciences  
University of Tennessee**

Vomiting, diarrhea, and weight loss are classic signs of feline chronic enteropathy and are common reasons for cats to be presented to private practitioners. However, these clinical signs are not specific for gastrointestinal disease and can be triggered by a variety of systemic diseases. Creating a plan to quickly and correctly identify and treat the cause of these clinical signs in light of the long list of differentials can be challenging for practitioners and frustrating and financially burdensome for owners. However, consideration of the signalment, acquisition of a tailored GI medical history questionnaire, performance of a comprehensive physical exam, and use of a structured diagnostic and therapeutic algorithm will help guide a more successful outcome for the patient and the practitioner.

This presentation will review the author's diagnostic and therapeutic approach to feline enteropathy. In this seminar, the author will cover enteropathies seen more commonly in specific breeds (e.g. feline gastrointestinal eosinophilic sclerosing fibroplasia in Ragdolls) and will introduce a tailored GI history questionnaire that can be used by the veterinarian or veterinary technician to minimize error and obtain an accurate and complete GI history more efficiently. Interactive case presentations will be purposefully entered into the presentation to provide context, to demonstrate how the questionnaire can be used, and to point out subtleties that might be missed in the physical examination, diagnosis, and treatment of a cat with enteropathy. The author's diagnostic algorithm, divided into 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> tier diagnostics, will also be presented. The diagnostic plan is based on the chronicity and severity of the GI signs. For cats with acute diseases that do not respond to supportive therapy or those that have more severe disease or chronic disease, I recommend performing a complete blood count, serum chemistry, urinalysis, tT4 and FeLV/FIV (if appropriate), and abdominal imaging. If no abnormality can be identified and supportive care does not eliminate the symptoms, additional testing is recommended based on clinical signs and results of the first tier diagnostics. These

may include but are not limited to evaluation of serum gastrin, bile acids, thoracic radiographs, urine and/or bile culture, infectious disease testing, heartworm serology, fPLI, TLI, cobalamin, folate, diet, antibiotic, or probiotic trial, and exploratory endoscopy or surgery with biopsies. If concern for GI lymphoma exists, surgical biopsies are preferred. The most common sites of GI lymphoma, the jejunum and ileum, are in places that may be hard to impossible to reach via endoscopy. The final half of the seminar will be dedicated to the therapeutic approach to feline enteropathy. Advantages and disadvantages of therapeutics used in the treatment of feline enteropathy will be discussed. Therapies to be covered will include diet (novel protein versus hypoallergenic; fat versus no fat restriction), supplements (vitamins, minerals, amino acids), anthelmintics, fish oil, prebiotics, probiotics, gastroprotectants, and anti-emetics. Novel therapies showing promise in human medicine (e.g. curcumin, stem cells, fecal transplant) will also be reviewed. Strategies for monitoring patients with feline enteropathy will be reviewed at the end of the seminar.

## MANAGEMENT OF THE CONSTIPATED CAT - 2017 CENTRAL FLORIDA ACADEMY OF VETERINARY MEDICINE

**Katie Tolbert, DVM, PhD, DACVIM**  
**Assistant Professor, Sm Animal Clinical Sciences**  
**University of Tennessee**

Feline constipation (FC), defined by infrequent bowel movements, tenesmus, hard stools, and abdominal pain, is a common gastrointestinal disorder in cats. FC can occur secondary to a wide range of diseases and/or be a side effect of medical therapy. Several risk factors have been identified or proposed for FC including season, age, hydration status, inactivity and/or hospitalization, metabolic disease, orthopedic or neurologic disease, colonic neoplasia or structural disease, idiopathic megacolon, and/or  $\mu$ -opioid receptor agonists) administration.<sup>1</sup> Additional risk factors for constipation that have been identified in humans but may be difficult to appreciate in cats include anxiety, depression, and stress. A variety of other drugs including NSAIDs, antihypertensives, anticholinergics, and antiemetics are also associated with chronic constipation in humans,<sup>2,3</sup> however, the role of these drugs in the development of FC are unknown.

Severe FC can negatively affect the cat's quality of life and lead to life-threatening complications. Identification and removal, if possible, of the underlying cause is the most effective remedy for FC. Thus, a thorough diagnostic workup to evaluate for risk factors of FC is recommended in addition to initiation of medical management. A careful history should be taken to rule out acute causes of constipation (e.g. immobility, dehydration). To the extent possible, medications associated with constipation should be discontinued. **Coinciding with removal of the offending agent, management of FC should begin with promoting adequate hydration and encouraging activity.**

### **Conventional therapies**

Pharmacologic management of FC can be difficult especially with drug shortages and aversion of some cats to dietary modification and oral therapies. The majority of FC pharmacologic treatments are given orally and work by acting as bulking agents, laxatives, or colonic motility stimulants.

**Dietary fiber** is one path towards ameliorating or preventing FC and should be considered as a frontline treatment for FC in combination with laxative therapy. Fiber can be divided into two major categories, insoluble and soluble. Insoluble (e.g. cellulose) fiber is bulk-forming and improves intestinal motility by distending the intestinal lumen. However, insoluble fiber is characterized by a lower nutrient digestibility and reduced fecal moisture content which may lead to excessively dry stool. Soluble (e.g. pectins from

carrots or fruits, canned pumpkin, guar gum; psyllium) fiber often undergoes bacterial fermentation resulting in short-chain fatty acid (SCFA) production. These fatty acids have prokinetic effects on colonic smooth muscle. Too much SCFA production can lead to very liquid stools and lower nutrient digestibility,<sup>4</sup> thus the addition of soluble fiber should be titrated carefully. In one uncontrolled study of 66 cats, addition of a psyllium-enriched diet improved stool consistency in 56 cats receiving laxative therapy.<sup>4</sup>

**Laxatives** aid in the prevention or treatment of constipation by increasing fecal water content and promoting movement of feces through osmotic, lubricant, or stimulatory mechanisms.

**Polyethylene glycol 3350** (PEG 3350; e.g. Miralax), a bulking and fecal hydration agent, contains large molecules that cannot be absorbed by the gastrointestinal tract. Therefore, it works as an osmotic laxative, pulling water into the colonic lumen. In an uncontrolled, open-label study of six healthy cats with no history of gastrointestinal disease, PEG3350, given at a median daily dose of  $3.0 \pm 1.1$ g, resulted in the desired fecal consistency in all six cats within 1 month of therapy. Mild hyperkalemia was the only side effect noted in some of the cats. No other adverse effects were noted as a result of PEG 3350 administration.<sup>5</sup> Although there are no published reports on the use of PEG 3350 in cats with FC, I use it often and find it to be an effective prophylactic treatment for cats at risk for FC and may be a more palatable option as it can be added to the cat's food without imparting a major taste change.

**Lactulose** is a semi-synthetic disaccharide that, like PEG 3350, acts as an osmotic laxative and draws water into the colonic lumen in addition to stimulation of colonic motility. Lactulose may also have a prebiotic effect. There are a paucity of studies evaluating the efficacy of lactulose in the treatment of FC. However, lactulose is inexpensive, is a very effective laxative and is often used as a first-choice laxative for FC. The major disadvantage to lactulose is that it must be administered orally which may not be an option for some cats.

**Liquid paraffin (mineral oil):** Mineral oil, like white petroleum, acts as a lubricant laxative. In my opinion, it is not effective for severe cases of FC. Mineral oil should only be administered per rectum as oral administration is associated with a risk of aspiration pneumonia.

**Promotility drugs** may aid in the treatment of FC through stimulation of colonic motility and via increased fecal water content due to decreased amount of time for water absorption. **Cisapride**, a serotonin 5-HT<sub>4</sub> agonist, stimulates motility of the entire GI tract. Unfortunately, because of its association with cardiac arrhythmias in people, sources of cisapride can be difficult to obtain. We obtain our cisapride from a local compounding pharmacy. A newer drug, **mosapride**, is not associated with cardiac arrhythmias in people, however it does not stimulate motility in the large intestine and therefore it is not as effective for treatment

of FC compared to cisapride. **Metoclopramide**, a dopaminergic drug, stimulates GI motility but it is far less potent than cisapride as a promotility drug. **Misoprostal**, a prostaglandin analog, may increase fluid secretion and improve colonic transit time. Based on these mechanisms, it would seem to be a rational consideration for a multi-drug approach to FC.

### **Novel therapies**

**Probiotics:** The GI microbiota play an enormous role in the regulation of GI motility and secretion and therefore are a potential target for the treatment of FC. Studies evaluating the GI microbiota in human patients with chronic idiopathic constipation (CIC) demonstrate a reduced *Lactobacillus* and *Bifidobacterium* spp. compared to individuals without the disease. Administration of probiotics containing these bacterial spp. has resulted in improvement of clinical signs in some patients with constipation including those with constipation associated with irritable bowel syndrome. However, the dose and appropriate bacterial composition of probiotics for the treatment of constipation remains under investigation. Dysbiosis in cats with FC is likely but has not been established. I do administer probiotics containing both *Lactobacillus* and *Bifidobacterium* to cats with FC, however there is currently a lack of evidence for this practice. Clinical studies of the microbiome in cats with FC as well as clinical trials investigating the use of probiotics as an adjunctive therapy for FC are needed.

**Stimulant laxatives** are used in human medicine but have not been studied for the treatment of FC. Stimulant laxatives are often combined with osmotic laxatives for advanced cases of constipation in humans. **Biscodyl** (e.g. Dulcolax) is a stimulant laxative that is available in oral and rectal suppository form. Biscodyl increases fluid secretion and colonic motility via promotion of colonic secretion and stimulation of the myenteric plexus. The safety of prolonged administration of stimulant laxatives has not been investigated in cats, therefore these drugs should only be used as a last alternative and should be used in combination with other therapies. Prolonged administration should be avoided when possible. Biscodyl is generally my first choice when cats fail first-line medical management with diet, cisapride, and miralax. **Senna** (e.g. Senacot) is a stimulant laxative that like PEG 3350 is available over-the-counter. It is harvested from the leaves and fruit of the Senna plant and irritates the inner lining of the intestine resulting in fluid secretion.

**Novel promotility drugs:** Prucalopride and tegaserod are serotonin 5-HT<sub>4</sub> agonists that have shown promise as promotility drugs in cats and/or dogs. No studies have evaluated these drugs in the treatment of FC, however some studies in human medicine suggest that these drugs may be comparable to the effects of commonly used laxatives (e.g. PEG 3350). Tegaserod, like cisapride, has been associated with

cardiac arrhythmias, and therefore may be difficult to obtain. Prucalopride is marketed in the European Union and Canada.

**Intestinal secretagogues:** Lubiprostone and linaclotide are intestinal secretagogues that stimulate the release of Cl<sup>-</sup> and H<sub>2</sub>O into the intestinal lumen resulting in fecal hydration. These drugs are approved for the use of chronic idiopathic and opioid-induced constipation in humans but have not been investigated for use in the treatment of FC.

**Selected references (Additional references can be provided upon request):**

1. German AC, Cunliffe NA, Morgan KL. Faecal consistency and risk factors for diarrhoea and constipation in cats in UK rehoming shelters. *Journal of feline medicine and surgery* 2015.
2. Chang JY, Locke GR, Schleck CD, et al. Risk factors for chronic constipation and a possible role of analgesics. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2007;19:905-911.
3. Prichard D, Bharucha A. Management of opioid-induced constipation for people in palliative care. *International journal of palliative nursing* 2015;21:272, 274-280.
4. Freiche V, Houston D, Weese H, et al. Uncontrolled study assessing the impact of a psyllium-enriched extruded dry diet on faecal consistency in cats with constipation. *Journal of feline medicine and surgery* 2011;13:903-911.
5. Tam FM, Carr AP, Myers SL. Safety and palatability of polyethylene glycol 3350 as an oral laxative in cats. *Journal of feline medicine and surgery* 2011;13:694-697.

## **DIAGNOSIS AND TREATMENT OF FELINE INFECTIOUS DIARRHEA - 2017 CENTRAL FLORIDA ACADEMY OF VETERINARY MEDICINE**

Katie Tolbert, DVM, PhD, DACVIM  
Assistant Professor, Sm Animal Clinical Sciences  
University of Tennessee

Feline infectious diarrhea can be a frustrating problem for many reasons. First, there are many potential causes of feline infectious diarrhea that vary from extremely common to rare. Moreover, the presence of these pathogens does not always mean they are the cause of the diarrhea. Finally, the number of tests available to the practitioner to diagnose infectious diarrhea continues to increase. In this seminar, we will discuss which pathogens are significant, how to recognize clues in the signalment, history, and physical exam that suggest which pathogens are in play, and how to prioritize the tests you can use to detect the relevant pathogens causing feline infectious diarrhea.

### **Clinical Presentation**

Consideration of the history, signalment, and physical exam findings often helps to direct the diagnostic plan. For example, *Strongyloides* is generally an uncommon cause of diarrhea in the cat but may be an appropriate top consideration for a cat that comes from a wet, unsanitary environment. *Campylobacter* is commonly found in healthy cats but may be considered as the cause of diarrhea in a cat that presents with bloody diarrhea and signs of systemic illness. Localization of the origin of diarrhea (small versus large bowel) will also help direct the diagnostic plan. *Giardia* induces small bowel diarrhea whereas *Tritrichomonas foetus* is a large bowel pathogen. However, care is recommended when using this approach as cats with both infections can also present with mixed-bowel diarrhea perhaps as a result of concurrent dysbiosis or presence of co-infections.

### **Diagnostic Plan**

The diagnostic plan for evaluation of infectious diarrhea can be divided into front-line, second, and thirdline diagnostic tests. Considerations for front-line diagnostics for small bowel diarrhea include wet-mount fecal cytology, fecal flotation, and Giardia SNAP ELISA. When possible, feces should be obtained for wet mount cytology from the proximal colon by a fecal loop or colonic flush (*video of colonic flush available at:*

<http://www.youtube.com/watch?v=JMfZ9M80V8E>). However, fresh fecal samples obtained immediately after voiding are acceptable. Empirical deworming with fenbendazole is also recommended even when fecal testing is negative because of intermittent shedding of ova and oocysts and the low sensitivity

associated with fecal testing for certain pathogens. Minimum data base blood work may also be included if the cat is older or presents with signs of systemic or severe illness (e.g. fever, inappetance, lethargy). FeLV/FIV testing should be performed in young cats with diarrhea or those with an unknown vaccination history or coming from highdensity housing environment. For a cat with large bowel diarrhea, testing for common infectious diseases in your area (e.g. *Histoplasma*, *Tritrichomonas foetus*) and cytologic examination of a rectal scrape would also be considered. The latter can be obtained by scraping the mucosa with a gloved finger or conjunctival spatula.

In this seminar, we will also discuss when to prioritize testing for bacterial enteropathogens with fecal culture or PCR (“feline diarrhea panel”). Although these tests are widely available and easy to perform, many of these bacteria (e.g. *Campylobacter*, *Clostridium perfringens*, *E. coli*) can be found in the healthy cat and therefore, their presence must be interpreted in light of the signalment and clinical signs.

## UPDATE ON THE APPROPRIATE USE OF GASTROPROTECTANTS - 2017 CENTRAL FLORIDA ACADEMY OF VETERINARY MEDICINE

**Katie Tolbert, DVM, PhD, DACVIM**

The gastric mucosa is repeatedly exposed to noxious substances including an acidic pH, mechanical and chemical irritants, and digestive enzymes. The gastric mucosal barrier (GMB) is comprised of defense mechanisms that protect the gastric mucosa against these noxious substances. The GMB includes a single layer of highly resistant epithelial cells that repel gastric acid and are capable of rapid repair, a double mucus layer that is rich in bicarbonate ions, the local production of prostaglandins that serve to regulate blood flow and stimulate the secretion of mucus and bicarbonate ions, and a rich mucosal blood supply. Gastric and proximal duodenal erosion and ulceration develops when there is an imbalance of increased injurious agents and/or a decrease in these protective mechanisms.

The most common cause of gastrointestinal (GI) ulceration in the dog is NSAID administration whilst the most common cause in the cat is GI neoplasia (i.e. mast cell tumor, gastrinoma, lymphoma, adenocarcinoma). Thus, the diagnostic approach and direct treatment of the underlying cause of ulceration often differs between species. However, the approach to the treatment of ulcerative and erosive disease with mucosal gastroprotectants is very similar. A summary of gastroprotectant drugs used for the treatment of GUE can be found below. Additional details and less commonly used drugs (e.g. nutraceuticals, conventional antacids, etc.) will be provided in the presentation.

### **Acid suppressants**

The development of gastric erosion and ulceration (GUE) is multifactorial, however excessive gastric acidity is closely associated with ulcer development. Thus, the clinical goal for the medical treatment of ulcerative disease in people is to reduce gastric acidity and maintain the intragastric pH at or above 3 for at least 18 hours per day. Although no goals have been established for the treatment of GUE in companion animals, it is widely accepted that increasing gastric pH aids in healing of GUE in dogs and cats. For this reason, acid suppressant drugs are used as a first line treatment for dogs and cats with GUE. There are 2 major classes of acid suppressant drugs used in veterinary medicine, the **histamine-2 receptor antagonists** (H2RAs) and the **proton pump inhibitors** (PPIs). The H2RAs, which target the histamine-2 receptor on the acid-producing gastric parietal cells, have some advantages. The H2RAs are maximally effective within hours of administration, have a good safety profile, and, unlike the PPIs, has a bioavailability that is unaffected by food. However, the PPIs, which target the final pathway for acid production, are significantly more effective at acid suppression than the H2RAs. Although PPIs can take up to 4 days to reach peak effect, evidence suggests they are likely as effective as H2RAs on day 1 of

administration. The disadvantages of PPIs are that the majority of them are cytochrome P450 (CYP) inhibitors and thus can result in interactions with other drugs dependent on CYP metabolism. The PPIs are also associated with some serious adverse effects when given chronically to humans. These adverse effects are covered in more detail in the proceedings on acid suppressants. Dogs and cats with documented or suspected GUE should be treated with a PPI (e.g. omeprazole, esomeprazole, pantoprazole) at 1 mg/kg q 12 hr.<sup>1-3</sup> A variety of omeprazole formulations (tablet, capsule, reformulated paste, suspension) have been evaluated and demonstrated to be effective in raising the intragastric pH in healthy dogs and cats. With the exception of self-limiting diarrhea, PPIs appear to be well-tolerated during short-term administration in dogs and cats. However, based on the evidence for adverse effects in humans, I would advise avoiding long-term administration of PPIs when possible.

### **Coating agents**

Coating agents include sucralfate, barium, and alginate-antacids (e.g. Gaviscon). **Sucralfate**, a polyaluminum sucrose sulfate, forms a protective layer on the esophageal and gastric mucosa. Sucralfate is activated in the presence of an acid to form a gel-like substance that covers areas of denuded epithelium. Sucralfate may also stimulate the production of protective prostaglandins. There are very few studies which have evaluated the efficacy of sucralfate in the treatment of GUE in dogs and cats. However, studies investigating the use of sucralfate in the polypharmacy treatment of GUE and muscositis in humans suggest there is a benefit to this practice. Moreover, sucralfate is associated with very few adverse effects aside from constipation. Sucralfate does change the pH of the stomach and therefore may interfere with the metabolism of drugs that are dependent on an acidic gastric pH (e.g. PPIs). It also may interfere with drugs affected by the aluminum component of sucralfate (e.g. tetracyclines, ciprofloxacin). Therefore, these drugs should be administered at least two hours before or after sucralfate administration.<sup>4</sup>

**Barium**, like sucralfate, is proposed to have mucosal protecting effects. It has also been proposed to have hemostatic properties although neither of these mechanisms have been proven in the treatment of dogs and cats with GUE. I do not use barium in my practice but many of my colleagues use it often for the treatment of GI hemorrhage. Barium should be withheld at least 24 hours prior to gastrointestinal endoscopy and should not be used in animals where GI perforation is suspected.

**Alginate-antacid** drugs are acid-neutralizing drugs that also contain sodium bicarbonate and alginic acid. The alginic acid and bicarbonate combine to target acid-pockets in the stomach to prevent reflux of gastric acid into the esophagus. In humans with gastroesophageal reflux disease, alginate-antacids significantly decreased reflux and symptoms of dyspepsia compared to placebo.<sup>5</sup> No studies have evaluated the use of this medication for the treatment of reflux esophagitis or GUE in dogs and cats.

Alginate-antacids are likely inferior to acid suppressant therapy and should not be used as the sole treatment for GUE. Moreover, they may lead to rebound gastric acid hypersecretion if not administered frequently and in the absence of an acid suppressant.

### **Prostaglandin agonists**

The most commonly used prostaglandin agonist in veterinary medicine is misoprostal, a PGE1 analog. By stimulating endogenous eicosanoids, misoprostal increases mucosal blood flow and epithelial repair and stimulates mucus and bicarbonate secretion. Despite its mechanism of action, misoprostal is only effective for NSAID-induced injury and has no effect with steroid-associated ulceration. Misoprostal may increase GI and urogenital smooth muscle contractions leading to side effects of cramping, diarrhea, and abortions.<sup>6</sup>

### **Selected references (additional references provided on request):**

1. Tolbert K, Bissett S, King A, et al. Efficacy of oral famotidine and 2 omeprazole formulations for the control of intragastric pH in dogs. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2011;25:47-54.
2. Parkinson S, Tolbert K, Messenger K, et al. Evaluation of the Effect of Orally Administered Acid Suppressants On Intragastric pH in Cats. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2014.
3. Tolbert K, Odunayo A, Howell R, et al. Efficacy of intravenous administration of combined acid suppressants in healthy dogs. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2015;in press.
4. KuKanich K, KuKanich B. The effect of sucralfate tablets vs. suspension on oral doxycycline absorption in dogs. *Journal of veterinary pharmacology and therapeutics* 2015;38:169-173.
5. Thomas E, Wade A, Crawford G, et al. Randomised clinical trial: relief of upper gastrointestinal symptoms by an acid pocket-targeting alginate-antacid (Gaviscon Double Action) - a double-blind, placebo-controlled, pilot study in gastro-oesophageal reflux disease. *Alimentary pharmacology & therapeutics* 2014;39:595-602.
6. Hanson SM, Bostwick DR, Twedt DC, et al. Clinical evaluation of cimetidine, sucralfate, and misoprostol for prevention of gastrointestinal tract bleeding in dogs undergoing spinal surgery. *American journal of veterinary research* 1997;58:1320-1323.

## **APPROPRIATE AND RATIONAL USE OF ACID SUPPRESSANTS AND ANTACIDS - 2017 CENTRAL FLORIDA ACADEMY OF VETERINARY MEDICINE**

**Katie Tolbert, DVM, PhD, DACVIM**

Acid-related tissue injury arises from multifactorial and often overlapping mechanisms related to an impaired mucosal barrier and/or overproduction of injurious substances (e.g. gastric acid, pepsin, bile salts). Gastroduodenal ulceration and reflux esophagitis are two of the more commonly recognized causes of acid-related tissue injury in dogs and cats. As in people, it is widely accepted that intragastric pH is closely associated with the healing of gastroduodenal ulceration and reflux esophagitis in dogs and cats. Clinical pH goals have been established that suggest that the gastric pH should be at or above 3 for at least 18 hours per day to promote healing of gastroduodenal ulceration in humans. Although there are no goals for the treatment of acid-related tissue injury in dogs and cats, acid suppression is recommended for these conditions

Two major classes of drugs, antacids and acid suppressants, can be used to increase the gastric pH. Antacids are acid-neutralizing drugs that are significantly less effective in sustaining a high intragastric pH. Moreover, they need to be administered frequently to prevent rebound gastric acid hypersecretion. Thus, acid suppressants are the preferred drug for raising intragastric pH. Most commonly used acid suppressants in human and veterinary medicine include the histamine-2 receptor antagonists (H2RAs) and the proton pump inhibitors (PPIs).

Histamine-2 receptor antagonists target the histamine-2 receptor on the acid producing cell of the stomach, the parietal cell. Peak serum concentration and effect occur within hours of H2RA administration. In vitro studies suggest that the H2RA drugs may also have effects independent of their action on inhibition of acid secretion including stimulation of bicarbonate and mucus secretion. The potency of the H2RA drugs varies with famotidine being more effective than ranitidine. Cimetidine is not an effective H2RA in dogs and is associated with acute liver injury in people. Unlike the PPIs, the bioavailability of H2RAs is not affected by food. Because H2RAs target only one pathway of acid secretion, they are significantly inferior to PPIs in raising intragastric pH. Studies in our lab suggest that dogs may develop tolerance to famotidine as early as day 3 of administration. However, H2RAs may be a good choice for prevention of anesthesia-induced esophageal reflux and for as needed symptom control.

The PPI drugs target the enzyme responsible for the final production and secretion of gastric acid. These drugs inhibit gastric acid secretion irrespective of the stimulus. Because there is a delay to peak effect, maximal effect of the PPI drugs may take up to 4 days. However, studies in healthy dogs suggest

that PPIs have acid suppressant activity comparable to H2RAs on day 1. Additionally, there is no evidence in dogs to suggest that combined therapy (H2RA + PPI) results in better acid suppressant activity even in the first few days of PPI administration. Studies in healthy dogs and cats as well as clinical experience suggest that PPIs should be dosed twice-daily at 1.0mg/kg/dose when treating gastroduodenal ulceration or esophagitis. Many formulations (e.g. capsule, tablet, reformulated paste, suspension) of PPIs are effective in raising intragastric pH in dogs and cats. During this presentation, I will discuss potential risk factors that can be used to determine which dogs and cats may be considered “high risk” and therefore may benefit from prophylactic, transient acid suppressant therapy.

Acid suppressants are efficacious for the treatment of acid-related tissue injury but the rationale for and efficacy of acid suppressant administration for the adjunctive treatment of metabolic and inflammatory diseases are less clear. In this seminar, I will discuss the pros and cons for use of PPIs in metabolic and inflammatory conditions including chronic kidney disease, liver failure, pancreatitis, and thrombocytopenia.

#### **Selected references:**

1. Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression for healing of duodenal ulcers? A model of the relationship between ulcer healing and acid suppression. *Gastroenterology* 1990;99:345-351.
2. Huang JQ, Hunt RH. Pharmacological and pharmacodynamic essentials of H(2)-receptor antagonists and proton pump inhibitors for the practising physician. *Best practice & research Clinical gastroenterology* 2001;15:355-370.
3. Bersenas AM, Mathews KA, Allen DG, et al. Effects of ranitidine, famotidine, pantoprazole, and omeprazole on intragastric pH in dogs. *American journal of veterinary research* 2005;66:425-431.
4. Tolbert K, Bissett S, King A, et al. Efficacy of oral famotidine and 2 omeprazole formulations for the control of intragastric pH in dogs. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2011;25:47-54.
5. Parkinson S, Tolbert K, Messenger K, et al. Evaluation of the Effect of Orally Administered Acid Suppressants On Intragastric pH in Cats. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2014.
6. Sutalo S, Ruetten M, Hartnack S, et al. The Effect of Orally Administered Ranitidine and Once-Daily or Twice-Daily Orally Administered Omeprazole on Intragastric pH in Cats. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2015;29:840-846.
7. Zacuto AC, Marks SL, Osborn J, et al. The influence of esomeprazole and cisapride on gastroesophageal reflux during anesthesia in dogs. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2012;26:518-525.
8. McLeland SM, Lunn KF, Duncan CG, et al. Relationship among serum creatinine, serum gastrin, calcium-phosphorus product, and uremic gastropathy in cats with chronic kidney disease. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2014;28:827-837.
9. Lazarus B, Chen Y, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA internal medicine* 2016:238-246.

10. Mazaki-Tovi M, Segev G, Yas-Natan E, et al. Serum gastrin concentrations in dogs with liver disorders. *The Veterinary record* 2012;171:19.
11. Parente NL, Bari Olivier N, Refsal KR, et al. Serum concentrations of gastrin after famotidine and omeprazole administration to dogs. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2014;28:1465-1470.
12. Tolbert MK, Graham A, Odunayo A. Repeated famotidine administration results in a diminished effect on intragastric pH in dogs. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 2017.

## EVIDENCE-BASED APPROACH TO THE USE OF PROBIOTICS IN CANINE AND FELINE GI DISEASE - 2017 CENTRAL FLORIDA ACADEMY OF VETERINARY MEDICINE

**Katie Tolbert, DVM, PhD, DACVIM Assistant Professor, Sm Animal Clinical Sciences University of Tennessee**

There are approximately 10 fold more bacteria than cells in the body. Thus, mammals and not the microbiota could be considered as the parasites! Regardless, it is clear that both provide benefit to each other. Mammals provide a nutrient-rich environment for the microbiota to live and, in turn, intestinal bacteria provide a number of benefits to the host such as synthesis of nutrients (e.g SCFAs) and vitamins (B vitamins), regulation of the intestinal epithelial barrier, promotion of digestion, crosstalk with the host immune system, influence of host-cell proliferation, vascularization, and neurologic signaling, and protection against pathogens. Many factors influence the microbiome in humans including genetic background, infections and its associated immune response, environmental exposures, and most importantly, diet, sex and age, previous xenobiotic administration, and intestinal biopsy sample collection. Perhaps it comes as no surprise, given the ratio of bacteria to host cells, that “dysbiosis” or alteration of the native microbiota is associated with a wide variety of diseases. The onset of microbial shifts and reduction in biodiversity are well-described in canine and feline enteropathies. For this reason, manipulation of intestinal bacteria with probiotic administration represents a potential therapeutic target for a variety of diseases. Probiotics are live microorganisms, which when administered in appropriate concentrations, are intended to colonize and interact with the host intestinal epithelium and immune system and confer a physiological health benefit to the recipient (e.g. anti-inflammatory activity, antagonize enteric pathogens, etc). Probiotics, therefore, must survive not only processing and storage in vitro but also gastric and bile acid degradation in vivo. Most probiotics contain lactic acid-producing bacteria (i.e. *Bifidobacterium*, *Lactobacillus*, *Enterococcus spp*). Lactic acid-producing bacteria are normal inhabitants of the colon. They maintain anti-microbial properties as a result of secretion of bioactive compounds and induction of changes in environmental pH that may be unfavorable to certain pathogens. These bacteria tend to be decreased in inflammatory bowel disease. Although a variety of veterinary probiotics containing lactic-acid producing bacteria are now available, many animals are still treated with probiotics intended for human use as these are more widely available. Thus, practitioners should have a good understanding of the probiotics that are available, both those intended for human and animal use. Probiotic strains derived from dogs can adhere to the human and canine GI tract similarly. Moreover, the use of probiotics intended for humans can transit the canine and feline GI tract. Thus, despite differences in resident bacteria among species (e.g. cats have more anaerobic bacteria in their intestine compared to dogs and humans), probiotics do not necessarily need to be derived from the species being treated. However, they must be shown to survive GI transport and colonize the intestinal tract of the species of interest. Practitioners should also be aware of dosing and storage guidelines for each probiotic as they vary greatly between products. Practitioners should make clients aware that probiotics are classified as dietary supplements, not pharmaceuticals, and therefore are not regulated by the FDA. Proof of efficacy is not required. Several studies had demonstrated that a substantial number of probiotics on the market for human or animal use may not contain the claimed organism, may contain additional species not listed on the label, and/or may contain markedly lower concentrations than stated on the label. Thus, practitioners and clients should scrutinize probiotic products and only choose probiotics produced from companies with good quality control measures.

### **Probiotics in intestinal diseases**

Evaluation of the effect of probiotics as adjunctive therapies for the treatment of animals with naturally occurring diseases is still in its infancy. Most work to date has been focused on the use of probiotics for the treatment of intestinal diseases with the treatment of acute idiopathic diarrhea showing the most promise. For example, administration of the probiotic *Enterococcus faecium* SF68 to shelter cats resulted in a significantly lower percentage of cats with diarrhea for  $\geq 2$  days compared to cats that received

placebo. Administration of the canine-derived probiotic containing *Bifidobacterium animalis* AHC7 to dogs with acute idiopathic diarrhea resulted in significantly reduced time to resolution of diarrhea and reduced percentage of dogs administered metronidazole compared to dogs receiving placebo. Similar results were found in a study investigating the effects of a probiotic cocktail orally administered to dogs with acute vomiting and diarrhea. In this study, dogs who received the probiotic cocktail had a quicker resolution of diarrhea, but not vomiting, compared to dogs who received placebo. The beneficial effects of probiotics and microbial therapy for infectious diarrhea (e.g. *C. diff*-associated diarrhea) has been well established in people. However, the beneficial effects of probiotics for infectious diarrhea in dogs and cats have been underexplored. To the author's knowledge, only one published report has described the use of probiotics for infectious diarrhea in dogs wherein treatment of dogs with subclinical chronic giardiasis with the probiotic *Enterococcus faecium* SF68 did not reduce giardial cyst or fecal antigen shedding compared to dogs receiving placebo.

It stands to reason the probiotics would also be helpful in the treatment of intestinal disorders where dysbiosis is thought to play a major role (i.e. antibiotic-induced diarrhea, antibiotic-responsive diarrhea, inflammatory bowel disease). Unfortunately, at the time of this writing, only one published study has evaluated the use of probiotics in dogs with presumed IBD. No dogs were hypoproteinemic prior to treatment. In an open-label, randomized design, ten dogs each were treated with either a high-dose ( $1-2 \times 10^{11}$  lyophilized bacteria per 10 kg per day) probiotic cocktail intended for human use which contains 8 different bacterial strains or metronidazole and prednisone for 60 days. Before therapy and 30 days following completion of the drug trial, the clinical disease activity index (CIBDAI) scores, duodenal histology scores as well as presence of inflammatory cells, and fecal bacteria were compared. All dogs regardless of treatment improved clinically. Moreover, the group treated with probiotics had an increase in T-regulatory cells as well as an increase in the potentially protective bacteria, *Faecalibacterium prausnitzii*, in fecal samples. Caution is advised when drawing definitive conclusions about this study given its open-label design and the lack of a clearly defined patient population. Dogs had not been treated with steroids or other immunosuppressants so it is difficult to know how many dogs truly had IBD. Thus, at this time, the presenter does not recommend withholding immunosuppressive treatment to dogs with a diagnosis of inflammatory bowel disease. However, although more studies are needed, this early data suggests that certain probiotics might have a steroid-sparing effect in a population of dogs with chronic enteropathy. Until additional studies with a larger, clearly defined patient population are performed, the author recommends probiotics as an adjunctive, but not sole, therapy in dogs and cats with IBD. The benefit of probiotic therapy for dogs and cats with food responsive diarrhea (FRD) has not been demonstrated likely because dogs and cats with FRD often respond quickly to diet alone making it difficult to evaluate for a potential beneficial effect of the probiotic. In one placebo-controlled study evaluating a synbiotic containing *Enterococcus faecium* for dogs with food-responsive diarrhea, no effect was observed compared to diet alone over a 6-week treatment period however the study only included 12 dogs (7=synbiotic, 5=placebo) and thus was underpowered. In another placebo-controlled study evaluating the administration of an elimination diet and probiotic containing a combination of different *Lactobacilli* spp., the elimination diet (with or without concurrent probiotic administration) resulted in clinical improvement in dogs with FRD. Moreover, the effect of the administration of probiotics on intestinal mucosal cytokine profiles was highly variable. Thus, at this time, the presenter does not recommend probiotics to cats and dogs with presumptive FRD.

### **Probiotics in extra-intestinal diseases**

The few studies that have investigated the effect of probiotics in extra-intestinal diseases in veterinary patient are as follows:

- 1) Early life exposure to a *Lactobacillus*-containing probiotic resulted in long-term decrease in clinical signs in dogs with experimentally-induced atopic dermatitis. Oral administration of *Lactobacillus paracasei* probiotic had a steroid-sparing effect in dogs with naturally occurring canine atopic dermatitis.
- 2) The effect of probiotics for the treatment of feline herpes virus infection has also been studied in an investigator-blinded, prospective study. 12 shelter cats were treated with either *Enterococcus*

*faecium* SF68 or placebo once daily for 140 days. Although the sample size was low and there was no crossover in this study, *Enterococcus faecium* was well-tolerated and seemed to have a benefit in decreasing conjunctivitis in some cats.

- 3) Probiotics have also been purported to provide benefit in the treatment of canine and feline lower urinary tract infections (UTIs). Vaginal colonization with lactic-acid producing bacteria is thought to reduce the risk of recurrent UTIs in human women. However, administration of an oral probiotic containing *Lactobacillus*, *Bifidobacterium*, and *Bacillus* spp. to 35 healthy, spayed female dogs for either 14 or 28 days failed to increase the prevalence of vaginal lactic acid-producing bacteria.<sup>13</sup> Moreover, lactic acid-producing bacteria were not commonly isolated from the vaginal vault of healthy dogs and there were no significant differences in isolation of lactic-acid producing bacteria in healthy dogs compared to dogs with recurrent UTIs. Thus, more studies evaluating the role of specific bacteria in the development of UTIs in dogs and cats as well as the beneficial effect of probiotics, if any, in the treatment of UTIs in companion animals are warranted.
- 4) No studies have investigated the effectiveness of probiotics in reducing the incidence of uroliths in dogs. However, *Lactobacillus* spp. containing probiotics were able to decrease oxalate concentrations in vitro.<sup>15</sup> Thus, further studies are warranted to determine if probiotics could play a role in reducing risk of calcium oxalate urolith formation.

### Cautions with use

Probiotics are considered supplements and therefore are not subject to regulatory oversight by the FDA. Demonstration of effectiveness is not mandated. Generally speaking, most probiotics are safe and are associated with few to no side effects. However, probiotics might be inappropriately labeled, contain organisms at the incorrect concentration, or contain organisms that might be pathogenic or have not been demonstrated to possess probiotic properties. Clients should be notified of these concerns as well as the lack of efficacy data in veterinary medicine. Some probiotics intended for human use are manufactured in enteric-coated capsules to prevent premature acid degradation and to assist in delivery of bacteria to the distal intestine prior to activation. A study performed in cats with CKD demonstrated that opening an enteric-coated synbiotic capsule and sprinkling its contents on food or delivering as a slurry resulted in ineffectiveness of the synbiotic. Thus, this form of delivery, unless otherwise indicated by the manufacturer, is not recommended.

### Conclusions

The culmination of this early work suggests that probiotics might have a place in the adjunctive treatment of a variety of diseases. However, much work is needed to determine which diseases will respond and which type and how much of the probiotic is needed to induce such a favorable response. At this time, the presenter does use probiotics for the treatment of acute idiopathic diarrhea, antibiotic-induced diarrhea, and as an adjunctive treatment in dogs and cats with chronic enteropathies other than food-responsive disease.

### Selected reading:

1. Weese JS, Anderson ME. The Canadian veterinary journal La revue veterinaire canadienne 2002;43:771-774.
2. Garcia-Mazcorro JF, Lanerie DJ, Dowd SE, et al. FEMS microbiology ecology 2011;78:542-554.
3. Marshall-Jones ZV, Baillon ML, Croft JM, et al. American journal of veterinary research 2006;67:1005-1012.
4. Bybee SN, Scorza AV, Lappin MR. Journal of veterinary internal medicine 2011;25:856-860.
5. Kelley RL, Minikhiem D, Kiely B, et al. Veterinary therapeutics : research in applied veterinary medicine 2009;10:121-130.
6. Simpson KW, Rishniw M, Bellosa M, et al. Journal of veterinary internal medicine 2009;23:476-481.
7. Rossi G, Pengo G, Caldin M, et al. PloS one 2014;9:e94699.
8. Schmitz S, Glanemann B, Garden OA, et al. Journal of veterinary internal medicine 2015;29:533-543.

9. Sauter SN, Benyacoub J, Allenspach K, et al. *Journal of animal physiology and animal nutrition* 2006;90:269-277.
10. Marsella R, Santoro D, Ahrens K. *Veterinary immunology and immunopathology* 2012;146:185-189.
11. Ohshima-Terada Y, Higuchi Y, Kumagai T, et al. *Veterinary dermatology* 2015;26:350-353, e374355.
12. Lappin MR, Veir JK, Satyaraj E, et al. *Journal of feline medicine and surgery* 2009;11:650-654.
13. Hutchins RG, Bailey CS, Jacob ME, et al. *Journal of veterinary internal medicine* 2013;27:1368-1371.
14. Hutchins RG, Vaden SL, Jacob ME, et al. *Journal of veterinary internal medicine* 2014;28:300-304.
15. Cho JG, Gebhart CJ, Furrow E, et al. *American journal of veterinary research* 2015;76:801-806.
16. Weese JS. *Journal of the American Veterinary Medical Association* 2002;220:794-797.
17. Rishniw M, Wynn SG. *Journal of feline medicine and surgery* 2011;13:405-409.