Nutritional Management of Chronic Diarrhea

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The major functions of the gastrointestinal tract are nutritional (digestion and absorption of food and water) and protective (providing both a physical barrier and immunological defense from potential pathogens or toxins). While the focus is often on digestive functions, it is important to remember that the gastrointestinal mucosa is the largest surface area that provides a barrier to the external environment and contains the largest and most complex part of the immune system, the gut-associated lymphoid tissue.[1] Compromise to either digestive or protective function can lead to systemic manifestations of disease, including specific or generalized malnutrition and/or immune compromise such as disruption of oral tolerance to dietary proteins or commensal microorganisms. A common clinical manifestation of intestinal pathology is diarrhea. While diarrhea may occur secondary to diseases involving the pancreas, kidneys, liver, or endocrinopathies such as Addison's disease, this discussion will focus on the nutritional management of chronic diarrhea defined as persistent or recurrent diarrhea lasting three or more weeks due to primary intestinal dysfunction.

Nutrition plays an important role in the management of patients with chronic enteropathy. Approximately 50% of cats[2] and 64% of dogs[3] with chronic enteropathy respond favorably to dietary intervention. The role of dietary management in patients with gastrointestinal (GI) disease is to maintain an adequate plane of nutrition to meet the patient's overall nutritional needs, to support GI regeneration, and to provide symptomatic relief of clinical signs. Correction of malnutrition can improve GI function and help protect against bacterial translocation and other complications. The patient evaluation must include a complete nutritional assessment consisting of diet history, physical examination including assessment of body condition and muscle condition, and appropriate diagnostic testing to recognize malnutrition and to identify clinical signs that may benefit from nutritional management. The appropriate dietary modifications are dependent upon the severity of disease, anatomic location of the underlying pathology, and physical examination and diagnostic findings. Patients with signs of systemic disease (significant weight loss, febrile, debilitated) or clinical pathology findings associated with more severe disease (e.g. hypoalbuminemia or hypocobalaminemia) need a more aggressive initial diagnostic work-up with concurrent medical management and may have a poorer prognosis.[4] Younger relatively healthy patients with no significant abnormalities on physical examination with normal baseline laboratory findings may first undergo diagnostic food trials before advancing to more invasive and costly diagnostics.

The clinical signs and nutritional status of the patient should direct the selection of the diet. The appropriate modifications depend upon several factors such as:

1) Current caloric intake, patient's body weight and body condition score. This information will help determine the initial daily caloric goals.
2) Localization of intestinal dysfunction. Patients with primarily small bowel diarrhea may respond better to a highly digestible, moderate fat, lower fiber diet whereas patients with primarily large bowel diarrhea may respond to an increased amount of fiber, specific types of fiber, &/or modulation of the intestinal microbiota with prebiotics or probiotics.
3) Concurrent dermatologic signs of pruritus may raise the index of suspicious for a cutaneous adverse food reaction that warrants a dietary elimination food trial with a novel or hydrolyzed protein diet.
4) Specific clinical pathology or histopathologic findings. Hypocobalaminemia needs to be addressed with supplementation. Evidence of lymphangiectasia warrants a lower dietary fat intake.

As with any aspect of medical management, the patient should be reevaluated at appropriate intervals to assure achievement of desired results. Patients with chronic enteropathy may require a series of logical systematic food trials to determine the nutritional plan that best meets that individual's needs. In addition to provision of complete nutrition, key dietary components of importance in GI disease

include fat, carbohydrates, fiber, protein, probiotics, and cobalamin. Each of these will be discussed in more detail.

ROLE OF DIETARY FAT IN DIARRHEA

Fat is the most caloric dense nutrient and therefore important to consider for inappetant malnourished patients. Fat is also necessary for optimal absorption of fat-soluble vitamins. Certain fats play an important physiological role such as long-chain polyunsaturated fatty acids that are eicosanoid precursors. Most dietary fat present in pet foods is in the form of long-chain triglycerides (LCT). The bulk of fat digestion begins with the emulsification of fats by bile acids, creating minute, water-soluble particles, which can be readily digested by pancreatic and enteric lipase. Pancreatic lipase is the enzyme of primary importance in the normal digestion of fats; however, gastric lipase, secreted by the stomach, and enteric lipase, which is secreted by the intestinal mucosa, are also capable of digesting LCTs. These become more important in patients with exocrine pancreatic insufficiency. Bile acids, secreted by the liver, are also important in facilitating fat digestion and absorption.

Absorbed fatty acids and monoglycerides are re-esterified within the enterocyte to form new triglycerides. The newly formed LCTs are packaged along with cholesterol, fat-soluble vitamins, and other lipids into chylomicrons. These protein-coated, water-soluble chylomicrons are then absorbed into the intestinal lacteals and transported via the lymphatic system to the venous blood.

The intestinal cells most specialized for absorption of fat are located at the tip of the microvilli. These are also the cells most susceptible to mucosal injury. Therefore fat malabsorption or maldigestion may occur as a result of mucosal damage or atrophy, enzymatic deficiency, or biliary deficiency. Severe fat malabsorption is evident as steatorrhea, but fat malabsorption may occur in the absence of obvious steatorrhea, contributing to weight loss even without diarrhea. Malabsorbed fats can be fermented by colonic bacteria to produce hydroxy fatty acids, which can stimulate a secretory diarrhea thereby worsening the clinical signs.[5] For patients with evidence of fat malabsorption, a highly digestible diet with moderate to lower fat may be indicated.

A low-fat diet will help limit the diarrhea associated with fat malabsorption. Unfortunately, since fat provides a significant proportion of calories in the normal diet, patients may lose weight on a low-fat diet unless there is adequate caloric compensation. For some animals, this can be achieved by providing adequate quantities of highly digestible carbohydrates and proteins. Others may require a more concentrated source of energy. For some dogs, supplementation with medium chain triglycerides (MCT) can provide essential dietary calories. MCTs can be absorbed even in the absence of bile acids and pancreatic lipase, and are readily oxidized as a source of energy.

It is worth mentioning two clinical conditions in the dog that typically require dietary fat modification. Intestinal lymphangiectasia may be either a primary disorder seen in certain breeds including Yorkshire terriers or secondary to significant mucosal inflammation (e.g. inflammatory bowel disease) or neoplasia (e.g. alimentary lymphoma). Obstruction of lacteals can result in a net loss of lipid and protein from the lacteals into the gastrointestinal tract resulting in hypoalbuminemia or panhypoproteinemia.[6] Dietary fat restriction is recommended and has been shown to be beneficial.[7] Dietary recommendations for acute canine pancreatitis continue to evolve. The historical recommendation for prolonged fasting has been replaced with the recommendation to provide early enteral nutrition.[8,9] The optimal nutrient profile for dogs with acute pancreatitis remains unknown. While studies have shown that dietary fat intake does not impact pancreatic enzyme secretion in healthy dogs,[10] avoiding high fat diets is prudent.[8] A recent review article provides dietary fat guidelines based on the patient's serum triglyceride level.[9]

While dietary fat intake may have a clinical impact on dogs with various enteropathies, the same may not apply to cats. A study in cats indicated that cats with chronic diarrhea do not benefit from a low fat diet.[11] In that study, cats were fed either high fat (23% dry matter) or low fat (10% dry

matter), highly digestible diet. Over 75% of the cats showed a positive response, but there were no differences in response rate between the two diets.

ROLE OF DIETARY CARBOHYDRATES IN DIARRHEA

There is a perception that cats do not digest carbohydrates well. Cats, like dogs, do not have salivary amylase, but intestinal digestion of starches is initiated by pancreatic amylase, and completed by enzymes at the intestinal brush border. Normal, healthy cats are able to digest properly processed carbohydrates with greater than 90% efficiency.[12]

With intestinal disease, however, carbohydrate digestion may decrease. The disaccharidases that complete the digestion of carbohydrates are located in the small intestinal brush border, which may be damaged due to disease. Increased carbohydrate fermentation, indicative of carbohydrate malabsorption, has been confirmed in cats with inflammatory bowel disease (IBD).[13] Carbohydrate malabsorption may occur in IBD if inflammation inhibits production of digestive enzymes or if inflammatory infiltrates inhibit nutrient absorption.[13]

When carbohydrate malabsorption does occur, it can contribute to osmotic diarrhea, as well as bacterial overgrowth. In such cases, modulating carbohydrate intake may help manage the clinical signs of diarrhea.

Dietary Fiber

While dietary fibers are carbohydrates, their physiological effect is very different from digestible carbohydrates. Unlike digestible carbohydrates, which are linked with an alpha linkage that is easily cleaved by mammalian alpha-amylase, the sugars in dietary fiber are linked by a beta linkage. Beta links between sugar molecules are not digestible by mammalian digestive enzymes, but are cleaved by bacterial enzymes, so these substrates remain intact until digested (fermented) by bacteria.

Dietary fibers can be classified in many different ways, although the most common are based on the water solubility of the fiber or fermentability by microorganisms. Although there are exceptions, it is generally recognized that more soluble fibers tend to be more fermentable. The functionality of dietary fibers is related to these two characteristics. Soluble fibers tend to form viscous gels, which can slow gastric emptying and GI transit. Insoluble fibers tend to adsorb water and increase fecal bulk, which can help normalize GI motility. Many fibrous ingredients in foods and pet foods contain differing degrees of both soluble and insoluble fiber.

A subset of fermentable fibers includes “prebiotics.” By definition, these fibers are selectively fermented by health-promoting bacteria, especially strains of *Lactobacillus* and *Bifidobacteria*. This results in their ability to increase the number or percentage of these organisms, while decreasing the prevalence of potential pathogens, such as Salmonella, Clostridia or *E. coli*. Prebiotics and dietary fibers produce such health benefits as reducing blood lipids and cholesterol, reducing constipation, and aiding in various types of diarrhea and inflammatory conditions of the GI tract, as well as being a substrate for SCFA production.[14-16] Among the many fibers available for use as prebiotic supplements are beta-glucans; pectin; resistant starch; various oligosaccharides, such as inulin, fructooligosaccharides (FOS) and mannan-oligosaccharides (MOS); and others.[16-18]

ROLE OF DIETARY PROTEIN AND AMINO ACIDS IN DIARRHEA

Enterocytes are continuously renewed from stem cells in the crypts such that intestinal epithelial cells are replaced about every 3 days. This rapid regeneration helps the intestine heal quickly following an injury, but the continuous turnover of cells exerts a high demand for nutrients. These cells use between 10% and 20% of the individual’s daily energy intake and approximately 50% of ingested protein, with more than 90% of the aspartate, glutamate and glutamine utilized by the intestinal tissues.[19] Thus, the GI tract is highly sensitive to protein or amino acid deficiency.

Inadequate intake of dietary protein or essential amino acids can cause GI tract atrophy with a decrease in absorptive cells, alterations in digestive enzymes, reduction in immunoglobulins and

immune cells in the intestine, and an increased risk for colonization and translocation of pathologic microorganisms.[20-23]

The amino acids glutamine and glutamate are critical for the health of the GI tract, where they serve as key energy sources and promote the natural barrier function of the intestinal mucosa.[24] If dietary glutamine is excluded following intestinal injury, the intestinal mucosa atrophies and bacterial translocation from the intestinal lumen can occur. However, glutamine is found abundantly in meat and other proteins and is normally made in the body from other amino acids. So long as dietary protein intake is sufficient, supplemental glutamine should not be necessary.

Some patients may have an adverse reaction to a component of the diet. A subset of adverse food reactions is a "food allergy" or "food hypersensitivity" defined as an aberrant immune response characterized as an IgE antibody dependent, cell mediated, or a mixed immunological response.[1] Most dietary antigens are proteins or glycoproteins of 10 to 70 kDa in size.[1] Two recent metanalyses report the most common dietary antigens for the dog are beef, chicken, dairy and wheat[25] and egg[26] while the most common food allergens for the cat are beef, chicken, fish,[25] and dairy.[26] Dietary elimination trials followed by provocation trials remain the gold standard for the diagnosis of both food-responsive enteropathy and food-induced cutaneous manifestations including food-induced atopic dermatitis.[1,27,28] Most dogs with gastrointestinal signs of food hypersensitivity improve within 2 weeks[1] while the current recommendation for cutaneous signs of food hypersensitivity is an 8 week elimination food trial.[29] Currently serological or intradermal testing to determine food allergens is not recommended.[27] Veterinary therapeutic diets designed for elimination diet trials should be fed since over the counter diets may contain trace amounts of ingredients not listed on the label that could be potential antigens.[30] Either single protein novel or hydrolyzed protein diets can be utilized for a food trial. However for some patients it is extremely difficult to find a truly "novel" protein that the pet has not previously consumed. A comprehensive diet history is required to determine if a "novel" commercial or home-cooked recipe is an option for that individual. When the diet history is unclear or a truly novel protein is not available, a hydrolyzed diet may be the most viable option for that patient. Hydrolyzed protein diets have undergone enzymatic hydrolysis to cleave the protein molecules into smaller peptide fragments to reduce antigenicity compared to corresponding intact protein.[1,31] One study showed 79% of dogs hypersensitized to soy and corn tolerated a commercially available hydrolyzed soy and cornstarch diet.[32] A pilot study evaluated 6 dogs with a histological diagnosis of inflammatory bowel disease previously refractory to various dietary and/or medical interventions. Four out of six dogs had marked clinical improvement with dietary therapy alone using a hydrolyzed soy diet and did not require additional therapy while one dog required pancreatic enzyme supplementation for concurrent exocrine pancreatic insufficiency and the sixth dog required metoclopramide to resolve vomting.[33] A three-year prospective randomized clinical trial in dogs with chronic small bowel enteropathy compared a hydrolyzed soy diet to a highly digestible therapeutic diet indicated for gastrointestinal disease. In this study, dogs responded favorability to both diets with no difference in initial response rate. However long-term efficacy was better for the hydrolysate diet.[34] Positive results to a hydrolyzed soy diet have also been reported in cats with chronic enteropathy.[35]

Can we assume patients that improve on a hydrolyzed diet have a "food allergy"? It is plausible that other factors such as the overall digestibility of these diets or the omission of certain non-antigenic ingredients could play a role in the positive response. In addition certain ingredients such as soy, a common protein hydrolysate, may have immunomodulatory properties that could contribute to a positive response. It may be more appropriate to consider some of these patients as having a food-responsive enteropathy rather than a true "food allergy" or "inflammatory bowel disease."[36] Furthermore diet, including protein, can influence the intestinal microbiota.[37-40] This is an important consideration since there is an association between mucosal bacteria and intestinal inflammation in both the cat[41] and dog[42] leading to emerging evidence that dysbiosis of commensal

intestinal microbiota plays a role in inflammation associated with chronic enteropathy including idiopathic inflammatory bowel disease.[43,44]

ROLE OF PROBIOTICS IN DIARRHEA

Although not a nutrient, probiotics are potential dietary components that may be of value for GI health. Probiotics are live microorganisms when consumed in adequate quantities confer a health benefit to the host.[45] Probiotics benefit the host by improving microbial balance and by interacting with the gut associated lymphoid tissue (GALT). The GALT is the largest immunological organ in the body as it contains about 70% to 80% of the immunoglobulin-producing cells in the body.[18] Stimulation of the immune system within the GI tract also can result in effects throughout the body. Activated plasma cells migrate to the bloodstream and to other parts of the body. Thus, antigen priming at one surface area (the intestinal mucosa) can result in antibodies being synthesized and secondary responses occurring at other sites. Via this mechanism, probiotics interacting with the GALT can influence GI and systemic health and immune function.

Some of the most commonly fed probiotics include *Lactobacillus* species, *Bacillus subtilis*, and *Enterococcus faecium* SF68.[46] Multiple metanalyses of clinical trials in humans have confirmed the benefit of probiotics in the control of antibiotic-associated diarrhea.[47,48] In humans probiotics have proven useful in the management of acute diarrhea, viral and bacterial diarrhea, and inflammatory bowel diseases by reducing either the duration or severity of diarrhea, or both.[49-51] In a murine model of sepsis, probiotics were able to prevent the breakdown in colonic barrier function and reduced bacterial translocation and liver injury.[52]

Several studies have been published evaluating various probiotics or synbiotics (probiotic plus prebiotic) for dogs and cats with diarrhea. Most studies to date have demonstrated some benefit for patients with acute diarrhea in the shelter[53-55] or colony[56] setting. For example, in kittens, *Enterococcus faecium* SF68 increased fecal bifidobacteria and decreased *C. perfringens*, increased serum IgA concentrations, and significantly reduced the severity and incidence of diarrhea during a natural outbreak in the colony.[56] Decreased time to resolution of acute diarrhea has been demonstrated in dogs receiving certain probiotics.[57,58] Positive outcomes have also been reported in sled dogs with exercise-induced diarrhea receiving a probiotic[59] or synbiotic.[60] The data in dogs with food-responsive enteropathy managed concurrently with an elimination diet and a probiotic is less straightforward due to the significant clinical improvement due to the elimination diet.[61,62] One open-label trial in 20 dogs with idiopathic IBD compared a probiotic to combination drug therapy with metronidazole and prednisolone. Clinical activity, duodenal histology scores and CD3+ lymphocytes decreased post-treatment in both groups but enhancement of regulatory T-cell markers was only observed in the probiotic group.[63] The authors concluded the probiotic treatment induced a differential anti-inflammatory immune response compared to the combination drug therapy group. However this study had a small number of patients and the dogs receiving the probiotic had a lower clinical activity score indicating milder disease compared to the drug treatment group. Further research should help the clinician better select an appropriate probiotic(s) for a given individual with a given condition.

Selecting a probiotic requires evaluation for both safety and efficacy. This includes evaluating the product label. The label should include a guaranteed analysis stating the number of live probiotic bacteria, a list of the specific genus, species, and strain and an expiration date.[64] Unfortunately previous studies have shown many commercial available products contain labeling errors including failure to list specific microorganisms, misspellings, and failure to list expected bacterial numbers.[65,66] Furthermore comparison of actual content versus label claims demonstrated some products did meet viable organism claims, contained organisms without probiotic effect, or contained potentially pathogenic organisms. The veterinarian should select a probiotic from a reputable manufacturer and ask questions regarding product quality including manufacturing practices and stability studies to ensure the probiotic survives production, storage prior to

consumption, and passage through the gastrointestinal tract. Safety is of upmost concern. Safety includes testing for virulence and antibiotic-resistance genes as well as patient tolerance. Caution is advised when considering probiotics in patients with marked intestinal mucosa compromise, or those who are immune-compromised or critically ill.[67]

ROLE OF COBALAMIN IN DIARRHEA

Normal uptake of cobalamin (vitamin B12) requires a binding factor (intrinsic factor), which is secreted from the pancreas of cats and dogs, followed by a receptor-mediated uptake in the ileum. These receptors are located on the brush border of ileal enterocytes. A compromise in either pancreatic or ileal function can lead to B12 deficiency resulting in GI mucosal atrophy and reduced GI function. Inflammatory bowel disease, lymphoma, cholangiohepatitis or cholangitis, and pancreatic inflammation have been associated with B12 deficiency in cats.[68] Among cats with low B12, weight loss, diarrhea, anorexia, and vomiting were the most common signs. In dogs, intestinal bacterial overgrowth also may contribute to B12 deficiency.

Since cobalamin functions as a co-factor in many processes involved in cellular turnover, a deficiency can lead to atrophy of the rapidly dividing cells of the intestinal mucosa, further decreasing function and compromising recovery. Correcting a cobalamin deficiency via parenteral supplementation (250µg subcutaneously, once weekly for 4 weeks) resulted in clinical improvement in one study of cats with GI disease and low B12.[69] More recently two clinical studies have suggested that oral cobalamin may be considered as well.[70,71]

SUMMARY:

Treat underlying condition when possible. Provide nutritional support, monitor response to the nutrition plan, and adjust the plan as needed. A summary of typical nutrient modifications for common conditions is provided below.

Condition	Nutrient modifications
Chronic small bowel diarrhea	Highly digestible, moderate or low fat in dogs. In cats, consider low carbohydrate. Consider probiotics. Consider B12
Chronic large bowel diarrhea	Elimination diet trial (hydrolyzed protein/ single novel protein); Moderate to high fiber – soluble & insoluble; Consider probiotics and/or prebiotics
Food-responsive enteropathy or Inflammatory bowel disease	Elimination diet trial (hydrolyzed protein/ single novel protein);Consider omega-3 fatty acids, probiotics.
Protein Losing Enteropathy / Lymphangiectasia	Ultra low fat; Highly digestible; Elimination diet trial; Consider parenteral vitamin supplementation

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