

Managing Chronic Enteropathies in Dogs (Parts 1 and 2)

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Dogs with chronic intestinal disease typically present for investigation of clinical signs such as diarrhea, weight loss or vomiting. Diarrhea that has lasted 3 weeks or more is usually considered chronic. The initial approach to chronic diarrhea is based on determining the nature and severity of the diarrhea and the presence of specific or localizing clinical findings. The presence of additional clinical signs often points to the underlying cause: e.g. tenesmus and dyschezia (large bowel disease), melena (upper GI bleeding/ulceration), abdominal pain (structural disorders, perforation, thrombosis), and abdominal distension, difficulty breathing and peripheral edema (enteric protein loss). This information is integrated to determine whether diarrhea is most likely due to large bowel disease (dyschezia, tenesmus, increased frequency of defecation, small volume of feces with mucus and blood) or a consequence of small intestinal disease or exocrine pancreatic insufficiency (large volume of diarrhea, weight loss, may also be vomiting). In patients with abdominal pain, dehydration, frequent vomiting, or localizing findings such as an abdominal mass, these problems are pursued ahead of an in-depth work up for chronic diarrhea. In patients with chronic diarrhea and no obvious cause it is best to adopt a systematic approach, 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 will review the diagnosis and management of dogs with chronic enteropathies that are 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.

Table 1. Initial diagnostic approach to chronic small bowel diarrhea

Integrate signalment, history and physical examination	Breed predisposition, environment, diet other clinical signs, localizing findings Fecal analysis(e.g. Giardia)
Detect endoparasites and enteric pathogens	
Perform clinicopathological testing:	
Detect non-GI disease	CBC, profile, UA ± TLI, ACTH stim, freeT ₄ /TSH, bile
acids	
Detect/characterize intestinal disease	hypoproteinemia, hypocalcemia, hypocholesterolemia, leucopenia, leukocytosis
Perform diagnostic imaging:	
Detect non-GI disease	Radiographs, ultrasound (liver, spleen pancreas, lymph nodes, masses, effusions)
Detect and characterize intestinal disease	Radiographs, ultrasound (obstruction, intussusception, focal masses, thickening, loss of layering, hyperechoic striations (Gaschen 2008)

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

The approach to this group of patients is usually determined by the severity of clinical signs (frequent severe diarrhea, excessive weight loss, decreased activity or appetite) and the presence of hypoalbuminemia, intestinal thickening, or mesenteric lymphadenopathy. In patients with these abnormalities intestinal biopsy is required to define the cause (e.g. IBD, lymphangiectasia, lymphoma,) and to optimize therapy. Controlled studies have shown that hypoalbuminemia is associated with a poor outcome in dogs with chronic enteropathy (Craven 2004, Allenspach 2007). Serum concentrations of cobalamin and folate can be measured to determine if supplementation is required and low serum cobalamin concentration (<200ng/L) has also been associated with a negative prognosis (Allenspach 2007). Evaluation of hemostatic function is recommended to determine if hypo- or hyper- coagulability have arisen as a consequence of enteric protein loss.

The clinical severity of intestinal disease can be quantified by determining the clinical disease activity index (attitude activity, appetite, vomiting, stool consistency, stool frequency, weight loss) (Jergens 2003). Measurement of serum C- reactive protein (has been shown to correlate with clinical disease activity (CIBDAI) and implies that severe clinical disease is accompanied by a systemic

inflammatory response (Jergens 2003). Measurement of clinical disease activity or CRP can also serve as a baseline for determining the response to treatment.

In stable patients with chronic diarrhea (i.e. good attitude, appetite, mild weight loss, normal serum proteins and no intestinal thickening or lymphadenopathy) measurement of serum cobalamin and folate can be performed to evaluate disease severity, aid localization of intestinal disease, and to determine if supplementation is required. Intestinal biopsy is indicated in dogs with low serum cobalamin to determine the nature of the intestinal disease.

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 below). Failure to respond to empirical therapy, or worsening of disease, is an indication for intestinal biopsy.

Intestinal biopsy

Intestinal biopsies can be acquired endoscopically or surgically. In patients without an indication for surgery e.g. intestinal masses, anatomic or structural disease, perforation, the authors prefer to perform diagnostic endoscopy to visually inspect the esophageal, gastric and intestinal mucosa and to procure endoscopic biopsies. Guidelines for biopsy acquisition have recently been published (Willard 2008). Operator experience, and biopsy quality and number are of key importance in enabling effective histopathological evaluation. Surgical biopsy is usually performed where intestinal disease is suspected to involve the submucosa or muscularis and where the results of endoscopic biopsies do not adequately explain the clinical picture.

Unfortunately the interpretation of gastrointestinal histopathology varies considerably among pathologists (Willard et al 2003). To try to correct this problem a working group established by the WSAVA has formulated a scheme to standardize the evaluation of intestinal histopathology (Day et al 2008). The ability of this scheme to increase agreement between pathologists, and the clinical relevance of the criteria it evaluates remain to be determined, but it is a step in the right direction.

The most common histopathological diagnoses in dogs with chronic diarrhea are inflammatory bowel disease, lymphangiectasia and lymphoma. The most commonly described histopathological lesion in the intestines of dogs is increased cellularity of the lamina propria that is usually referred to as inflammatory bowel disease (IBD). The extent of inflammation is variable 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 and severe. 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 Basenji, Lundehund and Chinese Sharpei. However, recent studies have called into question the appropriateness and clinical relevance of the term lymphocytic plasmacytic enteritis. Dogs have similar numbers of CD3+T cells before and after clinical remission (Schreiner 2008), and cats with and without signs of intestinal disease have similar numbers of lymphocytes and plasma cells (Waly 2004).

The presence of moderate to large numbers of eosinophils in intestinal biopsies, which is often accompanied by circulating eosinophilia, suggests possible parasitic infestation or dietary intolerance. Moderate to high numbers of macrophages and neutrophils raise the possibility of an infectious process, and culture and special stains are indicated.

Changes in mucosal architecture such as mucosal atrophy and fusion are less frequently commented on than cellularity, but appear to be important indicators of disease severity. A recent study in cats with signs of gastrointestinal disease measured mucosal cytokine levels to identify histological correlates of mucosal inflammation. In this study villus atrophy and fusion correlated with severity of clinical signs and degree of proinflammatory cytokine upregulation in the duodenal mucosa (Janeczko 2008).

Dilatation of lymphatics and the presence of crypt abscesses and crypts cysts are most commonly encountered in dogs with protein losing enteropathies, and often are accompanied by lymphoplasmacytic inflammation of varying severity (Peterson 2003, Willard 2003).

Treatment

The therapeutic approach to chronic enteropathies 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; the presence of bacteria or fungi; and presence of architectural changes, such as atrophy, ulceration, lymphangiectasia/crypt cysts. Therapeutic intervention is directed at correcting nutritional deficiencies (e.g. cobalamin) and counteracting inflammation and dysbiosis. The clinical severity of disease, nature and severity of histopathological lesions, and the presence or absence of hypoalbuminemia guides treatment.

Minimal change enteropathy

Low clinical disease activity, normal intestinal histopathology, normal serum cobalamin serum albumin >2.0g/l,

1. Empirical treatment for Giardia and endoparasites if not already performed (e.g. fenbendazole 50mg/kg PO x 5d)
2. Dietary trial (see Table 2). A positive response suggests diet responsive enteropathy. If a good response, continue diet, consider re-challenge, and defining basis of dietary intolerance.

3. Antibiotic trial: tylosin (10-15mg/kg TID PO), oxytetracycline (20mg/kg TID PO), or metronidazole (10mg/kg PO BID). A positive response suggests antibiotic responsive enteropathy, maintain on antibiotics for 28days then discontinue. If a good response consider transition to probiotics? If signs recur after stopping antibiotics chronic therapy with tylosin at 5mg/kg PO SID can be used to maintain dogs that are tylosin responsive (Elias Westermarck 2010, personal communication).
4. If response is poor reappraise before considering other treatments.

Inflammatory bowel disease

Treatment of any disease is ideally directed at the underlying cause, which is problematic for IBD as the etiopathogenesis is unclear.

IBD in people 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.

In people, 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 the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation (Packey 2008). While the mucosa-associated flora is implicated frequently as a pivotal factor in the development of IBD in people and animals, the specific bacterial characteristics that drive the inflammatory response have remained elusive. The clinical responses of some dogs with idiopathic chronic diarrhea to antibiotics such as tylosin or oxytetracycline, and the predisposition of certain breeds, e.g. German Shepherd, points to a similar interaction of host susceptibility and microflora in dogs (Batt 1988, Westermarck 2005, German 2003). As the numbers of cultivable aerobic and anaerobic bacteria in the duodenal juice of dogs that respond to antibiotics is similar to dogs that respond to food or immunosuppression it is plausible that dogs with antibiotic responsive enteropathy are more susceptible to their resident microflora (German 2003, Simpson 1994), but this remains to be determined.

Recent advances in molecular microbiology have enabled the analysis of complex bacterial communities without bacterial culture. Culture-independent analyses of bacterial 16S rDNA libraries in people reveal that only 30% of the fecal flora appears cultivable, and there is significant variation in the flora in different gastrointestinal segments and luminal contents versus the mucosa of healthy individuals (Eckburg 2005). The application of these culture independent techniques to people, dogs and cats has revealed that intestinal inflammation is associated with a floral shift from Gram-positive Firmicutes to Gram-negative bacteria, predominantly Enterobacteriaceae (Baumgart, 2007, Janeczko 2008, Xenoulis 2008). It is noteworthy that increased numbers of Enterobacteriaceae have been found to correlate with mucosal inflammation and clinical signs in cats with signs of gastrointestinal disease (Janeczko 2008), and a novel group of adherent and invasive *E. coli* (AIEC) have been associated with intestinal inflammation in people and Boxer dogs with granulomatous/histiocytic ulcerative colitis (Baumgart 2007, Simpson 2006). While it remains to be determined if these floral alterations are a cause or a consequence of the inflammation, their discovery has provided new opportunities for therapeutic intervention.

There is also growing evidence to support an important role for diet in the development of canine IBD. In controlled studies of 65 dogs with diarrhea of at least six weeks duration, 39/65 dogs responded to dietary modification (10 days of Purina Veterinary Diets LA Salmon and Rice), and the remaining dogs were treated with corticosteroids (2mg/kg /24hrs for 10 days followed by a tapering dose over 10 wks (Luckschander 2006). The CIBDAI and histopathological 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 dogs that did not 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.

Taken as a whole the results of studies in dogs with chronic diarrhea to date provide reasonable evidence that various subsets of dogs will respond to treatment with antibiotics, diet or immunosuppressive therapy. At present there is no reliable means for predicting which dogs will respond to which treatment, and a treatment consists of a series of therapeutic trials.

Lymphocyte and plasma cell predominant IBD

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. At present, because there is no reliable means for predicting which dogs will respond to which treatment, treatment consists of a series of therapeutic trials.

Mild to moderate disease activity, mild to moderate histopathology (lymphocytes and plasma cells are predominant cell type), serum albumin >2.0g/L (inflammatory bowel disease):

1. Empirical treatment for Giardia and helminths if not already performed
2. Dietary trial with a hydrolyzed diet for 2 weeks. If a good response then maintain on diet, consider re-challenge, and defining basis of dietary intolerance.
3. Poor response to diet perform antibiotic trial with tylosin for 2 weeks. If a good response maintain on antibiotics for 28 days then discontinue. Consider transition to probiotics? If signs recur after stopping antibiotics chronic therapy with

tylosin at 5mg/kg PO SID can be used to maintain dogs that are tylosin responsive (Elias Westermarck 2010, personal communication).

4. Immunosuppression with glucocorticoids (2mg/kg PO/d x 21d, 1.5mg/kg PO/d x 21d, 1mg/kg PO/d x 21d) and or azathioprine (2mg/kg PO /d x5d, then 2mg/kg PO EOD)
5. If poor response reappraise before considering escalating immunosuppression (e.g. add azathioprine, or substitute with cyclosporine (5mg/kg PO SID: Allenspach 2006, if already on azathioprine)
6. If good response taper immunosuppression, then stop antibiotics

Moderate disease activity, moderate to severe intestinal histopathology (atrophy, fusion, lymphocytes and plasma cells are predominant cell type), serum albumin <2.0g/L (inflammatory bowel disease):

1. Empirical treatment for Giardia and helminths if not already performed
2. Concurrent dietary modification (hydrolyzed diet), antibiotics (tylosin), and immunosuppression (glucocorticoids and /or azathioprine)
3. Reappraise if poor response before considering escalating immunosuppression (e.g. cyclosporine)
 - a. Consider failure to absorb oral prednisolone and switch to injectable corticosteroids
 - b. Dexamethasone may be preferable to prednisolone in patients with ascites to avoid increased fluid retention
 - c. Concurrent therapy with ultra low dose aspirin (0.5mg/kg) and judicious use of diuretics (lasix and spironolactone) are often used in patients considered at risk for thromboembolic disease, and those severely distended with tense ascites respectively.
 - d. The use of elemental diets and PPN may be required in some dogs with severe PLE.
4. If good response taper immunosuppression, then stop antibiotics

This approach has been evaluated on 27 dogs with a histopathological diagnosis of IBD: 26/27 dogs have responded to standardized treatment: 16 dogs were diet responsive, 3 steroid responsive, 3 were partially responsive to a combination of food and antibiotics, and three to food steroids and antibiotics.

Granulomatous or neutrophilic enteritis

Enteropathies characterized by neutrophilic or granulomatous inflammation are described infrequently in dogs. Some may be associated either with bacterial infections, such as from *E. coli* (granulomatous colitis in boxers), *Streptococcus*, *Campylobacter*, *Yersinia*, and *Mycobacteria*, or fungal (e.g. *Histoplasma*) or algal (e.g. *Prototheca*) infections. Culture of mucosal biopsies, intestinal lymph nodes, and other abdominal organs; and imaging of chest and abdomen should be undertaken in cases of granulomatous or neutrophilic enteritis to detect infectious organisms and systemic involvement. Special stains such as GMS, PAS, Gram and Modified Steiner are traditional cytochemical methods used to search for infectious agents in fixed tissues. Fluorescence in situ hybridization (FISH) with a probe directed against eubacterial 16S rRNA is a more contemporary and sensitive method of detecting bacteria within formalin fixed tissues. It is imperative not to immunosuppress patients with granulomatous or neutrophilic infiltrates until infectious agents have been excluded.

Eradication of mucosally invasive *E coli* in Boxers and French Bulldogs 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 guarded to poor if an underlying cause is not identified.

Lymphangiectasia and crypt cysts / abscesses

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 the 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.

The Yorkshire terrier (4.2-10-fold relative risk), soft-coated wheaten terrier (concurrent proteinuria), and Norwegian Lundehund seem to be overrepresented, supporting a familial cause in some dogs.

Clinical findings

Clinical findings are essentially a consequence of the intestinal loss of protein and range from weight loss to chronic diarrhea, vomiting, ascites, edema, and chylothorax. In a study of 12 Yorkshire terriers 14 hypoalbuminemia (< 3.1g/dl) was present in all 12 dogs (median 1.6g/dl), and hypoglobulinemia (<1.9g/dl) in 7 dogs (median 1.7g/dl). Additional biochemical abnormalities included hypocalcemia (n=12), hypocholesterolemia (n=11) hypomagnesemia (n=9), hypokalemia (n=5) and hypochloremia (n=5). Hypocalcemia and hypomagnesemia have been attributed to hypovitaminosis D. Hematological abnormalities in 12 yorkshire terriers included mild anemia (n=5), thrombocytosis (n=8), mature neutrophilia (n=6), and neutrophilia with a left shift (n=3).

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 attention to potential for bleeding, exacerbation of hypppoteinemia by fluid therapy, and potential for 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 (highly digestible, restricted antigen or hydrolysate). Fat restriction has been emphasized as a mainstay of treatment but there is little evidence to support this. 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. The use of MCT improves outcome in children with primary lymphangiectasia () but there are no studies in dogs.

Prednisolone is often employed at 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 cyclosporine at 5 mg/kg PO Q 24 H³) may be tried if the patient is unresponsive. However patients with lymphangiectasia appear more prone to sepsis than other forms of IBD so it is imperative not to over immuno suppress these patients and concurrent therapy with metronidazole or tylosin is frequently initiated to decrease the risk of bacterial translocation through the markedly impaired gut. Aspirin at 0.5 mg/kg PO Q 24 H is often 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. In a recent study of 12 Yorkshire terriers¹⁴ empirical therapy with corticosteroids (11/12), azathioprine (2/12), antibiotics (amoxicillin-clavulanate, n=6, metronidazole, n=6, tylosin n=5, enrofloxacin n=2), plasma and diuretics was associated with a poor outcome. 7/12 cases died or were euthanased within 3 months of diagnosis (thromboembolism was suspected in 3). Long-term survival was achieved in 3 dogs, (36, 24, and 8 months), and 2 are alive at 3 and 4 months after diagnosis.

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