

RECENT ADVANCES IN THE DIAGNOSIS AND MANAGEMENT OF CHRONIC GASTROINTESTINAL DISEASES OF CANINES

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Chronic gastrointestinal disorders, collectively known as inflammatory bowel diseases (ISO), are common in canine general practice. They are characterized by persistent or recurrent gastrointestinal signs and inflammation of GI tract. It is widely accepted that chronic enteropathies involves a complex interplay among host genetics, the intestinal microenvironment, the immune system and the environmental triggers of intestinal inflammation (Packey and Sartor, 2008). Many of these diseases do not have clearly defined underlying cause despite thorough diagnostic investigation. This paper describes recent developments on etiology, diagnosis and therapeutic management of various chronic enteropathies that are associated with chronic diarrhea in dogs.

(a)Lymphocytic-Plasmacytic Enterocolitis

Lymphocytic-plasmacytic enterocolitis (LPE) is the most common form of IBD. A breed predilection has not been confirmed, although purebred dogs seem to be overrepresented in the veterinary literature. Varying degrees of vomiting, weight loss, and diarrhea are observed clinically. Although most clinical signs are referable to small intestinal disease, any part of the GI tract can be affected. Intestinal inflammation with altered lymphatic function can cause GI protein loss, resulting in pan hypoproteinemia. The pathophysiology of this disease is incompletely understood. An increased number of IgG- and IgA-producing plasma cells and T lymphocytes have been identified in dogs with LPE compared with control dogs. Furthermore overproduction of nitric oxide in dogs with LPE is suggested by increased colonic luminal nitrite levels and increased mucosal expression and concentrations of inducible nitric oxide synthase in endoscopic biopsy specimens. (Ettinger and Feldman, 2005, Simpson and Jergens, 2011).

(b)Eosinophilic Enterocolitis

Eosinophilic enterocolitis (EE) is less common than LPE in dogs. It is clinically indistinguishable from LPE, although eosinophilia is sometimes found on a complete blood count. Eosinophilic infiltration can occur anywhere along the GI tract. Eosinophilic intestinal disease has been reported in mixed-breed and a variety of purebred dogs. Rottweilers and German shepherds may be predisposed to EE. One report suggests that most affected dogs

are younger than 5 years of age. However, the exact sex and age distributions are uncertain.

(Ettinger and Feldman, 2005, Simpson and Jergens, 2011).

Clinical signs

The most frequently observed clinical signs in dogs and cats are chronic diarrhea (large volume) accompanied by weight loss or vomiting. IBD of the small intestine is characterized by small bowel disorder, which involves a large volume of stool, a mild increase in frequency of defecation, and little or no straining, mucus, or blood present. The vomit often contains bile. If the large bowel is involved, there may be mucus, blood, and straining at defecation with little matter produced. There are other clinical signs such as changes in appetite, excessive burbling noises in the intestine (borborygmi), and abdominal discomfort. It is important for owners to understand that the severity of inflammatory bowel disease is variable, ranging from intermittent diarrhea and vomiting in mild cases to intractable diarrhea, refusal to eat, and weight loss in severe cases. The severity of the disease is believed to reflect the degree of cellular infiltrate into the intestine. (Simpson and Jergens, 2011).

Diagnosis

Initial diagnostic approach to chronic diarrhea Integrate Signalment, history and physical examination, Breed predisposition, environment, diet, other clinical signs, localizing findings. Fecal analysis for endoparasites and enteric pathogen (e.g. Giardia).

Clinical pathology

Detect non GI disease- CBC, biochemistry profile, urinalysis, ACTH stimulation test, Free T4/TSH levels, bile acid levels. Detect GI disease- Hypoproteinemia, hypocalcaemia, hypocholesterolemia, leucopenia, leucocytosis, low cobalamin or folate levels.

Diagnostic imaging

Detect non GI disease- Radiography, ultrasonography of liver, spleen, pancreas, lymph node, masses and effusions, obstruction intussusceptions, focal masses, thickening, loss of layering, hypoechoic appearance, hyperechoic striations. The clinical severity of intestinal disease can be quantified by determining the clinical disease activity index (e.g. attitude, activity, appetite, vomiting stool consistency, stool frequency, weight loss). Measurement of C-reactive protein (CRP) levels has been shown to correlate with clinical activity disease activity index. (Grutzner *et al.*, 2011, Simpson and Jergens, 2011). Measurement of serum cobalamin and folate concentration can help determine the need for intestinal biopsy, localize the site of intestinal disease, determining the need of cobalamin supplementation and establish a prognosis (Grutzner *et al.*, 2011).

Intestinal biopsy

It is noteworthy that in some but not all studies the endoscopic appearance of the small intestine correlate better with outcome than the histopathologic appearance. If there is suspicion of ileal involvement, transcolonic ileoscopy is performed in addition to the standard upper GI tract endoscopic examination. Cellular infiltrate-Intestinal infiltration with macrophages or neutrophils raises the possibility of an infectious process and culture, special staining and FISH are indicated. The presence of moderate to large number of eosinophils in intestinal biopsy samples, often accompanied by circulating eosinophils, suggests possible parasitic infestation or dietary intolerance. Increased numbers of lymphocytes and plasma cells, indicate lymphoplasmacytic enteritis (Simpson and Jergens, 2011).

Treatment

Empirical treatment of giardia and helminths if not already initiated. Cobalamin and folate supplementation if their levels are subnormal. Dietary modification pending biopsy result; concurrent dietary modification

(hydrolyzed or antigen restricted diet), antibiotics and immunosuppression. If there is poor response, reappraise before considering escalating immunosuppression. The use of elemental diets and partial parenteral nutrition may be indicated in some dogs that have severe protein losing enteropathy.

(c)Granulomatous colitis of boxer dogs

It is an uncommon type of inflammatory bowel disease, predominant in boxer dogs younger than 4 years. There are sporadic reports of GC in other dog breeds, particularly young French bulldogs. Affected dogs typically present with signs of colitis, hematochezia and weight loss progressing to Cachexia in severe cases.

GC and invasive Escherichia coli- The application of culture independent molecular methods like immunohistochemistry and fluorescent in situ hybridization (FISH) enabled the identification of mucosally invasive E. coli. Also immunostaining of colonic mucosa gave positive results with antibodies against Salmonella, Campylobacter and Lawsonia intracellularis. (Simpson *et al.*, 2006, Mansfield *et al.*, 2009).

Genetics- Because GC is breed specific and rare, it is suspected to be an autosomal recessive genetic defect involving the immune system that confers susceptibility to E. coli invasion. Research is currently being undertaken to identify the genetic basis of GC and a genome wide association scan (GWAS) is under way. (Craven *et al.*, 2010, Craven *et al.*, 2011).

Clinical features

GC typically affects Boxer dogs younger than 4 years with no sex predilection and some reports describe clinical signs in animals as young as 6 weeks. Clinical signs are typical of colitis that is frequent small volume diarrhea, hematochezia, mucoid feces and tenesmus. The degree of hematochezia is often significantly greater than for other types of colitis, and affected dogs may fail to thrive or may lose weight. Affected dogs are usually clinically well and afebrile but may be lethargic with severe disease (Craven *et al.*, 2011).

Diagnosis

Diagnosis could reflect anemia of chronic disease or hemorrhage if hematochezia is severe. Hypoalbuminemia may also occur in some

affected dogs because of hemorrhage, protein exudation via diffusely ulcerated mucosa, anorexia and inflammation. Definitive diagnosis is usually achieved by ruling out other causes of clinical signs and histologic confirmation on colonic mucosal biopsies. The histologic appearance of GC is unique relative to other types of colitis in dogs because of severe mucosal ulceration and infiltration of the submucosa and lamina propria with macrophages that stain positive with PAS. (Craven *et al.*, 2011).

FISH analysis- Demonstration of invasive E.coli in GC is now integral to disease diagnosis and management and is best accomplished using FISH.

Antimicrobial susceptibility testing- It is also necessary to culture colonic mucosa, particularly when invasive E. coli are documented in order to determine antimicrobial susceptibility.

Treatment

The administration of enrofloxacin alone, 5mg/kg once daily for a total of 6-8 weeks daily has been associated with long term remission. Currently, the suggested treatment regimen for cases with enrofloxacin sensitive E. coli is 5-10mg/kg every 24 hour for a minimum of 6 weeks. Post treatment colonoscopy and biopsy are advisable to demonstrate remission of disease and successful eradication of E. coli invasion. Aside from the spectrum of activity, it is of critical importance that the antimicrobial used is capable of penetrating macrophages. Agents likely to do so include chloramphenicol, florfenicol, TMPS, tetracyclins, clarithromycin, and rifampin. When a multi drug resistant strain of E. coli is present, the recommendation is to use combination of antimicrobial protocol, to include a fluoroquinolone and several others of these macrophage penetrating agents. (Mansfield *et al.*, 2009, Craven *et al.*, 2011).

(d)Chronic idiopathic large bowel diarrhea (CILBD)

In dogs, large bowel diarrhea is usually characterized by small amount of feces often admixed with mucus and/or fresh blood, frequent defecation with urgency and tenesmus. These signs reflect colonic dysfunction with decreased water reabsorption and decreased fecal storage capacity as well as mucosal damage and response

to inflammation. Acute colitis is most commonly associated with whipworm infestation, dietary indiscretion and Clostridium perfringens and Clostridium difficile infections.

Clinicopathological findings

The clinical signs displayed by dogs with CILBD are indicative of a large bowel disorder, but are in no way pathognomonic. Unlike what has been reported earlier, hematochezia occurs in large proportion of dogs with CILBD, even in those with behavioral disorders. Therefore, CILBD is a diagnosis that can only be made by exclusion of all other causes of large bowel diarrhea. In one study, colonoscopy revealed minimal mucosal changes in slightly less than half of dogs, which included very slight focal increases in friability, granularity or hyperemia, decreased or increased numbers of lymphoid follicles, decreased visualization of submucosal blood vessels, localized colonic spasm, and localized small superficial erosions. It is noteworthy that many dogs with CILBD occasionally vomit, have a decreased appetite and show abdominal pain during episodes of diarrhea (Khan and Chang, 2010).

Diagnosis

Chronic or recurring diarrhea for at least 4 weeks. Diarrhea of large bowel origin with increased frequency, excess mucus, tenesmus and hematochezia. No abnormal findings on physical examination, CBC, biochemical profile and urinalysis or if minor changes observed on physical examination, CBC count, chemistry panel, urinalysis, absence of a severe systemic disorder. No identifiable cause of large bowel diarrhea. No or only minimal changes are observed on colonoscopy. Histopathologic evaluation of colonic mucosal; biopsies unremarkable.

Treatment

Fiber- Psyllium- daily dose- 0.5T for toy breeds, 1 T for small breed dogs, 2T for medium breed dogs, 3T for large breed dogs. Special diets commercially available supplemented with fiber. Motility modifying agents-loperamide- 0.1 mg/kgPOq6-8h, Diphenoxylate- 0.1 mg/kgPOq6-8h. Antispasmodics (neurotropic)- chlordiazepoxide (5mg) and clidiniurn bromide(

2.5mg)- 0.1 - 0.25mg/kg elidinium POq 8-12h for few days. Given at time of onset of clinical signs or when stressful situations are anticipated for a few days only. Propantheline- 0.25mg/kg PO TID, Hyoscyamine- 0.003-0.006mg/kg PO BID to TID, Dicyclomine- 0.15mg/kg BID to TID. Antispasmodics(muscolotropics)- Mebeverine- 2.5-5mg/kg PO BID, Pinaverium- 1 mg/kg PO BID, Trimebutine- 0.33mg/kg PO TID. Behavior modifying agents- Selegiline- starting dose 0.5mg/kg PO once daily. Dose can be increased upto 2mg/kg once daily if no response after 2 months. Clomipramine- starting dose 1 mg/kg PO BID. Increase gradually upto 3 mg/kg PO BID if necessary after 14 days. Tryptic hydrolysate of alpha casein- 15mg/kg PO once daily.

(e)Protein losing enteropathies in dogs

Protein losing enteropathy (PLE) is a syndrome associated with an abnormal loss of albumin through the gastrointestinal mucosa. PLE is identified when hypoalbuminemia occurs because the loss of albumin can not be compensated by liver synthesis.

Inflammatory bowel disease

PLE is associated with IBD in dogs. Recently colonic IBD in dogs has been associated in dogs with upregulation of claudin, a protein associated with paracellular colonocytes junctions suggesting that alterations of paracellular intestinal permeability may occur in canine IBD.

Crypt disease

Recently PLE has been associated with crypt disease. The hallmark of crypt disease is a severe dilation of the intestinal crypts that are filled with mucus, sloughed epithelial cells and some times inflammatory cells.

Regional enteritis

It is characterized by focal transmural granulomatous infiltration mostly localized in the distal small intestine. It has been associated with hypoproteinemia in dogs.

Infectious diseases associated with PLE.

GI tract infection with Histoplasma capsulatum can induce severe granulomatous intestinal infiltration and secondary PLE in dogs.

In patients with histoplasmosis, hypoalbuminemia is frequently associated with hyperglobulinemia (Oossin and Lavoue, 2011).

Parasitism

Severe intestinal parasitism especially hookworm infestation may induce PLE with ascites and edema. It has been suggested that parasites may induce an inflammatory reaction that eventually lead to IBD. In humans, giardiasis has been associated with PLE.

Gastrointestinal neoplasia

Mild to marked hypoalbuminemia is reported in dogs with alimentary lymphoma. The prevalence seems high, with 11 of 18 dogs and 24 of 30 dogs affected in two different studies. (Dossin and Lavoue, 2011).

Clinical findings

The classical clinical presentation of PLE is a combination of chronic relapsing digestive signs with weight loss and edematous signs associated with chronic hypoalbuminemia. Some affected dogs have concurrent abdominal and pleural effusions, chylothorax, or even isolated pleural effusion. Pleural effusion is especially prevalent in Yorkshire terrier with PLE. PLE should always be considered in hypoalbuminemic dogs, even in the absence of digestive signs. Other less frequent clinical signs are related to complications resulting from the protein loss (Dijkstra *et al.*, 2010).

Complications

A hypercoagulable state may occur in dogs with PLE. It has been associated with reduced antithrombin III plasma concentration, increased thrombin-antithrombin complexes or an abnormal thromboelastogram. Hypocalcaemia may be associated with hypomagnesaemia that may induce secondary hypoparathyroidism. Granulomatous lymphangitis and gut wall edema are other possible complication of canine PLE .(Dijkstra *et al.*, 2010, Dossin and Lavoue, 2011).

Diagnosis

Identifying the origin of the protein loss

The only available test for GI protein loss is the measurement of fecal alpha1- proteinase inhibitor. a 1- PI is a protease inhibitor of similar

size to albumin and is also synthesized in the liver. a 1- PI is neither actively absorbed nor secreted in the normal gut. It can leak with other protein through the gut. Fecal at- PI is increased in dogs with chronic GI signs but does not correlate with plasma albumin. Hypoalbuminemia is the hallmark of PLE and concurrent hypocholesterolemia, hypoglobulinemia, and lymphopenia are frequently observed. Fecal parasite screening with floatation, and antigen test for giardia using 3 different samples should be performed. A coagulation panel including prothrombin time , activated partial thromboplastin time, AT III and D- dimmers is recommended to evaluate patient for hypercoagulability and thrombosis{Simpson and Jergens, 2011}. (Grutzner *et al.*, 2011). Perinuclear anti neutrophil cytoplasmic autoantibodies{ pANCA} are early markers of PLE in soft coated wheaten terriers. Serum pANCA are positive in affected dogs on average 2.4 years before the onset of hypoalbuminemia but unfortunately this test is not routinely available{Mancho *et al.*, 2010}.

Diagnostic imaging

Abdominal ultrasound is essential in most cases of PLE. Abdominal ultrasound is a prerequisite to select the biopsy method, identification of focal or patchy lesions that can not be reached by an endoscope provides a good indication for surgical biopsy. Specific findings such-as hyperechoic mucosal striations can be suggestive of PLE. (Umar and DiBaise, 2010).

Intestinal biopsies

Bidirectional endoscopy including gastric , duodenal and ileal biopsies is the preferred method because histologic diagnosis can be different between duodenal and ileal samples in upto 73% of the cases of canine IBD and lymphangiectasia may only be found on ileal biopsies in some cases. Deeper lesions especially those located in the muscularis or serosa may not always be associated with more superficial changes in the mucosa and may not appear in endoscopic biopsies. For the same reason, diagnosis of crypt disease requires good endoscopic biopsies that include sufficient numbers of intestinal crypts.

Treatment

Providing nutritional support

Dogs with PLE are usually in severe negative energetic and protein balance. The goal of the nutritional support is to provide a high energy density with a combined low fat and high carbohydrate content. Current recommendations for dogs with PLE are below 10-15% of fat, above 25-30% of protein, less than 5% of crude fibers and above 87% and 90% digestibility for the protein and fat/carbohydrate sources, respectively. Intramuscular injection of an adequate vitamin supplement solution with 300 IU of vitamin E, 100,000 IU of vitamin A. and 10,000 IU of vitamin D should be sufficient for 3 months in dogs (Peterson and Willard, 2003, Dijkstra *et al.*, 2010, Dossin and Lavoue, 2011).

Providing oncotic support

Hydroxylethyl starches are used at a maximal dosage rate of 20-30ml/kg/day, although they provide short term oncotic support only. Aggressive oncotic support is also advocated in case of PLE associated with severe gut edema that may further worsen GI protein loss. Albumin can be provided through plasma transfusion. Canine purified albumin has recently become available in 5 g vials and might be a good option to benefit from the colloid support while avoiding allergic reaction to human albumin (Peterson and Willard, 2003).

Addressing complications

Coagulation should be monitored in patients with PLE because hypercoagulability and thrombosis have been reported. When antithrombin is severely reduced, supplementation with fresh frozen plasma transfusion may be beneficial. In case of suspected thrombosis, heparin (200-250 IU/kg s/c 3 times a day) treatment combined with low dosage of aspirin(0.5mg/kg/day orally in dogs) is recommended. If plasma antithrombin III is decreased, fresh frozen plasma combined with 10 IU/kg of standard heparin should be administered before starting heparin therapy. Vitamin K is a fat soluble vitamin whose absorption may be decreased in dogs with PLE. Intravenous supplementation with calcium and magnesium salts is required in cases of hypocalcaemia and /or hypomagnesaemia. (Peterson and Willard, 2003, Dossin and Lavoue, 2011).

Treating intestinal lesions

Standard treatment includes steroids at immune suppressive dosages or azathioprine. A recent study demonstrated the efficacy of cyclosporine (5mg/kg/d) orally in dogs with steroid refractory PLE. Sodium chromoglycate (100mg/dog 3 or 4 times daily orally) has been recommended in soft coated wheaten terriers with PLE. An antibiotic trial with Metronidazole or tylosin is probably a reasonable option when starting treatment of PLE in antibiotic responsive cases. (Dijkstra *et al.*, 2010, Dossin and Lavoue, 2011).

(f)Lymphangiectasia

Lymphangiectasia is caused by abnormal dilation of the mucosal and submucosal lymphatics within the GI tract. The two basic classifications are primary and acquired lymphangiectasia. Primary lymphangiectasia is caused by abnormally formed lymphatics and is considered a congenital disorder. Acquired lymphangiectasia results from lymphatic blockage or elevated venous pressure. Lymphatic blockage is caused by inflammatory or neoplastic infiltrates.

Clinico-pathological findings

Diarrhea seems to be the most consistent clinical finding in dogs with lymphangiectasia. Small bowel diarrhea is more common; however, large bowel diarrhea or a combination of both may occur. Vomiting, weight loss, and ascites occur frequently but may not be present in all cases. Abnormal laboratory findings, including hypoalbuminemia, hypoglobulinemia, lymphopenia, hypocholesterolemia, and hypocalcaemia, may not always be present. The severity of hypoalbuminemia roughly correlates with the severity of histopathologic lesions. Hypocalcaemia consistently occurs in dogs with lymphangiectasia and appears to be multifactorial. (Kull *et al.*, 2001).

Diagnosis

A diagnosis of lymphangiectasia can be made following evaluation of intestinal biopsy specimens, which can be obtained endoscopically or surgically; each method has advantages and disadvantages. Affected dogs that are fasted before anesthesia can have empty, undilated lymphatics.

Feeding a small amount of corn oil or cream the night before anesthesia may make the dilated lymphatics more visible on gross and, possibly, histopathologic examination (Kull *et al.*, 2001).

Treatment

The treatment of primary lymphangiectasia is targeted mainly toward reducing the amount of fat in the diet. Diet should be highly digestible, restricted antigen, or hydrolysate. Fat restriction has been emphasized as a mainstay of treatment. Commercial fat-restricted diets are the logical choice in treating less severe cases. Prednisolone, 1 mg/kg every 24 hour is often administered orally and may work by decreasing lipogranulomatous inflammation or concurrent mucosal inflammation. Aspirin 0.5mg/kg every 24 hour is often given orally to dogs with low antithrombin III levels if they are considered at risk for thromboembolism. Diuretics are used if ascites is problematic (Simpson and Jergens, 2011).

(g)Canine alimentary lymphoma

Alimentary lymphomas are less common in dogs than in cats, representing only 7% of all canine lymphomas. Alimentary lymphoma in dogs may be part of the syndrome of multicentric lymphoma but most commonly it is confined to the GI tract. The majority of dogs have rapidly progressive clinical signs associated with lymphoblastic lymphoma including vomiting, diarrhea, weight loss, anorexia and lethargy. (Rassnick *et al.*, 2009).

Chemotherapy and supportive treatment are the mainstays of the treatment of alimentary lymphomas in dogs. The overall response rate to treatment with a multidrug chemotherapy protocol was 56% in the largest published study of dogs with alimentary lymphoma. For the responders, the overall median first remission duration was 86 days and the MST was 117 days (Rassnick *et al.*, 2009).

(h)Antibiotic-Responsive Enteropathy and Diarrhea

A recent trend in the veterinary literature is to rename or redefine the syndrome known as small intestinal bacterial overgrowth (SI80) as ARD. This is because of a lack of consensus on what defines SI80, and patients that are responsive to antibiotic therapy may not have bacterial overgrowth. ARD/SI80 may be secondary to other disease processes, such as exocrine pancreatic

insufficiency or IBD. Greater than 10⁵ CFU/ml of aerobic bacteria or 10⁴ CFU/ml of anaerobic bacteria cultured from duodenal juice was historically considered to be consistent with SIBO. The clinical relevance of these numbers is questionable because many healthy dogs have had much higher culture results. In addition, cobalamin (vitamin B12) and folate concentrations have not been found to reliably correlate with bacterial culture results or a response to antibiotic therapy. (German *et al.*, 2003, Ettinger and Feldman, 2005).

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