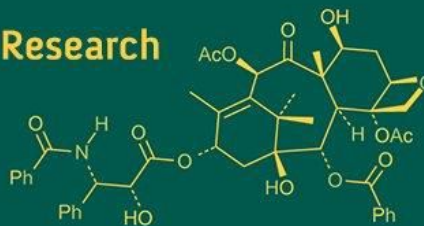


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Pathologic features of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic condition characterized by persistent gastrointestinal inflammation in dogs. The etiology involves a complex interplay between genetic susceptibility, the intestinal microbiota, and the mucosal immune system. The clinical signs include vomiting, diarrhea, weight loss, and abdominal discomfort. Endoscopic findings revealed mucosal changes such as redness, erosions, and ulcerations. Histologically, IBD is characterized by inflammatory cell infiltrates, primarily lymphocytes and plasma cells, within the lamina propria. The World Small Animal Veterinary Association (WSAVA) has established standards for histological assessment of IBD. Diagnostic tools include endoscopy with biopsy, serological markers (e.g., pANCA and CRP), fecal markers (e.g., calprotectin and α 1-PI), and immunohistochemical markers (e.g., caspase 3, P-glycoprotein, and NF- κ B). Treatment strategies include dietary modifications, antibiotics, prebiotics, and immunosuppressive drugs such as corticosteroids. Novel therapies include grape seed proanthocyanidins, glycosaminoglycans, fecal microbiota transplantation, and mesenchymal stem cell therapy. These approaches aim to reduce intestinal inflammation, improve clinical signs, and enhance the quality of life in dogs with IBD.

Keywords: Inflammatory bowel disease, lymphocytic-plasmacytic enteritis, fecal microbiota transplantation, endoscopy

1. Introduction

Inflammatory bowel disease (IBD) refers to a collection of chronic inflammatory conditions affecting the intestines, marked by ongoing or recurrent gastrointestinal (GI) symptoms lasting over three weeks (Eiro *et al.*, 2022; Jergens and Heilmann, 2022) [16, 29]. A definitive diagnosis is made when histological evidence of mucosal inflammation is present and all other potential causes of enteritis or infiltrates have been ruled out (Hall and German, 2009) [23]. The classification of this disease varies between humans and their companion animals. In humans, IBD is primarily categorized as ulcerative colitis and Crohns disease. In veterinary medicine, classification is based on the predominant cell types infiltrating the intestinal wall and their location (German *et al.*, 2003) [19]. Chronic small intestine diseases classified as IBD include lymphocytic-plasmacytic enteritis, eosinophilic enteritis, and eosinophilic gastroenteritis (Hall and German, 2009) [23]. For the large intestine in dogs, four main conditions have been identified as IBD: lymphocytic-plasmacytic colitis, eosinophilic colitis, histiocytic ulcerative colitis (HUC) characterized mainly by PAS-positive macrophages, and regional granulomatous colitis with mainly PAS-negative macrophages (Hall and German, 2009) [23]. It is important to note that these diseases often affect both the small and large intestines and may also involve the stomach, as seen in lymphocytic-plasmacytic enterocolitis, eosinophilic enterocolitis or gastroenterocolitis, and granulomatous gastroenteritis (Kleinschmidt *et al.*, 2007; Hall and German, 2009) [35, 23].

IBD is believed to occur equally in both male and female dogs, with a higher prevalence in middle-aged dogs (Hall and German, 2009; Benvenuti *et al.*, 2020) [23, 6]. Certain breeds are thought to be predisposed to specific types of IBD, such as immunoproliferative enteropathy in Basenjis, protein-losing enteropathy and related protein-losing nephropathy in Soft-Coated Wheaten Terriers, and HUC in boxers (German *et al.*, 2003; Hall and German, 2009) [19, 23]. Although boxers show a greater tendency for HUC (Davies, 2004), this condition has also been identified in other breeds such as French Bulldog, Doberman Pinscher, Mastiff, and Alaskan Malamute (Stokes *et al.*, 2001) [57]. Kathrani *et al.* (2010) [33] indicated that Weimaraners, Rottweilers, German Shepherds, Border Collies, and Boxers are particularly

prone to IBD. Epidemiological data indicate that IBD is prevalent worldwide, especially in countries such as England (O'Neill *et al.*, 2014) [46], USA (Collins, 2013) [8], Poland (Marchesi *et al.*, 2024) [42], and India (Kedia and Ahuja, 2017) [8, 42, 34]. However, the precise cause of IBD remains unknown. Evidence gathered from companion animals suggests that intestinal inflammation results from a disrupted interaction between environmental factors, the intestinal microbiota, and the mucosal immune system in genetically susceptible hosts (Washabau *et al.*, 2010; Holmberg *et al.*, 2022) [63, 26]. The current criteria for diagnosing IBD include (1) chronic (>3 weeks) persistent or recurrent gastrointestinal symptoms; (2) histopathological evidence of mucosal inflammation; (3) exclusion of other causes of gastrointestinal inflammation; (4) insufficient response to dietary, antibiotic, and anthelmintic treatments alone; and (5) clinical improvement with anti-inflammatory or immunosuppressive medications (Washabau *et al.*, 2010) [63].

2. Etiopathogenesis

Researchers have suggested that the origin of the disease is probably initiated by a failure in immunological tolerance to luminal antigens, including commensal microorganisms and food elements (Dias *et al.*, 2019) [15]. An imbalance in microbiota often arises when the immune system cannot distinguish between commensal and pathogenic bacteria (Redfern *et al.*, 2017) [50]. The intestinal mucosal immune barrier consists of gut-associated lymphoid tissue, secretory antibodies, and mesenteric lymph nodes that react to toxins, antigens, and potentially harmful pathogens (Zhang *et al.*, 2022) [6]. Despite exposure to numerous intraluminal microbial and dietary allergens and a high concentration of lymphoid cells, the intestine typically shows low physiological inflammation. This is due to the interaction between the epithelial mucosal barrier, innate immune system, and adaptive immune system (del Pilar Martínez-Montiel *et al.*, 2014) [13]. In both human and animal IBD, the intestinal barrier becomes more permeable due to improper control of tight and adherent junctions, leading to increased exposure of immune cells to luminal antigens (Ohta *et al.*, 2014) [45]. Intestinal Epithelial Cells (IECs) are crucial in modulating the immune response by expressing pattern recognition receptors (PRRs) for microorganisms, such as Toll-like receptors (TLRs), and by producing various humoral factors, including cytokines (del Pilar Martínez-Montiel *et al.*, 2014) [13]. The non-specific innate immune response is driven by the interaction of IECs, neutrophils, macrophages, dendritic cells, and eosinophils, along with their secreted products, which facilitates the differentiation of pathogen-associated molecular patterns (Eissa *et al.*, 2019) [17]. Neutrophils serve as one of the initial cellular defense lines and can eliminate infections by enhancing inflammation through phagocytosis, generating reactive oxygen species (ROS), and releasing intracellular substances known as neutrophil extracellular traps (NETs), which aid in mucosal healing and reduce inflammation. However, NETs can also induce epithelial cell death and ROS can damage lipids and proteins in the mucosal barrier, impairing their function (Zhang *et al.*, 2022) [69]. Lymphocytes are the main effector cells in the adaptive immune response and are activated in the gut to eliminate harmful antigens (Eissa *et al.*, 2019) [17]. Dendritic cells present antigens to specific lymphocytes, such as naïve CD4

+ T helper cells, within secondary lymphoid organs such as the mesenteric lymph nodes (Allenspach *et al.*, 2011) [32]. Based on the cytokine profile, T helper cells can evolve into Th1, Th2, Th17, or regulatory T cells (Tregs), each producing various cytokines with distinct functions (Allenspach *et al.*, 2011; Eissa *et al.*, 2019) [32, 17]. Once antigens are cleared, lymphocytes are typically downregulated to preserve the intestinal balance (del Pilar Martínez-Montiel *et al.*, 2014) [13]. In IBD, these lymphocytes are persistently stimulated, leading to ongoing inflammation, which in turn activates macrophages and B cells and attracts circulating leukocytes to the gut (Grégoire *et al.*, 2017) [21]. In one study, 6 out of 18 authors could not clearly demonstrate Th1 or Th2 cytokine expression in dogs and cats with chronic intestinal enteropathy (Jergens, 2012; Jergens and Heilmann, 2022) [31, 29], and there was no evidence of a Th17 signature (Schmitz *et al.*, 2012) [52]. This observation in canine and feline chronic intestinal enteropathy contrasts with human IBD, where Crohn's disease patients exhibit significant Th1/Th17 (cell-mediated) cytokine polarization and ulcerative colitis shows a pronounced Th2 (humoral) cytokine profile (Jergens and Heilmann, 2022) [29]. Genetic anomalies of the innate immune system have been associated with IBD susceptibility in both dogs and humans. Mutations in NOD2/CARD15 in humans and TLR4 and TL5 in dogs, along with the presence of enteric microbiota, may lead to increased proinflammatory cytokine production and reduced bacterial clearance, exacerbating chronic intestinal inflammation. The pathophysiology of IBD in cats remains unclear (Jergens, 2012; Kathrani *et al.*, 2010) [31, 33].

In dogs with IBD, intestinal dysbiosis is frequently characterized by a reduction in both bacterial richness and diversity. Metagenomic studies have revealed a diminished presence of Firmicutes, while Proteobacteria are more prevalent in dogs with IBD than in healthy dogs (Suchodolski *et al.*, 2005) [58]. Additionally, the levels of *Faecalibacterium* spp. and *Fusobacterium* spp. are notably lower in dogs with IBD than in their healthy counterparts (Guard *et al.*, 2019) [22]. Furthermore, an increased presence of adherent and invasive *Escherichia coli* has been observed in colonic biopsies from dogs with granulomatous colitis, suggesting a possible connection to gut inflammation (Simpson *et al.*, 2006) [55]. Metabolic changes have also been documented, such as the reduced production of short-chain fatty acids and tryptophan metabolites, which could affect intestinal balance and immune tolerance (Vich Vila *et al.*, 2018) [60]. Fecal samples from dogs with IBD showed decreased levels of acetate and propionate compared to those from healthy dogs (Derrien *et al.*, 2019) [14].

3. Clinical findings

The clinical signs in dogs with IBD are highly variable. The clinical signs associated with canine IBD are primarily GI symptoms, such as vomiting, small and large bowel diarrhea, weight loss, alterations in appetite (Bhavani *et al.*, 2023) [7], lethargy, abdominal discomfort, polyuria, polydipsia, and polyphagia (Rana, 2020) [7, 49]. These signs are attributed to mucosal cellular infiltration, inflammatory mediators, inflammation-associated enterocyte dysfunction, and intestinal dysmotility. Moreover, the clinical condition at a particular time may be influenced by the presence of active intestinal inflammation as well as secondary consequences of inflammation, including anemia and

vitamin deficiencies, which contribute to the diverse signs of GI disease (Bhavani *et al.*, 2023) [7].

4. Clinical scoring indices

The clinical IBD activity index (CIBDAI) was created and validated to assist in the management of canine IBD (Collins, 2013) [8]. This index evaluates six key gastrointestinal symptoms-attitude and activity, appetite, vomiting, stool consistency, stool frequency, and weight loss-by assigning scores from 0 to 3 based on their deviation from normal in a specific IBD case. These scores were summed to produce a total CIBDAI score, which was then used to categorize the disease as clinically insignificant, mild, moderate, or severe (Collins, 2013) [8]. The CIBDAI was an initial effort to create a straightforward scoring system for assessing dynamic changes that indicate the progression of IBD in dogs, serving as a valuable measure of clinical signs resulting from intestinal inflammation. Another clinical activity index, the CCECAI, includes six clinical signs from the CIBDAI and considers albumin levels and the presence of ascites, peripheral edema, and pruritus (Collins, 2013) [8].

5. Gross finding during endoscopy

Endoscopic examinations often reveal non-specific lesions, and nearly 50% of cats and dogs with IBD show no lesions (Lecoindre, 2006) [38]. In dogs with IBD, typical endoscopic findings include mucosal changes such as redness, increased fragility, greater granularity, erosions, ulcers, and unusual blood vessel patterns (Lecoindre, 2006; Benvenuti *et al.*, 2020) [38, 6]. The extent of these lesions can be assessed using semi-quantitative scoring systems that are linked to the clinical activity of the disease (Heilmann *et al.*, 2014) [25]. In more advanced cases, endoscopy may reveal significant changes in the intestinal wall, such as distended crypts, dilated lacteals, and fibrotic mucosa (Benvenuti *et al.*, 2020) [6]. In Boxer dogs with HUC and some instances of suppurative colitis, the endoscopic lesions are extremely severe, featuring numerous ulcerations of varying sizes, often covered with mucus or mucopus. Mucosal lumps, often referred to as pseudopolyps, have been commonly observed. The folds are significantly enlarged and covered with a brownish mucosa (Lecoindre, 2006) [38].

6. Histological features of canine IBD

6.1 WSAVA standards

There is significant variability in the interpretation of GI histopathological findings by pathologists (Willard *et al.*, 2002) [66]. To address this issue, the World Small Animal Veterinary Association (WSAVA) formed a working group to create a standardized approach for evaluating intestinal histopathological results (Day *et al.*, 2008) [54]. The WSAVA Gastrointestinal Standardization Group was initially established to develop a global standard for histological assessment of GI tract diseases in cats and dogs (Washabau, 2005) [62]. According to the WSAVA, IBD is histologically characterized by the type of inflammatory infiltrate (neutrophilic, eosinophilic, lymphocytic, plasmacytic, granulomatous), mucosal pathology (villus atrophy, fusion, crypt collapse), lesion distribution (focal or generalized, superficial or deep), severity (mild, moderate, severe), mucosal thickness (mild, moderate, severe), and topography (gastric fundus, gastric antrum, duodenum, jejunum, ileum, cecum, ascending colon, and descending colon). Similar to small-intestinal IBD, the subjective

interpretation of large-intestinal IBD lesions complicates the comparison of tissue findings among pathologists. This subjectivity in histologic evaluation has prompted the creation of various IBD grading systems (Washabau, 2009) [61].

6.2 Types of cellular infiltrates

The main histopathological observation is the infiltration of inflammatory cells within the lamina propria, primarily composed of lymphocytes and plasma cells (Jergens *et al.*, 1992) [30]. These infiltrates are confined to the lamina propria and can be found in various parts of the gastrointestinal tract, including the stomach, duodenum, and colon (Jergens *et al.*, 1992) [30]. Moderate-to-severe lymphoplasmacytic enteritis is frequently associated with protein-losing enteropathy (Peterson and Willard 2003) [48]. A significant monomorphous infiltration of lymphocytes eliminates any uncertainty regarding the presence of primitive lymphoma, and repeat endoscopic biopsies or full-thickness intestinal biopsies are recommended (Kojima *et al.*, 2021) [36]. Neutrophils are not typically present in IBD lesions (Lecoindre, 2006) [38]. When neutrophils infiltrate the intestine, they suggest a potential infectious process, warranting culture, special staining, and FISH (Simpson *et al.*, 2006; Janeczko *et al.*, 2008) [55, 28]. Predominant neutrophil infiltration in the colonic mucosa is indicative of chronic suppurative colitis (Roth *et al.*, 1990; Lecoindre, 2006) [51, 38]. The presence of moderate to large numbers of eosinophils in intestinal biopsy samples, often with circulating eosinophils, indicates possible parasitic infection or dietary intolerance (Kleinschmidt *et al.*, 2007) [35]. Histiocytic infiltration is the least common characteristic of granulomatous IBD. These histiocytes were PAS positive. This is observed in the histiocytic infiltration of HUC in Boxer dogs (Nolte *et al.*, 2017) [44]. In cases of granulomatous or regional enteritis, histiocytes are PAS-negative, with a polymorphous transmural infiltrate of lymphocytes, granulocytes, and eosinophils (Lecoindre, 2006) [38].

6.3 Mucosal architecture

Numerous studies have suggested that alterations in mucosal structure, such as changes in villous shape, lymphatic expansion, goblet cell mucus levels, and crypt abnormalities, are linked to the presence and severity of gastrointestinal diseases (Peterson and Willard, 2003; Mansfield *et al.*, 2009; Janeczko *et al.*, 2008; Simpson *et al.*, 2011) [48, 41, 28, 56]. Significant associations have been found between various histological characteristics, including crypt enlargement, lamina propria lymphocytes and neutrophils, mucosal scarring, lacteal expansion, and villus shortening (Allenspach *et al.*, 2019) [2]. Other studies have identified crypt swelling, lacteal expansion, mucosal scarring, and intraepithelial lymphocytes as prominent histological features of canine IBD (Benvenuti *et al.*, 2020) [6]. In the colon, the reduction in mucus and goblet cells has been associated with the presence of GC and the severity of lymphoplasmacytic colitis (Roth *et al.*, 1990; Mansfield *et al.*, 2009; Simpson *et al.*, 2011) [51, 41, 56]. Lymphatic expansion and crypt abscesses and cysts are most commonly observed in dogs with protein-losing enteropathies and are frequently accompanied by varying degrees of lymphoplasmacytic inflammation (Peterson and Willard, 2003; Willard *et al.*, 2003) [48, 67].

7. Ancillary diagnostic tools

7.1 Endoscopy and biopsy

Endoscopy accompanied by biopsy is regarded as the gold standard for diagnosing canine IBD. This technique enables direct observation of the gastrointestinal tract and collection of tissue samples for histopathological analysis (Irving *et al.*, 2023) [27]. Endoscopic biopsies are especially beneficial for distinguishing IBD from other conditions such as intestinal lymphoma, which can exhibit similar clinical symptoms (Irving *et al.*, 2023) [27]. However, endoscopic biopsies have certain limitations. Although it is effective in diagnosing gastric lymphoma, it may not be sufficient to differentiate IBD from lymphoma in the small intestine, particularly in the jejunum and ileum (Evans *et al.* 2006) [18]. In these instances, obtaining full-thickness biopsy specimens through laparotomy or laparoscopy may be required for accurate diagnosis (Evans *et al.*, 2006) [18].

7.2 Serological markers

Perinuclear antineutrophilic cytoplasmic autoantibodies (pANCA) are IgGs that target antigens in the cytoplasm of neutrophil granulocytes and monocytes. pANCA are instrumental in diagnosing human inflammatory bowel disease (IBD), especially in distinguishing between Crohn's disease and ulcerative colitis (Bahari *et al.*, 2009) [5]. In dogs, pANCA have been shown to be highly specific markers for IBD; however, their sensitivity is insufficient for use as a general screening tool (Allenspach, 2011) [32]. C-reactive protein (CRP) has been widely studied as a biomarker for canine IBD. Numerous studies have demonstrated that CRP levels are higher in dogs with IBD than those in healthy controls (Heilmann *et al.*, 2012; Otoni *et al.*, 2018) [24, 47]. CRP levels generally decrease following treatment, indicating their potential utility in monitoring disease activity and therapeutic response (Otoni *et al.*, 2018) [47].

7.3 Urine and fecal markers

Fecal calprotectin has become a reliable indicator of intestinal inflammation in dogs with IBD, as research has demonstrated its effectiveness in both diagnosing and tracking disease progression (Krzystek-Korpacka *et al.*, 2020), with a sensitivity of 82.4% and a specificity of 68.4% (Heilmann *et al.*, 2012) [37, 24]. Another fecal marker that may be useful for monitoring canine IBD is the α 1-proteinase inhibitor (α 1-PI). This plasma protein, which is similar in size to albumin, indicates the extent of albumin loss in the gastrointestinal tract. α 1-PI remains largely unchanged within the GI lumen, allowing it to be detected in feces using an immunoassay. However, since GI protein loss can occur under various gastrointestinal and systemic conditions, measuring α 1-PI in feces is not specific to canine IBD (Collins, 2013) [8]. N-methylhistamine (NMH), a stable histamine metabolite, can serve as a marker for mast cell degranulation and GI inflammation (Wdowiak *et al.*, 2013) [65]. An increase in urinary NMH levels has been observed in patients with ulcerative colitis and Crohn's disease, with a notable correlation with endoscopic findings, clinical activity index, and CRP (Winterkamp *et al.*, 2002) [68].

7.4 Immunohistochemical markers

Immunohistochemical markers are crucial for diagnosing and understanding canine IBD. Apoptosis markers were

assessed using immunohistochemistry. The expression levels of caspase 3 (Casp3), poly (ADP-ribose) polymerase (PARP), and the anti-apoptotic marker Bcl-2 were examined in the duodenal villous tips, base of the duodenal villi, and colonic mucosa (Dandrieux *et al.*, 2008) [10]. In Boxers with HUC, an increase in IgG + , IgG3 + , IgG4 + plasma cells, CD3 + T cells, MHC class II cells, L1 + , and PAS-positive cells was observed in the lamina propria through immunohistochemical analysis, compared to the control group and unaffected colon regions (German *et al.*, 2001) [37]. P-glycoprotein (P-gp), a transmembrane protein, acts as a drug efflux pump in the intestinal epithelium. Previous research has suggested that mucosal expression of P-glycoprotein could be a useful predictor of therapy response in dogs with chronic enteropathies (Allenspach *et al.*, 2006) [1]. Quantitative analysis of nuclear factor kappa B (NF- κ B) in activated B cells revealed a higher number of NF- κ B-positive macrophages in the lamina propria of dogs with chronic enteropathy than in the controls. An increase in NF- κ B-positive epithelial cells was noted in dogs with FRD compared with those with IBD (Luckschander *et al.*, 2006) [39]. Recently, the number of CD11c + integrin-expressing cells in the duodenum, ileum, and colon of dogs with IBD was assessed (Kathrani *et al.*, 2011) [32]. Researchers have observed a significant reduction in CD11c + cells in the intestines of dogs with IBD compared to healthy controls, suggesting that this may contribute to the breakdown of mucosal tolerance in IBD.

7.5 Other non-invasive, indirect evaluation methods

A reduction in folic acid levels may indicate inflammation in the proximal intestine, whereas a decrease in cobalamin levels may indicate inflammation in the distal intestine. A simultaneous reduction in both suggests a widespread disease. Although changes in these levels are not specific to IBD, they should be considered in a patient's treatment plan (Wdowiak *et al.*, 2014) [64]. A recent study indicated that the count of monocytes and the hematological ratios-neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, and platelet to lymphocyte ratio-ould be valuable in distinguishing between dogs with IBD and healthy dogs (Marchesi *et al.*, 2024) [42].

8. Therapeutic strategies

The treatment plan for canine IBD, as informed by pathology, involves a comprehensive approach. The primary strategies include dietary and pharmacological interventions (Jergens, 2012) [31]. Hydrolyzed diets are frequently used to minimize adverse reactions to immunostimulatory proteins in dogs with food-responsive diarrhea (Ambrosini *et al.*, 2020) [4]. Additionally, modifying the enteric microbiota with antibiotics and prebiotic supplements is recommended (Jergens, 2012) [31]. Notably, new methods for the treatment of canine IBD are being explored. Grape seed proanthocyanidin (GSP), a plant-derived polyphenol, has shown potential in reducing intestinal inflammation by enhancing inflammatory markers and decreasing intestinal permeability in Labrador Retrievers with mild IBD (Zhang *et al.*, 2023) [70]. Recent research indicates that combining hydrolyzed diets with glycosaminoglycans (GAGs) and prebiotics (PRBs) improves the serum metabolomic profiles of dogs with IBD, particularly lipid metabolism, suggesting better intestinal membrane integrity (Ambrosini *et al.*, 2020) [4]. Similarly, a new oral supplement containing chondroitin

sulfate and prebiotics, when used alongside a hydrolyzed diet, demonstrated improvements in certain serum biomarkers without adverse effects, although larger studies are necessary to confirm its effectiveness (Segarra *et al.*, 2016) [53]. The pharmacological management of canine IBD often involves immunosuppressive drugs, with corticosteroids being a common initial treatment. Prednisone, an oral corticosteroid, is commonly used to reduce mucosal inflammation and alleviate gastrointestinal symptoms in dogs with IBD. The dosage typically starts as immunosuppressive therapy and gradually decreases as clinical improvement is observed (Cristóbal *et al.*, 2021) [9]. Glucocorticoids (prednisolone at an initial dose of 2 mg/kg PO q12-24h, then tapered by 25% q2-4 weeks) have catabolic, hyperlipidemic, and prothrombotic effects. Therefore, other immunosuppressive drugs (e.g., cyclosporine at 5 mg/kg PO q12-24h or chlorambucil at 4-6 mg/m² PO q24h for 1-3 weeks, then tapered) might be preferable as first-line steroid-sparing options. Mycophenolate poses the risk of significant gastrointestinal side effects (Swann *et al.*, 2019) and is generally not recommended for treating inflammatory PLE (and CIE in general) (Jergens and Heilmann, 2022) [29].

9. Another innovative approach

Fecal microbiota transplantation (FMT) has also emerged as a potential treatment for canine IBD. FMT has shown efficacy and safety in the long-term periodic treatment of canine IBD. A study found that FMT increased diversity in the fecal microbiome, particularly the proportion of *Fusobacteria*, which was linked to improvements in clinical signs (Niina *et al.*, 2021) [43]. Mesenchymal stem cell (MSC) therapy has demonstrated significant potential in the treatment of canine IBD. A previous study showed that a single infusion of MSCs in dogs with IBD, both with and without prednisone treatment, led to reduced disease severity and improvements in albumin and cobalamin levels over a 12-month period (Cristóbal *et al.*, 2021) [9]. This therapy allowed for gradual reduction and eventual cessation of steroid dosage in all patients, indicating long-lasting benefits.

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