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Case Report

Successful Management of a Dog with Protein-Losing Enteropathy and Concurrent Protein-Losing Nephropathy with Repeated Fecal Microbiota Transplantation

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Abstract

Protein-losing enteropathy (PLE) is a spectrum of gastrointestinal disorders in which protein loss occurs through the gastrointestinal tract. One of the underlying causes is chronic inflammatory enteropathy (CIE). Conventional therapies for CIE often include diet, immunosuppressives, anti-microbials, probiotics, and, recently, fecal microbial transplantation (FMT). This case report highlights the use of lyophilized material-based FMT through oral capsules and enema in a dog with PLE and concurrent protein-losing nephropathy (PLN). The patient initially had a significantly increased dysbiosis index (DI) and required repeated FMT treatments, resulting in a positive clinical response through improvement in body weight, serum albumin concentrations, fecal scores, and normalization of the DI over time. To maintain clinical responses, FMT had to be performed monthly. Approximately 1 year after starting FMT therapy, the patient then developed an episode of acute hemorrhagic diarrhea syndrome (AHDS) associated with netF-gene-encoding *Clostridium perfringens* strains, after which the DI became abnormal again. The patient responded clinically well to monthly FMT treatments again, but it took several months for normalization of the DI after the AHDS episode. In summary, this case report highlights the continued use of adjunct lyophilized FMT in a dog with PLE resulting in improved clinical control over time.

Keywords: chronic inflammatory enteropathy; protein-losing enteropathy; fecal microbiota transplant; dog

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1. Introduction

Protein-losing enteropathy (PLE) is a group of gastrointestinal (GI) disorders where protein loss, mainly of albumin and globulins, occurs across the enteric mucosa. Clinical signs may include vomiting, diarrhea, borborygmi, hyporexia, abdominal pain, nausea, and/or weight loss [1,2]. The most common causes are chronic inflammatory enteropathy (CIE) and lymphangiectasia [3]. Chronic inflammatory enteropathies are diagnosed based on the presence of chronic gastrointestinal signs (≥3 weeks), histopathological evidence of intestinal mucosal inflammation, and exclusion of other GI disorders (such as infectious, parasitic, mechanical, and neoplastic causes) and extra-GI disorders [3–5]. Chronic enteropathies (CEs) are currently subcategorized into groups based on clinical response to treatment. These include food-responsive enteropathy (FRE), immunosuppressant-responsive enteropathy (IRE), antibiotic-responsive enteropathy (ARE), and non-responsive

enteropathy (NRE), with 13–18% of dogs with CIE being categorized as having NRE [6,7]. A system modified by replacing ARE with microbiota-related modulation-responsive enteropathy (MrMRE) has been proposed by another author group [8]. However, overall, this is a clinical classification system and the underlying pathophysiology among these subgroups is often overlapping [9], and dogs within one subgroup can potentially also respond to other treatments. For example, in recent literature, some NRE dogs were still recategorized as FRE when another diet was trialed [10]. Similarly, a subset of dogs with NRE can also respond to FMT [11,12] or treatment with bile acid sequestrants as adjunct therapy [13].

Protein-losing nephropathy (PLN) describes a kidney disease that causes persistent proteinuria. Proteinuria can be pre-glomerular, glomerular, or post-glomerular in origin. When the urine protein/creatinine ratio (UPC) is >2.0, the amount of albumin loss in urine can sometimes result in a decrease in serum albumin and is more often attributed to glomerular diseases [14]. The most common causes of glomerular disease in dogs include immune complex glomerulonephritis (ICGN), amyloidosis, and glomerulosclerosis, with roughly 50% being ICGN and responsive to immunosuppression [15,16]. This can lead to chronic kidney disease (CKD) where there are structural and/or functional abnormalities in one or both kidneys that have been continuously present for $\geq$3 months [13], resulting in accumulation of nitrogenous blood products.

Fecal microbiota transplant (FMT) is an emerging treatment in humans, with high success rates for recurrent *Clostridioides difficile* infection [17–21]. More recent investigations in veterinary medicine have been conducted for a variety of disorders including canine parvovirus [22], chronic inflammatory enteropathy [11,12,23,24], acute diarrhea [25], and acute hemorrhagic diarrhea syndrome (AHDS) [26,27]. Other initial studies have also explored the use of FMT in extraintestinal disorders, such as atopic dermatitis [28], diabetes mellitus [29], and epilepsy [30,31]. FMT involves taking the feces of a healthy donor and administering them to a diseased recipient, often as an adjunct therapy. A subset of dogs with CE have severe shifts in their microbiome, as demonstrated by an increased dysbiosis index (DI), and these are associated with more severe functional changes in the host and the microbiome, such as malabsorption of fatty acids, carbohydrates, and bile acids [9,12,32–34]. Therefore, FMT may be useful as an adjunct therapy for the improvement of clinical signs, although success may vary, as was noted in a recent study that highlighted that animals with an increased DI often have a short-lived response to FMT, necessitating multiple treatments due to relapses [12]. Proposed mechanisms for improvement with FMT include niche exclusion, where fecal donor strains may compete for the same intestinal niches more successfully than the recipient's pathogenic strains; increased nutrition competition with pathobionts that reduces the survival of these organisms; production of antimicrobials; and lastly, normalization of bile acid conversion and secondary bile acid concentrations [35]. Other perceived effects include helping restore the integrity of the intestinal barrier through secretions of mucin [36] and shifting of microbial diversity to butyrate-producing bacterial species, which can decrease inflammation via induction of regulatory T cells and IL-10 production [37,38]. In various studies, animals who have received FMT have been reported to exhibit improvements in fecal consistency, clinical signs, appetite, weight gain when underweight, reduction in corticosteroid dosages, and mentation [11,12,22,23,25]. Side effects reported in humans such as bloating, worsening of diarrhea/stool consistency, abdominal pain, nausea, vomiting, or low-grade fever [25–27,32] are typically mild or transient in dogs [12]. Currently, there is no clear evidence on the efficacy of different procedures to prepare feces for FMT (e.g., fresh versus lyophilized feces), nor the administration route (oral versus enema) [39]. Some studies have shown clinical benefits of administering FMT with oral capsules [40,41], although

long-term follow-up data are still limited. Several studies using repeated enemas reported clinical improvement lasting for more than 6 months in many patients [11,12]. Therefore, FMT administered through rectal enemas was chosen as the primary delivery mode. This is based on our clinical experience and also the fact that an enema will introduce more volume to the recipient compared to oral capsules.

This case report describes the clinical course of a dog with concurrent PLE and PLN that was treated successfully with diet and repeated FMT administered via rectal enema. FMT was considered first before immunosuppressive therapy was attempted due to the concurrent co-morbidity of PLN (see Section 3). Furthermore, we also describe the clinicopathological impact that an episode of AHDS had on the patient.

2. Case Description

A 32.3 kg, 4-year-old, female spayed American Pit Bull Terrier presented to the Internal Medicine service as a second-opinion consultation for PLN and hypoalbuminemia. Her prior diagnostics, 8 months prior to presentation, included complete blood count (CBC), serum chemistry, urinalysis, and urine protein/creatinine ratio (UPC), which revealed hypoproteinemia (4.4 g/dL, reference range (RR) 5.2–8.2 g/dL) characterized by hypoalbuminemia (1.9 g/dL, RR 2.3–4.0 g/dL) and low-normal globulin (2.5 g/dL; RR 2.5–4.5 g/dL), azotemia (creatinine 2.1 mg/dL, RR 0.5–1.8 mg/dL and blood urea nitrogen (BUN) 52 mg/dL, RR 7–27 mg/dL), hyperphosphatemia (7.4 mg/dL, RR 2.5–6.8 mg/dL), mildly elevated alanine-aminotransferase (ALT) (174 U/L; RR 10–125 U/L), low urine specific gravity (USG) of 1.025, and an elevated UPC (12.6). Prior diagnostics also included abdominal ultrasound, which showed a diffusely thickened gastric wall (1.56–1.86 cm) with mild heterogeneous echotexture, and small intestinal ileus with mild segmental fluid dilation. Other relevant diagnostics included infectious disease testing via *Dirofilaria*/*Anaplasma*/*Lyme*/*Ehrlichia* serology testing (SNAP 4Dx Plus, IDEXX, Westbrook, ME, USA) and a rapid Leptospirosis IgM-detection immunochromatographic test (WITNESS® Lepto, Zoetis, Parsippany, NJ, USA), both of which were negative; a normal blood pressure (136 mmHg); and an adrenocorticotropic hormone (ACTH) stimulation test that was not consistent with either hypoadrenocorticism or hyperadrenocorticism (pre- and post-cortrosyn cortisol of 1.8 µg/dL and 6.4 µg/dL, respectively). Gastroduodenoscopy showed an edematous gastric mucosa with a mildly hyperemic and irregular duodenal mucosa. Gastric and duodenal endoscopic biopsies revealed sections of histologically normal stomach with focal, moderate lymphoplasmacytic (LP) gastritis with focal gland atrophy and gland fibrosis, and chronic moderate LP and eosinophilic enteritis. She was started on telmisartan 20 mg (0.7 mg/kg) PO q24h, clopidogrel 37.5 mg (1.3 mg/kg) PO q24h, omeprazole 10 mg (0.35 mg/kg) PO q12h, a probiotic (Visbiome®, ExeGI Pharma® Rockville, ML, USA), and a mixture of JustFoodForDogs® Irvine, CA, USA (JFFD) Renal Support Low Protein diet and Royal Canin Renal Support dry food. One month later, albumin and UPC had improved to 2.4 g/dL and 0.3, respectively, and ALT had normalized. At that time, her telmisartan dose was decreased to 10 mg (0.34 mg/kg) PO q24h.

The patient presented one month later for the second opinion consultation, and was reported to have soft stools with mucus, a picky appetite, and ptyalism. Physical examination showed mild peripheral edema of the distal limbs, good body and muscle condition scores (BCS 5/9, MCS 3/3), and a weight of 31.6 kg. Diagnostics included serum chemistry, urinalysis, UPC, and serum cobalamin, folate, trypsin-like immunoreactivity (TLI), and pancreatic lipase immunoreactivity (PLI). Results revealed worsening hypoalbuminemia (1.2 g/dL; RR 2.5–4 g/dL), static globulin (2.8 g/dL; RR 2–3.6 g/dL), hypercholesterolemia (324 mg/dL; RR 120–310 mg/dL), hypocalcemia (8.8 mg/dL; RR 9–12.2), urine specific gravity of 1.032, with 4+ proteinuria on dipstick, pyuria (4–10 WBC/hpf),

UPC of 2.6, normal cobalamin (781 ng/L; RR 251–908 ng/L), hypofolatemia (5.6 µg/L; RR 7.7–24.4 µg/L), normal TLI 29.1 µg/L (RR 5.7–45.2 µg/L), and normal PLI (74 µg/L; RR ≤ 200 µg/L). Abdominal ultrasound revealed mild ascites and resolved gastric wall thickening. She was transitioned from a renal diet to a novel protein (white fish), moderately protein-restricted (5.2 g/100 kcal), and low-fat (1.8 g/100 kcal) commercially available diet (JustFoodForDogs® Hepatic Support Low Fat). Other treatment adjustments included adding psyllium husk 3 teaspoons PO q12h, folic acid 400 mcg PO q24h, and omega-3 supplementation of 4 capsules per day (Nordic Naturals® Watsonville, CA, USA, total 660 mg EPA/420 mg DHA, 1320 mg total omega-3 fatty acids), and telmisartan was increased back to 20 mg (0.63 mg/kg) PO q24h.

One month later, she had lost 1.1 kg (30.5 kg) and had an improvement in stool consistency (Purina® St. Louis, MO, USA fecal score*, PFS, 4). The owner ran out of Visbiome® and replaced it with Proviable® (Nutramaxx® Lancaster, CA, USA). Serum chemistry showed improved albumin (2.1 g/dL), decreased globulin (2.4 g/dL), and improved UPC (2.0) with resolved ascites on point-of-care ultrasound (POCUS). Telmisartan dose was further increased to 30 mg (0.98 mg/kg) PO q24h.

Another month later, there was progressive weight loss (30.1 kg) and more flatulence. Serum chemistry showed improved albumin 2.6 g/dL, static globulin 2.4 g/dL, and improved UPC (1.3). Telmisartan dose was increased to 40 mg (1.32 mg/kg) PO q24h, along with a further increase in psyllium husk to 4 tsp BID two weeks after that visit.

Four days after increasing her psyllium husk dose, the patient presented for a 24 h history of regurgitation, hyporexia, and urinary incontinence. Thoracic radiographs were unremarkable. Abdominal ultrasound revealed trace ascites, gastric ileus, and mild gastric wall thickening that were previously resolved for 3 months, suspected to be gastritis. Spec cPL was 78 µg/L (normal ≤ 200 µg/L). Urinalysis showed isosthenuria (USG 1.008), 2+ proteinuria, trace hematuria, with no growth on culture. She was hospitalized on a metoclopramide continuous-rate infusion (CRI) at a dose of 1.5 mg/kg/day and was discharged within 24 h with cisapride 15 mg (0.53 mg/kg) PO q8h and maropitant 60 mg (2.11 mg/kg) PO q24h, with further weight loss at 28.4 kg.

One week after discharge, she had continued weight loss of 0.3 kg (28.1 kg), worsening diarrhea (PFS 6) with increased frequency/urgency, continued flatulence, and resolved regurgitation. Recheck ultrasound revealed mild gastric ileus and trace ascites but normal gastric wall. Recheck labwork showed a new non-regenerative anemia (hematocrit (HCT) 29%, RR 35–57%) and panhypoproteinemia (albumin 2.2 g/dL, globulin 2.2 g/dL), despite a UPC of 0.6 indicating sufficient control of the patient's PLN. Mycophenolate was initiated for treatment of CIE at a lower dose of 250 mg (8.9 mg/kg) PO q24h due to concern for possible side effects such as diarrhea.

Two weeks later, her stools had firmed up (PFS 4) but were still intermittently soft. Her weight had improved by 0.6 kg (28.7 kg) and her energy was better, and she was strictly on her JFFD diet. Mild ascites noted on POCUS were thought to explain the minor weight gain. CBC and serum chemistry showed static anemia (HCT 30%) and progressive panhypoproteinemia (albumin 1.8 g/dL, globulin 2.0 g/dL). The fecal microbiota Dysbiosis Index® (Texas A&M University, Gastrointestinal Laboratory, College Station, TX, USA) was increased (2.9, normal < 0). The cisapride dose was decreased to 20 mg (0.7 mg/kg) PO, but at q12h since the owner was unable to administer q8h. Due to the persistent soft stool, worsening panhypoproteinemia, muscle mass, and weight loss that were suspected to be related to poorly controlled CIE, treatment escalation was deemed necessary. However, in order to decrease the risk of worsening the management of the PLN, a decision was made not to initiate steroid and/or cyclosporine therapy; therefore, FMT was scheduled for the

following week, with the plan to administer a series of 2 FMTs approximately 14 days apart as initial induction therapy, as suggested based on previous data [12].

A few days before the scheduled first FMT, the patient presented with a 2-day history of regurgitation, vomiting, diarrhea (PFS 6–7), hyporexia, and further weight loss of 1 kg (26.7 kg). Gastrointestinal ileus and trace ascites were noted on POCUS. Recheck CBC and chemistry showed static to minimally improved serum proteins (albumin 1.9 g/dL, globulin 2.3 g/dL) and persistent anemia (HCT 33%). She was hospitalized on supportive care (intravenous [IV] fluids and metoclopramide CRI 1.5 mg/kg/day) and ate well. FMT was then performed using feces from a donor that was screened based on current guidelines [39]. The donor was a 4-year-old female spayed Golden Retriever and deemed healthy based on history and physical exam with a BCS of 4–6/9 and a BW of 34 kg. The donor underwent regular screening at least every 6 months, which included a normal DI (typically below −4) and fecal testing for *Salmonella* spp., *Campylobacter jejuni*, *Giardia* spp., *Cryptosporidium* spp., and other intestinal parasites via centrifugal fecal floatation. Fecal samples were lyophilized without preservatives and stored in a −20 °C freezer for up to 6 months, as described previously [42]. Briefly, fecal samples were divided into multiple aliquots, each containing approximately 10 g of feces in 15 mL plastic tubes. The tubes were covered with Kimwipes secured by rubber bands and frozen at −80 °C for 2–24 h. Frozen samples were then transferred to lyophilizer beakers and freeze-dried overnight using a freeze-drying system (Labconco 710401000 FreeZone 4.5 L –84 C Complete Freeze Dryer System) set to −80 °C and 0.014 mbar (1.4 Pa). The following day, Kimwipes and rubber bands were removed, and the lyophilized feces were gently ground into a fine powder using a spatula. The powdered feces were then used for fecal enemas or capsules and stored at −20 °C for up to 6 months. During this study period, 5 batches of lyophilized fecal materials were from the same fecal donor, with bacterial viability verified after reconstitution with propidium monoazide (PMA)-qPCR in every batch and routine culturing for *P. hiranonis* as described previously [42]. For each procedure, the patient was walked to defecate before and after being administered a warm water enema (about 20 mL/kg); then, FMT was performed under mild sedation (butorphanol 0.3 mg/kg IV) using 25 g lyophilized feces (approximately 1 g lyophilized feces/kg BW, equaling approximately 3 g fresh feces/kg BW based on previously published protocols [11,12]), which was re-suspended in 150 mL saline and administered via retention enema into the colon over 10 min, and manually held for 10–15 min. The patient then rested in her kennel for at least 90 min. She had hematuria prior to her discharge the next day, so a 1-week course of prazosin 2 mg (0.07 mg/kg) PO q12h was dispensed pending urine culture, which grew *Escherichia coli* (*E. coli*). However, her hematuria had resolved, so anti-microbial therapy was not instituted.

The patient had a decreased appetite for 24 h after the FMT, after which she vomited once, but was noted to have improved energy and appetite and improved PFS (3–4). The patient received her second FMT approximately 2 weeks later and again had transient inappetence for 24 h, which resolved with maropitant. FMT was then performed at 4-weekly intervals due to the patient improving clinically after each FMT but then exhibiting worsening energy and stool quality by week 5. Subsequent FMTs and their clinical data are highlighted in Table 1 and Figure 1. Dysbiosis indexes were submitted after the second and third FMT, which showed an initial persistence of dysbiosis (DI = 5.5 after 2 FMTs) and then progressive normalization (<0) over time in response to repeated FMTs without other changes in treatment (Figures 1 and 2).

Table 1. Timeline of events throughout the case report with presenting complaints/history from prior recheck, treatment changes, and changes to body weight (BW), albumin (alb), globulin (glob), canine chronic enteropathy activity index (CCECAI), and dysbiosis index (DI).

Date	FMT#	History/Presenting Complaint	Treatment Changes	BW (kg)	Alb (2.7–4.4 g/dL)	Glob (1.6–3.6 g/dL)	CCECAI	DI (<0)
23 December 2022	--	Lethargy, distended abdomen ×1 week, morning bile vomiting ×1 day, soft stool ×4 day, slower eating	On: telmisartan 10 mg, clopidogrel 37.5 mg PO q24h Started: Visbiome® 450 bcfu, maropitant 30 mg PO q24h	32.3	1.2	2.8	9	--
26 December 2022	--	Second opinion consult for PLN	Increased: maropitant to 60 mg PO q24h, telmisartan to 20 mg PO q24h Added 4 Nordic Naturals Omega 3 capsules PO q24h	31.6	--	--	--	--
24 January 2022	--	Recheck PLN & suspected PLE Soft stool	Increased telmisartan to 30 mg PO q24h Started folic acid 400 mcg PO q24h, psyllium husk 2–3 tsp q12h	30.5	2.1	2.4	5	--
19 February 2023	--	Fecal score 4, malodorous flatulence Licking foot mass	Increased: telmisartan to 40 mg PO q24h, psyllium husk to 4 tsp PO q12h (2 weeks after) Prescribed Douxo® wipes for foot mass	30.1	2.6	2.4	5	--
11 March 2023	--	Regurgitation clear fluid & pollakiuria ×1 night, owner gave omeprazole (dose unknown), fecal score 4, gastritis/gastric ileus	Discharged the next day Started cisapride 15 mg PO q8h	29.5	--	--	--	--
20 March 2023	--	No regurgitation post-discharge until this AM, fecal score 6 since discharge, nocturnal fecal urgency Non-regenerative anemia, progressive panhypoproteinemia	Increased cisapride to 20 mg PO q8h Added mycophenolate 250 mg PO q24h	28.1	2.2	2.2	5	--
3 April 2023	--	Fecal score 4, no regurgitation/vomiting Gastric ileus resolved	Owner increased psyllium husk to 4 tsp PO q8h with feedings decrease to 3 tsp PO q8h Decreased cisapride to 20 mg PO q12h	28.7	1.8	2	6	--

Table 1. *Cont.*

Date	FMT#	History/Presenting Complaint	Treatment Changes	BW (kg)	Alb (2.7–4.4 g/dL)	Glob (1.6–3.6 g/dL)	CCECAI	DI (<0)
8 April 2023	--	Acute regurgitation, vomiting, diarrhea, hyporexia, lethargy, GI ileus	Hospitalized	26	--	--	--	--
9 April 2023	1	Transfer to IM	Discharged the next day Increased cisapride to 23 mg PO q8h Added prazosin 2 mg PO q12h for hematuria Pending urine culture	25.5	1.9	2.3	15	2.9
24 April 2023	2	No progression of diarrhea, vomited 1× prior week, improved energy	--	26.5	1.9	2.6	9	--
8 May 2023	--	Hyporexia after FMT #2—responded to maropitant	--	27.4	1.9	2.4	3	5.5
23 May 2023	3	Fecal score 4, Weight loss, Pruritic paws	Cytopoint® (Lokivetmab)	26.6	2.1	2.6	4	--
13 June 2023	--	PLE and paw wound. Increased food intake Fecal score 5, no vomiting	Discontinue mycophenolate. Taper cisapride to 17 mg PO q8h	27.3	2.3	2.5	1	--
3 July 2023	4	Leaking urine and pollakiuria past 48 h No change in energy or GI signs Weight loss over the past 2 weeks	--	26.4	2	2.7	3	0
13 July 2023	--	Fecal score 5 since last recheck, leaking urine	Add Proin® (phenylpropanolamine) Taipei, China, 50 mg PO q12h	26.8	2.3	2.4	4	--
31 July 2023	5	No urinary incontinence, fecal score 4	--	27.1	2.2	2.4	1	--
5 September 2023	6	Fecal score 4–5, increased stool frequency 5 weeks since last FMT	Discontinue cisapride	26.5	2.4	2.6	3	2.6
2 October 2023	7	Fecal score 4, Defecates 3× daily	--	27.2	2.4	2.4	1	--
30 October 2023	8	Regurgitated 2× the week prior	--	27.7	2.2	2.2	2	--
27 November 2023	9	Improved energy	--	27.9	2.3	2.4	2	--
24 December 2023	10	Self-resolving mixed bowel diarrhea after eating chicken legs from the trash	Increase FMT interval to 5 weeks	27.9	2.3	2.4	2	1.1

Table 1. *Cont.*

Date	FMT#	History/Presenting Complaint	Treatment Changes	BW (kg)	Alb (2.7–4.4 g/dL)	Glob (1.6–3.6 g/dL)	CCECAI	DI (<0)
28 January 2024	11	Intermittent softer stool, increased flatulence, licking paws more (owner stopped Apoquel® (oclacitinib) Kalamazoo, MI, USA)	Restart Apoquel® 16 mg PO q24h Start Advantix topical monthly	27.9	2.3	2.4	5	−2.1
25 February 2024	12	--	--	--	--	--	--	--
12 March 2024	13	Increased defecation frequency on day 5 after FMT (typically at least 2–3 weeks after q4 week FMT), lethargy, pica, possible nausea responsive to maropitant	Started 6 lyophilized fecal capsules/day ×3 weeks	27.6	2.5	2.3	5	--
7 April 2024	14	Nocturnal fecal urgency resolved 1 vomiting episode the week prior	Discontinued folic acid	27.9	2.5	2.3	2	−1.3
12 April 2024	--	AHDS hospitalization— Large bowel diarrhea on 4/10/24, vomited undigested food, abdominal discomfort, neutropenia with fever	Started ampicillin/sulbactam and enrofloxacin Gave psyllium husk 1–2 tsp PO q8h via gel capsules	--	2.4	3.2	--	5.2
14 April 2024	--	--	--	--	1.4	2.9	--	--
15 April 2024	--	Persistent diarrhea with mild hematochezia, improved appetite, afebrile	Discharged 16 Apr 2025	--	1.6	2.7	--	--
29 April 2024	15	Resolved hematochezia	--	27.4	2.7	2.8	--	--
5 May 2024	--	Large bowel diarrhea, vomiting Owner gave loperamide 3 mg, subsequent regurgitation and hyporexia Ate after maropitant and ondansetron	Discussed leflunomide— owner never started as diarrhea resolved	28.9	--	--	--	--
29 May 2024	16	Improved appetite Mild worsening of diarrhea 3–4 d post-FMT, then fecal score 3–4	--	27.8	2.8	2.8	--	6.3

Table 1. *Cont.*

Date	FMT#	History/Presenting Complaint	Treatment Changes	BW (kg)	Alb (2.7–4.4 g/dL)	Glob (1.6–3.6 g/dL)	CCECAI	DI (<0)
26 June 2024	17	--	--	28.3		2.7	--	--
22 July 2024	18	Vomited 2–3× overnight since last FMT, but no vomiting for last 2 weeks, fecal score 4–5	Restart FMT capsules—6 capsules/day × 3 weeks	27.8	2.9	2.6	6	--
19 August 2024	19	Lethargic ×1 week more soft stool, vomited 2× last week Urinary incontinence	--	27.7	2.8	2.7	5	2.6
16 September 2024	--	Regurgitation	Restart cisapride 15 mg PO q8h	--	2.9	2.5	0	--
14 October 2024	20	Periodically needs freeze-dried cod treat to eat, owner giving cisapride intermittently q12h	--	29.4	2.9	2.3	1	2
11 November 2024	21	Fecal score 2, urinated/defecated middle of night 2 nights prior	Taper cisapride	30.5	3.3	2.4	0	--
9 December 2024	22	Nausea on 23/12/24, responded to maropitant & ondansetron ×1 day Owner abruptly stopped cisapride	--	30.7	3.1	2.6	0	−2.5
6 January 2025	23	Regurgitated 3× since last visit Fecal score 5 at time of regurgitation but improved without intervention	--	30.7	3.2	2.4	0	--
3 February 2025	24	Hyporexia few days, ate with cod treats as a food topper Fecal score 4 with some undigested food, vomit vs. regurgitation 3 consecutive days post-FMT	--	30.4	3.3	2.5	1	--
28 February 2025	--	--	--	--	--	--	--	--
3 March 2025	25	Depressed/slower to eat, pollakiuria (no stranguria)	Restart cisapride 16 mg PO q12h	31.5	3.1	2.6	2	--
31 March 2025	26	Regurgitated 2× last week, eating without cod treats	--	30.7	3.1	2.7	0	--

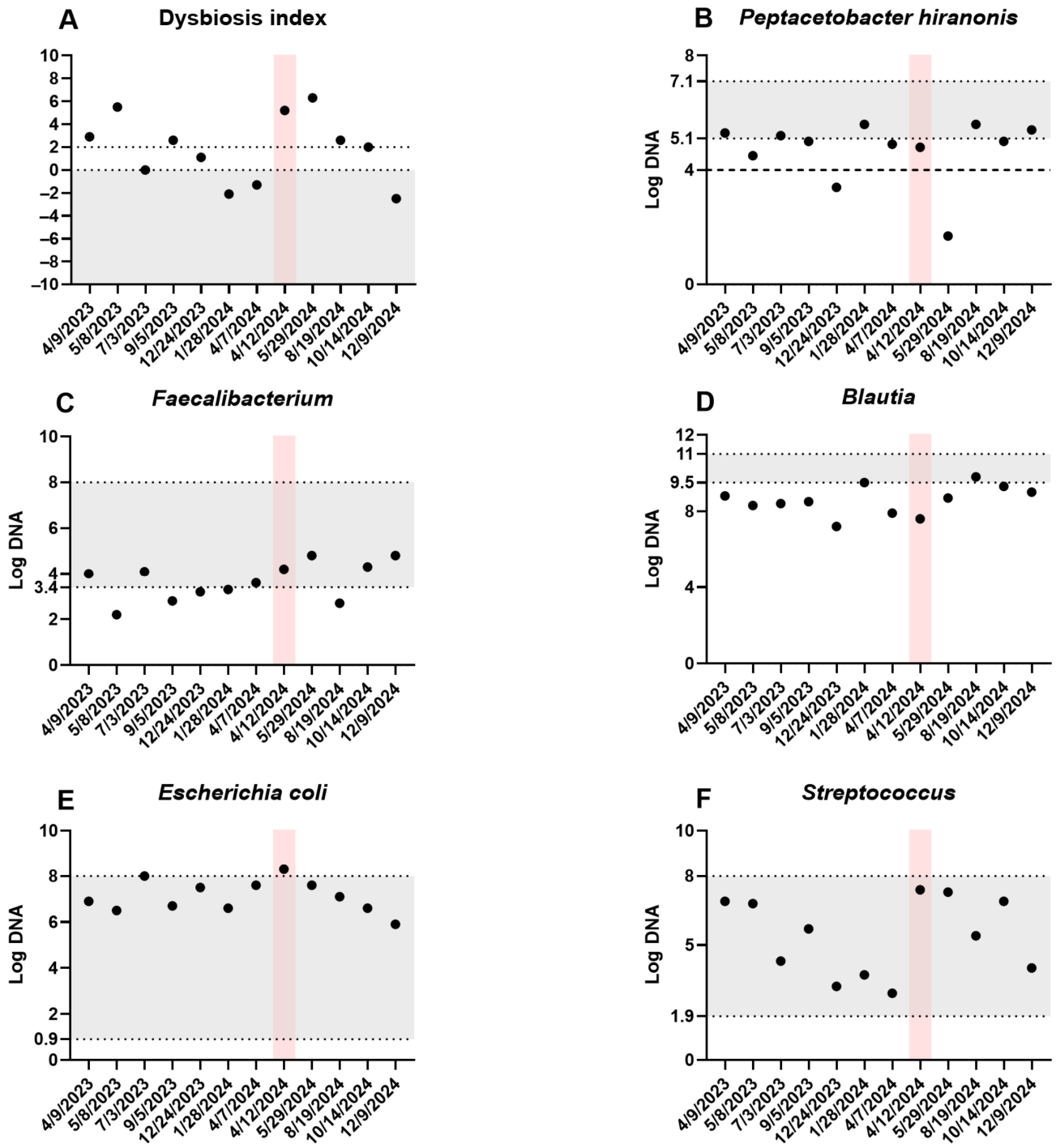


Figure 1. Fecal dysbiosis and bacterial taxa. The dysbiosis index (**A**) and five bacterial taxa showing the greatest temporal variation (**B**–**F**) are displayed. Each sample was collected prior to a fecal microbiota transplantation (FMT) procedure. The patient experienced an episode of acute hemorrhagic diarrhea syndrome from 12 to 15 April 2024, indicated by the red shaded area. The gray shaded area represents the reference intervals. For *P. hiranonis* (**B**), the dashed line at log DNA 4 marks the bile acid conversion cutoff, with values below associated with abnormal conversion of primary to secondary unconjugated bile acids.

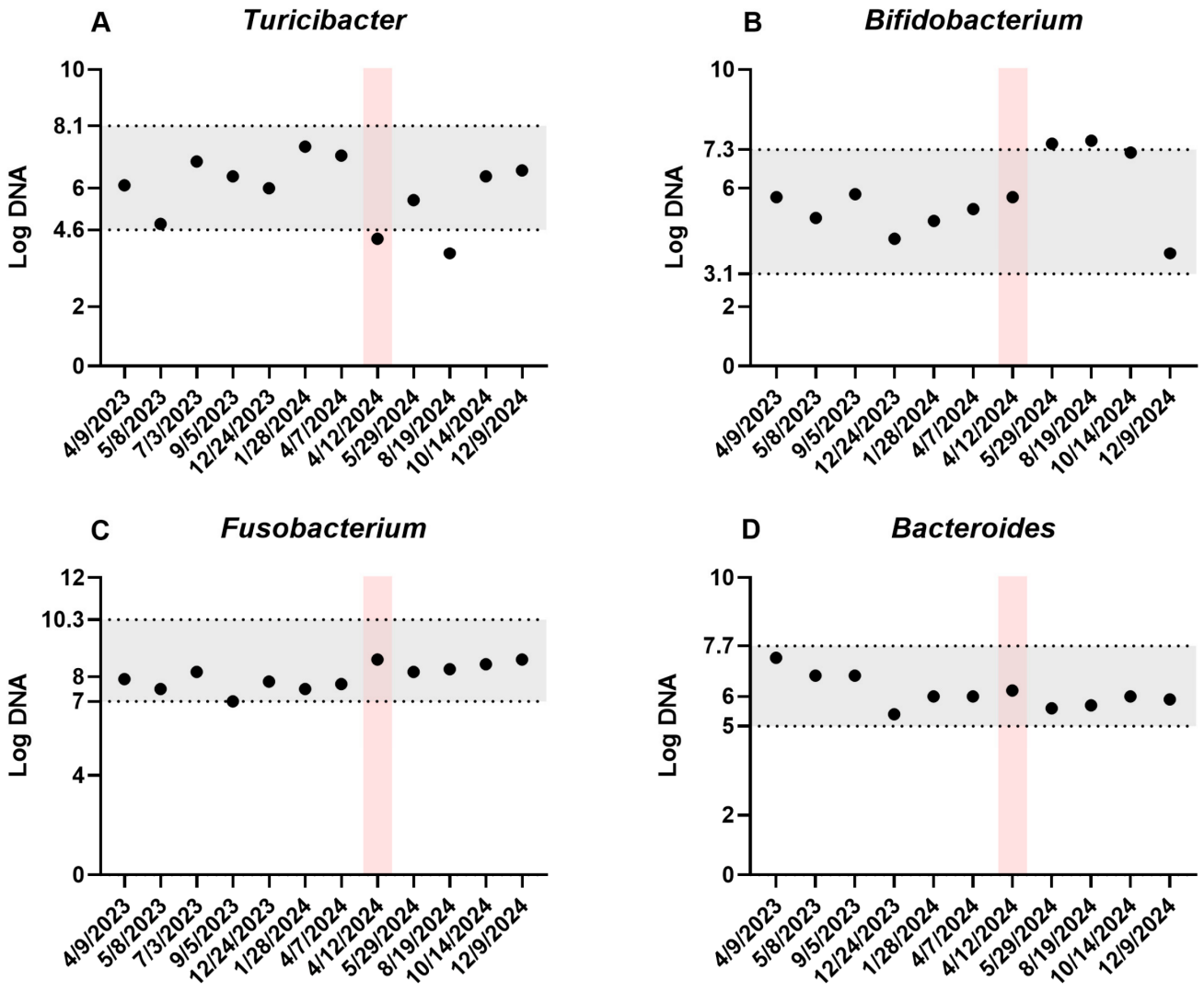


Figure 2. Additional core bacterial taxa. Four additional bacterial taxa (**A**–**D**) were quantified at multiple timepoints, with each sample collected prior to a fecal microbiota transplantation (FMT) procedure. The pink shaded area indicates an episode of acute hemorrhagic diarrhea syndrome (12–15 April 2024), and the gray shaded area represents the reference intervals.

Mycophenolate was discontinued after the third FMT as it was felt not to have made any clinical impact. No adverse effects were associated with its discontinuation. Since the patient was doing well clinically, the FMT interval was extended to 5 weeks at the 11th FMT. The DI at this visit was normal at −2.1. Unfortunately, the patient relapsed in clinical signs (lethargy, inappetence, and diarrhea) after only 5–6 days after the 11th FMT. At the time of the 12th FMT visit, lyophilized fecal capsules were also initiated at six capsules PO per day (six size #3 capsules each filled with 85 mg (510 mg total) of lyophilized feces per day) for 3 weeks to see if it could help control clinical signs and eventually extend rectal enema FMT treatment intervals. The oral FMT dosage was based on previously published studies and clinicians' experiences [29,39]. During and after oral FMT, the patient did well during the 4-week interval between enema FMTs apart from one episode of vomiting. Her serum proteins remained static (albumin 2.5 g/dL, globulin 2.3 g/dL). Folic acid was also discontinued. At the 14th FMT visit, the DI was −1.3.

Five days later, roughly 12 months from the first FMT, the patient presented for acute onset of vomiting and hemorrhagic diarrhea. Diagnostics included a mildly elevated Spec cPL (357 ug/L). The patient had mild leukopenia (4.11 × 10^9/L; RR 6–17 × 10^9/L) characterized by neutropenia (2.79 × 10^9/L; RR 3–12 × 10^9/L), increased BUN 31.8 mg/dL

(RR 9–29 mg/dL), mild hypotriglyceridemia (29 mg/dL; RR 30–130 mg/dL), hyponatremia 136 mEq/L (RR 141–152 mEq/L), and overall static albumin and globulin at 2.4 g/dL and 3.2 g/dL, respectively. Because an infectious cause for hemorrhagic diarrhea was suspected, a fecal enteropathogen panel was requested, which was negative for *Giardia* and *Cryptosporidium* on immunofluorescence, and PCR-negative for *C. difficile*, *Salmonella*, *Campylobacter jejuni*, and canine parvovirus. However, the patient was positive for *Clostridium perfringens* encoding the netF toxin gene on PCR, consistent with acute hemorrhagic diarrhea syndrome (AHDS). The dysbiosis index was markedly abnormal (5.2, previously −1.3), with an increase in *E. coli* (8.3; RR 0.9–8 log DNA), and a slight decrease in *P. hiranonis* (4.8 log DNA; RR 5.1–7.1 log DNA).

The patient was hospitalized with supportive care, which included isotonic fluid therapy, maropitant 27.9 mg (1.02 mg/kg) IV q24h, ondansetron (14 mg; 0.51 mg/kg) IV q8h, and clopidogrel 35 mg (1.28 mg/kg) PO q24h was continued. The next day, the patient became progressively neutropenic (1.10×10^9/L; RR 3–12 $\times 10^9$/L), monocytopenic (0.08×10^9/L; RR 0.2–1.5 $\times 10^9$/L), thrombocytopenic (137×10^9/L; RR 165–500 $\times 10^9$/L), and mildly anemic (HCT 36.82%; RR 37–55%). Antimicrobials, including ampicillin/sulbactam (819 mg IV q8h; 30 mg/kg) and enrofloxacin (227 mg IV q24h; 8.32 mg/kg), were administered due to concern for bacterial translocation. Abdominal ultrasound revealed gastric wall thickening (0.88 cm), colonic wall thickening (0.38 cm), small intestinal ileus, and trace ascites. Enteral nutrition with Vivonex® (Nestlé Health Science, Bridgewater, NJ, USA) via nasogastric tube, psyllium husk 1–2 teaspoon via gel capsules PO q8h, Visbiome® probiotic 1 packet PO q12h (450 billion cfu/packet), and capromorelin 90 mg PO q24h (3.3 mg/kg) were initiated on day 3 of hospitalization. The patient was discharged on day 6 of hospitalization with a recheck chemistry 3 days prior showing decreased serum albumin and globulin of 1.6 g/dL and 2.7 g/dL, respectively.

The patient presented two weeks later for ongoing 4-weekly intervals of FMT. Weight loss of 0.5 kg was noted since discharge (27.4 kg). Serum albumin had improved (2.7 g/dL), with static to slightly improved globulin (2.8 g/dL). Recheck DI showed 5.2 with decreased *Blautia*, and increased *E. coli*. Repeated PCR for netF toxin gene was negative.

The patient re-presented for transient large bowel diarrhea 6 days later. Weight gain of 1.5 kg (28.9 kg) was noted. Leflunomide was discussed as another immunomodulatory agent for CIE management, but was never started as her diarrhea quickly resolved.

The patient presented for the 16th FMT 3 weeks later with a 1.1 kg weight loss (27.8 kg). Her submitted DI (6.3) showed decreased *P. hiranonis* (1.7 log DNA). During the following two FMT visits, her weight and serum proteins remained relatively stable. Due to soft stools (PFS 4 with occasional 5 noted), a 3-week course of lyophilized FMT capsules (six capsules for a total of 510 mg lyophilized feces PO daily) was dispensed at her 18th FMT in addition to her regular enemas.

One month later (19th FMT), the patient's weight and serum protein remained stable. The patient was doing well for 2 weeks after starting the 3-week course of FMT pills. However, the patient became lethargic, had softer stool (PFS 5), and vomited twice prior to presentation. Serum albumin was decreased (2.5 g/dL). A Fecal Keyscreen® GI PCR (Antech Diagnostics, Fountain Valley, CA, USA) was not suggestive of bacterial or parasitic infection. The recheck DI at that time was 2.6.

A week before the 20th FMT, the patient began regurgitating for 3 days, which improved on cisapride (15 mg PO q8–12 h; 0.51 mg/kg). At the visit, she was noted to be the heaviest she had been (29.4 kg) since the initial FMT. POCUS showed mild gastric ileus, so cisapride was continued. Her serum chemistry showed improved albumin 2.9 g/dL with decreased globulin (2.3 g/dL). Her dysbiosis index was 2. At the 21st FMT visit, the patient showed another 1.1 kg weight gain (30.5 kg) and her PFS was 2, with further improved

serum albumin (3.3 g/dL) and similar globulin levels (2.4 g/dL). Her regurgitation and gastric ileus had resolved, so cisapride was tapered.

At the time of writing this manuscript (after the 34th FMT), the patient continues to do well with good energy, stable weight, stable albumin and globulin, and normal stools (PFS 2–3). Her last DI improved markedly at the time of writing (DI −2.5), with normalization of all taxa besides a mild decrease in *Blautia* spp.

3. Discussion

This case report describes a dog with PLE and PLN that showed clinicopathological improvement with multiple consecutive FMTs. In veterinary medicine, FMT has been reported in case reports or case series as an adjunct treatment in gastrointestinal diseases, where various improvements in weight gain, diarrhea, fecal scoring, vomiting, lethargy, and improved canine inflammatory bowel disease activity index (CIBDAI) scores have been observed [11,18,22,23,25,43]. Various routes of FMT administration include oral, retention enema, or endoscopic [39]. The fecal transplant in this study was delivered primarily via retention enema. Due to soft stools between the patient's FMT enemas, two courses of oral FMT capsules were added on 12 March 2024 and 22 July 2024. To date, there are no studies comparing the two methods. However, most case reports and canine FMT studies utilize rectal enema or oral capsules [11,12,39,40,42]. Additionally, different forms of fecal material, including fresh, fresh-frozen, and lyophilized feces, have been used in FMT studies [39]. In this report, lyophilized fecal material without cryoprotectants was chosen due to its storage convenience and ease of preparation and reconstitution before procedures. Although lyophilization without cryoprotectants reduces microbial viability compared to fresh feces, the viability was shown to be stable under our storage conditions [42] and was verified for each batch. Currently, there is no established guideline in veterinary medicine defining the minimum viable microbial load required for a successful FMT. And it is possible that the therapeutic effect is driven by multiple factors, including the colonization of live microbes, bacterial cell components, and metabolites present in the fecal material. Furthermore, in two studies using fresh-frozen feces without cryoprotectants, the clinical response was associated with improvement of the DI, which aligns with the overall shift of the gut microbiome and functionality. Therefore, it is reasonable to suspect that the response to FMT is likely related to the severity of the underlying pathophysiology, rather than the microbial viability alone. Nevertheless, future studies are needed to directly assess both the clinical efficacy and microbial viability of FMT materials and correlate with clinical long-term outcomes.

In our case report, the patient experienced clinical improvement, in particular, improved energy and weight gain, along with eventually normalized serum proteins. Two to three initial FMTs were required for the patient to start exhibiting more consistent clinical improvement, which we suspect was related to a markedly increased DI at presentation, as described in previous retrospective studies as well as a recent prospective [11,12]. For example, in one study [44], three dogs with CE were treated with one single FMT, and the DI was analyzed weekly for eight weeks. After FMT, the DI decreased but increased again 3–4 weeks later, and disease activity increased in some dogs. This clinical data shows that repeated FMT is needed to normalize the microbiome, and while there may not be an initial improvement in some patients, there can still be a clinical benefit later on with repeat treatments. This is likely due to underlying persistent pathology, as dogs with an increased DI have more functional changes that are associated with abnormal mucosal absorption due to chronic mucosal remodeling [9].

Therefore, in our case, continuous repeated FMT also led to progressive improvement/normalization in the DI, with increases in *Blautia*, *Turicibacter*, and *Faecalibacterium*,

and decreases in *E. coli* and *Streptococcus* species. One of the described beneficial mechanisms of FMT is the reestablishment of bile acid metabolism. In dogs, *P. hiranonis* is the main converter of primary to secondary bile acids and is decreased in a subset of dogs with CIE [24]. There is a significant interplay between host bile acids and the microbiome; for instance, secondary bile acids inhibit the growth of certain pathobionts, which may otherwise contribute to further dysbiosis [45]. However, our patients had normal or just slightly decreased *P. hiranonis* most of the time, with values above the cut-off for abnormal bile acid conversion (Figure 1). Another positive effect of FMT can be due to the re-establishment of short-chain fatty acid (SCFA)-producing bacteria. Short-chain fatty acids help reduce inflammation, regulate intestinal motility, and maintain intestinal barrier integrity [39,46–48]. Replenishment of the microbiome would help promote an anti-inflammatory state. However, with the underlying inflammatory process of CIE being persistent and multifactorial, it is to be expected that, over time, dysbiosis would likely return after cessation of the FMT, particularly in the absence of other therapies to address, which further emphasizes that FMT should be an adjunct rather than sole/primary therapy in CIE cases [11,12].

The DI is a quantitative PCR-based assay that has been validated to assess overall shifts in the fecal microbiome by quantifying seven core bacterial taxa and the total bacterial abundance, which are commonly altered in both canine and feline chronic enteropathies [33]. In this case report, FMT was performed every 4 weeks due to the timeline of recurrence of clinical signs such as worsening of energy and stool consistency, often by the end of the fourth week or by the fifth week. This illustrates that in some CIE dogs, FMT could be considered as an ongoing adjunct treatment, and this was demonstrated in one study where the DI in dogs receiving FMT was significantly decreased one week post-FMT, but then started to worsen by the four-week mark in one quarter of the dogs enrolled [49]. The findings in our case demonstrate the need for some patients to have repeated FMT, with responses noted after multiple FMTs likely due to the ongoing attempts to correct a significantly dysbiotic microbiome, which was also highlighted in two studies in which dogs with higher DIs, indicating severe dysbiosis, were less likely to respond to FMT [11,12].

Of note, other treatment modalities such as cyclosporine and steroids were not prescribed in our patient due to her concurrent PLN. In our case, steroids were also elected not to be used as a treatment due to the possibility of increased proteinuria [50] as to not confound monitoring of the dog's PLN, and also due to the risk of worsening hypercoagulability [51] in an animal already at higher risk for thromboembolic disease due to both of her major conditions (PLE and PLN) [52,53]. Cyclosporine was also not utilized due to available human data suggesting possible nephrotoxicity with chronic use [54]. In humans, cyclosporine has been shown to cause renal damage through inflammatory cell infiltration, tubular shrinkage, arteriolopathy, increased immunogenicity and tubular interstitial fibrosis [55]. However, data is lacking in dogs, and discussion of this is beyond the scope of this paper.

During the case report, one year after starting FMTs, the patient experienced an episode of acute hemorrhagic diarrhea syndrome (AHDS). Pancreatitis was considered less likely given only a mild elevation in Spec cPL, which was likely secondary to acute gastroenteritis, and a lack of pancreatic abnormalities on ultrasonography [56]. AHDS is a disease that results in an acute onset of hemorrhagic diarrhea with possible vomiting and anorexia preceding the event [57]. Although not present in every dog with AHDS, a higher prevalence of netF-encoding *Clostridium perfringens* strains has been shown in fecal samples of dogs with AHDS compared with healthy dogs or dogs with other intestinal diseases [58,59]. The netF toxin is a pore-forming toxin that can cause necrosis of the intestinal mucosa, leading to acute vomiting, hemorrhagic diarrhea, and hemoconcentration with discordant serum protein levels [27,60]. For each batch, the same material was analyzed

immediately before lyophilization for *netF* toxin gene-carrying *Clostridium perfringens* using qPCR, making the possibility of transferring this organism to the recipient unlikely. In dogs with acute hemorrhagic diarrhea, shifts in the microbiome can be seen in dogs, although these are typically milder compared to CIE, and the DI remains < 0 in most dogs, with *P. hiranonis* remaining within the reference interval [61]. *C. perfringens* and *E. coli* are increased, but they normalize relatively quickly, independent of treatment [61]. In our patient, we saw a marked increase in the DI, which may be because the acute episode reactivated the underlying disorder, leading to more severe dysbiosis than would be expected from an AHDS episode alone. This was likely compounded by anti-microbial therapy, as some animals can remain dysbiotic for a prolonged timeframe, as was highlighted in one study where 3/8 dogs were dysbiotic even at 42 days post-event, characterized by increased *Bifidobacterium* and decreased *P. hiranonis*, as also seen in this patient [61]. After the next FMT, *P. hiranonis* increased again to similar levels as before the AHDS and antibiotic administration, further suggesting that the temporary change in this organism was in part due to antibiotic administration. Nevertheless, the DI remained high and again required multiple FMTs to normalize, indicating that the acute episode exacerbated the underlying disease. It is difficult to determine if the patient's underlying CIE led to the occurrence of the AHDS episode per se. However, we do suspect that the underlying significant microbiome derangement common in CIE may make a patient more susceptible to acute GI episodes, and may take longer to recover from episodes such as AHDS compared to a dog that was previous clinically normal. Interestingly, it took almost 8 months, during which there were continued improvements and declines in the clinical presentation, for the patient's microbiome to recover from the AHDS event, further highlighting the effect of these acute events on an animal that has also had pre-existing chronic enteropathy and dysbiosis. The acute event did not alter the treatment frequency, as the patient still responded well to the established timeline for repeated FMTs. However, possible consideration could have been given to attempting repeated oral FMT capsules if the patient had required more frequent therapy than what was given prior to the event.

Dogs with CIE with the same disease process can present heterogeneously, so while our management of this patient has led to an ongoing positive outcome, treatment for each CIE patient should be individualized and adjusted based on treatment response. At the time of writing this manuscript, the patient is clinically doing well but still requires repeated monthly FMT enemas.

4. Conclusions

This case report highlights the continued use of adjunct FMT in a dog with CIE, resulting in improved clinical control over time and further highlighting the therapeutic benefits and alternative treatment modality to immunomodulatory therapy that adjunct FMT can provide. The patient suffered from an episode of AHDS, which negatively impacted the overall clinical control of the patient's CIE with prolonged dysbiotic effect for the following 8 months, illustrating the long-lasting impact of an acute condition on a CIE patient with underlying significant global GI dysfunction.

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Institutional Review Board Statement: Ethical review and approval were not necessary for this study, as a signed informed consent form was considered adequate in the circumstance of a case report. A signed informed consent form was obtained from the owner, allowing the abovementioned procedures to be performed and the use of data for scientific purposes.

Informed Consent Statement: Informed consent was obtained from the owner.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACTH	Adrenocorticotropic hormone
AHDS	Acute hemorrhagic diarrhea syndrome
ALT	Alanine-aminotransferase
ARE	Antibiotic-responsive enteropathy
BCS	Body condition score
BW	Body weight
BUN	Blood urea nitrogen
CBC	Complete blood count
CCECAI	Canine chronic enteropathy activity index
CE	Chronic enteropathy
CIBDAI	Canine inflammatory bowel disease activity index
CIE	Chronic inflammatory enteropathy
CKD	Chronic kidney disease
CRI	Continuous rate infusion
FMT	Fecal microbial transplantation
FRE	Food-responsive enteropathy
GI	Gastrointestinal
HCT	Hematocrit
ICGN	Immune complex glomerulonephritis
IRE	Immunosuppressant-responsive enteropathy
IV	Intravenous
LP	Lymphoplasmacytic
MCS	Muscle condition score
NRE	Non-responsive enteropathy
PFS	Purina fecal score
PLI	Pancreatic lipase immunoreactivity
PLN	Protein-losing nephropathy
POCUS	Point-of-care ultrasound
PLE	Protein-losing enteropathy
PO	Per os
RR	Reference range
SCFA	Short-chain fatty acid
TLI	Trypsin-like immunoreactivity
UPC	Urine protein/creatinine ratio
USG	Urine specific gravity

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