

First Case Report of Fecal Microbiota Transplantation in a Cat in Israel

Furmanski, S.^{1,*} and Mor, T.²

¹Medi-Vet Veterinary Hospital, 8 Einstein St., Haifa 3460506, Israel.

²Veterinary Endoscopic Services, 2 Reuven Rubin St., Tel Aviv 6941253, Israel.

* **Corresponding Author:** Dr. Shirley Furmanski, B.Sc, DVM, Dipl. ABVP (C/F), Medi-Vet Veterinary Hospital, 8 Einstein St., Haifa 3460506, Israel. Phone: +972-4-834-2887. Email: shirley.furmanski@gmail.com

ABSTRACT

This case report describes a 10-year-old, 2.9 kg, female spayed Abyssinian cat diagnosed with ulcerative colitis (UC), unresponsive to conventional therapy. A fecal microbiota transplantation (FMT) through rectal (enema) administration was performed as a last therapeutic option for the cat before euthanasia, and there was an immediate improvement after the procedure in regards to fecal texture, odor and color. After the initial successful response, the cat developed a clinical relapse of the diarrhea, and a second FMT procedure was performed five weeks thereafter. Gradually, during a 3-month period the cat started passing normal stools. On a follow-up, 11 months into the procedure, a prolonged clinical cure of the diarrhea has been achieved with the cat passing normal feces. This report describes the criteria for choosing FMT for the cat, the selection process and the screening tests performed for the fecal donor for infectious bacterial and parasitic diseases, the preparation and the methodology for the FMT and the outcome of the procedure. According to our clinical assessment, in this cat, FMT was a safe, beneficial and promising novel therapeutic procedure, and should be considered when a patient fails to respond to conventional therapy for UC. To the best of the authors' knowledge this is the first report of FMT in a cat performed in Israel.

Keywords: Cats; Feline; Fecal Microbiota Transplantation; Ulcerative Colitis; Inflammatory Bowel Disease; Fecal Donor Selection; Dysbiosis; *Clostridium difficile*.

INTRODUCTION

Chronic diarrhea of numerous etiologies is a common frustrating disorder in cats (1, 2). Chronic colitis is characterized by large-bowel diarrhea with frequent defecation of small volumes of soft to watery stool, often mixed with mucus and hematochezia (3, 4). Feline lymphoplasmacytic colitis is the most common form described, followed by eosinophilic, neutrophilic, granulomatous and ulcerative colitis (UC) (2, 3, 5). The exact etiology is unknown, and may be different between feline patients, but it is widely accepted that the pathogenesis of colitis involves complex interplay of host genetics, intestinal mucosal immune system, environment, and intestinal microbiota (3, 4, 6).

Many conventional and newly introduced therapeutic measures of enteropathies have been described in the veterinary literature. Fecal Microbiota Transplantation (FMT) is one of a newly emerged novel targeted microbiome-based therapy for gastrointestinal diseases, which has received considerable attention in human medicine (7, 8), as well as in veterinary medicine (9-11).

FMT is the introduction of fecal suspension, obtained from a selected healthy individual (donor), into the gastrointestinal tract (GIT) of an ill patient (recipient), most commonly suffering from GIT disease characterized predominantly by dysbiosis (12, 13). FMT is being carried out commonly in humans and is effective for treating *Clostridium*

difficile infection (CDI) unresponsive to antibiotics (7, 14, 15) as well as for non-GIT disorders (8). FMT has been carried out for many decades in animals, including horses, cattle and monkeys (9), as well as in cats and dogs with a variety of chronic enteropathies (1, 10, 11, 13). However, in contrast to the extensive studies of the use and efficacy of FMT in humans, information in dogs and cats is very limited, comprising mainly of anecdotal reports and a few case series (1, 10, 11, 13).

The rationale of using FMT in humans and animals is similar to the rationale of using prebiotics, probiotics or their combination (i.e., synbiotics), with their potential to modify and improve the intestinal microbiota and affecting the host's immune response (8, 16). It has been hypothesized that, in humans, FMT restores the colonic normal microbial community structure, thereby protecting against colonization of pathogenic bacteria such as *Clostridium difficile*, and suppressing its growth and its production of disease-causing toxins. However, the exact mechanism leading to the restoration of intestinal function is incompletely understood (8). This hypothesis is supported by evidence of the beneficial effects of intestinal microorganisms on health, and by the observation, in humans, that an FMT recipient can adopt, restore and maintain the transplanted microbiota (7, 15). Supportive evidence of the protective role of the microbiota was described in a recent case-series of three dogs with chronic enteropathy, where the microbiota analysis (i.e., 'dysbiosis index'; DI) was assessed prior to and after FMT. The results suggested correlations between the DI values and the absence, presence or improvement of the clinical signs of diarrhea (13).

Currently, there are no pre-set consensus guidelines regarding performance of FMT in dogs and cats. Veterinarians may consider FMT when other, conventional therapeutic options of GIT disorders have failed (17, 18). Studies in cats and dogs have demonstrated the potential to improve various acute and chronic GIT disorders, including inflammatory bowel disease (IBD), colitis and idiopathic diarrhea (10, 11, 13). Similar alterations in small intestinal and fecal microbial populations in dysbiosis observed in human IBD or in animal models of intestinal inflammation associated with dysbiosis, suggests that the microbial responses to intestinal inflammation are similar across different mammalian species (13, 19-21).

This report describes FMT in a cat with chronic diarrhea, unresponsive to conventional therapy.

CASE REPORT

A 10-year-old, 2.9 kg, female spayed Abyssinian cat diagnosed on histopathology with ulcerative colitis (UC), unresponsive to conventional therapy for over one year, was presented for FMT procedure as the last therapeutic option before euthanasia. The cat was currently vaccinated and dewormed. It had queened several times in the past, and shortly after the last two parturitions and prior to being spayed, transient self-limiting diarrhea was noted. In addition, twice previously, and 5 years prior to the onset of chronic mucoid large-bowel bloody diarrhea, giardiasis and *Tritrichomonas foetus* were detected by direct fecal wet mount-smears. The cat was treated with metronidazole (Flagyl Suspension, Unither Liquid Manufacturing, Colomiers, France; 20 mg/kg BID PO for 7 days) and Ronidazole (compounded by Vetmarket, Shoham, Israel; 30 mg/kg BID for 10 days), respectively, which led to resolution of the diarrhea in both episodes.

Six months before the cat was diagnosed with UC, signs of bloody, mucoid and malodorous large-bowel diarrhea were noted. Repeated complete blood counts, serum biochemistry profiles, direct fecal smears and fecal flotations over the period from onset of the clinical signs of large bowel diarrhea to the FMT were unremarkable. Serology for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) (FeLV Antigen/FIV Antibody Test Kit, SNAP* Combo Plus, IDEXX Laboratories, Westbrook, ME, USA) were negative. Total serum T4 (VetScan VS2, Abaxis Inc., Global Diagnostics, Union City, CA, USA) was within reference interval (RI). A gastrointestinal parasitic and infectious agents' screen (Laboratory Animal Department, American Medical Laboratories, Herzliya Pituach, Israel) was negative. Serum cobalamin and folate concentrations were within their RIs. Biopsies obtained via enteroscopy and colonoscopy were sent for histopathology (Patho-Vet Diagnostic Veterinary Pathology Services, Rehovot, Israel). The microscopic findings in the colonic biopsies included extensive ulceration and loss of the mucosal architecture, with numerous bacterial colonies and food material on the ulcerated mucosal surface (Figure 1). In one section, moderate diffuse infiltration with macrophages was noted. Biopsies obtained from the distal small intestines were unremarkable. PAS stain was performed for the endoscopic biopsies. There was no evidence of positive staining of macrophages infiltrating – the ulcerated colon. The findings were compatible with severe ulcerative colitis.

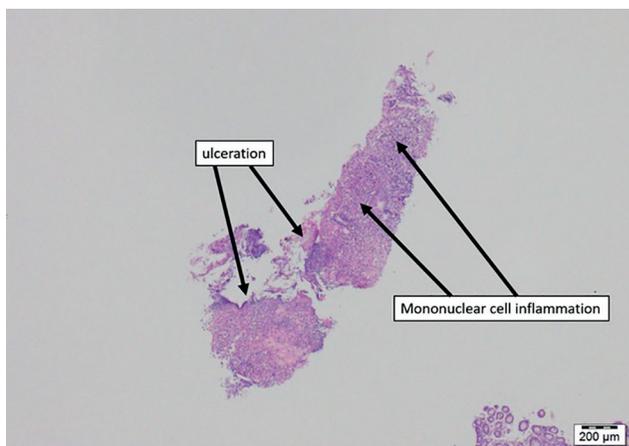


Figure 1: Extensive ulceration and loss of the mucosal architecture in the colon with moderate diffuse infiltration with macrophages (H&E X40).

The cat was then treated with multiple oral medications, at times combined, for varying periods, including metronidazole (Flagyl, Unither Liquid Manufacturing, Colomiers, France; 15 mg/kg BID), sulfamethoxazole/trimethoprim (compounded by Vetmarket, Shoham, Israel; 15 mg/kg BID), prednisone (Rekah Pharmaceuticals, Holon, Israel; 2 mg/kg BID, then tapered to 1 mg/kg BID), maropitant (Cerenia, Fareva, Amboise, France; 1 mg/kg SID for 5 days and then twice a week), sulfasalazine (compounded by Vetmarket, Shoham, Israel; 10 mg/kg TID), mirtazapine (compounded by Vetmarket, Shoham, Israel; 2 mg SID), ranitidine (Aspen, Bad Oldesloe, Germany; 2.2 mg/kg BID), chlorambucil (Leukeran, Excella GmbH, Feucht, Germany; 2 mg every 3 days administered late in the disease course) and cobalamin (Bedodeka, Teva, Godollo, Hungary; 250 µg subcutaneously (SC) every 7 days for 6 weeks, and then every 30 days for several months).

The diet had been changed during this period. The diets included a high fiber diet (canned Hill's Prescription Diet feline w/d, Hill's Pet Nutrition, Topeka, KS, USA), an intestinal diet (canned Hill's Prescription Diet feline i/d, Hill's Pet Nutrition, Topeka, KS, USA) and a hypoallergenic diet (canned Hill's Prescription Diet feline z/d, Hill's Pet Nutrition, Topeka, KS, USA). The latter had been fed for the last 3 months prior to the FMT, and thereafter. Dietary fibers (Psyllium 95% and Fusidic acid powder, Rafa, Jerusalem, Israel; 1 teaspoon SID-BID with food) and probiotics (Florentero paste, Candioli Pharma, Turin, Italy; 1 mL SID PO) were also given but were discontinued 4 months before the first FMT. Despite the chronic large bowel diarrhea, the

cat did not lose weight and had a good appetite throughout the disease course. However, as there was no improvement in response to any of the above mentioned treatments over a 12-month period, the owner had considered euthanasia. It was at this stage that the FMT was scheduled as a novel microbiome-based therapeutic technique for UC. The cat was taken off all medications 7 days before the FMT.

The donor used in this case was a healthy 3-year-old, 6.2 kg, female spayed domestic shorthair cat, with a body condition score (BCS) of 5/9 with no history of gastrointestinal disease, which was currently vaccinated and routinely dewormed. The donor cat did not have a history of a recent (past 3 months) antibiotic use, and the only antibiotic use was at time of being spayed at 6 months of age. The donor cat was fed a commercial dry adult cat (Friskies, Purina-Nestle, Vevey, Switzerland). Serology for FIV and FeLV was negative. Direct fecal smear and floatation were negative for worms, egg worms, *Giardia* spp. and other protozoa and fecal



Figure 2: (A) The donor feces was passed through a strainer; (B) A slurry of the fecal suspension with no visible large particles; (C) The administration of the 30 mL fecal cocktail via a lubricated 8 FR 2-way standard balloon Foley catheter which was introduced rectally and gently advanced until it reached the estimated location of the transverse colon while the anus held closed by an assistant. The recipient cat was placed in right lateral recumbency with its caudal body slightly elevated.

cultures were negative for *Campylobacter* spp., *Salmonella* spp., *Clostridium difficile* spp. and common aerobic bacterial pathogens (Kimron Veterinary Institute, Beit Dagan, Israel).

It was necessary to synchronize between the collection of the donor's fresh fecal sample and the essential preparation of the recipient cat. Immediately before the FMT procedure, a fresh (still warm and moist) fecal sample was obtained from the fecal donor. The donor cat was hospitalized and fasted the night before FMT. The stool was obtained through a direct removal of feces from the donor's rectum while the donor cat was slightly sedated, and the donor cat was doing well thereafter.

Five grams of the donor's stool was then diluted at a 1:6 ratio with a non-bacteriostatic sterile saline solution at room temperature, and mixed manually and then by blender. Large particles in the suspension were filtered through a strainer (Figure 2A), yielding a large particle-free slurry (Figure 2B). The 30 mL fecal slurry to be administered was transferred to a 60 mL catheter-tip sterile syringe to which was attached the 8 FR 2-way standard sterile balloon silicone-coated 100% latex Foley catheter.

The recipient cat was fasted overnight before the FMT procedure. At presentation, it was bright, alert and responsive, with normal vital signs. Physical examination was unremarkable. Its BCS was 3/9. It had a bloody, mucoid and malodorous diarrhea (Figure 3A). Once the donor stool sample was obtained, the recipient cat was premedicated (medetomidine; Domitor, Orion Pharma, Espoo, Finland; 10 µg/kg IM, butorphanol; Butomidor, Richter Pharma AG, Wels, Austria; 0.2 mg/kg IM and midazolam; Midolam, Rafa Laboratories, Jerusalem, Israel; 0.3 mg/kg IM). With sedation, approximately 15 minutes later, a 23 G over-the-needle IV catheter was placed into the left cephalic vein, and general anesthesia was induced with propofol (Diprofol; Synthon Hispania SL,

Barcelona, Spain; 2 mg/kg IV to effect), and maintained with isoflurane (Piramal Critical Care, Bethlehem, PA, USA) and 100% oxygen (2 L/min) delivered via an endotracheal tube. During anesthesia lactated Ringer's solution (Teva Medical, Ashdod, Israel; 5 mL/kg IV) was administered. The cat was stable throughout the procedure.

The recipient cat was placed in right lateral recumbency with its caudal body slightly elevated. A warm water enema was administered via a lubricated 8 FR 2-way standard balloon catheter attached to a 60 mL catheter-tip syringe, pre-filled with warm water (to avoid introduction of air into the colon), introduced up to the estimated location of the transverse colon. Immediately after the enema, the donor's fecal slurry was administered via a lubricated 8 FR 2-way standard balloon Foley catheter which was introduced rectally and gently advanced until up to the estimated location of the transverse colon (Figure 2C). Some of the fecal slurry was pushed into the catheter prior to its administration into the cat, to avoid introducing air into the colon. A total volume of 30 mL (10 mL/kg body weight) were administered slowly, while the anus held closed by an assistant. No discomfort signs were noted. It took 35 minutes from the beginning of the preparation of the fresh donor stool and until the prepared fecal slurry was fully administered. After completing the FMT infusion, the recipient was kept in right lateral recumbency for 15 additional minutes, and was then placed in sternal position for another 15 minutes, and then in left lateral recumbency for additional 15 minutes (total retention period of 45 minutes). The cat recovered uneventfully from the anesthesia, was observed in hospitalization for 6 hours, was fasted, and its activity was restricted, to decrease the likelihood of premature bowel movements. The cat was then discharged. A hypoallergenic diet (canned Hill's Prescription Diet feline z/d, Hill's Pet Nutrition Inc., Topeka, KS, USA) was prescribed.



Figure 3: (A) The recipient (bloody, mucoid and malodorous) stool immediately before the FMT procedure; (B) The recipient stool 48 hours after FMT: soft with no evidence of blood; (C) The recipient stool 4 days after FMT: stool with normal texture and color.

Over the first 24 hours post-FMT a bloody diarrhea was noted. At 48 hours post-FMT the stool was soft with no evidence of blood (Figure 3B) and over the next 2 days fecal consistency gradually improved. On day 4 post-FMT the cat passed a stool with normal texture and color for the first time after over a year (Figure 3C). After several additional days loose stool was noted again. Five weeks post-FMT no substantial fecal texture improvement was noted, while occasional fresh blood and mucus were noted as well. A second FMT was scheduled, and performed as described above, using the same donor, using 6 grams of feces. No medications were given between the two FMTs, and the cat was fed exclusively the same hypoallergenic diet. On the day of the second FMT, the recipient cat was bright, alert and responsive with normal vital signs, and weighed 2.7 kg. The cat recovered uneventfully from the anesthesia, and discharged home on the same day. No immediate improvement in fecal texture and consistency was noted immediately after the second FMT procedure.

One month post-FMT, in a phone follow-up, the owner reported some inconsistent improvement in fecal texture, color and odor. Sometimes the stool was loose and every once in a while it was more formed with occasional fresh blood and mucus noted. Three months after the second FMT procedure, the owner reported that the cat had been passing normal stool consistently. At the last recheck, 11 months after the second FMT, the owner reported that the cat was doing well and passing normal stools. During the whole period from the second FMT procedure and until the 11-month follow-up, the cat was not treated with medications and was fed exclusively the same hypoallergenic diet.

DISCUSSION

This report describes the use of FMT for the treatment of UC unresponsive to conventional therapy in a cat. Although no accepted guidelines or protocol of FMT in dogs and cats are available, the present favorable response to FMT as well as previously published preliminary results in dogs and cats (9–11, 13) are encouraging, suggesting that FMT is a safe and effective procedure, and should be considered in selected unresponsive cases of chronic diarrhea. More research is needed to determine the exact donor fecal components which play a role and exert a beneficial effect of FMT in the recipients. In human medicine, FMT protocols vary in the quantity of used donor stool, the recipient preparation, donor stool infusion methods and assessment of the outcome (7, 22, 23).

The methodology of the present FMT was adapted from the recommendations and experience published in the veterinary literature in FMT treatment of chronic enteropathy (1, 10, 11, 17, 18) as well as recommendations in humans (7, 20, 22, 24).

The approach to fecal donor selection is variable and has been evolving, and while the selection process characteristics are undetermined, the present reported method was aimed to adhere to available recommendations (1, 10, 11, 17, 18) and standardize the different and multiple parameters of the procedure. Nevertheless, certain limitations were encountered regarding the donor's screening process. The *Giardia* antigen ELISA was unavailable at the time and *Giardia* was screened for by fecal direct wet mount-smear and centrifugation flotation, which have a lower sensitivity. In addition, a special request was made for the outside laboratory for isolation of *Clostridium difficile*, although its presence in the gastrointestinal tract of dogs (4, 21) and cats (21, 24) is often a part of the normal intestinal microbiota and is detected with similar frequency in the feces of healthy and diarrheic dogs and cats (4, 21, 24).

Furthermore, there are several different techniques for preparing the donor's feces infusion for FMT, and the amount of donor stool used varies (23,25). In this case, a human protocol describing the fecal infusion was adapted (22), as it was recommended previously for dogs and cats (17, 18). However, this protocol suggested using ~50 grams of feces with ~250 mL of normal saline, while presently, 5 and 6 grams of fresh donor stool (approximately 2 g/kg body weight) were used in the two FMTs respectively. The amount of fresh feces used in FMT procedure is limited by the amount of fresh feces that can be obtained from the donor cat immediately before the FMT. It is recommended to avoid any delay when using fresh feces, because delay exposes the fresh feces to air, which presumably could result in progressive loss of some anaerobic microbial components which may be important components in the normal desired microbiota (17). In addition, there is conflicting evidence regarding the volume of infusion. Various volumes of fecal infusions have been used in humans (23, 25). A recent study has suggested low volume enema FMT is effective and safe in human patients with chronic relapsing CDI (25). However, a systematic review of FMT for treating recurrent CDI in humans has concluded that the resolution rate increased with the volume of donor fecal infusion to 97%

when the volume was >500 mL vs. 80% when <200 mL was infused (7). Although larger volume may be beneficial, by allowing the clinician to deposit multiple aliquots in multiple locations in the GIT, it might correspondingly increase the likelihood of straining in the recipient, resulting in rapid post-transplantation defecation (17).

In this case, the FMT was administered as rectal 30 mL fresh fecal enema (1, 17). In humans, both fresh and frozen preparations for FMT have been successfully used in managing recurrent CDI, introduced orally or rectally (15, 23). A recent study has reported the use of frozen donor stool stored at -80°C was equally beneficial compare to fresh donor stool (22). Using frozen feces preparations is more convenient than fresh stool since it is not necessarily tied to the timing of FMT procedure (17). In addition, the use of frozen stool allows standardization of the calculated stool volume to be used based on the recipient's body weight. However, since the preparation, storage and shipment of frozen feces is more complex and time consuming, and is definitely of greater cost, currently, until centralized stool banks become available in veterinary medicine, it is probably more feasible to perform the FMT with fresh stools for dogs and cats.

A recent collaborative analysis of 305 individual human patient data from 14 studies has revealed that FMT delivered via the lower GIT is a more effective route for the prevention of the recurrence of CDI compared to FMT delivered via the upper GIT route (12), although no similar evidence-based data in the veterinary literature is available.

In this case, two FMT procedures were performed, five weeks apart. Patients with confirmed chronic enteropathy, such as IBD and UC, may show improved stool quality several days to a week post FMT, but the clinical signs may relapse and therefore more than one FMT procedure might be required to achieve sustained clinical cure (1, 10, 13). With no consensus protocol, no specific recommendations regarding the frequency and time interval of the FMTs can be presently made in animals, although it may be useful to repeat the FMT every 3-4 weeks in some animals, to improve the clinical signs (10, 13). The recurrence of clinical signs in this cat after their initial improvement after the first FMT might suggest recurrent dysbiosis due to the underlying UC. This hypothesis might be supported by the results of a recent small case-series that evaluated three dogs with a history of chronic enteropathy treated by FMT via nasoduodenal tube, in which the fecal microbiota was evaluated using the DI. A DI was

calculated for each fecal sample using quantitative PCR analysis. While the DIs drastically dropped to the donor-like value after the FMT procedure in all three dogs, implying improvement of the dysbiosis, in three weeks, the DI of one of the dog increased. This was correlated with the recurrence of diarrhea, suggesting that in the future, the DI may be used as a quick screening tool for GIT dysbiosis and disease. In addition to fecal parasite and microbial pathogens screening, DI may be used to monitor the intestinal microbiota before and after FMT (13). Furthermore, molecular methods for calculating microbial DIs will potentially lead to a better understanding of the pathophysiology of GIT diseases, and necessitate new diagnostic and therapeutic approaches for dysbiosis (26).

The correlation between the prolonged clinical remission in the cat after the second FMT and the period of time until improvement of fecal color and consistency was noted, can be attributed to the process of normalization of GI dysbiosis, by restoring the colonic normal microbial community structure and its effect on the host's immune response (13). Currently, since the information regarding FMT in dogs and cats is very limited and comprising mainly of anecdotal reports and a few case series with no comprehensive studies, there is no available data regarding the considerable time it may take to notice an improvement in the clinical signs and in restoring gastrointestinal homeostasis after the FMT. In addition, a stool consistency score to directly evaluate the FMT outcome was not used in this case, and should be used in future FMTs in order to get a more precise, objective and better quantitative evaluation of the feces described by the owner. Further well-designed studies about the role of microbiota and FMT treatment using a larger scale of higher numbers of cats with more intestinal biopsies and fecal PCR for DI before and after each FMT as well as multiple donors are needed to help in better evaluating the role of FMT in various enteropathies and disease processes and not just as the last resource when other treatment options have been exhausted (13).

CONCLUSIONS

Although this is a single clinical case report, the favorable outcome post FMTs which resulted in a prolonged clinical cure for the cat, suggests that FMT is a promising novel therapy in chronic non-responsive enteropathies in cats, failing conservative therapy, and supports performing further

studies. The technique offers a safe and effective treatment with a potentially favorable outcome.

Nevertheless, currently, there are limited evidence-based objective data in the veterinary literature regarding the recommended protocol and guidelines for FMT. Further research is therefore necessary to clarify and evaluate microbial changes as a consequence of FMT and to study the immune and metabolic changes as an outcome of this procedure.

Furthermore, dogs and cats may serve as models to study this therapeutic approach to spontaneous inflammatory conditions of the gastrointestinal tract in humans.

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