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Trial of Fecal Microbial Transplantation for the Prevention of Canine Atopic Dermatitis

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***Abstract*—**The skin-gut axis defines the relationship between the intestinal microbiota and the development of pathological skin diseases. Low diversity within the gut can predispose to the development of allergic skin conditions, and a greater diversity of the gastrointestinal microflora has been associated with a reduction of skin flares in people with atopic dermatitis. Manipulation of the gut microflora has been used as a treatment option for several conditions in people, but there is limited data available on the use of fecal transplantation as a preventative measure in either people or dogs. Six, 4-month-old pups from a litter of 10 were presented for diarrhea and/or signs of skin disease (chronic scratching, otitis externa). Of these pups, two were given probiotics with a resultant resolution of diarrhea. The other four pups were given fecal transplantation, either as a sole treatment or in combination with other treatments. Follow-up on the litter of 10 pups was performed at 18 months of age. At this stage, three out of the four pups that had received fecal transplantation had resolved all clinical signs and had no recurrence of either skin or gastrointestinal symptoms, the other pup had one episode of Malassezia otitis. Of the remaining six pups from the litter, all had developed at least one episode of Malassezia otitis externa within the period of five to 18 months of age. Two pups had developed two Malassezia otitis infections, and one had developed three Malassezia otitis infections during this period. Favrot's criteria for the diagnosis of canine atopic dermatitis include chronic or recurrent Malassezia infections by the age of three years. Early results from this litter predict a reduction in the development of canine atopic disease in dogs given fecal microbial transplantation. Follow-up studies at three years of age and within a larger population of dogs can enhance understanding of the impact of early fecal transplantation in the prevention of canine atopic dermatitis.

***Keywords*—**Canine atopic dermatitis, fecal microbial transplant, skin-gut axis, otitis.

I. Introduction

ATOPIC dermatitis is a condition in which there is an immune system hyperreactivity to environmental triggers resulting in a chronic inflammatory skin disease [1]. The prevalence of atopic dermatitis in human medicine is reported to be rising in many parts of the world [2] with rates as high as 15-20% of children and 1-3% of adults now affected worldwide [3], [4]. The incidence in adults may be underrepresented due to the fact that sufferers may frequent their health care provider less as they age despite the severity of their symptoms [5]. Within veterinary medicine, there has been prevalence estimates of atopic dermatitis to occur in about 10-15% of the canine population [6], [7]. Under diagnosis of the condition due to owner's interpretation that the clinical signs are not severe enough to warrant veterinary attention may mean the incidence of the disease is higher than reported [7]. The Labrador retriever is highly represented within breeds diagnosed with canine Atopic Dermatitis (cAD) [7], [8].

The pathogenesis of cAD is complex within most breeds, involving multiple genes and environmental factors [8]-[10]. The genes implicated are those involving inflammation, immune regulation and skin barrier function [9]. Environmental factors include diet, supplementation with probiotics and prebiotics, average annual rainfall, rural vs. residential life and frequency of bathing [8], [10]-[14].

In people, development of the immune system can be heavily influenced by gut microbial dysbiosis especially within early-life [15], [16]. Antibiotics have a direct impact on the development of atopic dermatitis and asthma with maternal intake or usage within the first month of life increasing allergy diagnoses [15], [17]-[20]. Therapy with probiotics in early-life can reduce the incidence of atopic eczema and allergies in children with potential long-term benefits [21]-[23]. In dogs, providing probiotics for the first six months of life may help to protect against cAD [13].

Probiotics have been shown to transiently pass through the gastrointestinal tract rather than colonize the gut [24] although can confer beneficial effects within the host without changing the microbiome permanently [25].

Fecal microbiota transplantation (FMT) is the infusion of the microbiota from a healthy donor, via a fecal suspension, into a recipient to restore normal gut microbial diversity [26], [27]. FMT has been used for centuries for treatment of diarrhea and constipation, however, it is only in recent times that it has been used for specific conditions [26]. Standard treatment for *Clostridium difficile* infection (CDI) involves combination antibiotic therapy that has a reported relapse rate of 20-30% [28]-[30]. Those that fail to have complete remission of disease and developed chronic relapsing CDI have been successfully treated with FMT. Published average success rate of FMT for CDI is around 90% [31]. FMT in humans has extended to include success in treatment of autoimmune diseases such as ulcerative colitis, irritable bowel disease and myoclonic dystonia [27].

Clinical reports in dogs receiving FMT are based on gastro-intestinal complaints and have had varied responses [32]-[37]. FMT was performed in 16 dogs with inflammatory bowel disease unresponsive to routine therapy. The treatment was administered by endoscopic or oral methods and there was clinical improvement in most patients [33].

A study of 25 dogs compared therapy of uncomplicated

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diarrhea with FMT or metronidazole. Better fecal scores were evident at both 7 days and 28 days with the FMT treatment as opposed to metronidazole. Fecal microbiome post therapy in the FMT treated dogs clustered more towards healthy dogs than those treated with metronidazole [34]. Two studies report on FMT therapy for individual dogs with long histories of inflammatory bowel disease refractory to standard therapies [35], [36]. These dogs showed clinical improvements and increased diversity of their fecal microbiome [35], [36].

cAD has a heritability of 0.47 in British Guide Dogs [9], which indicates that estimated breeding values should be able to reduce the incidence in breeding populations. Identification of genomic estimated breeding values in cattle has shown to greatly improve genetic selection [38] and is likely to do so in cAD, but due to the suspected complexity of the genotype and influence of the environment, total elimination of cAD from canine breeding programs is thought to be unlikely to occur [9]. Identification of targeted prevention and treatment strategies is key to improving canine health and welfare associated with atopic dermatitis [9]. Investigation of environmental influences on the immune system in early life may identify methods to decrease the risk of developing cAD [39]. FMT may potentially be used as a prophylactic tool for either gastrointestinal diseases or non-gastrointestinal diseases in the future [40].

II. Materials and Methods

Fecal Donor Selection

As fecal transplantation in dogs is in its infancy, there is little literature on required selection criteria for fecal donors, although one paper describes a recommendation for selection criteria of donors [32].

Our ideal criteria for donor selection are described in Table I. The dog that was selected to be a donor for the transplantation of the pups in this study met all the criteria.

TABLE I
CRITERIA FOR SELECTION OF FECAL MICROBIOTA DONOR

History and physical examination	Laboratory results
• No history of chronic disease • No history of systemic antibiotic therapy within previous 12 months • History of normal fecal consistency • Normal on physical examination • History of regular vaccination and recommended preventative medications	• Normal CBC and biochemistry results • Negative fecal PCR for *Salmonella, Cryptosporidium, Clostridium, Giardia, Circovirus, Enteric Coronavirus, Parvovirus, Distemper, Campylobacter* • Negative fecal oocyst analysis for *Coccidia* and Non-coccidial oocysts

Fecal Preparation

Different authors [32], [34] have published their processes for FMT and these have described varied fecal amounts, type of liquid used as a diluent and procedure [32]. Preparation of the fecal material used for these cases is described in Table II.

Other authors have discussed the varied procedures for preparation of FMT and the impacts on bacterial viability [41], [42]. In other studies, the feces have been processed with a blender and either drawn through a catheter tip or cheesecloth in order to avoid organic material in the donor sample [37], [43]. One study in human literature has found that blending stool in ambient room air for homogenization has a large impact on the viable bacterial composition [41]. Storage of the feces at -20 °C for periods of between three and six months has required the addition of glycerol to maintain adequate bacterial viability [32]. In these cases, the feces used had been stored at -20 °C for four months when used.

TABLE II
PROCEDURE FOR PREPARATION OF DONOR FECES.

- Fresh feces collected from donor within 1 hour of defecation
- Portion of sample sent to laboratory for fecal analysis
- Rest of sample is diluted with tap water in approximate ratio of 1:1 according to volume.
- Sample is mixed thoroughly until it forms a slurry.
- A 5 ml syringe is used to divide the solution into 5 ml aliquots.
- Particles that are too large to be drawn up by a syringe are discarded.
- The aliquots are frozen in sterile tubes at -20°C.

Fecal Transplantation Procedure

Implantation of the FMT was performed without any form of sedation. The recipient dogs were handled gently and given positive reinforcement throughout the procedure with use of voice and kibble treats. No dogs were adversely affected or injured during the procedures. There were no negative side effects associated with the FMT.

Description of the procedure is outlined in Table III.

TABLE III
FECAL TRANSPLANTATION PROCEDURE

- 10 ml of prepared feces is utilized for each 15kg pup.
- Frozen feces are defrosted by removing from freezer and placing into a kidney dish with lukewarm water.
- Recipient is allowed to toilet.
- Recipient is gently restrained by the veterinary nurse and given treats as required.
- Veterinarian lubricates an open suction catheter and measures the length from the anus to the last rib.
- The catheter is gently inserted into the anus of the recipient dog and advanced slowly to the measured length approximately middle of the descending colon.
- The fecal preparation is inserted slowly.
- 5 ml of room air is inserted to clear the catheter.
- The catheter is held in place for approximately 5 minutes to allow time for the solution to be retained.
- The catheter is slowly removed from the colon and anus.

Case Reports

A two-year-old female Labrador required a caesarean section for whelping concerns. She was administered a 10-day course of Amoxycillin Clavulanate starting from the day of surgery due to concerns in regards to potential infection. Weaning of pups onto solid food began at three weeks of age with initially just fingertip amounts of yoghurt, psyllium and a multi-strain synbiotic, and gradually increasing amounts of dog kibble were added. The pups were well without any clinical signs and weaned off mother's milk at five to six weeks of age. Kibble with added multi-strain synbiotic was continued over the transition period into their puppy homes, away from the mother and littermates at eight weeks of age. The synbiotic was continued for approximately two to three weeks post transition to the new home. The pups were well during this time.

Within her litter of 10 pups, by four months of age, six had started to develop chronic intermittent or recurrent diarrhea.

Two of these pups had developed chronic scratching. Reports from two of the families were that clinical signs developed immediately after the synbiotic was ceased. An outline of treatment and responses for each of the pups is documented in Table IV.

TABLE IV
CLINICAL FEATURES OF EACH CASE

Dog	Clinical Signs	Previous Treatment	Treatment	Result	Non-routine vet visits (5-18 months)	Owner home report (18 months)
1	Chronic scratching, chewing front feet and recurrent diarrhea	Zyrtec™, Claratyne™, Predisolone™, Royal Canin Junior™ diet	Fecal transplant, Royal Canin Hypoallergenic™ diet (8 weeks), Cytopoint™ injection, Aloveen™ shampoo and conditioner	resolution of diarrhea and scratching		Normal dog
2	Intermittent diarrhea		Fecal transplant	no further diarrhea.	2 courses amoxycillin/ clavulanic acid for grass seed foreign body, Malassezia otitis x1	Normal dog
3	Chronic scratching and recurrent diarrhea, Malassezia otitis, erythematous ears		Fecal transplant, Royal Canin Hypoallergenic™ diet (8 weeks), Cytopoint™ injection, Dermotic™ ear ointment (10 days), Otoflush™ ear cleaner (5 days).	resolution of diarrhea and scratching		Normal dog
4	Chronic diarrhea started after symbiotic ceased		Fecal transplant, Royal Canin Junior™ diet (4 weeks)	resolution of diarrhea		Occasional scratch in different situations? Behavioral vs. medical
5	Intermittent diarrhea		Synbiotic (4 weeks)	resolution of diarrhea	Malassezia otitis x2	Normal dog
6	Diarrhea started after symbiotic ceased		Probiotic paste (4weeks)	resolution of diarrhea	Malassezia otitis x3	Scratches face a lot in the mornings, chews paws on occasion and rubs head on ground for a minute in mornings. Preventative ear medication used fortnightly - no further ear infections.
7	Nil		Nil		Malassezia otitis x1	Rubs ears and head on ground every night, chews at paws each night. Seems like an itchy dog but not enough to require medication.
8	Nil		Nil		Malassezia otitis x1	Normal dog
9	Nil		Nil		Malassezia otitis x2	Scratches at chin quite often. Otherwise, normal.
10	Nil		Nil		Malassezia otitis x1, acute moist dermatitis x1	Normal dog

Each case was treated individually according to severity of clinical signs, with the more severe cases requiring the higher level of treatment. The two pups that had both chronic diarrhea and scratching were given fecal transplants, lokivetmab injections at 1 mg/kg, and diet change to a hydrolyzed diet. The hydrolyzed diet was given for eight weeks then slowly transitioned back to the normal diet. One of these pups had previously been treated with anti-histamines, prednisolone and diet change with minimal success. The pup that had a Malassezia otitis externa, with erythematous ear canals and pinnae, diagnosed at presentation was also treated with ear cleaner for five days and medicated eardrops twice daily for 10 days. By 18 months of age, both these pups had shown no further skin or ear concerns. The owners reported no scratching within the home and considered them normal dogs.

One pup that had chronic diarrhea alone was treated with a fecal transplant and a diet change to a different non-prescription diet. This was then slowly transitioned back to the normal diet with no adverse reactions. Owner reported a dramatic improvement with treatment. By 18 months, the owner reported no skin or ear infections and no further diarrhea. She did have the occasional scratch in different environments that was still to be determined to have a behavioral or medical basis.

The fourth pup that was given a fecal transplant had a history of diarrhea alone, with no skin or ear complaints. This pup developed a skin abscess secondary to a foreign body three months after the fecal transplant. This was treated with two courses of antibiotics and surgical investigation. He developed a single episode of Malassezia otitis externa at 16 months.

Two of the pups that had diarrhea without skin or ear issues were treated with either a single or multi-strain symbiotic for approximately four weeks. This resulted in resolution of the diarrhea in both cases. By 18 months of age, one pup had developed two episodes of Malassezia otitis, and the other pup had developed three episodes of Malassezia otitis.

Of the remaining four pups, there were no clinical signs of gastrointestinal or skin concerns at four months of age so no treatment was given. By 18 months of age, all dogs had

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developed Malassezia otitis episodes. Two had one episode of Malassezia otitis with one of these dogs having daily bouts of rubbing his head on the ground, scratching ears and chewing paws. Owner discussed that he seemed like an itchy dog but not severe enough to require medication. One dog had one episode of Malassezia otitis and one acute moist dermatitis. The final dog had experienced two episodes of Malassezia otitis.

III. Discussion

Favrot's criteria are used universally to aid the diagnosis of cAD with a high degree of sensitivity and specificity [44]. These criteria use an endpoint of three years for the age of onset to clinically define cAD. This study is using the data from dogs at 18 months, being the halfway point, with a follow up study at three years of age to be performed. According to these two sets of criteria, none of the treated dogs (numbers 1-4 of Table IV) were diagnosed at 18 months with cAD. Of the six non-treated dogs, by 18 months two of these dogs met the criteria for cAD but had not yet undergone a food allergy trial.

Dog 6 fulfilled the following criteria of Favrot's Set 1 and other conditions had been ruled out for resembling diseases, aside from food-induced cAD through a traditional work-up.

- Age at onset < 3years
- Mostly indoor
- Chronic or recurrent Malassezia infections
- Non-affected ear margin
- Non-affected dorso-lumbar area

Dog 7 fulfilled the following criteria of Favrot's Set 2 and other conditions had been ruled out for resembling diseases, aside from food-induced cAD through a traditional work-up.

- Age at onset < 3 years
- Mostly indoor
- "Alesional" pruritus at onset
- Affected front feet
- Non-affected ear margins
- Non-affected dorso-lumbar area

Food-induced cAD and environmental-induced cAD have very similar clinical pictures but the presence of gastrointestinal signs such as diarrhea is more typically seen in food-induced cAD [45]. The next step for dog 6 and dog 7 is an elimination trial to determine if remission can be achieved through diet management.

Human studies discuss the development of adverse food reactions depending on several factors occurring during infancy. These factors include genetic predisposition, early exposure to allergenic proteins, increased gut permeability and immaturity of local and systemic immunological responses [46]. Associations between the diversity of an infant's diet and the development of recurrent or chronic eczema have been found with an early exposure to four or more types of solid food before four months of age in children increasing the risk of eczema by 2.9 times [47]. Current guidelines support the restriction of solid food until at least four months, then the introduction of high-allergen foods between four and six months of age as a preventative measure against the development of food allergy [48].

Use of hydrolyzed formula diets were recommended to prevent allergic sensitization to cows' milk in children but more recent studies have debated its' effectiveness in preventing allergic disease, asthma, eczema or food allergy [48], [49].

There are currently no defined recommendations in dogs for the timing of introduction of different food types and the subsequent development of atopic dermatitis. One study investigated the use of non-commercial animal products during lactation. They reported that if the bitch did not receive non-commercial animal products during lactation and the puppy was exposed to non-commercial meat before six months, the pup had a significantly higher risk of developing cAD. If the bitch received non-commercial animal products during lactation, then the feeding of meat for the pup prior to six months had no effect on the development of cAD [50].

Hydrolyzed diets have been used for the treatment of food-induced cAD but not as a preventative trial. Within this study, the basis of using a hydrolyzed diet for eight weeks during the treatment phase of dog 1 and dog 2 was to reduce exposure to food allergens during the period of establishment of a normal gut microbiome. A diverse intestinal microbiome modulates immune responses, which are essential for the prevention of food allergy and gut hypersensitivity to gut-derived antigens [51]. A depleted normal gut microbiome can impair the gut-associated lymphoid tissue, which plays a crucial role in the development of oral tolerance to colon-derived antigens [51]. With dog 1 and dog 2, the aim was to restrict oral antigens for eight weeks after the FMT was performed to allow the establishment of a more normal microbiome prior to reintroduction of a normal diet. Early results at 18 months indicate that these dogs are less likely to develop cAD as their littermates that did not receive the combination therapy of FMT, hydrolyzed diet and lokivetmab injection. Determining whether this will be a long-term effect and whether this is related to the combination of therapies, or an individual therapy performed at the correct age, is a subject of future studies.

The two pups that received FMT without the hydrolyzed diet or lokivetmab injection exhibited no significant cAD symptoms at 18 months of age. Follow up studies at three years of age should give an indication as to whether they have a reduced incidence of development of cAD as compared to their untreated siblings.

The two dogs that received oral probiotic therapy had resolution of their diarrhea, but the incidence of Malassezia otitis does not appear to have been reduced by 18 months of age. A previous study reported a reduction of cAD in dogs given probiotic *Lactobacillus rhamnosus* for the first six months of life [12]. The dogs in our study were given a synbiotic for the first 10-11 weeks of life, then again for a month during the treatment phase at four months of age. Longer-term synbiotic use may have shown a reduction in clinical signs of Malassezia otitis.

IV. Limitations

Statistical analysis of the results of this study is not available as the case numbers are too low for analysis. The dogs for both FMT non-treated and treated groups are linked by genetics and environment, which reduces confounding elements and

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improves the reliability of results.

Whilst the FMT treated and non-treated groups were not divided randomly, the FMT group was clinically affected at a younger age, which would indicate they were at a higher risk of developing long-term atopic disease. Dogs not affected at four months of age were in the non-treatment group. If early preventative treatment was not effective, the affected dogs in the treated group would be expected to have continued to show clinical signs.

As multiple therapies were trialed at the same time in two of the four treated dogs, determination of the benefit of FMT alone cannot be evaluated in this study.

Determination of the microbiome signature of the donated feces and within the treated dogs was not performed, therefore results of this study can only be based on clinical recovery. True indication of the benefits of the FMT on the gut microbiome for these dogs cannot be interpreted within this study.

V. Conclusion

Results from this litter of 10 pups at 18 months of age show a reduced incidence of Malassezia otitis amongst those treated with FMT at a young age, either alone or in combination with other therapies. Further research projects such as a follow up study at three years of age, trials comparing individual FMT therapy with combination therapy or a therapy trial with a larger cohort of puppies can help define if these improvements can be longer lasting and have significant statistical benefits.

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