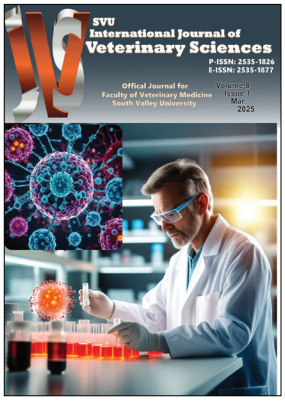
SVU-IJVS-8(1), 49-55 Print ISSN: 2535-1826 Online ISSN: 2535-1877
Research article Open Access

The utility of Fecal microbiota Transplantation for Feline Hyperesthesia Syndrome

Kerem Ural*[1], Hasan Erdoğan[1], Songül Erdoğan[1], Cemalattin Ayvazoğlu[2], Cansu Balikçi[1]
[1]Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Department of Internal Medicine, Aydın/TÜRKİYE
[2]Ardahan University, Nihat Delibalta Göle Vocational School, Department of Laboratory and Veterinary Health, Ardahan/ TÜRKİYE
*Corresponding author: Kerem URAL et al..; Kerem URAL, uralkerem@gmail.com, 0532 382 12 44,
https://doi.org/ 10.21608/svu.2025.349862.1360
Submit Date: Submit Date; 2025-01-02, Revise Date; 2025-03-02, Accept Date; 2025-03-08



ABSTRACT

Feline hyperesthesia syndrome (FHS) is a little-known syndrome characterized by skin texture fluctuations and behavioral disturbances (self-mutilation, excessive vocalization, jumping, running, tail chasing, etc.). In the present study, several long-term attacks of neurodermatological findings were evident in 23 cats of various breeds and both sexes. Depending on the respective clinical response, fecal microbiota transplantation (FMT) was used with heterologous origin between 1 and 4 sessions. Considering the frequency of attacks for clinical signs before FMT intervention, the vast majority of cats exhibited daily attacks/excessive grooming of the flank, lumbar or perineal region, lumbar hyperesthesia, vocalization, mutilation, alopecia, and allodynia. However, the disease phenotypes for FHS and the types of accompanying behavioral disorders recorded before and after FMT suggested that FMT was effective. Three different stress factors and environmental conditions were evaluated separately, showing that loud vocalization, struggling, panting, tremors and hyperesthesia decreased dramatically in response to FMT. In general interpretation, FMT was highly effective and no side effects were noticed or detected. The overall clinical response rate after FMT was 86.95%. Among them, 16 (69.56%) cats showed clinical remission, 4 (17.39%) cats showed clinical improvement and three (13.04%) cats had invalid clinical symptoms.

Keywords: *Behavioral disorders, Microbiome therapy, Neuro-dermatology.*

INTRODUCTION

Feline hyperesthesia syndrome (FHS) is an unexpected behavioral disturbance with an unclear etiology (Amengual et al., 2019; Gómez Álvarez and Soler Arias, 2021). A wide range of clinical signs linked to integumentary, neurological, and behavioral disorders (Ciribassi, 2009) were frequently observed, causing referral as atypical neurodermatitis, rolling skin syndrome, apparent neuritis, or disease of twitching (Tuttle, 1980). Related clinical signs were reported as pain linked with palpation, lumbar hyperesthesia (skin rippling and/or muscle spasms), attacking or over-grooming the flank, lumbar or perineal area, vocalisation, mutilation; alopecia and/ or allodynia (Amengual et al., 2019; Ciribassi, 2009; Gómez Álvarez and Soler Arias, 2021; Tuttle, 1980). Affected cats ranged from 1 to 5 years old, with no known sex predilection, whereas selected breeds, i.e. Abyssinian, Burmese, Siamese, and Persian are predisposed (Horwitz and Neilson, 2007). Treatment-refractory behavioral disturbances strongly affect both cats and their owners' health, making it necessary to investigate/establish novel therapeutical options for

achieving a primary therapeutic choice. In this study, to the present authors' knowledge, for the first time, FMT in heterologous origin was performed against FHS to those of cats with both presumed and tentative diagnosis. Clearly, and as a frontier therapeutical problem solving, 'treat to target' was purposed with FMT against FHS, which has been denoted as a behavioral/neurological disorder without any certain or proven therapy. It has emphasized that the Food and Drug Administration determined FMT treatment as an investigational new drug, which prompted the first author of this manuscript to perform this study.

MATERIAL AND METHODS

Study Population

The study was entirely performed at Intestinal Permeability Measurement Center (IPÖM) facilities available at a Feline Dermatology Group of selected researchers residing at Veterinary Internal Medicine Department, Faculty of Veterinary, Aydın Adnan Menderes University, history, relevant signalment, referral clinical reflection, laboratory work-up of cats with clinical signs compatible with FHS (Tuttle, 1980) similar to what have been described elsewhere (Amengual et al., 2019; Ruiz Suarez et al., 2021; Virga, 2003).

Inclusion criteria firstly involved evidence of proof for hyperesthesia, accompanied by attacking or over-grooming the flank, lumbar or perineal area, lumbar hyperesthesia (skin rippling and/or muscle spasms), vocalisation, mutilation; alopecia and/or allodynia, as shown in Table 1 below. Even if possible and did not match the initial diagnosis criteria, the owner was asked to video record a behavioral disturbance at any time in the day and recommended to observe daily, weekly, and monthly matching of each sign they visualize

Exclusion criteria and relevant testing

*Toxoplasma gondi*i, feline immunodeficiency virus/feline leukemia virus serology results were negative. Epidermal corneometric analytes, Quantum Pet Analysis, skin cytology, dermatoscopy, serum biochemistry, and relevant hematological laboratory work were deemed available for all cats enrolled.

Methodology for FMT

Previous descriptions and the same methodology (Ural et al., 2019) were used. The heterologous origin of other healthy relevant cats was in our archive of IPÖM facilities for their well-known previous microbiota analysis performed within the last 3 months. All heterologous origin of cats were on a low residue, low glycemic index diet with the lowest carbohydrate rates. Before FMT intervention all heterologue origin of healthy donor cats were free of medication or any drug usage, nor anesthesia/antibiotics for at least 3 weeks. Fecal material collected from the rectum or fresh defecation (not in contact with any solid substance or sand) sample was thoroughly and immediately combined with Lactated Ringer's Solution (as an equivalent volume of gr. feces; i.e. 20 gr fecal material was mixed with 20 ml Lactated Ringer's Solution), which was then manually blended, separated, extracted (the solid parts and the other relevant liquid one) and finally the obtained liquid part of FMT material was transferred from the rectal route with rectal catheter 15 cm apart from the rectum.

RESULTS

Study population

Twenty-three cats met the inclusion criteria, at which they were enrolled. Information on signalment and clinical findings is given in Table 1 above. Fifteen (6 were crossbred, 3 each British shorthaired and Scottish Fold, 2 Persian and 1 Van Cat) out of 23 cats were male, and the other relevant 8 ones were female (4 crossbred, 2 Angora cats, and 2 British short-haired). The median age of presentation was 2 years (range 1–6 years). Twelve cats were solely indoors.

Interestingly, it was shown in Table 2 above that all 23 cats demonstrated several different types of behavioral disturbances, in which hyperesthesia was evident in the entire population. Most cats, n=21 for each, showed loud vocalization, struggling, and vocalization, before FMT. Although in a less stressful environment (home), in contrast to harmful stress evident at veterinary clinics, most cases showed an increased density of clinical signs. For instance, during transport, five cats exhibited loud vocalization. However, following FMT, only one cat remained affected, whereas the other four were cured. Following

Table 1. Relevant clinical signs and inclusion criteria also involved demographic data of cats with feline hyperesthesia syndrome before therapeutical intervention with FMT.

Clinical Signs	Frequency of Episodes		
	Daily	Weekly	Monthly/Occasional
at	13/23	4/23	6/23
lh	17/23	6/23	
v	12/23	10/23	1/23
m	15/23	2/23	6/23
allo	20/23	2/23	1/23

at=attacking/over-grooming the flank, lumbar or perineal area; lh=lumbar hyperaesthesia (skin rippling and/or muscle spasms); v=vocalisation; m=mutilation; al=alopecia, allo=allodynia

Table 2. Disease phenotypes for FHS and demonstrated types of behavioral disturbances recorded prior to and thereafter FMT. Besides 3 distinct stressor environmental conditions were shown in the table and were separately evaluated.

Stressor Environmental Conditions	Loud Vocalisation		Struggling		Vocalisation		Panting		Shivering		Hyperesthesia	
	FMT		FMT		FMT		FMT		FMT		FMT	
	Prior	After	Prior	After		After	Prior	After			Prior	After
Less Stressful Area (namely residing home)	11	3	11	2	13	2	7	1	8	0	10	2
During Transport	5	1	6		5	1	3	0	6	1	4	1
At our Veterinary Department Facility (IPOM Unit)	5	2	4		3	0	4	1	5	1	9	3

FMT, cure rates were striking and showed diminished clinical findings (Table 2).

Treatment success

In overall interpretation, FMT was completely safe. No side effects were noticed, nor detected. The FMT was highly effective. The overall clinical response rate after FMT was 86.95%. Among them, 16 (69.56%) cats presented clinical remission, 4 (17.39%) exhibited clinical improvement, and three (13.04%) had invalid clinical symptoms. Figures 1-3 showed clinical records

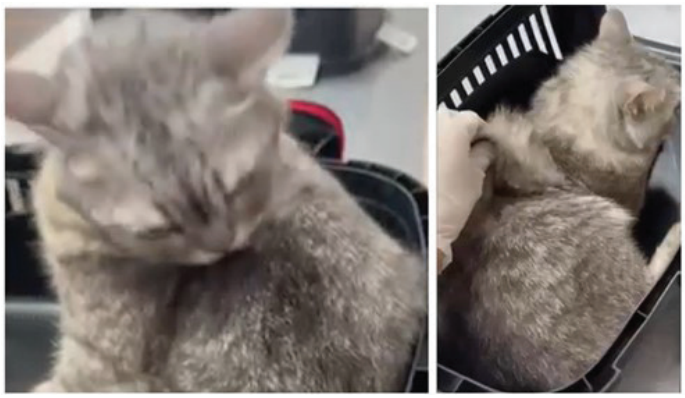


Figure 1. Before and thereafter FMT on days 0 and 10, respectively.

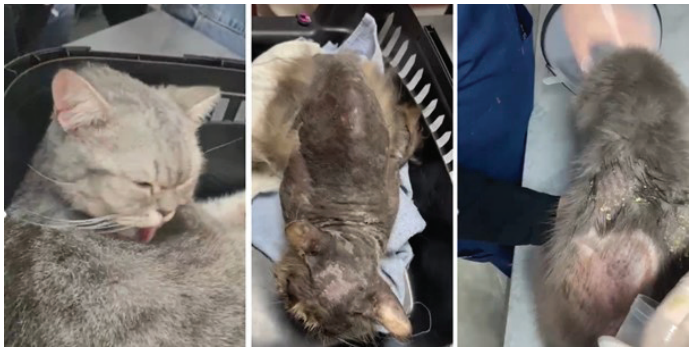


Figure 2. Three different and selected cases with hyperesthesia show distinct clinical signs.

of selected cases. Figure 3 belongs to a cat receiving FMT.

ETHICAL STATEMENT

In this study, dogs diagnosed with feline hyperesthesia were studied at the Animal Hospital of the Veterinary Faculty Animal Hospital. Ethical approval was obtained from the Animal Experiments Local Ethics Committee of Aydın Adnan Menderes University (date: 03/09/2024, no: 64583101/2024/90). Additionally, comprehensive information was provided to the owners of all dogs included in this study, and

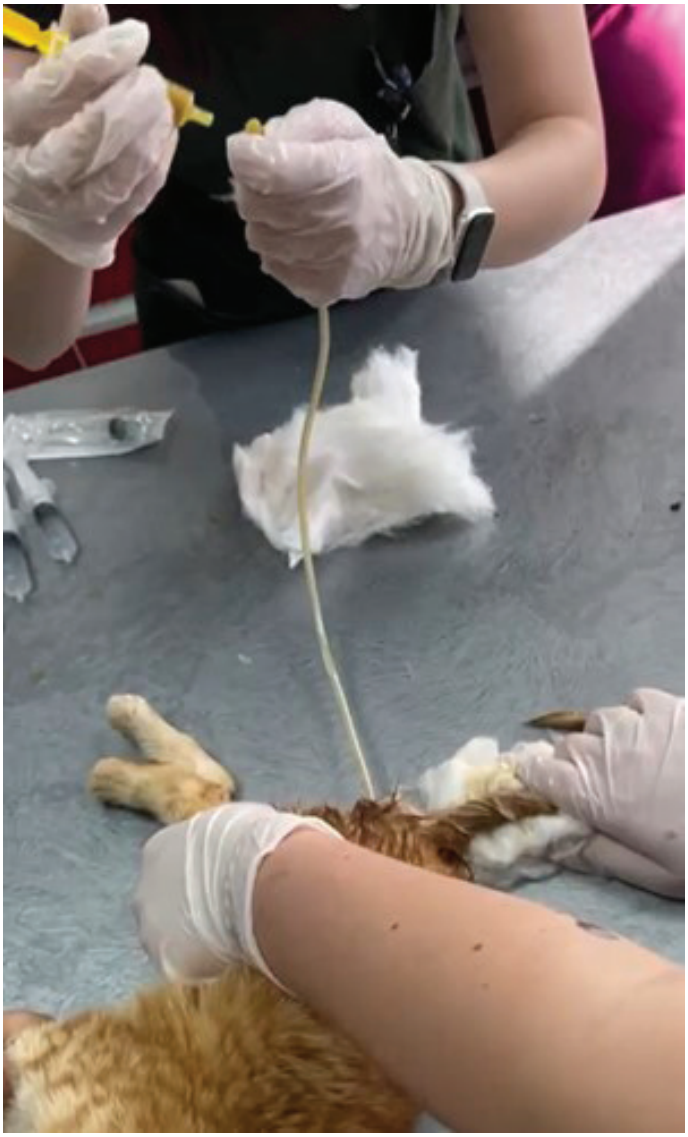


Figure 3. During fecal microbiota transplantation.

written consents were obtained from them.

DISCUSSION

Conducting this search primarily on the link or connection between neurological diseases and FMT, a well-written animal (Ural et al., 2019) and human literature (Jing et al., 2021) were deemed available for us to read. Preliminary literature suggests that FMT may be a promising treatment option for several neurological disorders. However, available evidence is still scanty, and some contrasting results were observed. A limited number of studies on humans have been performed or are ongoing, while for some disorders only animal experiments have been conducted. Large double-blinded randomized controlled trials are needed to further elucidate the effect of FMT in neurological disorders.

In a previous report, multiple sclerosis affected 3 people who received FMT in an attempt to resolve constipation and exhibited improvement in neurological signs (Borody et al., 2011)..The long-term efficacy of FMT against multiple sclerosis progression was reported. In that report, a woman with an exhibited inflammatory response, stimulated by recurrent C. difficile infections, probably linked to deteriorating neurological complications, which was responded to repaired gut dysbiosis by FMT (Makkawi et al., 2018). In the present study, we probably corrected and restored gut microbiota through FMT, in which clinical recovery might be hastened. However, we did not have any financial support for analyzing gut microbiota, which would be the purpose of our subsequent study. In this context, the next paragraph will discuss gut microbiota

The 'gut–microbiota–brain axis' denoted cross-talk of signalization comprising several/selected biological niches permitting a bidirectional network among gut microbiota and the brain. This is pivotal for the maintenance of homeostasis for the gastrointestinal/nervous and microbial systems of animals (Cryan et al., 2019a and 2019b; Martin et al., 2018). Several investigations on mammalians elucidated selected mechanisms of the way microbiota participated in several host life processes (i.e., energy output, metabolic pathway, immunology, and neuro-behavioral development, which is also the subject of this study). Perturbed gut microbiomes have been linked to several different disorders, also involving behavioral disorders. For fabric settings of host health, a balanced microbiome is crucial (Guard et al., 2017). On the other hand perturbed gut microbiota has been linked with behavioral disorders in autism (Chen et al., 2022). A novel study investigated the link between gut microbiota and behavior among children who exhibited varying microbiome status. In that study, behavioral disturbance has been linked to increased relative abundances of Bacteroides and Bifidobacterium species and selected functional encoded modules (Flannery et al., 2020). In this study, although we did not have the potential to analyze gut microbiota, a probable perturbation might be reversed with FMT, which could have hastened clinical recovery, at least for the cats herein involved.

Comparatively, animal research needs to be discussed. Germ-free male mice presented elevated

social alterations in contrast to conventionally colonized mice, denoting a significant contribution of gut microbiota linked to this behavior (Desbonnet et al., 2014). Germ-free wild-type mice received FMT, in which fecal samples were obtained from children with an autism spectrum disorder or from normally developed children. The autism spectrum disorder mice and their relevant offspring exhibited disease-similar clinical signs. Even if gamma-aminobutyric acid receptor agonists were prescribed to an autism spectrum disorder mouse model, clinical signs were diminished (Sharon et al., 2019). Furthermore, FMT was performed in normal hamsters and autism spectrum-disordered hamsters, and cerebral oxidative stress was diminished. Relevant efficacy was struck following Lactobacillus paracaseii administration (Aabed et al., 2019). In this study, one could easily speculate that the probiotic-rich FMT material belonging to previously detected gut microbiota analytes of donors selected could have been responsible for the clinical cure observed herein. Moreover, in the overall interpretation, FMT resulted in a clinical response rate of 86.95% in cats with FHS in this study. These results would encourage veterinary surgeons to seek eligible treatment options.

In general practice, it has been well accepted that in cats with FHS, alopecia or other relevant integumentary clinical reflection might not be evident (Virga, 2003). Taking into account the latter data, a state of not presenting selected clinical signs on referral is not adequate for excluding FHS as a probable underlying disease (Ruiz Suarez et al., 2021). The elevated response to lumbar palpation might be denoted as allodynia/alloknesis (Goich et al., 2019; Ruiz Suarez et al., 2021). Allodynia, as was determined through the Encyclopedia of Pain, is dedicated to establishing a description of pain stimulates that are naturally not painful, whereas allokinesis has been suggested to determine a sensational or pruritus behavior induced via stimuli that is naturally non-perceptive (LaMotte, 2007; Ruiz Suarez et al., 2021). In cases similar to this, diagnostic imaging techniques (Amengual et al., 2019) were suggested, which we were incapable of performing due to the economic budgets of animal owners and due to growing prices.

Taking into account the frequency of episodes of attacking/over-grooming the flank, lumbar or perineal area, lumbar hyperesthesia (skin rippling and/or muscle spasms), vocalisation, mutilation, alopecia and allodynia, the number of cats with daily symptoms were 13,17,12,15 and 20, respectively (Table 1). On the other hand, following FMT, as shown in Table 2, the number of cats with loud vocalisation, struggling, vocalisation, panting, shivering, and hyperesthesia were markedly diminished. This treatment modality should be taken into consideration by veterinary surgeons planning to battle FHS among cats.

In an attempt to clarify the long-term impact of FMT, we herein at this study monitored the cats for a 1-year duration, in which no recurrence was observed to those of cured cats. At the time of writing, there still exists no complication. However, we need to address concerns about the sustainability of FMT's therapeutic efficacy and potential for long-term remission. In 2013 a review reported and questioned whether FMT is sustainable (Vrieze et al., 2013), which did not clearly define conclusions. This was replaced or substituted by novel literature (Mahmoudi and Hossainpour, 2023; Nigam et al., 2022) still indicating further warranted studies and its necessity, however with satisfactory results. Although a 1-year duration was not enough for a sustainability search, we could speculate that our next study would thus be aimed also at the longer duration of monitoring for relieving behavioral disturbances by FMT.

In conclusion, taking into account FHS, a well-recognized and distributed disorder, has to be carefully and promptly treated due to its zoonotic nature in some circumstances. Moreover given the Food and Drug Administration's determination for FMT treatment as an 'investigational new drug', it should not be unwise to draw the preliminary conclusion that this treatment modality should be on the list of battling FHS among cats. However, it must be mentioned that this technique requires special knowledge, equipment, technical facilities, and management (donor selection, procedures of FMT preparation and then performance, etc.), which could be administered by specialists.

Availability of Data and Materials

The authors declare that data supporting the study findings are also available to the corresponding author

(Kerem URAL).

FUNDING SUPPORTS

There is no financial support for this study.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

AUTHORS' CONTRIBUTIONS

Motivation / Concept: KU. Design: KU. Control/ Supervision: KU. Data Collection and/or Processing: KU, HE, SE, CA, CB. Analysis and/or Interpretation: KU, HE, SE, CA, CB. Literature review: KU, HE, SE, CA, CB. Writing: KU.

REFERENCES

Aabed K, Bhat RS, Moubayed N, Al-Mutiri M, Al-Marshoud M, Al-Qahtani A, Ansary A (2019). Ameliorative effect of probiotics (Lactobacillus paracaseii and Protexin®) and prebiotics (propolis and bee pollen) on clindamycin and propionic acid-induced oxidative stress and altered gut microbiota in a rodent model of autism. Cellular and Molecular Biology, 65 (1): 1-7.

Amengual BP, Rusbridge C, Nuttall T, Heath S, Marioni-Henry K (2019). Feline hyperaesthesia syndrome with self-trauma to the tail: retrospective study of seven cases and proposal for an integrated multidisciplinary diagnostic approach. Journal of Feline Medicine and Surgery, 21 (2): 178-185.

Borody T, Leis S, Campbell J, Torres M, Nowak A (2011). Fecal microbiota transplantation (FMT) in multiple sclerosis (MS): 942. Official Journal of the American College of Gastroenterology, 106: S352.

Chen YC, Lin HY, Chien Y, Tung YH, Ni YH, Gau SS. (2022). Altered gut microbiota correlates with behavioral problems but not gastrointestinal symptoms in individuals with autism. Brain, Behavior, and Immunity, 106: 161–178.

Ciribassi J (2009). Understanding behavior: feline hyperesthesia syndrome. Compendium on Continuing Education for the Practicing Veterinarian, 31 (3): E10.

Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. (2019a). The microbiota–gut–brain axis. Physiological Reviews, 99: 1877–2013.

Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. (2019b). The gut microbiome in neurological disorders. Lancet Neurology, 1-16.

Desbonnet L, Clarke G, Shanahan F, Dinan TG, Cryan J (2014). Microbiota is essential for social development in the mouse. Molecular Psychiatry, 19 (2): 146-148.

Goich M, Bascuñán A, Faúndez P, Valdés A (2019). Multimodal analgesia for treatment of allodynia and hyperalgesia after major trauma in a cat. Journal of Feline Medicine and Surgery Open Reports, 5 (1): 2055116919855809.

Flannery JE, Stagaman K, Burns AR, Hickey RJ, Roos LE, Giuliano RJ, Fisher PA, Sharpton TJ. (2020). Gut feelings begin in childhood: The gut metagenome correlates with early environment, caregiving, and behavior. mBio, 11(2): e02780-19.

Gómez Álvarez CM, Soler Arias EA (2021). Feline hyperesthesia syndrome: epilepsy as possible aetiology in two cats. Veterinary Record Case Reports, 9 (3): e132.

Guard BC, Mila H, Steiner JM, Mariani C, Suchodolski JS. (2017). Characterization of the fecal microbiome during neonatal and early pediatric development in puppies. PLoS One, 12(4): e0175718.

Horwitz D, Neilson J (2007). Psychogenic alopecia/ overgrooming: feline. In: Blackwell's Five-Minute Veterinary Consult Clinical Companion: Canine and Feline Behavior. Wiley-Blackwell, Oxford, UK, 425-431.

Jing Y, Yu Y, Bai F, Wang L, Yang D, Zhang C, Qin C, Yang M, Zhang D, Zhu Y, Li J, Chen Z. (2021). Effect of fecal microbiota transplantation on neurological restoration in a spinal cord injury mouse model: Involvement of brain-gut axis. Microbiome, 9(59): 1-14.

LaMotte RH (2007). Allodynia and alloknesis. In: Schmidt RF, Willis WD, editors. Encyclopedia of Pain. Springer-Verlag, Berlin, Germany, 52-55.

Makkawi S, Camara-Lemarroy C, Metz L (2018). Fecal microbiota transplantation associated with 10 years of stability in a patient with SPMS. Neurology: Neuroimmunology and Neuroinflammation, 5 (4): e459.

Ruiz Suarez N, Mareyam Bhatti SF, Hermans M, Baptista Da Silva C, Hesta M (2021). Food hypersensitivity and feline hyperaesthesia syndrome (FHS): a case report. Veterinární Medicína, 2021.

Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim

YM, Zink EM, Casey CP, Taylor BC, Lane CJ, Bramer LM, Isern NG, Hoyt DW, Noecker C, Sweredoski MJ, Moradian A, Borenstein E, Jansson JK, Knight R, Metz TO, Lois C, Geschwind DH, Krajmalnik-Brown R, Mahmoudi H, Hossainpour H. (2023). Application and development of fecal microbiota transplantation in the treatment of gastrointestinal and metabolic diseases: A review. Saudi Journal of Gastroenterology, 29(1): 3-11.

Martin CR, Osadchiy V, Kalani A, Mayer EA. (2018). The brain–gut–microbiome axis. Cellular and Molecular Gastroenterology and Hepatology, 6: 133–148.

Mazmanian SK. (2019). Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. Cell, 177 (6): 1600-1618.

Nigam M, Panwar AS, Singh RK. (2022). Orchestrating the fecal microbiota transplantation: Current technological advancements and potential biomedical application. Frontiers in Medical Technology, 4: 961569.

Tuttle J (1980). Feline hyperesthesia syndrome. Journal of the American Veterinary Medical Association, 176 (1): 47.

Ural K, Erdoğan H, Adak Hİ, Ateş DS, Kahraman D (2019). Ataksik kedilerde fekal mikrobiyota transplantasyonu. Veterinary Journal of Mehmet Akif Ersoy University, 4 (1): 34-36.

Virga V (2003). Behavioral dermatology. Veterinary Clinics of North America: Small Animal Practice, 33 (2): 231-251.

Vrieze A, de Groot PF, Kootte RS, Knaapen M, van Nood E, Nieuwdorp M. (2013). Fecal transplant: A safe and sustainable clinical therapy for restoring intestinal microbial balance in human disease? Best Practice & Research Clinical Gastroenterology, 27(1): 127-137.