

Digest

VOLUME 3:
PUTTING
MICROBIOME SCIENCE
INTO PRACTICE



**Diagnosis and Clinical
Interpretation of Intestinal
Dysbiosis**

Jan Suchodolski
Dr. med. vet., PhD, AGAF,
Diplomate ACVM

**Antibiotic-Responsive
Enteropathy: Does It Exist?**

Julien Dandrieux
BSc, Dr. med. vet., PhD,
Diplomate ACVIM (SAIM), MRCVS

**Nutrition and FMT for
Chronic Enteropathy**

Kathrin Busch
Dr. med. vet.,
Diplomate ECVIM-CA



Diagnosis and clinical interpretation of intestinal dysbiosis

Jan S. Suchodolski, Dr. med. vet., PhD, AGAF, DACVM
Texas A&M University, College Station, Texas, USA

Microbiome assessment

As the majority of fecal bacteria are strict anaerobes requiring specialized media, routine **bacterial culture** is not useful, and a study showed no agreement between different laboratories.¹

Next-generation sequencing is useful in research studies, but lacks reproducibility for assessment of individual patients.

Dysbiosis Index (DI) is a commercially available PCR-based assay that quantifies core bacteria, and accurately predicts global microbiome shifts in individual patients.² The DI is interpreted together with the individual bacteria, especially the bile acid-converting *Clostridium hiranonis*, as a decrease in its abundance is a major contributor to dysbiosis (see Figure 1 for interpretation).³

Persistent dysbiosis is often seen in CE, and animals with non-specific clinical intestinal signs may also have an increased DI suggesting the presence of chronic intestinal dysfunction.⁴ The DI is also used to screen donors for fecal microbiota transplantation (FMT), as approx. 15% of clinically healthy animals may have subclinical dysbiosis.

Therapy

As dysbiosis is a common component of chronic intestinal disease, a multi-modal therapy approach is often needed. An increased DI in CE may reflect the severity and chronicity of mucosal remodeling, and dysbiosis typically persists even in clinical remission. Therapy should always consist of dietary manipulation as the first-line treatment, which can then be combined as needed with additional strategies such as probiotics, prebiotics, FMT, and in very rare cases, antibiotics. Nutritional therapy modifies the luminal microenvironment, leading to improvement in clinical signs, but

Of Note

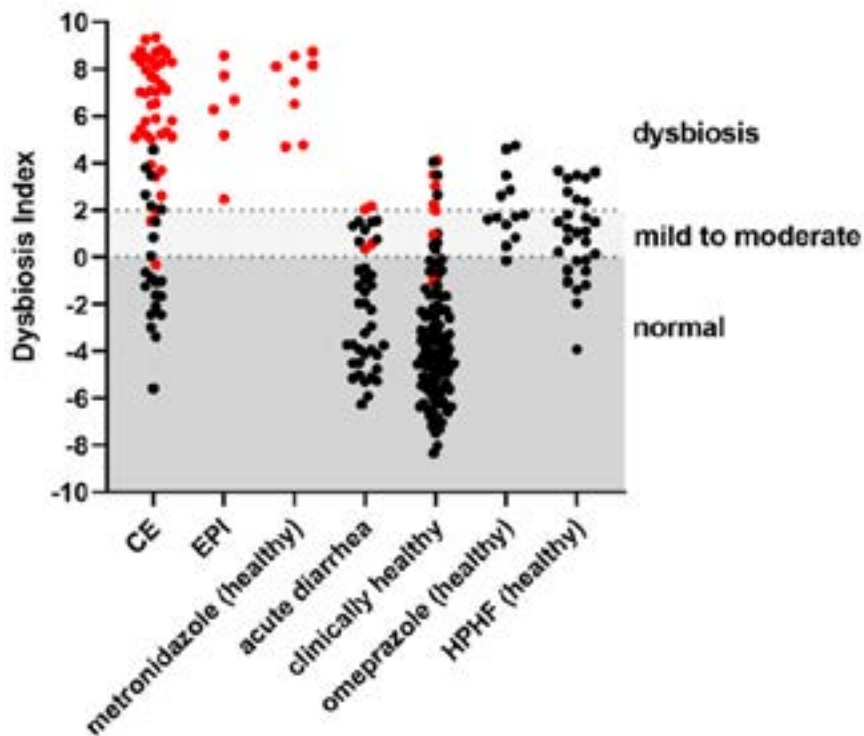
- Persistent dysbiosis is commonly due to chronic tissue remodeling in chronic enteropathy (CE).
- Broad-spectrum antibiotics induce significant dysbiosis.
- Acute diarrhea leads to minor and transient dysbiosis.
- Dietary modification should be a first-line treatment for CE.

it often does not directly reduce the dysbiosis. Anti-inflammatory therapy with corticosteroids in dogs with CE was shown to reduce the DI and normalize *C. hiranonis* after one year. FMT can lead to quick normalization of the microbiome, but in established CE the dysbiosis typically returns within a few weeks and multiple FMTs are typically required depending on recurrence of clinical signs.⁵

References

1. Werner, M., Suchodolski, J. S., Lidbury, J. A., Steiner, J. M., Hartmann, K., & Unterer, S. (2020). Diagnostic value of fecal cultures in dogs with chronic diarrhea. *Journal of Veterinary Internal Medicine*, 34(1), 199-208. doi: 10.1111/jvim.15982
2. Sung, C. H., Pilla, R., Chen, C. C., Ishii, P. E., Toresson, L., Allenspach-Jorn, K., . . . Suchodolski, J. S. (2023). Correlation between targeted qPCR assays and untargeted DNA shotgun metagenomic sequencing for assessing the fecal microbiota in dogs. *Animals*, 13(16), 2597. doi: 10.3390/ani13162597

Figure 1. Dysbiosis Index (DI) in dogs. Dogs in red have reduced abundance of *C. hiranonis*, a beneficial bile-acid converting bacterium important for maintaining a normal microbiome. A DI above 2 (dogs) or 1 (cats) indicates a significant dysbiosis, while a DI between 0 and 2 (dogs) and 0 and 1 (cats) indicates mild–moderate microbiome shifts. A subset of dogs with CE has persistently increased DI with reduced *C. hiranonis*. Some dogs with acute diarrhea have a mild and transient (1–2 weeks) altered DI. Broad-spectrum antibiotics induce dysbiosis that normalizes within 2–4 weeks after therapy in most animals, but some may have persistent dysbiosis for several months. Omeprazole leads to a transient increase in the DI, but with normal *C. hiranonis*, and the DI normalizes within 1–2 weeks after therapy. Also, some animals on very unbalanced home-made diets (e.g., high protein/high fat (HPHF) raw meat-based diets) may have an increase DI, but with normal *C. hiranonis*.⁶ Published with permission from The Purina Institute Handbook of Canine and Feline Clinical Nutrition, 2023.



- Wang, S., Martins, R., Sullivan, M. C., Friedman, E. S., Mistic, A. M., El-Fahmawi, A., De Martinis, E. C. P., O'Brien, K., Chen, Y., Bradley, C., Zhang, G., Berry, A. S. F., Hunter, C. A., Baldassano, R. N., Rondeau, M. P., & Beiting, D. P. (2019). Diet-induced remission in chronic enteropathy is associated with altered microbial community structure and synthesis of secondary bile acids. *Microbiome*, 7(1), 126. doi: 10.1186/s40168-019-0740-4
- Sung, C. H., Marsilio, S., Chow, B., Zornow, K. A., Slovak, J. E., Pilla, R., Lidbury, J. A., Steiner, J. M., Park, S. Y., Hong, M. P., Hill, S. L., & Suchodolski, J. S. (2022). Dysbiosis index to evaluate the fecal microbiota in healthy cats and cats with chronic enteropathies. *Journal of Feline Medicine and Surgery*, 24(6), e1-e12. doi: 10.1177/1098612X221077876
- Toresson, L., Spillmann, T., Pilla, R., Ludvigsson, U., Hellgren, J., Olmedal, G., & Suchodolski, J. S. (2023). Clinical effects of faecal microbiota transplantation as adjunctive therapy in dogs with chronic enteropathies—A retrospective case series of 41 dogs. *Veterinary Sciences*, 10(4), 271. doi: 10.3390/vetsci10040271
- Schmidt, M., Unterer, S., Suchodolski, J. S., Honneffer, J. B., Guard, B. C., Lidbury, J. A., Steiner, J. M., Fritz, J., & Kolle, P. (2018). The fecal microbiome and metabolome differs between dogs fed Bones and Raw Food (BARF) diets and dogs fed commercial diets. *PLoS One*, 13(8), e0201279. doi: 10.1371/journal.pone.0201279

Antibiotic-responsive enteropathy: Does it exist?

Julien Dandrieux, BSc, Dr. med. vet., PhD, DACVIM (SAIM), MRCVS
University of Edinburgh, Easter Bush Campus, Midlothian, Scotland, UK

Chronic inflammatory enteropathy (CE) is defined as primary gastrointestinal disease of three weeks' or more duration. Investigation is required to rule out extra-intestinal disease and parasitic disease, followed by sequential treatment trials. Although endoscopic biopsies were historically obtained during initial investigation, this is now reserved for cases not responding to treatment or those with severe disease. Many animals respond to dietary change and for this reason, the first treatment trial is typically a food trial with a hydrolyzed or novel protein diet.¹

Why not antibiotics as the next step?

Antibiotics, such as metronidazole, tylosin or oxytetracycline, were previously often used in cases unresponsive to a food trial. However, there are several arguments to discourage the use of antibiotics overall for CE:

- Intestinal dysbiosis is a hallmark of CE and antibiotics are a cause of further intestinal dysbiosis that can take months to resolve.
- Long-term follow up has shown that most dogs treated with antibiotics for CE will relapse and require ongoing or recurrent antibiotic treatment.
- There is rising concern for development of bacterial resistance with inappropriate antimicrobial use. In view of the short-term response, if any, and requirements for repeat use of antibiotics, CE should not be considered as a disease justifying antibiotic use.

When to consider antibiotics?

For the reasons listed above, antibiotic treatment should not be considered lightly and a proposal for rational use of antibiotics has been suggested.²

Antibiotics should be considered in animals presenting with signs suggestive of systemic inflammation, such as pyrexia, neutrophilia with

Of Note

- Dogs diagnosed with chronic inflammatory enteropathy (CE) will typically have a short-lived response to antibiotic therapy and there is concern for development of bacterial resistance. For this reason, antibiotics should not be considered in the majority of dogs with CE.
- Granulomatous colitis is a specific type of CE that has been reported mostly in Boxers and French bulldogs, where antibiotics are required to control the disease.
- Fecal microbiota transplant (FMT) is a new strategy that has been reported to improve the intestinal dysbiosis that is often reported with CE.

left shift, or neutropenia, especially if a bacterial infection has been documented.

In addition, a subtype of CE, granulomatous colitis, has been reported that affects mostly Boxers and French bulldogs. This disease is characterized by invasive *Escherichia coli* in the colonic mucosa. These dogs do not respond to standard treatment for CE, but typically have an excellent response to fluoroquinolones, although long treatment courses are often required and resistance has been reported.³ In view of the severity and the etiology of the disease, combined with lack of response to conventional treatment, appropriate antibiotics are recommended for this form of CE. Bacterial culture from the colonic wall can be useful to assess for antibiotic resistance and guide the choice of antibiotic.

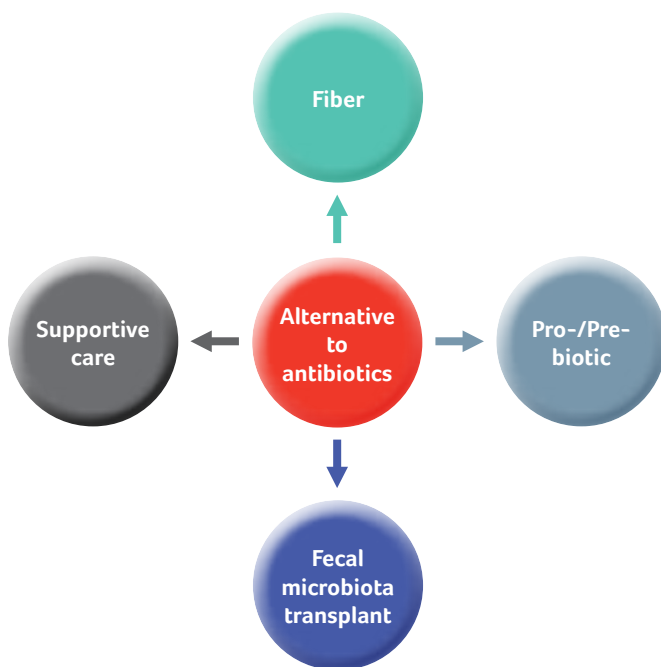
What should we consider instead of antibiotics?

Nutrition is a first-choice strategy and multiple diet trials might be required before patients are determined to be non-food responsive or partially food responsive. Different strategies can be considered instead of antibiotics in dogs that don't respond to a diet trial or that have recurrence of their gastrointestinal signs despite initial response (**Figure 1**).

If the episodes are infrequent and mild, supportive care at home, such as anti-emetics and/or appetite stimulants, is an option. For dogs with more pronounced signs, different strategies to modify the intestinal microbiome have been suggested.

Some dogs with large intestinal signs will respond to fiber supplementation. An alternative strategy is to consider the use of probiotics. However, there is currently little evidence-based literature on the utility of probiotics in dogs with CE.

Figure 1. Summary of the different strategies that are currently considered instead of antibiotics for pets not responding to diet trials.



More recently, there has been a strong interest in fecal microbiota transplant (FMT). This procedure involves transferring the intestinal microbiome from a healthy donor to a sick patient. Although the ideal donor, route of administration, and recipient is currently under investigation, there is some evidence that this strategy can be useful in some pets.⁴

In summary, there are several arguments that speak against the use of antibiotics in dogs with chronic enteropathy, in particular the short-term response to antibiotics and concerns about the development of antibiotic resistance that can impact both animal and human health. Different strategies are being actively researched and the use of FMT is of particular interest as CE is characterized by a bacterial dysbiosis.

References

1. Makielski, K., Cullen, J., O'Connor, A., & Jergens, A. E. (2019). Narrative review of therapies for chronic enteropathies in dogs and cats. *Journal of Veterinary Internal Medicine*, 33(1), 11-22. doi: 10.1111/jvim.15345
2. Cerquetella, M., Rossi, G., Suchodolski, J. S., Schmitz, S. S., Allenspach, K., Rodríguez-Franco, F., Furlanello, T., Gavazza, A., Marchegiani, A., Unterer, S., Burgener, I. A., Pengo, G., & Jergens, A. E. (2020). Proposal for rational antibacterial use in the diagnosis and treatment of dogs with chronic diarrhoea. *Journal of Small Animal Practice*, 61(4), 211-215. doi: 10.1111/jsap.13122
3. Manchester, A. C., Dogan, B., Guo, Y., & Simpson, K. W. (2021). *Escherichia coli*-associated granulomatous colitis in dogs treated according to antimicrobial susceptibility profiling. *Journal of Veterinary Internal Medicine*, 35(1), 150-161. doi: 10.1111/jvim.15995
4. Toresson, L., Spillmann, T., Pilla, R., Ludvigsson, U., Hellgren, J., Olmedal, G., & Suchodolski, J. S. (2023). Clinical effects of faecal microbiota transplantation as adjunctive therapy in dogs with chronic enteropathies—A retrospective case series of 41 dogs. *Veterinary SCEnces*, 10(4), 271. doi: 10.3390/vetsci10040271

Nutrition and Fecal Microbiota Transplantation (FMT) for Chronic Enteropathy

Kathrin Busch, Dr. med. vet., DECVIM-CA (Internal Medicine)

Ludwig Maximilians University, Munich, Germany

The etiology of chronic enteropathies is multifactorial. In addition to genetic predisposition and an excessive local immune response, the intestinal microbiome is particularly associated with the development of inflammatory bowel disease in humans.¹ It is also known that most dogs with chronic enteropathy (CE) have an altered microbiome compared to healthy individuals.²

Diet

Diet has a significant short- and long-term positive impact on the composition of the intestinal microbiota.³ Additionally, it can influence the mucosal immune system, intestinal permeability, and gut motility. Therefore, dietary management is the most important therapeutic measure in the treatment of dogs with chronic enteropathies (CE). Even in dogs with moderate to severe disease, a clinical improvement could be achieved solely through diet change.⁴

Nonetheless, it is crucial to recognize the underlying enteropathy often persists, even during clinical remission, with the potential for recurrence. Clinical improvement after diet change can be anticipated within 1–2 weeks. If a diet change fails to improve clinical signs, at least one more diet should be tried, including a hydrolyzed diet. Even if clinical signs do not significantly improve after trying multiple diets, including a hydrolyzed diet, maintaining the most appropriate diet is recommended. These dogs will also need to be supported by additional therapies such as fecal microbiota transplantation and/or immunosuppressive therapy.

Fecal microbiota transplantation (FMT)

FMT refers to the transfer of feces from a healthy donor into the intestine of a diseased recipient with the goal of influencing the intestinal

Of Note

- Nutritional modification and supplements should be the first management strategy in dogs and cats with CE.
- If the first diet trial fails, another diet change is recommended. Before starting immunosuppressive treatment or trying FMT, a hydrolyzed diet should be attempted.
- Diet should continue to be part of therapy even when only partial remission is achieved. FMT is an option for dogs that do not fully respond, as FMT can modulate intestinal microbiota in dogs with CE and can improve clinical signs.

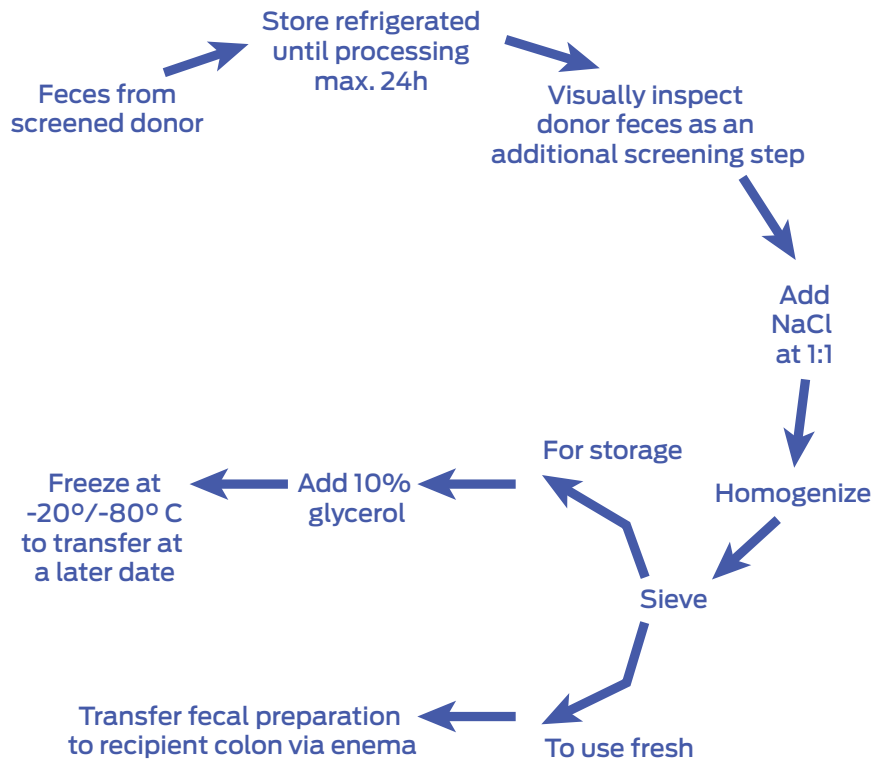
microbiome. In human medicine, FMT has proven more effective than antibiotics in treating *Clostridioides difficile* infection and shows promise in various other gastrointestinal as well as extra-gastrointestinal disorders like metabolic syndrome and obesity, neurological disorders, and liver diseases.⁵ In veterinary medicine, FMT shortened the time to normalization of fecal consistency and hospitalization time in puppies with parvovirus infection.⁶ In a recent study evaluating dogs with CE that did not respond to standard treatment, researchers observed decreased clinical signs like improved fecal consistency or overall activity after FMT in 31/41 dogs.⁷

Indications for FMT currently mainly include CE and diarrhea following antibiotic use. FMT can induce a change in the intestinal microbiome, which typically disappears after 3–4 weeks.

Especially in chronic conditions, we recommend concurrent therapy with dietary modifications to ensure long-term success. The use of FMT for extra-gastrointestinal diseases is currently not sufficiently substantiated, but it holds promise.

An ideal fecal donor is a healthy, adult, normal-weight dog with no chronic illnesses, displaying normal behavior, not taking any medications, and particularly not having received antibiotics in the last 6 months.⁸ The steps involved in FMT are shown in **Figure 1**.

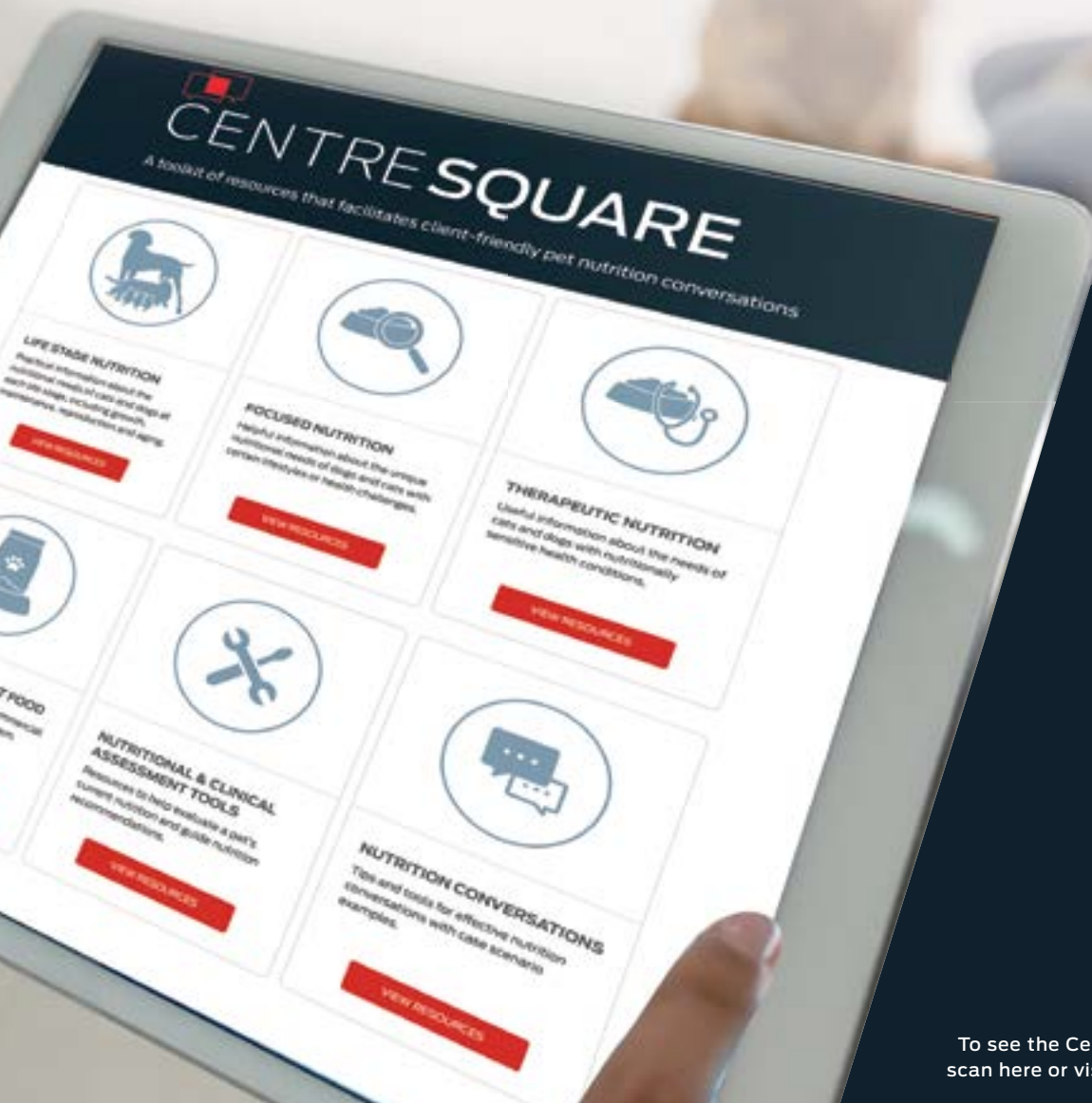
Figure 1. The steps involved in FMT.



References

1. Nishida, A., Inoue, R., Inatomi, O., Bamba, S., Naito, Y., & Andoh, A. (2018). Gut microbiota in the pathogenesis of inflammatory bowel disease. *Clinical Journal of Gastroenterology*, 11(1), 1-10. doi: 10.1007/s12328-017-0813-5
2. Pilla, R., & Suchodolski, J. S. (2019). The role of the canine gut microbiome and metabolome in health and gastrointestinal disease. *Frontiers in Veterinary Science*, 6, 498. doi: 10.3389/fvets.2019.00498
3. Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y. Y., Keilbaugh, S. A., Bewtra, M., Knights, D., Walters, W. A., Knight, R., Sinha, R., Gilroy, E., Gupta, K., Baldassano, R., Nessel, L., Li, H., Bushman, F. D., & Lewis, J. D. (2011). Linking long-term dietary patterns with gut microbial enterotypes. *Science*, 334(6052), 105-108. doi: 10.1126/science.1208344
4. Mandigers, P. J., Biourge, V., van den Ingh, T. S., Ankringa, N., & German, A. J. (2010). A randomized, open-label, positively-controlled field trial of a hydrolyzed protein diet in dogs with chronic small bowel enteropathy. *Journal of Veterinary Internal Medicine*, 24(6), 1350-1357. doi: 10.1111/j.1939-1676.2010.0632.x
5. Minkoff, N. Z., Aslam, S., Medina, M., Tanner-Smith, E. E., Zackular, J. P., Acra, S., Nicholson, M. R., & Imdad, A. (2023). Fecal microbiota transplantation for the treatment of recurrent *Clostridioides difficile* (*Clostridium difficile*). *The Cochrane Database of Systematic Reviews*, 4(4), CD013871. doi: 10.1002/14651858.CD013871.pub2
6. Pereira, G. Q., Gomes, L. A., Santos, I. S., Alfieri, A. F., Weese, J. S., & Costa, M. C. (2018). Fecal microbiota transplantation in puppies with canine parvovirus infection. *Journal of Veterinary Internal Medicine*, 32(2), 707-711. doi: 10.1111/jvim.15072
7. Toresson, L., Spillmann, T., Pilla, R., Ludvigsson, U., Hellgren, J., Olmedal, G., & Suchodolski, J. S. (2023). Clinical effects of faecal microbiota transplantation as adjunctive therapy in dogs with chronic enteropathies—A retrospective case series of 41 dogs. *Veterinary Sciences*, 10(4). doi: 10.3390/vetsci10040271
8. Chaitman, J., & Gaschen, F. (2021). Fecal microbiota transplantation in dogs. *Veterinary Clinics of North America: Small Animal Practice*, 51(1), 219-233. doi: 10.1016/j.cvsm.2020.09.012

YOUR CLIENTS HAVE QUESTIONS ABOUT PET NUTRITION.
CentreSquare™ makes it easy to provide credible answers backed by science.



CentreSquare offers a free online toolkit of resources to facilitate client-friendly pet nutrition conversations.

- Search a broad range of topics, including well-pet nutrition, brain health, gut health and more.
- Stay current on the most up-to-date scientific information.
- Easy-to-use tools and key messages written in language your clients can understand.
- Whether you have 5 minutes or 30 minutes you will find something helpful and relevant on CentreSquare.



To see the CentreSquare tools and topics in action, scan here or visit PurinaInstitute.com/CentreSquare.

SIGN UP FOR SCIENTIFIC COMMUNICATIONS AND RECEIVE A FREE E-BOOK

When you register for scientific communications from the Purina Institute, you will be among the first to receive:

- Information about the latest discoveries in nutritional science.
- Free nutritional resources and guides to support your conversations with clients.
- Invitations to events and webinars.
- New content alerts.
- Newsletters to keep you informed.

[Visit PurinaInstitute.com/Sign-Up](http://PurinaInstitute.com/Sign-Up)

