

Digest

VOLUME 12
SYSTEMIC EFFECTS OF
THE GUT MICROBIOME

The Interaction of Gut and Behavioral Health

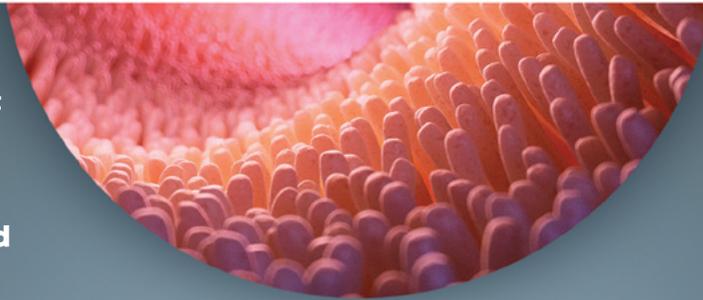
Julia Albright
MA, DVM, DACVB

The Gut-Skin Axis in Canine Atopic Dermatitis: Fact or Fiction?

Ana Rostaher
BVMS, PD, DECV, MRCVS

The Role of the Gut Microbiome in Chronic Kidney Disease

Jessica M. Quimby
DVM, PhD, DACVIM



The interaction of gut and behavioral health

Julia Albright, MA, DVM, DACVB

University of Tennessee, Knoxville, Tennessee, USA

Growing evidence demonstrates that bidirectional gut-brain communication regulates not only basic GI functions like digestion and elimination, but also higher-order processes including emotion, cognition, and behavior. The gut microbiome is an important intermediary of the gut-brain interaction due to its influence on host enteric, immune, neural, endocrine, and metabolic pathways. Microbiome-gut-brain axis (MGBA) activity provides a framework to explain the correlation between gut and behavioral health.¹

Gut microbial metabolites are principal factors in MGBA communication. For example, short-chain fatty acids (SCFAs), such as butyrate, are products of bacterial fiber fermentation and provide significant local and systemic anti-inflammatory effects.² Gut microbiota can also regulate the production of behaviorally relevant neurotransmitters (e.g., serotonin, gamma-aminobutyric acid (GABA), and catecholamines). Although metabolites and other neuroactive compounds may diffuse from the gut to act directly on the central nervous system, evidence suggests regulation of vagus nerve activity is the primary pathway for microbiome-CNS communication.³

Pathologic disruption of the MGBA

Psychological stress acts as a key risk factor for both GI and neurobehavioral disorders by initially triggering autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis activation. Acute stressors stimulate norepinephrine, corticotropin-releasing factor (CRF), and glucocorticoid release, transiently enhancing mental focus, energy metabolism, and immune function, including the inflammatory response. Under healthy conditions, cortisol provides negative feedback to resolve inflammation and initiate repair processes. However chronic or early-life stress can induce glucocorticoid receptor resistance and disinhibition of inflammation. These conditions also contribute to dysbiosis, or a shift in gut microbiota populations, resulting in reduced species diversity, lower abundance of anti-inflammatory bacteria (e.g., SCFA-producing *Faecalibacterium* species) and increases in species with pro-inflammatory effects. Pro-inflammatory cytokines act locally to further damage the intestinal barrier, dysregulate gut motility, and worsen dysbiosis. Chronic inflammation creates vagal

Of Note

- The microbiome-gut-brain axis (MGBA) involves complex interactions among the gut microbiota and host enteric, immune, neurologic, endocrine, and metabolic pathways.
- Psychologic stress and physical disease can create dysbiosis, inflammation, and disruption of the MGBA.
- Treatment approaches should address behavioral and GI signs for the best response.

withdrawal, allowing disinhibition of sympathetic and HPA activity.

Clinical signs

This persistent cycle of inflammation, dysbiosis, gut permeability, and vagal inhibition contributes to signs of gastroenteropathy, neuroinflammation, hypervigilance, enhanced fear responses, and mood/cognitive deficits.⁴ The co-occurrence of GI and behavioral disorders is common. People with anxiety disorders and depression report more GI symptoms than healthy controls, while those with chronic GI disorders, especially irritable bowel syndrome (IBS), have higher depression and anxiety rates.⁵

Other behavioral signs of GI disease include changes in an animal's elimination frequency or location (e.g., housesoiling), appetite alterations, and excessive licking (**Table 1**). GI disturbance should be strongly considered in dogs exhibiting air-licking or surface-licking behaviors, as some studies have shown most of these dogs have GI abnormalities on diagnostic imaging or histology.⁶

Pain from any GI location can contribute to a myriad of behavioral changes. Self-protective aggression may occur if an animal experiences or anticipates pain from a physical interaction. Pain from any etiology heightens anxiety levels and may manifest as stress-

Table 1. Behavioral signs of GI disease

Common signs of GI disease	Possible signs of GI disease
Elimination frequency or location changes	Destructive behavior
Appetite changes	Aggression
Pica	Nighttime waking
Excessive licking	Worsening separation or noise-related distress

displacement behaviors (e.g., destruction, repetitive behaviors) or intensify pre-existing behavioral concerns such as resource guarding or separation-related problems, given that painful and anxious patients can demonstrate reduced tolerance for stressors.⁷

Treatment approaches

A biopsychosocial treatment model addressing both GI and emotional issues provides optimal outcomes. Retrospective studies show that dogs with comorbid GI and behavioral signs demonstrated greater improvement when receiving comprehensive treatment compared to single-system focused therapy.⁸ A behavioral treatment plan typically includes addressing underlying morbidities, such as pain; ensuring the patient has underlying species-specific needs met (e.g., sufficient outlets for natural behavior); and formation of new emotional and behavioral responses to specific triggers of undesirable behaviors. Psychoactive medications can improve mood, resilience to stressors, and learning. Antidepressants are a common component of behavioral disorder management and may work partly through inflammatory regulation. They also have antimicrobial properties, which may reduce dysbiosis but potentially affect microbiota richness.⁹ Other therapies targeting the gut microbiome are gaining attention. Probiotics and “psychobiotics” (bacteria conferring neurobehavioral benefits) show promise, particularly those containing *Lactobacillus* and *Bifidobacterium* species. Limited veterinary studies suggest these may reduce fear responses and improve stress-related behaviors.¹⁰ Dietary fiber and other active anti-inflammatory compounds (polyunsaturated fatty acids [PUFAs], butyrate) have been associated with a healthy gut microbiome and improved psychological states.

References

1. Cryan, J. F., O’Riordan, K. J., Cowan, C. S. M., et al. (2019). The microbiota-gut-brain axis. *Physiological Reviews*, 99(4), 1877-2013. doi: 10.1152/physrev.00018.2018
2. Dalile, B., Van Oudenhove, L., Vervliet, B., & Verbeke, K. (2019). The role of short-chain fatty acids in microbiota-gut-brain communication. *Nature Reviews Gastroenterology & Hepatology*, 16(8), 461-478. doi: 10.1038/s41575-019-0157-3
3. Bonaz, B., Bazin, T., & Pellissier, S. (2018). The vagus nerve at the interface of the microbiota-gut-brain axis. *Frontiers in Neuroscience*, 12, 49. doi: 10.3389/fnins.2018.00049
4. Leigh, S. J., Uhlig, F., Wilmes, L., et al. (2023). The impact of acute and chronic stress on gastrointestinal physiology and function: A microbiota-gut-brain axis perspective. *The Journal of Physiology*, 601(20), 4491-4538. doi: 10.1113/jp281951
5. Keefer, L., Ballou, S. K., Drossman, D. A., et al. (2022). A Rome working team report on brain-gut behavior therapies for disorders of gut-brain interaction. *Gastroenterology*, 162(1), 300-315. doi: 10.1053/j.gastro.2021.09.015
6. Frank, D., Bélanger, M. C., Bécuwe-Bonnet, V., & Parent, J. (2012). Prospective medical evaluation of 7 dogs presented with fly biting. *The Canadian Veterinary Journal = La revue vétérinaire canadienne*, 53(12), 1279-1284.
7. Mills, D. S., Demontigny-Bédard, I., Gruen, M., et al. (2020). Pain and problem behavior in cats and dogs. *Animals*, 10(2), 318. doi: 10.3390/ani10020318
8. Jennings, R., Lilly, M., Bohland, K., et al. (2025). Concurrent management of behavioral and gastrointestinal disorders in dogs with early-life trauma improves clinical outcomes. 2025 ACVIM Forum Research Abstract Program. *Journal of Veterinary Internal Medicine*, 39(6), e70258, abstract GI19. doi: 10.1111/jvim.70258
9. Macedo, D., Filho, A. J. M. C., de Sousa, C. N. S., et al. (2017). Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. *Journal of Affective Disorders*, 208, 22-32. doi: 10.1016/j.jad.2016.09.012
10. McGowan, R. T. S., Barnett, H. R., Czarnecki-Maulden, G., et al. (2018, July 12). Tapping into those ‘gut feelings’: Impact of BL999 (*Bifidobacterium longum*) on anxiety in dogs. *Proceedings ACVB Veterinary Behavior Symposium*. Denver, CO, United States.

The gut-skin axis in canine atopic dermatitis: Fact or fiction?

Ana Rostaher, BVMS, PD, DECVD, MRCVS

University of Glasgow, Glasgow, UK

Atopic dermatitis (AD) is a prevalent chronic inflammatory skin condition characterized by its lifelong nature, resistance to therapy, and significant challenges for both veterinarians and pet owners. The condition significantly impacts the quality of life for both dogs and their owners, creating a cycle of stress and emotional strain.

Atopic dermatitis can only be diagnosed through clinical evaluation, which involves assessing the patient's signalment and clinical signs. This process must be followed by the exclusion of differential diagnoses, including sarcoptic mange, infections, hormonal disorders, sebaceous adenitis, and lymphoma. Elimination diet trials and allergen testing are only utilized to identify the triggers such as food, house dust mites, pollens or fungi/yeast.

Historically, canine AD was primarily associated with IgE antibodies to environmental allergens. Today it is accepted as a hereditary, typically pruritic, and predominantly T cell-driven inflammatory skin disease involving an interplay between skin barrier abnormalities, allergen sensitization, and microbial dysbiosis.¹

Atopic dermatitis is characterized by the involvement of various immune cells, including Th1, Th2, Th22, Th17, and T regulatory cells, as well as multiple cytokines, which are critical in the itch pathways (e.g., IL-4, IL-6, IL-13, IL-17, IL-31, IL-33).¹

The skin barrier can be compared to a well-constructed wall made of bricks (proteins such as keratins and filaggrins along with adhesion molecules) and mortar (lipids such as ceramides) and is compromised in AD. Recent studies have demonstrated that inflammation is the primary driver of barrier disruptions.²

Atopic dermatitis, dysbiosis, and the gut-skin axis

The hygiene and biodiversity hypotheses propose an inverse relationship between microbial exposure and the prevalence of immune-mediated diseases, highlighting the critical role of a diverse microbiome in the development and “training” of the host's immune system during early life (the early window

Of Note

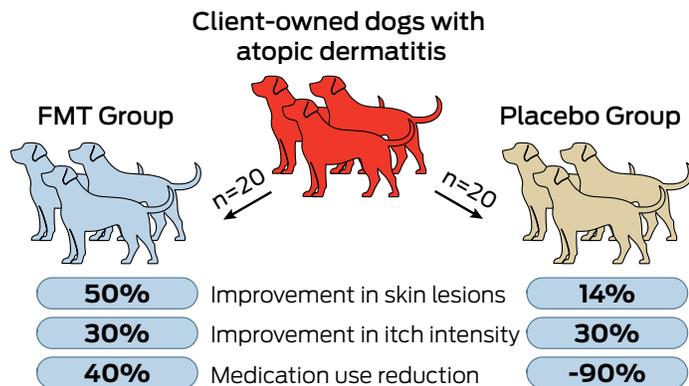
- The diagnosis of atopic dermatitis (AD) is strictly clinical; allergy tests are intended to identify specific triggers rather than the disease itself.
- Key components of the gut-skin axis include short-chain fatty acids, tryptophan, and pathogen-associated molecular patterns that interact with toll-like receptors.
- AD is a multifactorial condition that requires a multimodal approach, addressing not only immune and barrier dysfunction but also the role of the microbiome.

of opportunity). Furthermore, skin infections are frequently associated with exacerbations of AD. Recent technological advancements have facilitated a more comprehensive investigation of the skin and gut microbiomes and demonstrated that atopic dogs exhibit dysbiosis, with *Staphylococcus pseudintermedius* and *Malassezia* identified as key species associated with this microbial imbalance.³ However, findings from a birth cohort study involving West Highland White Terrier (WHWT) dogs suggest that the skin microbiota at the age of 3 months may not serve as the primary driver of AD development in this breed.⁴ These insights have prompted further research into the significance of gut microbiota, which has been shown to differ between allergic and healthy dogs.⁵

Currently, there is a significant gap in our understanding of the gut-skin axis in canine AD. However, its existence has been demonstrated through basic scientific research in other species.⁶ Three primary mechanisms have been identified as key components of the gut-skin axis:

1. **Short-chain fatty acids (SCFAs)** produced by the gut microbiota are transported across the intestinal

Figure 1. Use of FMT in dogs with atopic dermatitis. FMT is one way to modulate the microbiome.



wall, where they bind to T cells. This interaction reprograms naïve T cells to differentiate into regulatory T cells (Tregs), which promote immune tolerance. Additionally, SCFAs can circulate to the skin via the bloodstream or lymphatic system, where they interact with keratinocytes and immune cells to enhance immune function and improve skin barrier integrity.

- Tryptophan metabolites** generated by lactobacilli and bifidobacteria migrate to the skin, where they modulate cellular responses to reduce the production of inflammatory molecules and improve the skin barrier.
- Antigenic products** (pathogen-associated molecular patterns), such as endotoxins, influence the immune system to favor the development of Tregs and Th1 cells while suppressing inflammatory Th2 cells. This regulatory effect occurs in both the gut and the skin.

Interventions targeting the gut microbiome in canine atopic dermatitis

Microbiome-centric AD approaches include pre-, pro-, syn-, and/or postbiotics, leading to some improvements in pruritus and skin lesions and steroid-sparing effects. Fecal microbiota transplant (FMT) is one way to positively manipulate the gut microbiota, as shown in human AD patients.⁷ A recent randomized placebo-controlled study evaluated the effects of lyophilized FMT as enema and oral capsules in 40 client-owned dogs with AD (Felton V et al., manuscript in preparation). The FMT treated dogs showed significantly improved skin lesions, required significantly fewer symptomatic medications, and had improvement in life-quality scores after 3 months of treatment (**Figure 1**).

References

- Eisenschenk, M. C., Hensel, P., Saridomichelakis, M. N., et al. (2024). Introduction to the ICADA 2023 canine atopic dermatitis pathogenesis review articles and updated definition. *Veterinary Dermatology*, 35(1), 3-4. doi: 10.1111/vde.13183
- Combarros, D., Brahmi, R., Musaeffendic, E., et al. (2024). Reconstructed epidermis produced with atopic dog keratinocytes only exhibit skin barrier defects after the addition of proinflammatory and allergic cytokines. *JID Innovations*, 5(2), 100330. doi: 10.1016/j.xjidi.2024.100330
- Chermprapai, S., Ederveen, T. H. A., Broere, F., et al. (2019). The bacterial and fungal microbiome of the skin of healthy dogs and dogs with atopic dermatitis and the impact of topical antimicrobial therapy, an exploratory study. *Veterinary Microbiology*, 229, 90-99. doi: 10.1016/j.vetmic.2018.12.022
- Rodriguez-Campos, S., Rostaher, A., Zwickl, L., et al. (2020). Impact of the early-life skin microbiota on the development of canine atopic dermatitis in a high-risk breed birth cohort. *Scientific Reports*, 10(1), 1044. doi: 10.1038/s41598-020-57798-x
- Rostaher, A., Morsy, Y., Favrot, C., et al. (2022). Comparison of the gut microbiome between atopic and healthy dogs-Preliminary data. *Animals*, 12(18), 2377. doi: 10.3390/ani12182377
- Rios-Carlos, M., Cervantes-García, D., Córdova-Dávalos, L. E., et al. (2024). Unraveling the gut-skin axis in atopic dermatitis: Exploiting insights for therapeutic strategies. *Gut Microbes*, 16(1), 2430420. doi: 10.1080/19490976.2024.2430420
- Mashiah, J., Karady, T., Fliss-Isakov, N., et al. (2022). Clinical efficacy of fecal microbial transplantation treatment in adults with moderate-to-severe atopic dermatitis. *Immunity, Inflammation and Disease*, 10(3), e570. doi: 10.1002/iid3.570

The role of the gut microbiome in chronic kidney disease

Jessica M. Quimby, DVM, PhD, DACVIM

The Ohio State University, Columbus, Ohio, USA

Chronic kidney disease (CKD) is one of the most common and challenging conditions in cats, particularly in older populations. Traditionally, management has centered on dietary modification and symptomatic treatment of sequelae such as hypertension and anemia. However, recent research has illuminated the importance of the gut-kidney axis—the bidirectional relationship between intestinal microbiota and renal function—in the pathogenesis and progression of CKD.¹ This emerging perspective positions the gut microbiome not merely as a bystander but as an active contributor to disease morbidity, offering new therapeutic targets for feline patients.

Gut dysbiosis in feline CKD

The intestinal microbiome is a diverse ecosystem of trillions of microorganisms that support host health through nutrient assimilation, immune regulation, epithelial barrier maintenance, and production of metabolites. In CKD, this balance is disrupted, leading to dysbiosis—an altered microbial community with reduced diversity and functional capacity.²

Studies in cats with CKD (IRIS stages 2–4) have documented decreased fecal microbial richness and diversity compared to healthy cats.² This dysbiosis mirrors findings in human CKD, where uremia shifts the microbiota toward reduced abundance of beneficial short chain fatty acid (SCFA)-producing bacteria and increased prevalence of taxa associated with proteolytic metabolism.³ These alterations may compromise intestinal barrier integrity, promote systemic inflammation, and facilitate the accumulation of gut-derived toxins.

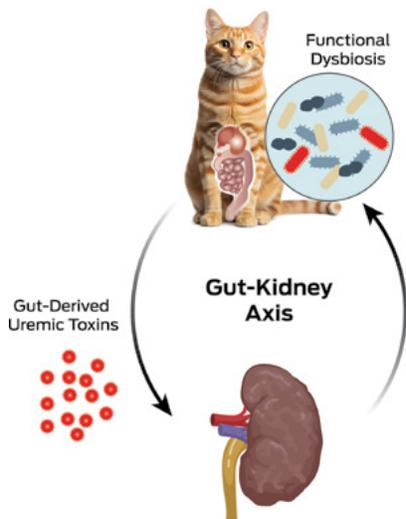
Uremic toxins and their impact

A central mechanism linking dysbiosis to renal dysfunction is the production of uremic toxins. Over 100 such compounds have been identified, many originating from microbial metabolism of dietary amino acids in the colon. Of particular relevance in cats are indoxyl sulfate (IS) and p-cresol sulfate (pCS), protein-bound toxins that accumulate in circulation as glomerular filtration declines.

Of Note

- **Gut dysbiosis in CKD:** Cats with CKD show reduced microbial diversity and richness, with shifts toward proteolytic bacteria that promote uremic toxin production, systemic inflammation, and intestinal barrier dysfunction.
- **Indoxyl sulfate as a biomarker:** Among gut-derived toxins, indoxyl sulfate (IS) consistently accumulates in cats with CKD and correlates with disease progression, making it a central focus for therapeutic intervention.
- **Therapeutic opportunities via the microbiome:** Strategies such as protein-modified but amino acid-fortified diets, soluble fiber supplementation, carbon-based adsorbents, and management of constipation offer promising ways to reduce toxin burden and improve outcomes in feline CKD.

Indole, derived from tryptophan metabolism, is converted in the liver to IS, while p-cresol from tyrosine and phenylalanine metabolism is sulfonated to pCS. These toxins exert deleterious effects including endothelial dysfunction, immune impairment, systemic inflammation, and renal fibrosis.^{1,2} In feline CKD, IS has been consistently shown to accumulate in serum, correlating with disease progression.⁴ Although pCS levels do not always differ significantly between healthy and CKD cats, the highest concentrations are observed in affected individuals. Metabolomic studies further confirm abnormal toxin profiles in CKD cats, highlighting the gut microbiome's role in driving systemic toxicity.¹

Figure 1. Gut-kidney connection

Fatty acid dysmetabolism

Beyond uremic toxins, CKD disrupts other microbial metabolites. Short chain fatty acids such as acetate, propionate, and butyrate are normally produced by saccharolytic fermentation of dietary fibers and confer anti-inflammatory, barrier-protective, and metabolic benefits. In cats with CKD, SCFA levels appear unchanged, but concentrations of branched-chain fatty acids (BCFAs)—products of protein fermentation—are elevated, especially in advanced stages.⁵ BCFAs are considered deleterious, promoting inflammation and reduced motility, and their increase reflects excessive colonic protein fermentation.

Constipation and the gut-kidney axis

Constipation is a frequent gastrointestinal manifestation in feline CKD, particularly in advanced stages. It arises from chronic dehydration, electrolyte disturbances, and altered motility. Importantly, constipation prolongs colonic transit, allowing more time for microbial conversion of amino acids into uremic toxin precursors (**Figure 1**). Human studies show higher serum pCS and indole acetic acid in constipated CKD patients, and similar mechanisms are likely operative in cats.

Therapeutic strategies targeting the microbiome

Recognizing the gut microbiome's role in CKD opens new avenues for intervention:

- **Dietary Management:** Cats are obligate carnivores, so diets must balance protein modification to reduce toxins with maintenance of lean body mass. Enhanced amino acid supplementation, particularly essential amino acids, has been shown

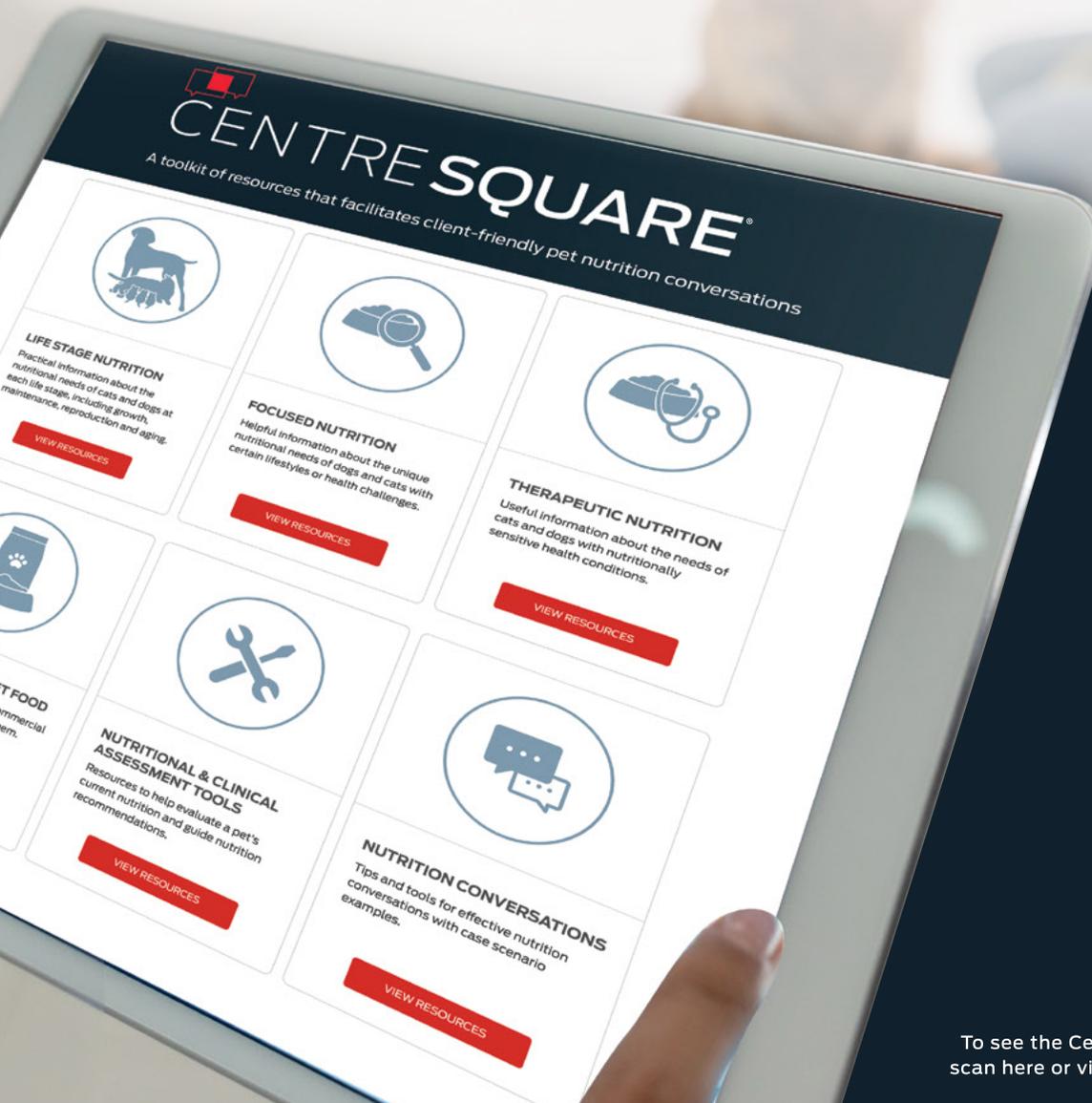
to preserve muscle mass and weight in CKD cats despite modified protein intake.⁶ Increasing soluble fiber also decreases circulating uremic toxins by promoting saccharolytic fermentation.

- **Adsorbents:** Carbon-based adsorbents bind indole and p-cresol precursors in the intestinal tract, reducing systemic IS concentrations in cats with CKD. These agents represent a promising adjunct to dietary therapy, though long-term outcomes remain under investigation.
- **Constipation Management:** Addressing constipation through diet, hydration, electrolyte correction, stool softeners, or promotility agents may not only improve quality of life but also reduce toxin accumulation.

References

1. Summers, S., & Quimby, J. (2024). Insights into the gut-kidney axis and implications for chronic kidney disease management in cats and dogs. *The Veterinary Journal*, 306, 106181. doi: 10.1016/j.tvjl.2024.106181
2. Summers, S. C., Quimby, J. M., Isaiah, A., et al. (2019). The fecal microbiome and serum concentrations of indoxyl sulfate and p-cresol sulfate in cats with chronic kidney disease. *Journal of Veterinary Internal Medicine*, 33(2), 662-669. doi: 10.1111/jvim.15389
3. Suliman, I. L., Panculescu, F. G., Fasie, D., et al. (2025). Gut microbiome in patients with chronic kidney disease stages 4 and 5: A systematic literature review. *International Journal of Molecular Sciences*, 26(21), 10706. doi: 10.3390/ijms262110706
4. Chen, C. N., Chou, C. C., Tsai, P. S. J., & Lee, Y. J. (2018). Plasma indoxyl sulfate concentration predicts progression of chronic kidney disease in dogs and cats. *The Veterinary Journal*, 232, 33-39. doi: 10.1016/j.tvjl.2017.12.011
5. Summers, S., Quimby, J. M., Phillips, R. K., et al. (2020). Preliminary evaluation of fecal fatty acid concentrations in cats with chronic kidney disease and correlation with indoxyl sulfate and p-cresol sulfate. *Journal of Veterinary Internal Medicine*, 34(1), 206-215. doi: 10.1111/jvim.15634
6. Hall, J. A., Fritsch, D. A., Jewell, D. E., et al. (2019). Cats with IRIS stage 1 and 2 chronic kidney disease maintain body weight and lean muscle mass when fed food having increased caloric density, and enhanced concentrations of carnitine and essential amino acids. *Veterinary Record*, 184(6), 190. doi: 10.1136/vr.104865

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

