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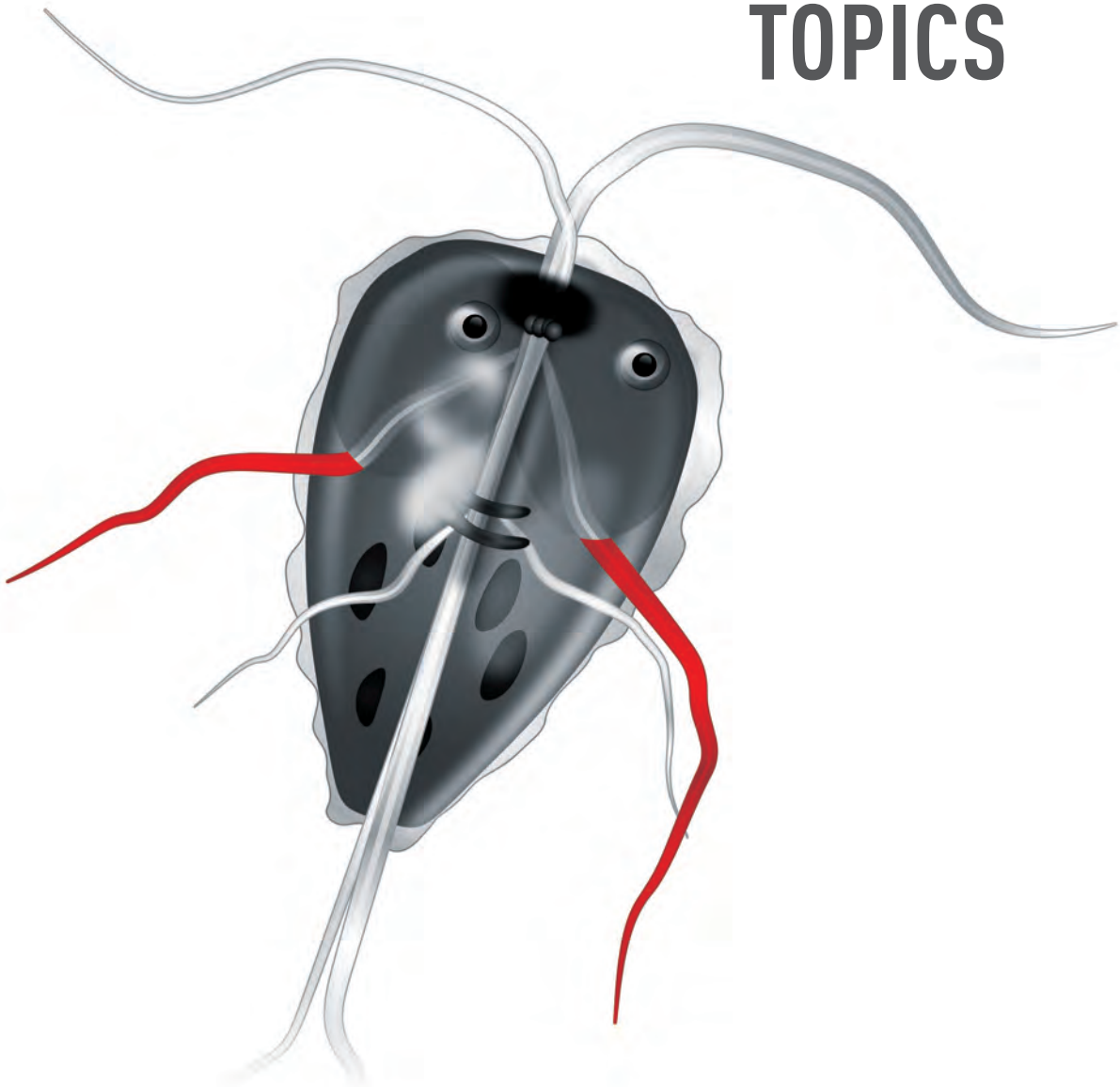

Feline exocrine pancreatic insufficiency – Treating constipation in cats – The feline gut-kidney axis: food for thought – Canine protein-losing enteropathy: an update – Giardiasis infection in dogs – Atypical canine hypoadrenocorticism – Fecal microbiota transplantation for GI disorders

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WHAT GOES AROUND COMES AROUND

"A work of the divine, (it) receives all the nutriment and subjects the food to its first elaboration, without which it would be useless and of no benefit whatever to the animal." **– Galen, 2nd Century BC**

The above quote, from probably the foremost physician of ancient times, refers to the stomach, and seems to combine both fact and fiction; there is no debate that without the stomach's actions, any nutritional intake would be useless, but to accord it as a holy creation (and apparently in isolation from all other bodily parts) may seem somewhat fanciful. Yet Galen regarded the stomach as an animate being: it could sense its own emptiness (and generate a feeling of hunger), break up food, and judiciously separate and utilize the dietary nutrients. But his idea that it was of divine conception was dismissed as knowledge grew, and medieval anatomists formed a more prosaic view. They recognized the importance of digestion, and agreed that if gastrointestinal function was impaired, all other body functions could be affected, but the stomach was now seen in a more passive light; they actually suggested it was the most unspiritual of the body's organs, possibly due to its aesthetically unappealing products. Thus, the perception shifted from the notion that the stomach was an active, almost intelligent entity to the idea that it – and indeed the entire gastrointestinal tract – was a natural but rather disreputable part of the body.

Yet just as many ideas are at first grasped eagerly, then dismissed before becoming popular again, the concept of the stomach as an animate object has almost returned. Some medical experts now refer to the organ as our "second brain" – and certainly there are strong neural, hormonal and immune-mediated links between the two; emotions such as excitement or nervousness can cause an all-too-familiar churning in the stomach, and gut disorders can lead to mental anxiety and stress. This issue of *Veterinary Focus* can be seen to extrapolate on this view by demonstrating that many gastrointestinal conditions may have effects far beyond its anatomical boundaries. Unlike Galen, we will offer no divine insights, but trust that the articles in the pages ahead will deliver food for thought.

Ewan McNEILL
Editor-in-chief

In this issue of *Veterinary Focus*

FELINE EXOCRINE PANCREATIC INSUFFICIENCY

Feline exocrine pancreatic insufficiency is more common than generally realized; this article offers pointers for successful diagnosis and treatment of the condition.

KEY POINTS

1. Exocrine pancreatic insufficiency (EPI) should be considered in cats with weight loss and/or loose stools, although concurrent disease can result in other signs being present.
2. Serum feline trypsin like immunoreactivity (fTLI) is the gold-standard for the diagnosis of EPI in cats; other tests, such as amylase or lipase activity, or even histopathology, are less sensitive and specific.
3. The management of feline EPI is mainly based on pancreatic enzyme and cobalamin supplementation.
4. Cats that do not respond to appropriate treatment for EPI should be re-evaluated for other potential diagnoses or concurrent diseases, such as a chronic enteropathy.

Introduction

Exocrine pancreatic insufficiency (EPI) results from inadequate production of enzymes from the pancreatic acinar cells, leading to maldigestion, malabsorption and subsequent clinical signs, such as weight loss and diarrhea. Although EPI has previously been considered rare in the cat, it is now recognized that many cases escaped diagnosis in the past due to the lack of sensitive and specific diagnostic tests, low awareness for the disease, and its co-existence with other gastrointestinal (GI) conditions that cause similar clinical signs. Until recently, the literature on feline EPI was sparse, consisting of reports of confirmed or suspected EPI in 10 individual cats published between 1975 and 2009 (1-9), as well as two small case series that together encompassed a total of 36 affected cats (10,11). More recently, a large retrospective study that evaluated 150 cats with EPI has been published (12), and in 2021 a small multicenter retrospective study described the ultrasonographic and clinicopathologic findings in 22 cats with EPI (13).

Epidemiology

The true prevalence of feline EPI is unknown, and (as noted above) the condition has traditionally been regarded as being rare in the cat, with only a few published case reports. However, since the introduction of the feline trypsin-like immunoreactivity (fTLI) test in 1995 (14), considerably more cases have been diagnosed. In a recent study, the Gastrointestinal Laboratory's database at Texas A&M University was searched over an approximately 2-year period (2008-2010), and 1,094 of 46,529 serum samples (2.4%) from cats submitted for fTLI measurement had levels consistent with a diagnosis of EPI (12). Despite the fact that the population used in this study is skewed (because it reviewed cats that had GI signs and therefore a possible suspicion of EPI), it appears that EPI is a condition that is not uncommon in cats. It is uncertain if these figures reflect a true increase in prevalence, or are merely an indication that clinicians now have a greater awareness of the disease and better means for arriving at a diagnosis. Therefore, although its true prevalence is still to be determined, EPI should be suspected in cases with a compatible clinical picture.

Etiology and pathophysiology

No studies have specifically investigated the potential causes of feline EPI, although chronic pancreatitis leading to gradual and extensive destruction of the acinar cells has almost always been traditionally cited as the sole etiology. However, this idea was based on a small number of case reports (13,15), and although chronic pancreatitis is still believed to be the most common cause of feline EPI, other etiologies may also exist. Although not proven, the belief is that a prolonged time period is necessary for chronic inflammation to cause almost complete destruction of the exocrine pancreas; however, recent studies have noted that young cats can develop EPI, making chronic pancreatitis a less likely cause, especially in this age group (12). Other potential etiologies for EPI could include pancreatic

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acinar atrophy (reported in a small number of cases), *Eurytrema procyonis* infestation (a fluke found in parts of the USA, and again reported in a small number of cases), pancreatic hypoplasia or aplasia, and pressure atrophy due to pancreatic duct obstruction (1-9,13). Whilst isolated pancreatic lipase deficiency has recently been reported as a cause of canine EPI (with other pancreatic enzymes remaining within normal parameters) (16), this has not yet been reported in cats.

The exocrine pancreas is thought to have exceptional functional reserve, and clinical signs of EPI are believed to develop only when > 90% of the secretory capacity is lost (13). Regardless of the cause, insufficient production and secretion of pancreatic enzymes into the small intestine leads to maldigestion of nutrients. The large amount of undigested nutrients in the intestine may lead to osmotic diarrhea, while decreased absorption of nutrients causes weight loss.

Of major importance is the pathophysiologic association between pancreatic function and cobalamin absorption. A cobalamin-binding protein, intrinsic factor, facilitates cobalamin absorption in the ileum, but in contrast to dogs, where intrinsic factor is also produced in the stomach, in cats it is produced exclusively in the exocrine pancreas. EPI therefore leads to reduced production and secretion of intrinsic factor, resulting in decreased intestinal absorption of cobalamin, and hence hypocobalaminemia and cobalamin deficiency (17).

Where EPI is a result of chronic pancreatitis, destruction of the endocrine portion of the pancreas may lead to concurrent diabetes mellitus. Additionally, many cats with EPI may have concurrent pancreatic inflammation, a chronic enteropathy (typically inflammatory bowel disease and/or GI small cell lymphoma) and/or hepatic disease.

Signalment and clinical signs

There is no significant breed or sex predisposition for EPI (12); most affected cats are middle-aged or older, but the reported age range is from 3 months to 19 years (12). This underlines the fact that EPI should be considered in cats of any age.

The clinical signs of affected cats are nonspecific and are the same as those seen with many other more commonly diagnosed conditions

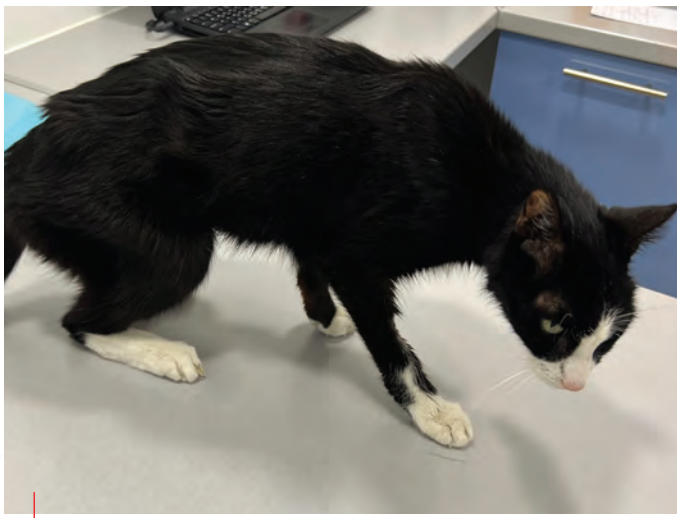

Figure 1. This cat was diagnosed with EPI and IBD; despite the low body condition score (2/9) and poor haircoat, the cat had a normal appetite.

(*e.g.*, hyperthyroidism, chronic enteropathies, pancreatitis, chronic kidney disease). Weight loss is by far the most common clinical sign **(Figure 1)** and was present in more than 90% of 150 cats in one study, and was the *only* clinical sign in 5% of the cases (12). Loose stools occurred in 62% of the cats, with 2/3 of them having occasional watery diarrhea **(Figures 2 and 3)**. This is in contrast with the typical EPI dog, where loose stools are reported in most cases (*e.g.*, 95% in one study (18)). Other clinical signs include poor haircoat (50%), polyphagia (42%), anorexia (42%), lethargy (40%), vomiting (19%), and a greasy haircoat (12). Some of the reported signs (*e.g.*, anorexia, depression, vomiting) are not typical of EPI and are likely associated with concurrent diseases (*e.g.*, chronic enteropathy, or inflammation of the liver and/or pancreas) than EPI *per se*. There is one report of a cat with EPI that developed D-lactic acidosis (presumably due to increased intestinal fermentation as a result of bacterial overgrowth) which presented with clinical signs of weakness, lethargy and ataxia (8), but this is considered to be rare.

It is clear that the clinical presentation of many cats with EPI differs from and is more confusing than the typical presentation seen in dogs. Clinical signs are more subtle and less specific in cats, and signs from comorbidities are more common. Therefore, EPI should be suspected in cases with unexplained

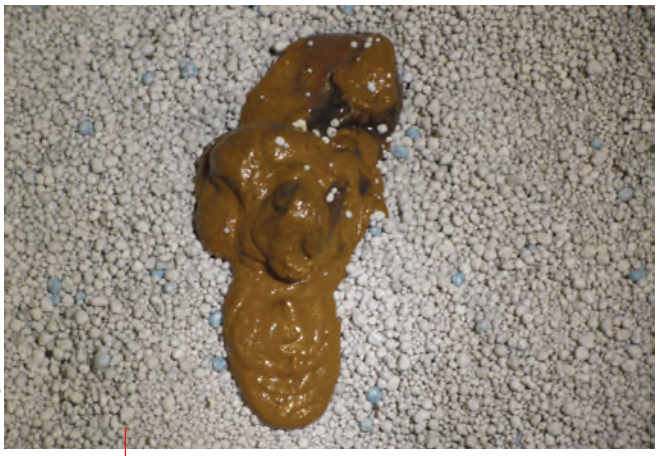

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Figure 2. Feces from the cat in **Figure 1**; note the loose, greasy appearance.

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Figure 3. Feces from a cat with EPI and gastrointestinal lymphoma. The chief complaint from the owner was watery diarrhea.

weight loss or anorexia, even when diarrhea or polyphagia are not present, or when vomiting or depression is the main presenting sign and where weight loss might be less noticeable.

Diagnosis

Exocrine pancreatic insufficiency will be initially suspected based on clinical presentation, but because various feline GI diseases can produce signs that overlap with those of EPI (and will often occur concurrently with EPI), every cat with a chronic GI disease or signs should ideally be tested for EPI. Cats with conditions such as IBD or GI small cell lymphoma that do not respond to appropriate treatment may have concurrent undiagnosed EPI. Therefore, any cat diagnosed with a chronic enteropathy or other GI problem that continues to lose weight or have loose stools despite appropriate treatment should have EPI included in the differential diagnosis list **(Figure 4)**.

Cats with EPI usually have normal or non-specific changes on complete blood count and serum biochemical profile, but again concurrent disease can result in various abnormalities (*e.g.*, anemia, increased liver enzymes, hyperglycemia, hypoalbuminemia), but none of these are specific for EPI. Serum cobalamin concentrations are decreased in most cats with EPI (80-100%) (12), but there is evidence that tissue cobalamin is depleted before hypocobalaminemia develops, and so even normocobalaminemic cats could still have cellular cobalamin deficiency (17). Although a common finding in cats with EPI, hypocobalaminemia is not specific for the condition, because it often occurs with other conditions such as IBD, GI lymphoma, and hyperthyroidism (17).

EPI is a functional disease that requires a definitive functional diagnosis (13). The gold standard is measurement of serum feline trypsin like immunoreactivity (fTLI) concentration (ideally performed on a fasting sample); this has 85-100% specificity, and although the sensitivity is unknown, it is considered to be high (10,12,13). TLI assays are species-specific, and therefore the tests developed and validated for dogs or humans are inappropriate for use in cats. fTLI assay measures the serum levels of trypsinogen produced by the exocrine pancreas, and the only validated assay currently available is provided by the Gastrointestinal Laboratory at Texas A&M University. In EPI, due to significant reduction in the functional capacity of the exocrine pancreas, subnormal serum fTLI concentrations are seen; the reference interval is 12-82 µg/L, and values ≤ 8 µg/L are considered diagnostic for EPI. Some cats with clinical GI signs have fTLI concentrations in the intermediate range (8-12 µg/L), and these cases should be retested a few weeks or months later to check whether values have normalized or have dropped into the diagnostic range for EPI. Because trypsinogen is excreted by the kidney, serum fTLI concentrations may be falsely raised in cats with decreased kidney function (19), which can hamper the diagnosis. In

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Figure 4. Any cat with chronic diarrhea that fails to respond to initial treatment should have EPI included in the list of possible differential diagnoses.

azotemic cats where EPI is suspected, re-evaluation of serum fTLI concentrations after improvement of the azotemia may be necessary.

Imaging modalities (radiography, ultrasound, computed tomography) are unhelpful for the diagnosis of EPI because they do not reflect the functional capacity of the pancreas. However, imaging can be useful for the diagnosis or exclusion of concurrent diseases, or conditions that can mimic EPI. In a recent multicenter study, it was shown that EPI causes minimal to no ultrasonographic changes in cats, although thin pancreatic parenchyma and pancreatic duct dilation were noted in some cases, which may raise the suspicion of EPI (13). Similarly, histopathology samples, or even a small pancreas noted on gross examination, are not indicative of a diagnosis of EPI, again because they do not reflect the functional capacity of the pancreas, although EPI may be suspected based on compatible findings.

Treatment

Enzyme replacement therapy

As in dogs, the mainstay of treatment in cats with EPI is pancreatic enzyme supplementation. There are several commercial products (dried extracts of porcine pancreas) available, but no studies have objectively evaluated the efficacy of the different products and preparations in cats. No difference was identified with regards to the specific product or type of pancreatic enzyme used for treatment of feline EPI in one study, and therefore all products may be equally effective (12). Although older reports supported the use of powdered products in dogs (with enteric-coated products being considered less effective), a recent prospective, placebo-controlled study showed that enteric-coated products may actually be more efficacious (20). Although raw pancreas from beef, pork, or game may also be used (13), these may contain potentially dangerous pathogens, and the author's preference is powdered or enteric-coated products.

Regardless of the product used, pancreatic enzymes should be administered with each meal. Enteric-coated products are ideally given immediately after a meal, while powdered products should be mixed thoroughly with food; preincubation with food does not appear to be necessary. Dosage is empirical, although initially 5 mL (1 teaspoon) of enzyme powder per meal is commonly used (13), and enteric-coated products can be started at 300 mg of pancreatin per day (divided in each meal); however, it is necessary to titrate the selected option for each cat based on response to treatment. This is expected to be quick, with resolution of loose stools usually seen within the first week, and once the clinical signs disappear a gradual reduction to the lowest effective dose should be attempted.

If raw pancreas is used, about 50 g per meal is appropriate as an initial dose, with subsequent adjustments as needed. Portions of raw pancreas can be kept frozen until use for several months without loss of efficacy, but owners must be aware that this option may be associated with a small risk of infectious and parasitic disease transmission (*e.g.*, bovine spongiform encephalitis, Aujeszky's disease, and parasites such as *Echinococcus* spp.) (13).

Due to their ability to break down protein and fat, pancreatic enzymes can cause irritation and ulcers if they have prolonged contact with the oral or esophageal mucosa. Therefore, powdered pancreatic enzymes should be mixed thoroughly with food, while administration of tablets or capsules should be followed by some food and water consumption to reduce the risk for stomatitis and esophagitis (13).

Cobalamin supplementation

Cobalamin supplementation is also of major importance and has been shown to favorably affect treatment response in both EPI cats and cats with chronic enteropathies, two conditions that often co-exist (12,21). Cobalamin deficiency can lead to intestinal inflammation and villus atrophy, disturbance of various biochemical pathways, and malabsorption of nutrients such as folate (17). In cats with GI disease and severe hypocobalaminemia, cobalamin supplementation led to significant increases in bodyweight and a lessening of vomiting and diarrhea (21). In a study of 150 cats with EPI, cobalamin supplementation favorably affected the response to treatment, even in cats with normal serum cobalamin concentrations (12). Finally, hypocobalaminemia associated with certain GI diseases in dogs has been shown to be a negative prognostic factor, and hypocobalaminemia in dogs with EPI is associated with shorter survival times (22,23).

The exact serum cobalamin concentration that indicates cellular cobalamin deficiency and a need for supplementation is currently

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unknown – hampered by the fact that normal serum cobalamin ranges vary greatly between laboratories. The use of markers of cobalamin deficiency – such as serum methylmalonic acid (MMA) – is more useful but not routinely available (24).

Whilst cats with hypocobalaminemia clearly require supplementation, some normocobalaminemic cats with EPI (especially those in the lower end of the reference range) may also benefit from a supplement, possibly because they have cellular cobalamin deficiency (12,17,24). Because virtually all cats with EPI either have or are prone to develop cobalamin deficiency due to lack of intrinsic factor, it might be recommended that all cases should be given a supplement, regardless of their serum cobalamin concentration.

Due to lack of intrinsic factor and the resulting impaired cobalamin absorption by the GI tract, parenteral cobalamin supplementation is typically recommended (13,17). Studies on the kinetics of parenteral cobalamin supplementation in cats with or without GI disease indicate that the serum half-life of cobalamin is 5 and 13 days respectively (25). Although protocols for supplementation have been published, the efficacy may be variable depending upon the underlying GI disease, the frequency of administration, and the formulation used (13,17), and no studies have specifically evaluated cobalamin supplementation protocols in cats with EPI. The author currently recommends either hydroxocobalamin (preferably) or cyanocobalamin at a total dose of 250 µg (500 µg for cats weighing > 5 kg) per cat, given either SC or IM every 2 weeks for 6-8 weeks. After this period cobalamin is administered at monthly intervals, with serum cobalamin re-evaluated every 3 months, and many cats will require long-term supplementation despite enzyme replacement treatment for EPI.

Recent evidence indicates that oral supplementation may be just as effective as parenteral administration for correcting cobalamin deficiency in cats with GI disease, but no studies have specifically evaluated the efficacy of this option in cats with EPI. Therefore, the author currently recommends parenteral cobalamin administration for all cats with EPI. If this is not possible, 250 µg of cobalamin per cat (either using a specific oral cobalamin preparation or the same injectable cobalamin preparations described above) may be given daily for 2-3 months, with subsequent re-evaluation of serum cobalamin concentrations.

Antibiotics and intestinal microbiota modification

Antibiotics have been used in some dogs as part of EPI treatment, supposedly to control concurrent intestinal dysbiosis, although no clear benefit for this practice has been established.

Antibiotic use was not found to affect treatment response in cats with EPI in one study (12), and since disturbances of the microbiota in feline EPI have not been fully described or confirmed, antibiotic use is of unknown benefit in these cases. Given that the above study did not show antibiotics had a positive effect on treatment response, and because they have been shown to cause long-term dysbiosis and antimicrobial resistance, the author currently does not recommend antibiotics for cats with EPI. In cases which do not respond to enzyme and cobalamin supplementation, further diagnostic investigation is required, as these cats may have concurrent small intestinal disease and antibiotic use is unlikely to improve the outcome. If antibiotic treatment is deemed necessary, a trial with metronidazole (15 mg/kg q12h PO) or tylosin (20 mg/kg, q12h PO) may be attempted, but this should be reserved as a last option.

Multi-strain, high-dose probiotics may be able to control intestinal dysbiosis and could be used if this is suspected, but again no studies are available. Finally, fecal microbiota transplantation (FMT) is gaining ground as a means of intestinal microbiota modification (and likely the most effective one) but studies in cats with EPI are lacking. FMT may also be attempted in cases where intestinal dysbiosis is suspected.

Dietary recommendations

No studies have evaluated the effect of different diets on the outcome of cats with EPI, but a good quality, high protein maintenance diet would seem appropriate in most cases, unless concurrent diseases are present that dictate the use of a specific clinical diet. Hypoallergenic or elimination diets are commonly used in cats with chronic enteropathies and these would also seem appropriate in cats with EPI, especially because of the likelihood of concurrent GI disease. In the past, low-fat diets have been recommended for the management of EPI (especially in dogs), but again no studies exist in cats.

Other treatments

Some clinicians recommend using a proton-pump inhibitor (*e.g.*, omeprazole or pantoprazole) concurrently with pancreatic enzyme replacement therapy to reduce gastric acidity and decrease enzyme inhibition in the stomach. However, the benefits of such treatment are unknown, and most cats seem to respond well without such intervention. However, it may be worthwhile giving a proton pump inhibitor to a cat that has not responded well to pancreatic enzyme and cobalamin supplementation to see if this improves matters.

Finally, there have been occasional reports of cats with EPI that presented with a coagulopathy that has responded to vitamin K supplementation (5). Although believed to be very rare, if a bleeding

condition is noted in an EPI cat, coagulation parameters should be measured, and vitamin K supplementation initiated if appropriate.

Prognosis

Overall, response to treatment is considered good in 60% of cats with EPI, and most cases that are treated appropriately typically have an excellent prognosis and a good quality of life (12). Only 13% of reported cases have had a poor response to treatment (12); the reasons for this are not clear. Lack of or partial response to treatment might be due to a lack of cobalamin administration, or the presence of inadequately managed concurrent diseases as previously mentioned. All cats that do not respond to appropriate treatment should be reevaluated for other possible diagnoses or significant concurrent disease.

CONCLUSION

Exocrine pancreatic insufficiency (EPI) in cats is likely more common than recognized in clinical practice, but is often missed because of non-specific clinical signs and limited availability of appropriate tests. Ideally, all cats with a chronic enteropathy, and especially those that do not respond to initial treatment, should be tested for EPI by measurement of feline-specific TLI. Cats with undiagnosed and untreated EPI as a concurrent component of other chronic GI conditions will likely have an inadequate response to treatment, while most cats diagnosed with EPI will have a good response to appropriate therapy.

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TREATING CONSTIPATION IN CATS

Is the constipated cat a simple "10-minute consultation"? Anything but, says Jonathan Lidbury, as he discusses a structured and careful approach to all such cases.

KEY POINTS

1. Constipation is common in the feline species, especially in older cats, obese cats, or those with chronic kidney disease; wherever possible, it is important to identify and treat the underlying cause(s) of the constipation.
2. Nutrition is an important part of management of constipated cats, and different types of dietary fiber may be beneficial.
3. Polyethylene glycol 3350 is a palatable, well tolerated and effective laxative in cats.
4. Subtotal colectomy to treat refractory cases of constipation is associated with long survival times and a high rate of owner satisfaction.

Introduction

"Constipation" is a commonly encountered problem in feline practice that can lead to significant morbidity, and can even be the reason some owners will opt for euthanasia of their pet, and it is firstly important to use the correct relevant definitions **(Box 1)** to aid accurate discussion and case management. There are many causes of constipation in cats, with idiopathic megacolon being the most common (1), and clinicians therefore need to be able to identify the etiology in order to initiate a patient-tailored management plan.

Etiopathogenesis

The causes of constipation can be classified mechanistically (see **Box 2**), although note that in any individual cat several of the listed mechanisms may simultaneously contribute to the problem. For example, a cat with constipation due to idiopathic megacolon may stop eating and drinking, consequently becoming dehydrated and hypokalemic, worsening the constipation. Although there are many potential causes, a review of published cases noted that 62% of cats with obstipation had idiopathic megacolon, 23% had pelvic canal stenosis, 6% had nerve injury, and 5% had Manx sacral spinal cord deformity (1). In a recent retrospective study, older cats, overweight cats, cats with chronic kidney disease, and those with a previous history of constipation were more likely to present to an emergency room for constipation (2).

By definition, the etiopathogenesis of idiopathic megacolon in cats is not fully understood. *Ex vivo* experiments using colonic tissue harvested from constipated cats has demonstrated generalized dysfunction of colonic smooth muscle, although it is not known if this was the initiating cause of constipation or a secondary effect (3). Additionally, histopathological assessment of the affected tissue did not reveal any abnormalities of the smooth muscle (longitudinal or circular) or myenteric plexus.

Box 1. Definitions (1).

Constipation	infrequent or difficult evacuation of feces (but does not necessarily mean that there is a permanent loss of function)
Obstipation	intractable constipation that has become refractory to management (associated with permanent loss of function)
Megacolon	abnormal dilation of the colon
Dilated megacolon	develops as an end-stage of idiopathic megacolon and implies permanent loss of colonic function and changes in structure
Hypertrophic megacolon	develops as a consequence of obstructive lesions and may be reversible if the obstruction is relieved in time (but can progress to dilated megacolon)

Note: these distinctions have important implications for patient management and prognostication.

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Clinical features

The signalment of constipated cats is very variable, as animals of either sex and any age or breed can develop this problem. In a review of published cases, the mean age was reported to be 5.8 years, with 70% of cats being male (although this gender bias has not been noted in the author's own experience), and commonly reported breeds included domestic shorthair (46%), domestic longhair (15%) and Siamese (12%) (1).

Affected cats are often observed to make multiple unsuccessful attempts to defecate **(Figure 1)**, and may vocalize while doing so. Sometimes they can pass small amounts of very firm feces, or they produce small amounts of liquid stool, or will have hematochezia (1). The latter two scenarios can lead to an owner believing that their cat's main problem is diarrhea. Constipation should also be differentiated from lower urinary tract disease, colitis, and anal sac disease, all of which can lead to apparent tenesmus and increased use of litter boxes. Conversely, any of the above signs of constipation can be easily missed in multi-cat households, so it is therefore important to be very careful when defining the patient's problems. With chronicity, vomiting, anorexia, or lethargy may occur, and if constipation is part of a multisystemic disease process (*e.g.*, dysautonomia) other systemic signs may be present. The owner also should be asked carefully about any medications/therapies that the cat has received, as some can lead to colonic hypomotility, dehydration, or iatrogenic hypothyroidism **(Box 2)**, as well as any recent environmental or behavioral changes.

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Figure 1. A constipated cat may be seen to make repeated visits to the litter tray, with prolonged attempts to pass feces.

Box 2. Causes of constipation in cats (1).

Physical obstruction (colon, rectum, or anus)	• luminal (*e.g.*, foreign bodies) • intramural (*e.g.*, masses of the colonic wall) • extraluminal (*e.g.*, displaced pelvic fractures, masses of other abdominal organs)
Neuromuscular dysfunction	• colonic smooth muscle disorders (*e.g.*, idiopathic megacolon) • spinal cord disease (*e.g.*, cauda equina syndrome, sacral spinal cord deformities [Manx cats], lumbosacral disease) • hypogastric or peripheral nerve disorders (*e.g.*, trauma, neoplasia, dysautonomia) • submucosal or myenteric plexus disease (*e.g.*, dysautonomia)
Systemic/ metabolic disease	• dehydration, chronic kidney disease, hypokalemia, hypercalcemia
Endocrine disease	• hypothyroidism (spontaneous or iatrogenic), nutritional hyperparathyroidism
Painful defecation	• anal sacculitis/anal sac abscessation, proctitis, bite wounds, degenerative joint disease
Pharmacological	• *e.g.*, opiates, cholinergic antagonists, diuretics
Environmental and behavioral	• soiled litter boxes, social interactions, inactivity, hospitalization, changes in environment

It is usually possible to transabdominally palpate impacted feces within the colon of constipated cats, but this can be challenging in severely obese or fractious patients. Affected cats may also show signs of nausea or dehydration. A neurological examination, including spinal palpation, and an ophthalmic examination should be performed to determine if constipation is part of a more widespread neuromuscular disorder (*e.g.*, dysautonomia, spinal cord disease). A careful rectal examination performed under sedation or anesthesia may reveal the presence of impacted feces, rectal masses, foreign bodies, displaced pelvic fractures, rectal strictures or anal sac disease. Occasionally, cats may develop perineal herniation as a result of prolonged fecal tenesmus.

Diagnostic testing

It is recommended to perform a complete blood count, chemistry panel and urinalysis in cats with recurrent or severe constipation. These usually do not lead to identification of an underlying cause, but can occasionally do so (*e.g.*, hypokalemia, hypercalcemia, dehydration, renal azotemia, or changes suggestive of hypothyroidism). If the cat's FeLV/FIV status is not already known, it should be determined.

Abdominal radiography should be performed for all constipated cats. This imaging modality allows the detection of impacted feces and assessment of the severity of impaction **(Figure 2)**. Luminal (*e.g.*, radiopaque foreign material) and extraluminal colonic obstruction (*e.g.*, pelvic canal stenosis due to a displaced fracture **(Figure 3)**) may also be appreciated. Obvious spinal cord lesions (*e.g.*, fractures or tumors) may also be apparent. Research has shown that the ratio of the maximal diameter of the colon to the length of the L5 vertebral body can help differentiate constipation from megacolon; a ratio < 1.28 indicates a normal colon, while a value of > 1.48 indicates megacolon (sensitivity 77%, specificity 85%) (4). Repeating abdominal radiographs after treatment also allows the clinician to assess the patient's response.

Further evaluation may be done as necessary. The clinician's first diagnostic aim should be to confirm the presence of constipation and to determine its chronicity and severity, and this can usually be achieved through a physical examination and radiography as described above. Given that idiopathic megacolon and pelvic canal stenosis account for about 85% of cases (1), an extensive diagnostic workup is not necessary for most constipated cats, but it is important not to miss a treatable underlying cause in an individual patient. Potential indications for further diagnostic testing include neurological deficits (*e.g.*, those associated with dysautonomia), palpable abdominal or recto-anal masses, radiographically detected abdominal/pelvic canal abnormalities, disproportionate dwarfism in young cats (consistent with congenital hypothyroidism), or other signs of systemic illness. Examples of additional tests that are sometimes needed include thyroid testing (*i.e.*, total T_4, free T_4, thyroid-stimulating hormone measurement) if hypothyroidism is a possibility, abdominal ultrasound if mural or extraluminal colonic masses are suspected, cross-sectional imaging if vertebral disease or intrapelvic masses are a concern, or colonoscopy to look for inflammatory lesions, recto-anal strictures or diverticula.

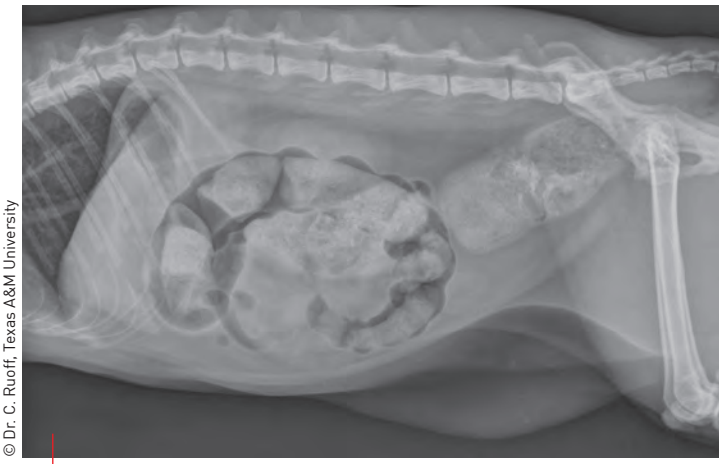

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Figure 2. Lateral abdominal radiography of a constipated cat, with the colon distended by dry feces. The maximal colon diameter to length of the L5 vertebral body ratio is 1.74 (> 1.48 indicates megacolon).

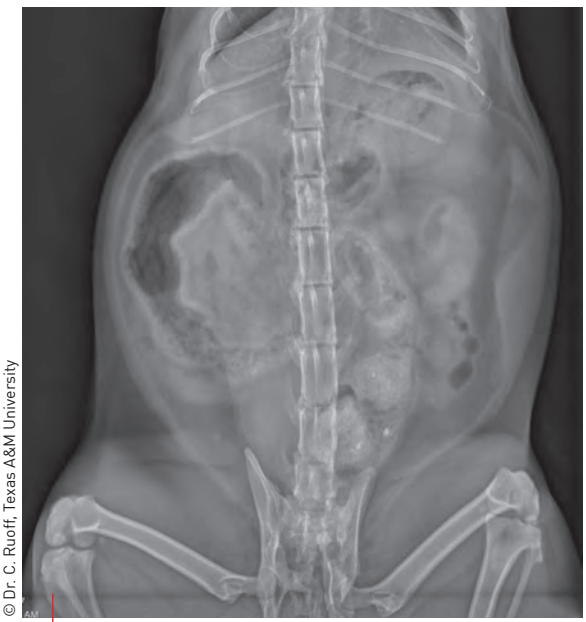

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Figure 3. Ventrodorsal abdominal radiograph of a constipated cat with a pelvic fracture. There is a large volume of heterogenous soft tissue opaque fecal material and gas throughout the colon, and moderate narrowing of the pelvic canal, with apparently healed fractures of the left ilium and the left and right pecten of the pubis.

Outpatient management

Nutrition

Initially, some mildly affected cats can be managed on an outpatient basis with dietary changes alone. Fiber supplementation is a commonly employed nutritional strategy in constipated cats, and there are various types of dietary fiber and fiber sources, each with different potential benefits. Fiber supplementation has shown to be beneficial in adult humans with chronic constipation (5), but supplementation with some types of fiber has the potential to worsen constipation. Fibers that are fermented by colonic bacteria lead to increased production of short-chain fatty acids, including butyrate which acts as an energy supply for colonocytes. Short-chain fatty acids also have anti-inflammatory properties and have been shown to stimulate longitudinal but not circular contractions of the canine and feline colon (6,7). Non-soluble,

non-fermentable fibers are bulk forming and potentially improve colonic motility by distending its wall, thereby stimulating contraction. These fibers have the potential disadvantage of reducing nutrient absorption and fecal water content, and the latter effect could potentially lead to worsened fecal impaction, especially in an already-dehydrated and obstipated patients, or in those that have a megacolon. Psyllium, a soluble but (mostly) non-fermentable fiber, leads to the formation of a gel **(Figure 4 and 5)** that provides lubrication and increases the frequency of defecation in humans with idiopathic constipation (with doses of 10 g/day and a duration > 4 weeks apparently optimal in human patients) (5).

In two field trials, a commercially available highly digestible moderately psyllium-supplemented dry extruded diet was shown to be palatable and allow the withdrawal of other medications in constipated cats (8). Note that neither trial was controlled, and so it was not confirmed that the improvement observed was due to the diet alone, therefore future randomized controlled clinical trials are needed. However, anecdotal experience with this diet is also positive, and it is the author's choice for managing constipation in most cats. Another option is to add unflavored psyllium husk (approximately 1-2 teaspoons/5-10 mL per meal) or other fiber sources to the cat's existing diet, but this can affect palatability.

An alternative nutritional strategy is to feed a highly digestible, low residue intestinal diet to reduce the volume of material reaching the colon. This strategy has been suggested to be particularly beneficial in cats with severe disease that cannot tolerate extra fecal volume. Gastrointestinal diets are also often supplemented with fermentable fiber.

Maintaining adequate hydration is crucial for successful treatment. Water (filtered/bottled if necessary) should be freely available in different shaped bowls or via a fountain to help ensure this, and feeding a canned (rather than dry) diet can also help.

Laxatives

In more severely affected cats, or those with recurrent bouts of constipation, it is often necessary to start medical therapy. There are a wide variety of different classes of laxatives available (*i.e.*, osmotic agents, bulk forming substances, emollients [stool softeners], or motility-stimulating [prokinetic] drugs). However, the author limits his use of laxatives in cats to the two osmotic agents discussed below.

The osmotic laxative agent polyethylene glycol (PEG)3350 is hydrophilic, binding water molecules to reduce the movement of water out of the colon, and consequently both softening and bulking its contents (9). Various forms of this agent without electrolytes are available over the counter in some countries for the treatment of constipation in humans. Metanalysis of clinical trials in adult and

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Figure 4. Milled flavored psyllium husk supplement for humans, which comes as a powder.

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Figure 5. Psyllium powder will absorb water to form a gel in the GI tract. Note that unflavored products are preferred for use in cats. Products containing xylitol are contraindicated.

pediatric human patients suggests that PEG3350 is more effective and better tolerated than lactulose (10-12) and this agent is the author's preference for treating cats with constipation because of its palatability and efficacy. A pilot study of PEG3350 in 6 healthy cats has demonstrated good palatability and stool softening, and no adverse effects were noted, although small non-clinically significant increases in serum potassium occurred in some cats (13). Therefore, rechecking serum electrolytes after initiation of therapy is recommended.

Lactulose is a non-absorbable disaccharide that is osmotically active, although it is fermented by colonic bacteria and can lead to bloating or flatulence in humans. This agent appears to be less palatable to cats than PEG3350 but it can also be effective.

The author recommends both products should be started at a low dose and then titrated to effect; PEG3350 can be given at an initial dose of 0.6-1.25 mL ($^1/_8$-$^1/_4$ tsp) of powder per cat q12H (mixed with food), whilst lactulose can be dosed at 0.5 mL ($^1/_{10}$ tsp)/kg q8-12H PO. It takes several days for either agent to have its full effect, and so dose escalation should be performed slowly. Overdosage of either agent can lead to diarrhea, dehydration, or electrolyte abnormalities.

Prokinetic drugs

In some cats prokinetic agents are also required; these are given as maintenance treatment once impacted fecal matter is no longer present in the colon. When available, the author's agent of choice is the serotonin (5-HT_4) receptor agonist cisapride at 0.5 mg/kg PO q12H. This drug has been shown to stimulate motility in *ex vivo* colonic tissue from cats with idiopathic megacolon (14), and anecdotally seems to be effective and well tolerated by constipated cats. It was withdrawn from the human market following reports of fatal cardiac arrhythmia (*torsades de pointes*) due to the drug's effects on other 5-HT receptor types present in the myocardium. This adverse effect has not been reported in feline patients, although one study did observe prolonged Q-T intervals in cats given 60 times the therapeutic dose for 7 days (15). Cisapride may be still sourced from accredited veterinary compounding pharmacies in many countries.

Tegaserod is another 5-HT_4 receptor agonist that has been shown to speed transit in the canine colon when given intravenously (16), although its effect in cats has not been described in the literature. Again, it was withdrawn from the US market because of cardiac safety concerns in humans, but was recently reintroduced under more selective labeling (17). Prucalopride is another, more specific, 5-HT_4 receptor agonist that has been shown to induce defecation in cats (18), but its use is off-label. The author has no personal experience using tegaserod or prucalopride and so cannot advocate their use. The histamine-2 receptor agonist ranitidine also has an anticholinesterase effect, and in one study (reported in the form of an abstract) has been shown to induce motility in feline colonic tissue *ex vivo* (19). However, efficacy has not yet been demonstrated *in vivo*.

Other strategies

Wherever possible, it is essential to address the underlying medical cause of constipation (*e.g.*, with thyroxine supplementation in hypothyroid cats). Interestingly, in a study of cats with pelvic fractures, of which 74% were surgically managed, constipation was an uncommon complication, occurring in only 8% of cases, and megacolon did not develop in any cats (19). Thus, surgery stabilization could be considered in a cat with a pelvic fracture that results in pelvic narrowing to avoid later development of megacolon.

Results of a pilot study suggested that a commercially available probiotic mixture may lead to improved signs and reduced colonic inflammation in cats with constipation (20), but further research is needed and it is not expected that all probiotics would have the same effect.

A variety of feline/pediatric enema products and suppositories of appropriate volumes for use in cats are available (*e.g.*, those containing dioctyl sodium sulfosuccinate and glycerin, or docusate sodium, PEG, and glycerin). However, the author does not typically advocate their use at home by clients due to the burden this places on the animal-human bond.

Finally, if environmental or behavioral factors are believed to have played a role in the development of constipation, these may also need to be addressed.

Inpatient management

More severely affected constipated cats require hospitalization. Dehydration is a contributing factor or a complication in many cases, and must be addressed for a successful outcome. Intravenous fluids (often initially balanced replacement crystalloid solutions) can be administered to restore/maintain adequate hydration and help correct any electrolyte abnormalities.

Warm water, physiological saline, or lactated Ringer's solution enemas (5-10 mL/kg) are usually well tolerated and are often helpful. If desired, a water-soluble lubricant can be added to these. A lubricated red rubber catheter is usually used to deliver the enema and must be advanced gently several centimeters into the colon, but this can be difficult with severe fecal impaction. Administration may need to be repeated several times with an appropriate interval (often 6-24H). Enema administration can lead to vomiting and subsequent aspiration of intestinal contents in cats, but the risk can be minimized by administering it under general anesthesia with an endotracheal tube in place. However, general anesthesia is not always possible or in the cat's best interests, in which case several small-volume enemas rather than a single high-volume enema should be administered. Pretreatment with the antiemetic maropitant (1 mg/kg IV) is advised before enema administration, and PEG3350 or lactulose can be given by mouth concurrently to cats that can tolerate oral medications. Note that phosphate-containing enemas are contraindicated in cats, as they can lead to potentially fatal hypernatremia, hyperphosphatemia or hypocalcemia.

Manual extraction of even severely impacted feces can be avoided in most cats by administering a PEG3350 solution (usually products which are used for pre-endoscopic colonic preparation in human patients) at a constant slow rate via an indwelling nasoesophageal tube. A study of 9 cats described using an administration rate of 6-10 mL/kg/H, with a median total dose of 80 mL/kg (range: 40-156 mL/kg) and reported a median time to significant defecation of 8 hours (range 5-24H) (21). Care must be taken to ensure proper placement of the nasoesophageal tube, including lateral radiographs of the cervical region and thorax, and the cat should be monitored carefully to avoid aspiration. It is also good practice to periodically check the cat's hydration status and serum electrolyte concentrations during hospitalization.

Occasionally, digital extraction of feces is required, but this should only be performed under general anesthesia with an endotracheal tube in place. First, warm water, physiological saline, or lactated Ringer's solution – again possibly mixed with a water-soluble lubricant – is given as an enema to rehydrate the feces. After allowing several minutes for rehydration to occur, manual extraction is attempted by gently using a finger to remove the feces while simultaneously moving more feces distally into the pelvic canal via caudal abdominal palpation. This cycle is repeated as necessary. The author does not use whelping forceps or other instruments during this process. Sometimes it is not possible to fully "deobstipate" a cat at the first attempt and the procedure needs to be repeated on a subsequent day; this is preferable to a single prolonged attempt. Possible complications include colonic trauma, colonic perforation, aspiration, and anesthetic-related problems. Some clinicians will administer pre-procedure antimicrobials (*e.g.*, metronidazole) because of the risk of bacterial translocation.

Surgical management

In cats where an underlying cause is not identified or cannot be adequately addressed and that fail to respond to rigorous medical management, subtotal colectomy may be the only remaining option. Whilst careful medical management will allow this major surgery to be avoided in many cats, it is also important not to wait until refractory patients are severely debilitated before recommending it. The specific protocol is, however, outwith the scope of this paper.

In a recent retrospective study of 151 cats undergoing subtotal colectomy, removal of the ileocolic junction was associated with less favorable outcomes than where it was preserved, and regardless cats often had diarrhea for several months after surgery. Encouragingly, the authors also found that subtotal colectomy was associated with long survival times and a high rate of owner satisfaction (22).

CONCLUSION

Constipation is a frequently encountered problem in small animal practice, and it is important to stress that it is not always easy to identify the underlying cause or to successfully treat the condition. Affected cats can develop significant morbidity over time, which can lead to an owner requesting euthanasia of their pet, so it is vital for the clinician to be proactive. Basic diagnostics will usually pinpoint if there is a primary cause, and the clinician can develop an appropriate management plan for each individual animal.

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THE FELINE GUT-KIDNEY AXIS: FOOD FOR THOUGHT

There is now strong evidence that there are significant links between the gut and the kidneys, and that gastrointestinal health may be a key consideration when treating kidney disease, as discussed in this article.

KEY POINTS

1. Interactions between the gut and kidney may have significant influences on the health of both organ systems, with subsequent clinical effects.
2. Cats with chronic kidney disease (CKD) have dysbiosis, with an altered composition of intestinal microbiota.
3. Uremic toxins accumulate even in the early stages of CKD; these have multiple deleterious systemic consequences and are associated with disease progression.
4. Targeting dysbiosis and accumulation of uremic toxins may be an important treatment strategy in feline CKD.

Introduction

A growing body of research supports the concept that there is significant connection in multiple species between the gut and the kidney (also known as the "gut-kidney axis") **(Figure 1)**, and that both systems have important influences upon the other, with potential significant clinical implications. Cats with chronic kidney disease (CKD) have dysbiosis, supporting the notion that the gut is a therapeutic target to potentially improve longevity and comorbidities. This article reviews the current understanding of the gut-kidney axis and strategies available to veterinarians to

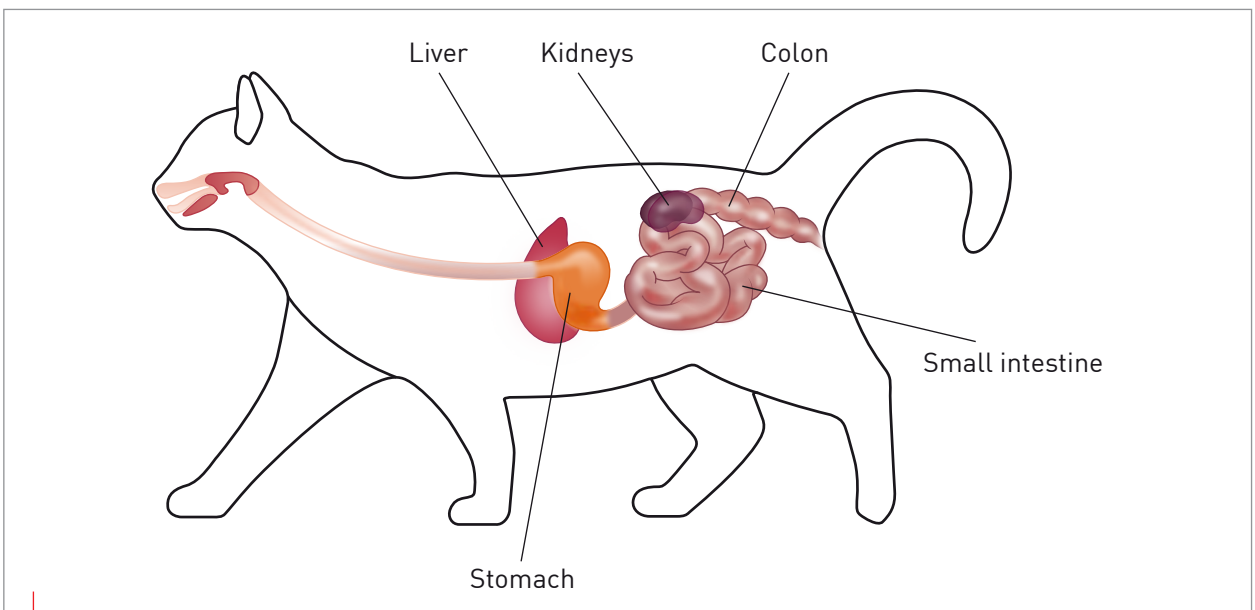

Figure 1. Feline gut-kidney axis. There is significant connection between the gut and the kidney, and it is thought that both systems have important influences upon the other, with potential significant clinical implications.

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potentially improve the health of the gut microbial community and thus reduce accumulation of harmful gut-derived uremic toxins.

The microbiome and dysbiosis

The intestinal microbiome is defined as the collection of microorganisms that consists primarily of bacteria. These microorganisms reside in the gastrointestinal tract and form an ecosystem that has complex interactions both with each other and the host. In cats, there are thousands of gut bacterial phylotypes, amounting to trillions of cells with an extensive functional capacity. This wide array of microorganisms plays an important role in maintaining host health via products of bacterial metabolism and by influencing gene expression in the gut. A healthy bacterial microbiota and communication between host and bacterial metabolites is vital for the development and maintenance of a healthy immune system, assimilation of nutrients from the diet, maintenance of the gut barrier, nutrient synthesis (*e.g.*, short-chain fatty acids, vitamin B12), and protection against invading enteric pathogens (1).

Dysbiosis is defined as an imbalanced intestinal microbial community, with alteration in the composition of the microbiota and its metabolic activities. In many conditions dysbiosis is not just a marker of disease, it also actively contributes to the pathology (2). Intestinal dysbiosis has been extensively documented in people with CKD and in laboratory modelling; uremia has been shown to negatively impact the microbiome, shifting the intestinal microbiota from a more evenly distributed and complex community to one that is simpler and dominated by certain bacterial families (2). Proposed reasons for intestinal dysbiosis in CKD patients – in addition to the direct effect of urea and subsequent increased production of ammonia by gut bacteria – include frequent use of antibiotics and phosphate binders, and dietary changes such as decreased fiber intake (2).

Uremic toxins

The term *uremia* refers both to the accumulation of substances in the blood that occurs as a result of a decline in glomerular filtration rate (GFR), and the clinical manifestations that result. Although this generally refers to imbalances in electrolytes, organic solutes and hormones, it also refers to uremic toxins. Creatinine and blood urea nitrogen (BUN) are the best known uremic toxins from a clinical perspective, but in reality these are only two of approximately 146 organic solutes that are putative uremic toxins (3). Importantly, many of these substances are not actively regulated by the body, and so progressively increase with declining GFR. Even for human patients these are particularly problematic, as some toxins are not amenable to removal by hemodialysis (3). Of particularly interest are uremic toxins that are waste products of protein catabolism by colonic microbiota (*e.g.*, indoxyl sulfate [IS], p-cresol sulfate [pCS]), as these are thought to not only have negative pathophysiologic effects, but also to contribute to the clinical syndrome of uremia.

Indole and p-cresol, which are uremic toxin precursors, are both products of protein catabolism which are produced in the colon via protein fermentation by microbiota (4,5). Indoles are derived from the metabolism of dietary tryptophan by tryptophanase in intestinal microbiota such as *Escherichia coli* (*E. coli*), *Proteus vulgaris*, and *Bacteroides* spp. **(Figure 2)**.

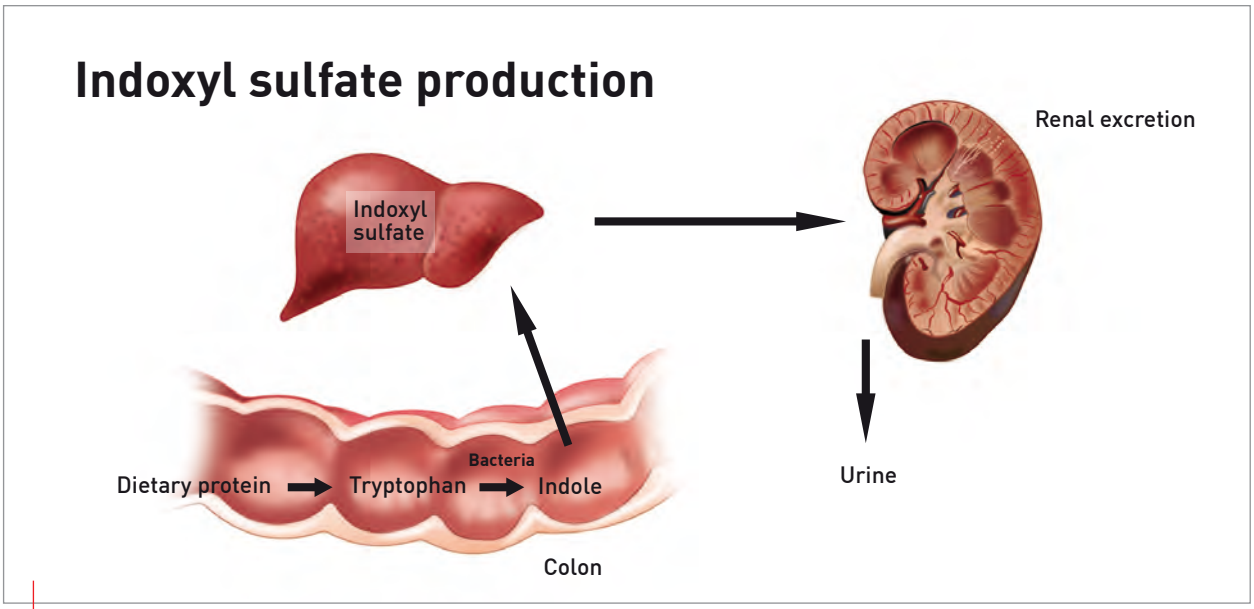

Figure 2. Colonic production of indoles, metabolism into indoxyl sulfate in the liver, and subsequent renal excretion.

P-cresol is generated via the partial breakdown of tyrosine and phenylalanine by many intestinal obligate or facultative anaerobes, including the genera *Bacteroides, Lactobacillus, Enterobacter, Bifidobacterium*, and *Clostridium*. Indol and p-cresol are absorbed and then sulfonated in the liver into the protein-bound uremic toxins IS and pCS respectively. These toxins are usually excreted by the kidneys, and thus accumulate in the systemic circulation of patients with renal disease. Dysbiosis further contributes to the production of colonic-derived uremic toxins, initiating a vicious cycle (4,5). The protein malassimilation in the small intestine that occurs in CKD patients increases protein substrate in the intestinal lumen, which promotes the expansion of proteolytic bacteria that produce the uremic toxin precursors. Constipation may also play a role due to sustained retention of fecal material in the colon; constipated human patients with CKD have higher levels of uremic toxins than patients with normal fecal scores (6).

Deleterious effects of uremic toxins

Although increased concentration of a substance does not imply pathology, numerous uremic toxins that accumulate in CKD are known to have deleterious effects. For example, the accumulation of IS and pCS in CKD has been associated with inciting the production of free radicals, activating the renin angiotensin aldosterone system (RAAS) which then promotes renal fibrosis, inducing inflammation and damaging renal tubular cells, and stimulating the progression of glomerular sclerosis (7). Other unwanted effects of uremic toxins also contribute to morbidity and mortality; these include impairment of the neurologic system, lowered erythropoietin production and bone turnover, accelerated muscle atrophy, and increased risk of cardiovascular disease (7) **(Figure 3)**.

Fecal fatty acids in CKD

Additional metabolites of colonic microbiota that could be disrupted by intestinal dysbiosis are fatty acids. The short-chain fatty acids (SCFA) produced by the colonic microbiota consist of the *straight-chain* SCFAs acetic acid, propionic acid, butyric acid and valeric acid, and the *branched-chain* (BCFA) SCFAs isovaleric acid and isobutyric acid **(Figure 4)**. Straight-chain SCFAs are major end-products of saccharolytic fermentation of complex polysaccharides (including non-digestible dietary fibers) and epithelial-derived mucus, and are essential nutrients vital for both intestinal and host health (8). They have several beneficial local and systemic effects, including promotion of colonic motility, lipid and glucose metabolism, blood pressure regulation, and anti-inflammatory properties. In contrast, BCFAs represent only a small portion of total SCFA production, and are

"Creatinine and blood urea nitrogen (BUN) are the best known uremic toxins from a clinical perspective, but in reality these are only a couple of approximately 146 organic solutes that are putative uremic toxins."

Stacie C. Summers

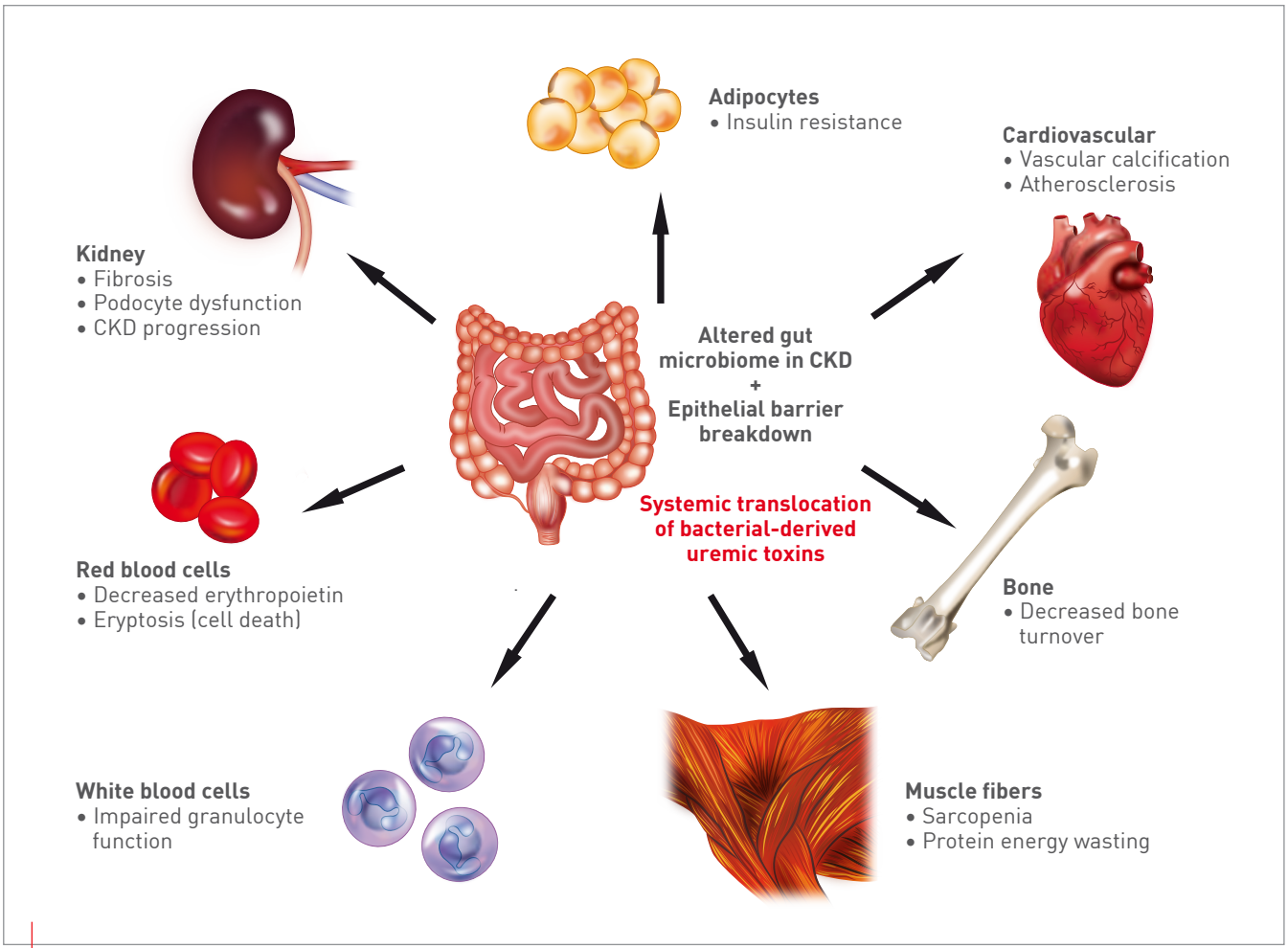

Figure 3. Multiple deleterious systemic effects of uremic toxins have been documented.

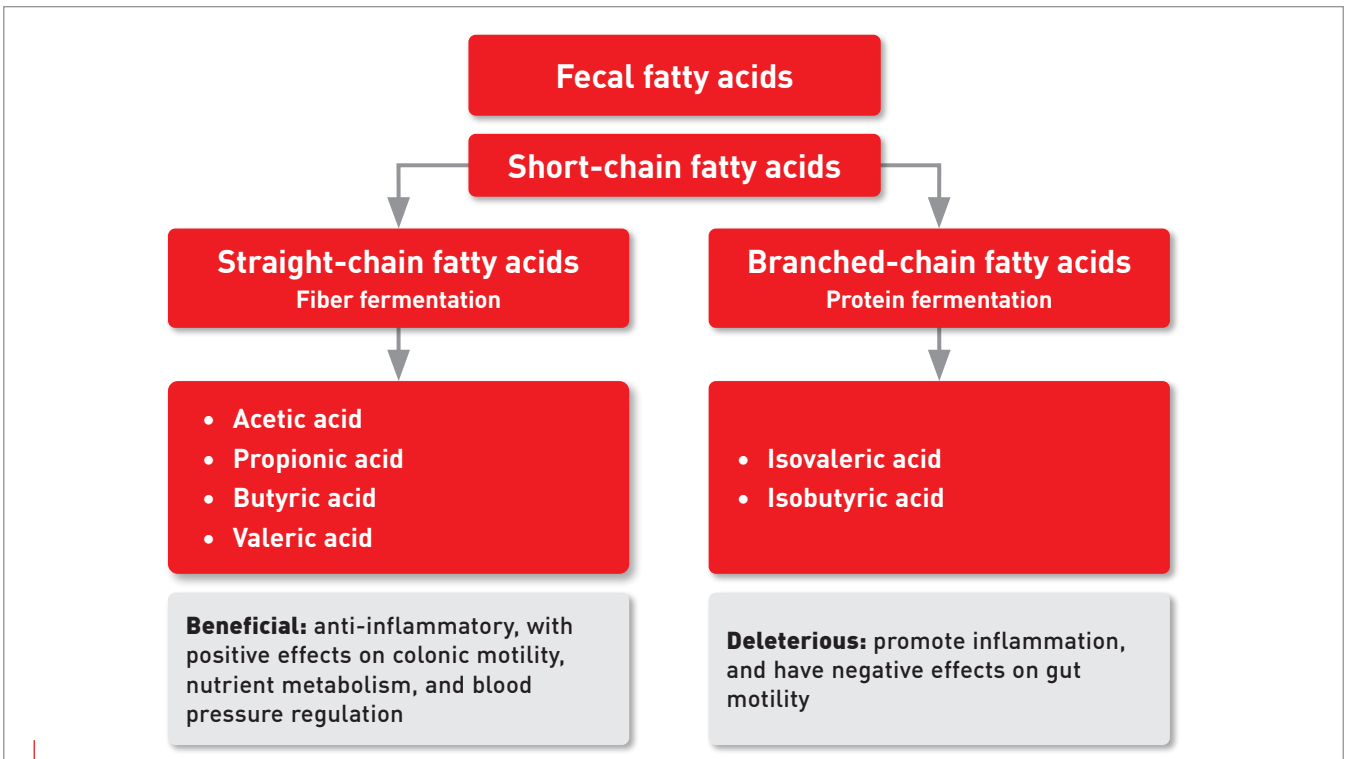

Figure 4. SCFA and BCFA are both products of colonic metabolism, but have differing effects.

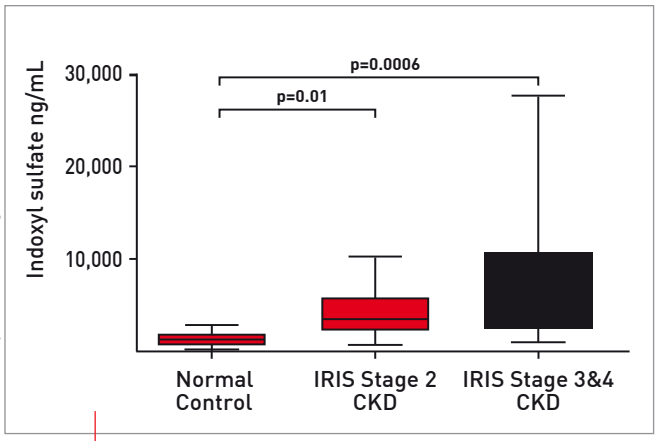

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Figure 5. Uremic toxins may increase in line with IRIS staging of CKD; for example, indoxyl sulfate levels are significantly higher in cats with CKD than in senior healthy cats (from 9).

produced when protein passes through the small intestine unabsorbed and protein-derived branched chain amino acids are fermented by microbiota in the colon (8). BCFAs and other products of protein fermentation in the colon are considered deleterious to the gut, and may serve as an instigator of inflammation as well as having negative effects on gut motility (8). In humans, dysbiosis in CKD is associated with a decrease in microbiota that produce SCFAs, but to the best of the authors' knowledge BCFAs have not been studied.

What do we know in cats?

There is relatively limited information regarding the microbiome and uremic toxins and their link to kidney disease in veterinary medicine, but our knowledge is more advanced in cats. In comparison to healthy cats (≥ 8 years), cats with CKD have been documented to have a dysbiosis characterized by decreased fecal microbial diversity and richness based on 16S rRNA gene sequencing (9). Additionally, cats with CKD accumulate gut-derived uremic toxins in the systemic circulation. Significantly elevated levels of IS have been shown to be present in feline CKD **(Figure 5)**, which is associated with disease progression (10-12). Although pCS concentrations did not significantly differ between healthy and CKD groups in one study, the highest concentrations were noted in CKD cats (9). Interestingly, even IRIS CKD Stage 2 cats have been documented to have uremic toxin concentrations that are significantly higher than control cats, implying this imbalance occurs relatively early in the disease process.

When fecal concentrations of straight-chain SCFAs (acetic acid, propionic acid, butyric acid, valeric acid) and BCFAs (isobutyric acid, isovaleric acid) were assessed in CKD cats and healthy controls, the first group had increased fecal isovaleric acid, and in particular the IRIS CKD Stage 3 and 4 cats (9). Cats with muscle atrophy had higher fecal BCFA concentrations compared to cats without muscle atrophy. Additional studies have demonstrated cats with CKD have a deranged fecal bile acid profile (13), and a deficiency in several essential amino acids in the serum (14). Together these findings support malassimilation of protein in CKD cats, but additional investigation is needed to more thoroughly understand the interplay between the gut and kidney in this species. However, these studies support the idea that the gut microbiome is a therapeutic target in CKD cats, with the goal of reducing production of detrimental gut-derived uremic toxins and restoring a more healthy gut microbial community.

The gut as a potential therapeutic target

Uremic toxins

Due to the potential negative effects of gut-derived uremic toxins, and their poor ability to be removed via hemodialysis due to protein binding, human medicine has focused on strategies to decrease production of IS and pCS, including modulation of microbial growth in the colon by dietary management, prebiotics, probiotics, and target adsorption of uremic toxins by the use of adsorbents (4,5). Generation of IS and pCS can be modulated by selectively increasing saccharolytic and reducing proteolytic bacteria in the colon, and by optimizing intestinal transit time (and hence addressing constipation is an important consideration). Prebiotics and probiotics have been shown to influence the composition of the colonic microbiota and have been successfully used to decrease IS and pCS concentrations in human CKD patients. In addition, increasing dietary levels of carbohydrate and fiber, and decreasing protein intake, have been shown to decrease IS and pCS concentrations. Adsorbents such as sevelamer hydrochloride and AST-120 are also used to limit intestinal absorption of these toxins (15,16). However, there has been little published on strategies to decrease gut-derived uremic toxins in veterinary CKD patients, and further exploration as a potential therapeutic target seems warranted.

"Cats with chronic kidney disease have dysbiosis, supporting the notion that the gut is a therapeutic target to potentially improve longevity and comorbidities."

Jessica M. Quimby

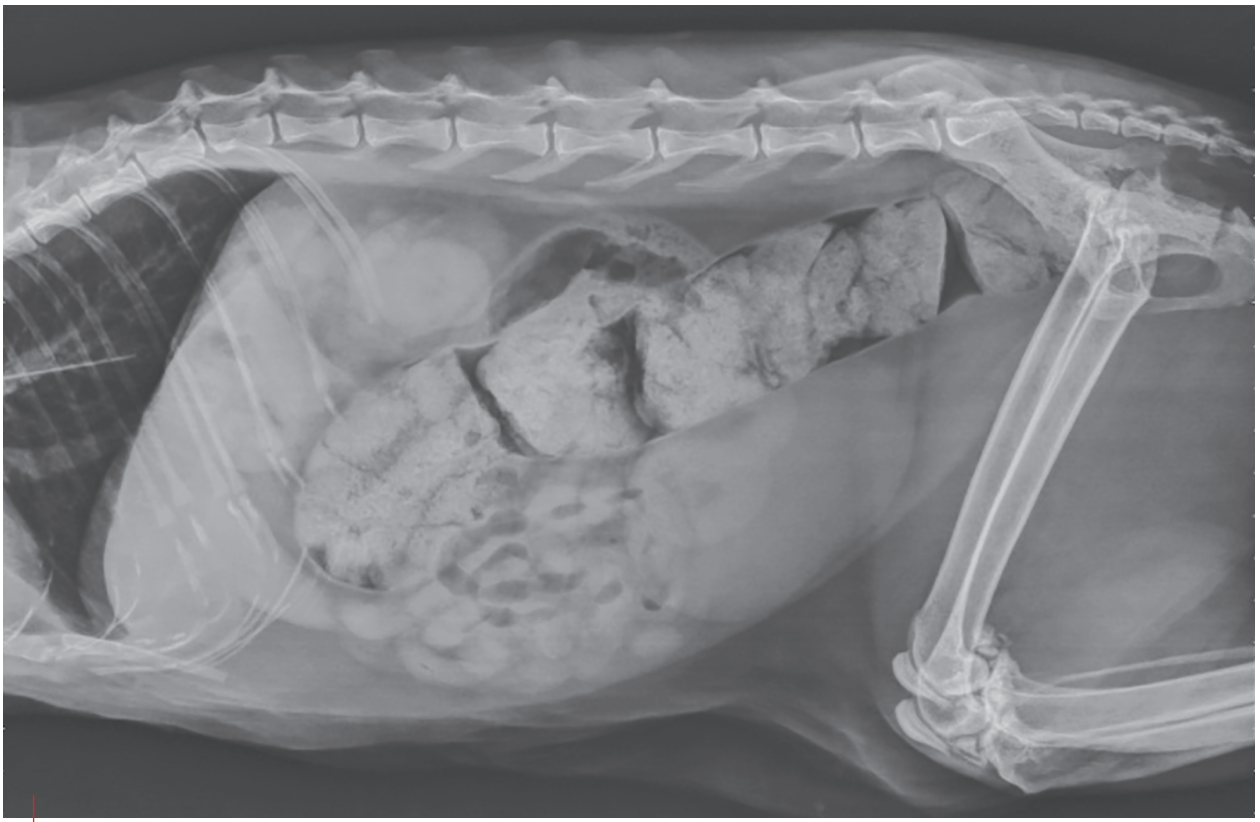

Figure 6. Constipation is a common finding in cats with CKD and should be treated appropriately, as otherwise it can have various negative consequences.

The concept of decreasing uremic toxins and clinical signs of uremia through palliation of the dietary protein load is the central tenet behind the historical protein modification in veterinary renal therapeutic diets. However, due to lack of studies, no strong evidence currently exists that show limiting protein results in palliation of uremic toxins or clinical signs of uremia, hence the more recent controversies, particularly in cats, about the ideal protein content in renal diets (17,18). Limited data on the effects of differing protein contents on uremic toxins in cats exists. In one study in healthy cats, a higher protein diet (10.98 g/100 kcal ME versus 7.44 g/100 kcal ME) was associated with increased concentrations of IS and relatively higher concentrations of pCS (19). Similarly, a study on cats with IRIS Stage 1 CKD that were fed three diets of differing protein levels showed that they had demonstrably higher IS and pCS concentrations when fed the highest protein diet (8.01 g/100kcal ME versus 6.95 g/100 kcal ME and 5.65 g/100 kcal ME) (20).

There is still a debate regarding the ideal protein content of renal diets for cats, as they are considered to be obligate carnivores and thus have increased protein requirements compared to dogs and humans. Studies suggest that senior cats may require more protein than younger cats and, in addition, many cats with CKD will show a decline in body weight, body condition score and/or muscle mass over time. Taking the information known to date into account, recommendations for dietary protein in cats with CKD likely consist of delicately balancing the protein content between limiting uremic toxin production and maintaining lean body mass. A key concept for success when feeding a modified protein diet is to ensure that an adequate caloric intake is also provided.

Prebiotic and probiotic treatments have been used in CKD cats in the hope that they will improve the health of the gut microbiome and reduce blood concentrations of gut-derived uremic toxins. The use of a commercial probiotic supplement (*Enterococcus faecium* SF68) was evaluated in cats with CKD, with the study reporting that it had no appreciable effect on the gut microbiome and serum concentrations of the major gut-derived uremic toxins (21). Another study evaluated the effect of fermentable fiber (a prebiotic) in experimental diets on the fecal microbiota in cats with CKD, and found that their microbiome was resistant to change when compared to healthy cats (22). The fiber did reduce relative concentrations of plasma uremic toxins in the CKD cats in comparison to healthy cats, which supports the notion that alteration of the gut microbiome can reduce the production of gut-derived uremic toxins, but species-specific evidence-based strategies are needed.

Some commercially available products are now available in many countries; these include a probiotic/prebiotic intended to beneficially target the microbiome by creating an environment with less uremic toxin production, and a carbon-based adsorbent designed to bind indole in the digestive tract to prevent uptake into the body. The latter product has been shown to reduce indoxyl sulfate in senior cats after eight weeks of administration (23), but data on the effectiveness of either product to decrease IS concentrations in cats with CKD is still forthcoming.

Constipation

The prevalence of constipation associated with feline CKD has not been reported, but anecdotally this appears to be a common medical concern **(Figure 6)**. Preliminary results of a survey studying fecal habits in cats suggest that defecation is less regular in CKD, and the cause of constipation in these cats is likely a dysfunction of water balance, possibly combined with abnormal GI motility. As the kidneys fail to provide appropriate urine concentrating ability, and the patient fights with chronic subclinical dehydration, water is reabsorbed from the colon to compensate. Hypokalemia and the use of phosphate binders may also contribute to constipation (24,25). Therapy for constipation may include correction of dehydration and electrolyte imbalance, diet, fiber, osmotic stool softeners or promotility agents such as lactulose. In addition to its clinical effects, constipation may have other negative consequences and is likely a classic example of the gut-kidney axis. As previously mentioned, constipated human patients with CKD have higher concentrations of uremic toxins than patients with normal fecal scores, and conversely such toxins may have negative effects on gastrointestinal motility (8). Laboratory modelling of CKD has demonstrated significant improvement in uremic toxins, creatinine and even kidney histopathology subsequent to a regimen of lactulose (26).

CONCLUSION

Although much work remains to be done, there is emerging evidence that the gastrointestinal tract and the kidneys interact and influence each other in both health and disease. Given that many cats with chronic kidney failure have dysbiosis of the microbiome, it is likely that the gut will become seen as a major focus to be proactively targeted with specific therapeutics in order to improve longevity and quality of life in affected cats.

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CANINE PROTEIN-LOSING ENTEROPATHY: AN UPDATE

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Protein-losing enteropathy is a heterogenous syndrome in dogs, which means that the clinician should approach each case as an individual.

KEY POINTS

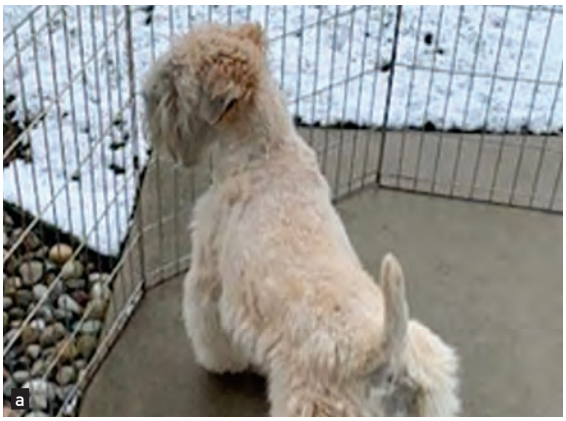
1. Canine protein-losing enteropathy (PLE) is a syndrome that occurs as a consequence of various disorders.
2. Chronic inflammatory enteropathy and intestinal lymphangiectasia are the most common causes of canine PLE.
3. Diagnosis requires careful exclusion of other causes of hypoalbuminemia, followed by a step-wise approach to determine the cause of the PLE.
4. PLE in dogs is a heterogenous disease process, but dietary modification is considered an important component of therapy in many cases.

Introduction

Protein-losing enteropathy (PLE) is a syndrome of excessive protein loss across the enteric mucosa. It occurs as a result of altered intestinal permeability and protein uptake, direct mucosal erosion or ulceration and secondary loss of protein, and/or in association with altered lymphatic function and direct loss of protein-rich lymph. Thus, PLE occurs as a consequence of a wide variety of disorders including neoplastic, infectious, mechanical, inflammatory and miscellaneous processes **(Table 1)**. Chronic inflammatory enteropathy (CIE) and intestinal lymphangiectasia (IL) are the most common causes of canine PLE (1). Chronic inflammatory enteropathy is a term used to describe conditions of the gastrointestinal (GI) tract characterized by signs of at least 3 weeks duration, with the exclusion of neoplastic, infectious, endocrine, mechanical, and extra-gastrointestinal causes, and histologic documentation of intestinal inflammation. The term inflammatory bowel disease (IBD) is typically reserved for dogs that have received a biopsy diagnosis of an enteritis and may have already failed food or antibiotic trials, and given that these strict criteria are met in very few patients, the broader terms chronic enteropathy (CE) or CIE are preferred. Intestinal lymphangiectasia is a condition characterized by variable intestinal lymphatic vessel dilation, lymphangitis, and/or lymphatic obstruction and rupture. A recent review reported that 314/469 (68%) of dogs with PLE were diagnosed with CIE and 214/469 (46%) were diagnosed with IL (1). While PLE can occur in cats, it is significantly more common in dogs. This review will focus on clinical findings, diagnostics, and therapies associated with the most common causes of canine PLE, with an emphasis on recent updates.

Table 1. Etiologies of protein-losing enteropathy in the dog.

Diseases that alter intestinal permeability and/or cause mucosal injury
Intestinal ulceration
Chronic obstruction of the intestine: • Foreign body • Intussusception
Intestinal crypt disease (unknown if primary disorder or secondary change)
Hypoadrenocorticism (Addison's disease)
Chronic enteropathies
Infectious enteropathies: • Fungal (Histoplasmosis, pythiosis) • Parasitic (Hookworm, shistosomiasis) • Viral (Parvovirus) • Bacterial – rare (*Campylobacter*, *Salmonella* spp.)
Neoplasia: • Intestinal lymphoma (solitary or diffuse) • Intestinal adenocarcinoma
Lymphatic disease
Primary lymphangiectasia (genetic predisposition)
Secondary lymphangiectasia: Common • Chronic enteropathies • Intestinal neoplasia Less common • Right heart failure • Constrictive pericarditis • Portal hypertension
Focal lipogranulomatous lymphangitis



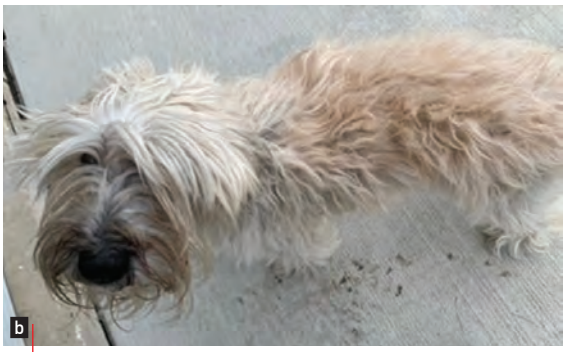


Figure 1. Images depicting the body condition of a 4-year-old, female neuter Soft-Coated Wheaten Terrier, before onset of clinical signs of PLE **(a)** and following diagnosis of PLE due to marked intestinal lymphangiectasia and moderate lymphoplasmacytic enteritis **(b)**.

Clinical findings

Protein-losing enteropathy may be diagnosed in dogs of any age, and no sex predilection is known. Breeds with the highest frequency of PLE reported across multiple studies include the Yorkshire Terrier, mixed breed, Border Collie, German Shepherd Dog, and Rottweiler (1). Breeds considered predisposed to the development of IL include the Norwegian Lundehund, Chinese Shar-pei, Rottweiler, and the Maltese, Soft-Coated Wheaten and Yorkshire Terriers (1-3).

Most commonly, PLE presents as chronic relapsing or progressive gastrointestinal signs, weight loss, and signs associated with hypoalbuminemia (*e.g.*, ascites, pleural effusion, subcutaneous edema). Diarrhea, weight loss, and decreased appetite are most frequently observed, while vomiting is less common. Gastrointestinal signs are noted to be absent in 5-10% of cases, with dogs presenting instead for evaluation of signs associated with hypoalbuminemia. Less commonly, cases may present due to systemic complications of PLE – for example, dogs with significant ionized hypocalcemia may exhibit tremors, facial rubbing or develop focal or generalized seizures, and thromboembolism secondary to PLE may result in respiratory, neurologic, or musculoskeletal signs (1,4,5).

Physical examination findings are variable; in some cases, the exam is unremarkable, and in others severe deviations are present. Frequently observed abnormalities include decreased body condition and/or muscle due to malnutrition **(Figure 1a & b)**, abdominal distension (and palpable "fluid-wave"), detection of peripheral edema, and/or decreased lung sounds secondary to pleural effusion. Chemosis secondary to hypoalbuminemia is seen rarely **(Figure 2)**. Rectal examination may reveal thickened or roughened rectal mucosa and/or diarrheic stool.

Hypoalbuminemia is the hallmark biochemical abnormality in cases of PLE. Additional common findings on complete blood count and serum

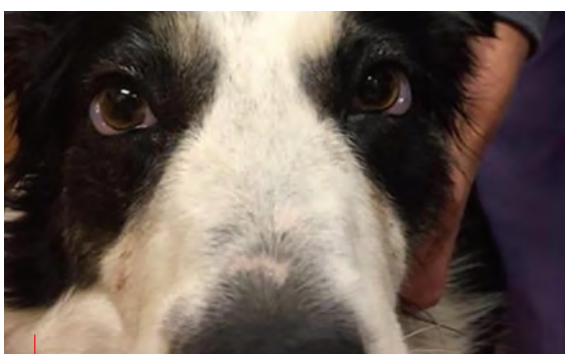


Figure 2. Chemosis (a rare clinical consequence of hypoalbuminemia) in a 5-year-old male neuter Border Collie with PLE due to moderate lymphoplasmacytic and neutrophilic enteritis and mild intestinal lymphangiectasia.

biochemistry include lymphopenia, various types and degrees of leukocytosis, hypocholesterolemia, decreased serum creatinine, increased liver enzyme activities (typically mild increases), decreased total serum calcium and magnesium, and hypoglobulinemia. Although the latter is frequently observed, some dogs with PLE will have normal or even increased serum globulin concentrations.

Observation of serum *total* hypocalcemia is expected secondary to hypoalbuminemia; however, *ionized* hypocalcemia also occurs, often associated with decreases in serum 25-hydroxyvitamin D. Concurrent ionized hypomagnesemia and secondary disorders of the parathyroid gland may also be present (6,7). Consideration should therefore be given to measurement of these variables. Hypocobalaminemia is also frequently observed in dogs with PLE, as are decreases in serum folate concentrations and increases in canine pancreatic lipase immunoreactivity (cPLI). Finally, viscoelastic testing has demonstrated a hypercoagulable state in dogs with PLE (8), but this finding has not been directly correlated to the development of thromboembolism.

Diagnostic work-up

The initial diagnostic work-up in cases of suspected PLE should involve careful consideration and exclusion of non-GI causes of hypoalbuminemia **(Table 2)**. When necessary, measurement of fecal alpha 1-proteinase inhibitor can confirm that loss of protein through the gastrointestinal tract is occurring. Alpha 1-proteinase inhibitor is similar in size to albumin, and as it is not normally actively absorbed or secreted in the intestine, and is resistant to hydrolysis, it is an ideal marker for intestinal protein loss (9). This test is probably most useful in patients that have concurrent renal protein loss or liver dysfunction which complicates the diagnosis of PLE. Following this step, a variety of tests are recommended prior to intestinal biopsy. This includes screening for hypoadrenocorticism; a serum basal cortisol >2 µg/dL rules it out, but if below this value ACTH stimulation testing should be performed to exclude hypoadrenocorticism.

Table 2. Non-GI causes of hypoalbuminemia and exclusionary tests.

Disorder	Test(s) for exclusion
Liver insufficiency/ dysfunction	Bile acids testing
Protein-losing nephropathy	Urinalysis +/- urine protein:creatinine ratio
Pancreatic insufficiency	Fasting serum trypsin-like immunoreactivity
Hemorrhage	Physical exam including rectal exam, evaluation for cavity effusions
Dilution or redistribution of albumin	Evaluation for renal and cardiac disease Evaluation for evidence of vasculitis or effusions

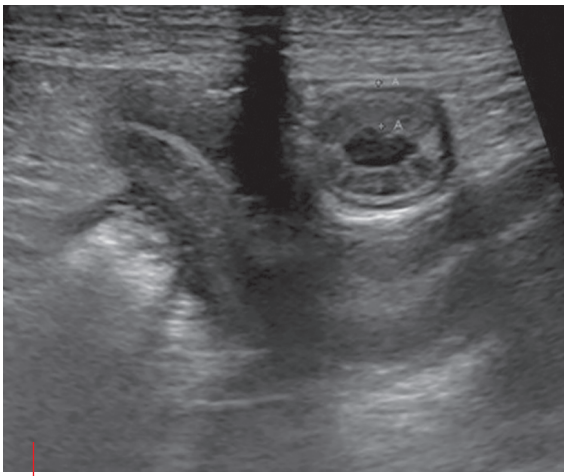


Figure 3. Transverse ultrasound scan of small intestinal hyperechoic mucosal striations in a 7-year-old female neuter Goldendoodle with PLE.

Other tests include fecal screening for helminths and *Giardia duodenalis*, diagnostic imaging, and specific testing for infectious diseases (*e.g.*, urine antigen test and rectal scraping with cytology for histoplasmosis) depending on exposure and clinical suspicion.

Thoracic radiographs may be useful to screen for evidence of pleural effusion, metastatic disease, or evidence of fungal disease. If chronic obstruction of the small intestine is a consideration, abdominal radiographs should be performed. Abdominal ultrasound may be helpful in excluding focal or extraluminal lesions that may change the diagnostic approach, and/or for fine-needle aspiration of masses or abnormal lymph nodes, which may allow a non-invasive diagnosis. Peritoneal effusion may be observed, and if present, fluid should be collected for analysis; a pure transudate is expected in cases of PLE. Hyperechoic mucosal striations **(Figure 3)** observed on abdominal ultrasound are supportive of, but not specific for, a diagnosis of intestinal lymphangiectasia (10). The diagnostic work-up should also include screening for abnormalities listed above – most importantly, ionized hypocalcemia and hypocobalaminemia.

Biopsy with histopathology is often required for definitive diagnosis of PLE, and remains an important step for several reasons. Primarily, biopsy can exclude infectious or neoplastic causes of PLE, but it will also help determine whether the dog is affected by CIE, IL or both (and if both, which process appears to predominate). Importantly, 76% of dogs with CIE and hypoalbuminemia will also have some degree of IL/lacteal dilation (11), so these processes are commonly present concurrently. Surgical exploration for biopsies provide the advantages of identifying focal areas of disease to biopsy and the ability to biopsy all segments of intestine, as well as other tissues as indicated (*e.g.*, liver, lymph node). However, collection of intestinal tissue via flexible endoscopy offers many advantages and is generally the preferred option, as it is much less invasive and post-biopsy recovery is hastened when compared to laparotomy. Additionally, endoscopy enables direct visualization of the mucosa

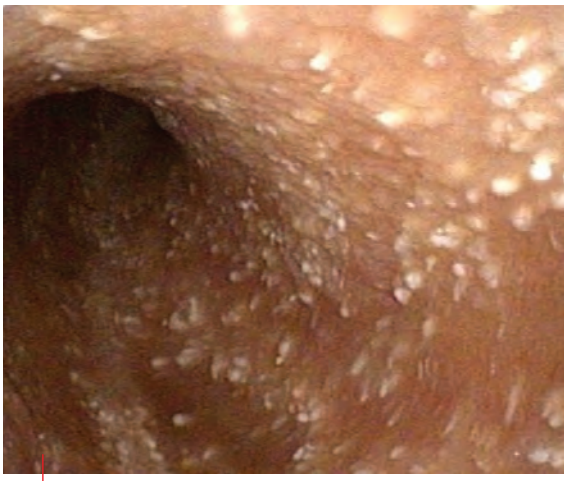


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Figure 4. Presence of small intestinal pinpoint to coalescing "white spots" consistent with dilated lacteals in a 5-year-old female neuter Soft-Coated Wheaten Terrier with histologically diagnosed marked intestinal lymphangiectasia and the clinical syndrome of PLE.

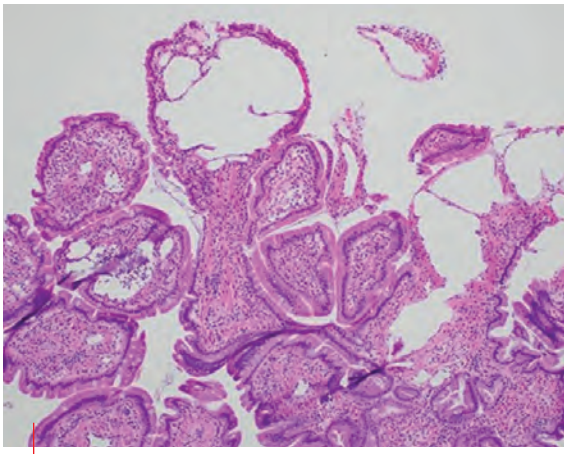

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Figure 5. Photomicrograph (x10 magnification) of marked intestinal lymphangiectasia and moderate lymphoplasmacytic, neutrophilic and eosinophilic duodenitis in a 5-year-old female neuter Soft-Coated Wheaten Terrier with PLE.

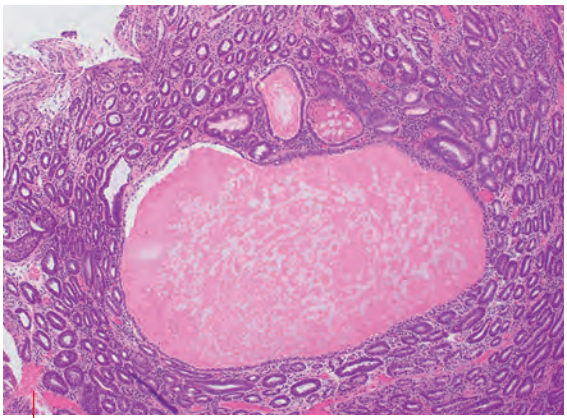

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Figure 6. Photomicrograph (x40 magnification) of a markedly dilated crypt with degenerate inflammatory cells intermixed with eosinophilic necrotic debris and mucous in a 6-year-old, MC, small mixed breed dog with PLE.

and allows for targeted collection of abnormal tissue. Specifically, "white spots" on the mucosa **(Figure 4)** have been associated with intestinal lymphangiectasia (12). Pathology can differ between intestinal sections, so it is highly recommended that both esophagogastroduodenoscopy ("upper") and ileocolonoscopy ("lower") endoscopy are performed (13). Importantly, endoscopy has limitations; the quality of endoscopic biopsies can impact the ability to make an accurate diagnosis, the jejunum typically cannot be sampled, and lesions deeper in the intestinal wall can be missed. Additionally, while guidelines for the interpretation of inflammatory and morphologic change in the GI mucosa of the dog and cat (WSAVA scoring system/template) are available (14), controversy and inter-observer variation exist in interpretation of intestinal biopsy samples. Additionally, histopathologic findings have not been consistently and accurately correlated to clinical signs and response to treatment. Some of the responsibility must be borne by the interpreting clinician to fully review the histopathology report, and to use their clinical judgment, particularly if samples are inadequate.

Common histopathologic findings in dogs with PLE include intestinal lymphangiectasia **(Figure 5)**, mucosal edema, various types and degrees of inflammatory infiltrates, and dilated, cystic crypts **(Figure 6)**. Intestinal lymphangiectasia has been detected in the villus, proprial mucosa and submucosa in endoscopic intestinal biopsies (15), therefore it is important that pathologists evaluate for lymphangiectasia in each of these areas. Crypt lesions seem to be especially common in the Yorkshire Terrier (2). If concern for bacterial adherence/invasion arises from biopsy assessment, fluorescent *in-situ* hybridization (FISH) can be considered to evaluate for bacteria within formalin-fixed tissue. In some cases, immunohistochemistry and PCR for antigen receptor rearrangements (PARR) may be necessary to help distinguish intestinal lymphoma from inflammatory infiltrates.

Management

The treatment of neoplastic, infectious, mechanical, and miscellaneous causes of PLE are beyond the scope of this review, and this section will focus on the treatment of PLE caused by CIE and IL. The severity of disease may influence the therapeutic approach to patients – so for dogs with suspected or confirmed PLE that are otherwise relatively stable, dietary treatment alone may be a reasonable approach. This approach has been shown to be successful in Yorkshire Terriers (16) and various other breeds (17). Additionally, it is critical to note that the treatment approach will often differ in individual cases of canine PLE, as it is a heterogenous disease process. In other words, there is no "cookbook" approach to treatment of PLE, and an individualized approach to therapy based on all available information is encouraged.

Although treatment should be directed towards the suspected or confirmed disease process, because PLE is a life-threatening disorder with a high rate of

mortality, the safest approach may be to assume all processes (*i.e.*, lymph fluid loss, increased intestinal permeability, mucosal injury) are occurring in a PLE patient, and treat accordingly. This is particularly true for patients with severe disease or those that are not responding to therapy.

Diet

Treatment of the underlying disease causing PLE starts with dietary modification, and many gastroenterologists consider this component of treatment to be the cornerstone of PLE management. One study suggests that dogs with PLE are more likely to respond to dietary therapy without the need for glucocorticoids if their canine chronic enteropathy clinical activity index (CCECAI) score is <8 (17). Dogs with PLE are in a catabolic state and may have marked negative energy and protein balance, so adequate nutrition is essential. Furthermore, treating PLE caused by CIE or IL relies on alterations to the diet. Anecdotally, the ideal diet is highly digestible, contains an adequate amount of protein, and is fat-restricted, but the dog's previous dietary history should also be taken into consideration when choosing the best approach. A low-fat diet is typically recommended for dogs with IL, while a novel protein or hydrolyzed diet is suggested for dogs with CIE. Note there is no definitive consensus on what constitutes a "low-fat" diet in veterinary medicine; commercially available "low-fat" diets contain between 17-26 g fat/Mcal ME (1.7-2.6 g/100 kcal), while diets considered "ultra low-fat" are typically classified as <15 g fat/Mcal ME (1.5 g/100 kcal). Dogs that have IL as the cause of their PLE will often improve considerably with low fat diet alone, but some may require fat restriction beyond what a commercial diet can provide. Additionally, many of the commercially available diets lowest in fat are poultry based, which may make them unsuitable for dogs with IL that have concurrent CIE. At least one commercially available canned low-fat diet is currently pork-based, which may be novel for some dogs. Dogs that require fat restriction beyond what a commercial diet provides, and dogs that have both significant CIE and IL, may require a veterinary-nutritionist formulated, home-cooked diet that can address both concerns. In dogs with PLE and CIE and limited to no IL, a hydrolysate or novel protein diet can be considered, but it is still suggested to consider ones with comparatively lower fat content, because IL can be missed and serum albumin concentrations have been consistently correlated with lacteal lesions in dogs with inflammatory PLE (11,18). Other nutritional considerations include the food form (dry or wet), frequency of feeding (it is often beneficial to feed PLE dogs multiple, small meals a day), volume fed, and fiber content. Some dogs may benefit from supplementary fiber. In all cases of PLE, whether or not a commercially available therapeutic diet or a home-cooked one is desired or anticipated, consultation with a veterinary nutritionist is helpful and recommended.

Finally, it is important to recognize that lack of response to one dietary approach does not mean that the dog will not be diet-responsive, or that the condition will not benefit from optimization of the dietary therapy. In one study 8/10 dogs with steroid-refractory inflammatory PLE responded to a dietary change (19). In the author's experience many dogs with PLE that have failed commercial diets and treatment with glucocorticoids and other immunosuppressive drugs have been rescued by feeding a novel, significantly fat-restricted (<15% by ME), veterinary-nutritionist formulated, home-prepared diet. In some cases, dogs with PLE may not require a novel protein diet, but simply need fat restriction beyond what a commercial diet can offer, and so a home-prepared diet becomes necessary. A summary of specific diets for PLE conditions is given in **Box 1**.

"Dogs with protein-losing enteropathy are in a catabolic state and may have marked negative energy and protein balance, so adequate nutrition is essential."

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Anti-inflammatory and immunosuppressive therapy

Although the pathogenesis of chronic inflammatory enteropathy is not completely understood, it is suspected that the GI tract has had a sustained immune reaction to endogenous or exogenous antigens (which may be food, bacterial and/or environmental). In addition, lymphangiectasia is associated with lymphangitis, and lymph leakage is known to induce secondary enteritis. Therefore, the initial approach to treating PLE typically involves the use of prednisone or prednisolone in either case. The exception may be in stable patients that are treated with diet alone initially and have shown a sustained clinical and biochemical response.

Importantly, side effects of steroid therapy in dogs with PLE can be significant, and glucocorticoids can worsen the catabolic and hypercoagulable states in some cases (20). Immunosuppressive doses of glucocorticoids may also be risky if a dog with PLE has a compromised enteric barrier, therefore in the author's opinion it is important to carefully consider the dose of glucocorticoid being prescribed and use the most conservative dose that could be successful. Budesonide has a high first-pass effect and a high affinity for intestinal steroid receptors, and may be considered as an alternative glucocorticoid.

Some cases of PLE are started on an immunosuppressive drug at the time of diagnosis, or if response to appropriate doses of glucocorticoids is inadequate or side effects severe. It is important to note that there is no evidence of an immune process in cases of primary IL, thus immunosuppressive therapy is not warranted in these dogs. Furthermore, a recent study comparing time to normalization of albumin and long-term outcome between dogs with inflammatory PLE treated with steroids alone versus steroids plus a second-line immunosuppressive agent found no differences between the groups (21). Thus, the author recommends utilizing immunosuppressive agents (*e.g.*, cyclosporine at 5 mg/kg PO q12-24H, or chlorambucil at 4-6 mg/m^2 PO q24H for 7-14 days, then dose reduction) in patients that have CIE and are steroid-refractory, or in those that are initially steroid-responsive but relapse when steroids are weaned. A summary of the above is given in **Box 2**.

If both CIE and IL appear to be contributing to a patient's PLE, it can be difficult to determine the best treatment approach, as one process may be driving the other. If IL is a significant component of the disease process it may be best to approach treatment for IL first and only escalate therapies if the patient fails to respond to therapies directed for IL.

Box 1. A summary of selected specific diets for PLE conditions.

Intestinal lymphangiectasia: A veterinary therapeutic low-fat diet, or a home-cooked low-fat or ultra low-fat diet formulated by a board-certified veterinary nutritionist.
Chronic inflammatory enteropathies: A veterinary therapeutic hydrolyzed or hypoallergenic diet, with priority given to those that are comparatively lower in fat, or a home-cooked diet formulated by board-certified veterinary nutritionist.
Combined lymphangiectasia and chronic inflammatory enteropathy: Hydrolyzed or hypoallergenic diets comparatively lower in fat could be considered, as can veterinary therapeutic low-fat diets. In some cases, management of one condition will allow for resolution of the other, but a home-cooked diet formulated by a veterinary nutritionist may need to be considered in cases where both disorders require dietary management.

Box 2. Drug recommendations for treating canine PLE.

Intestinal lymphangiectasia • Anti-inflammatory glucocorticoid therapy (*e.g.*, prednisone/prednisolone at 0.5-1 mg/kg/day) to decrease inflammation associated with lymph leakage and the formation of granulomas • Taper dose following clinical response every 3-4 weeks by 25% each time • No evidence that immunosuppressive therapy is useful in treating IL
Chronic inflammatory enteropathies • Anti-inflammatory to immunosuppressive doses of prednisone are recommended (0.5-2 mg/kg/day) • Taper dose following clinical response every 3-4 weeks by 25% each time • Additional immunosuppressive medications may be used in cases of steroid-refractory PLE or where there is relapse when steroids are weaned. The most commonly used medications are cyclosporine, chlorambucil, and azathioprine. Mycophenolate is generally not recommended due to its potential to cause significant adverse GI effects.

Supportive care and management of complications

Dogs with PLE may develop an altered enteric microbiota (intestinal dysbiosis), thus probiotics may be helpful in some cases; at least one commercial probiotic strain has been shown to have a beneficial effect (22). As cobalamin is important for GI health and function, any deficiency should be treated; this has traditionally been administered subcutaneously, but recent work has demonstrated that oral administration can be effective in dogs with intestinal disease (23). Supplementation of folic acid should be considered in dogs with folate deficiency (200 µg/kg PO q24H – if <20 kg – and 400 µg/kg PO q24H – if >20 kg), and human products are acceptable.

Treatment is recommended for dogs with significant ionized hypocalcemia. If clinical signs are observed (muscle twitching or tremors, facial rubbing), parenteral administration of 10% calcium gluconate may be necessary (0.5-1 mL/kg *slowly* IV over 10-30 minutes while monitoring heart rate, and optimally ECG). Oral calcium carbonate (25-50 mg/kg q24H, or elemental calcium at a divided dose q12H) can also be beneficial. It is important to remember that hypomagnesemia can impair calcium absorption, so if necessary oral magnesium hydroxide (1-2 mEq/kg q24H or as a divided dose q12H) can be given. Many dogs with ionized hypocalcemia have low 25-hydroxyvitamin D levels and may benefit from treatment with calcitriol (20-30 ng/kg PO q24H for the initial 3-4 days, followed by a maintenance dose of 5-15 ng/kg q24H, best given apart from steroids). It is unknown at this time whether dogs with PLE and hypovitaminosis D and normocalcemia would benefit from administration of vitamin D products. Dogs with PLE are classified as being at "high risk" for thrombosis (based on the 2022 CURATIVE guidelines) and thromboprophylaxis is recommended (24). Many dogs are administered clopidogrel at 2-3 mg/kg PO q24H; however, the use of factor Xa inhibitors (*e.g.*, apixaban, rivaroxaban) for thromboprophylaxis could also be considered.

Draining of abdominal or thoracic effusions is only recommended if there is discomfort or respiratory difficulty, use of diuretics is discouraged, as they are often ineffective and can promote dehydration. Any crystalloid fluid therapy should be judicious, due to the hypoproteinemia. The volume of plasma needed to increase a patient's albumin is substantial and typically not practical. Colloids, such as hydroxyethyl starches, are the most useful option for improving edema. Concentrated human albumin (25%) is not recommended in dogs (25). A canine albumin product is available in some countries and is anecdotally effective in dogs with PLE. Finally, dogs with PLE can often benefit from other supportive care, such as medications to reduce vomiting and nausea (*e.g.*, maropitant 2 mg/kg PO q24H).

Speculative treatment

If treating a dog without the benefit of an intestinal biopsy, a clinician should discuss with the client the risks involved (misdiagnosis, potential harms if the patient has an infectious enteropathy) and should also consider the breed involved and whether there are any known predispositions. In the absence of a biopsy or known breed predispositions, it may be best to assume that both IL and CIE are present, and treat accordingly.

Refractory cases and prognosis

Some dogs with PLE have no to minimal clinical or biochemical response to anti-inflammatory or immunosuppressive doses of steroids and second-line immunosuppressive agents. In these cases, the author recommends tapering the medications and focusing on dietary adjustment (ideally with the consultation of a board-certified veterinary nutritionist), treating deficiencies, and preventing complications. Anecdotally, some dogs with refractory PLE caused by intestinal lymphangiectasia have shown improvement in response to octreotide (5-10 µg/kg SC q8-12H), but limited information about the efficacy and possible side effects of this treatment is currently available.

In a review of 445 cases of canine PLE, disease-associated death occurred in 54.2% of dogs (1). However, increasing understanding of the heterogenous nature of this condition and the need for individualized therapy may lead to better outcomes. Despite the guarded prognosis, some dogs with PLE will have an excellent response to treatment, but even in patients that respond initially, relapse is always possible. Affected dogs should be frequently monitored, and treatment can be life-long.

CONCLUSION

Protein-losing enteropathy (PLE) is a heterogenous syndrome in dogs most commonly caused by chronic inflammatory enteropathy, intestinal lymphangiectasia, or a combination of the two disorders. Diagnosis requires the exclusion of other causes of hypoalbuminemia, followed by a systematic work-up to identify the specific cause. Treatment should be individualized depending on the specific cause of a dog's PLE, rather than a standardized approach, and dietary management is the cornerstone of therapy in many cases of canine PLE.

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GIARDIASIS INFECTION IN DOGS

Giardia infection is commonly identified in dogs, but deciding if it is a significant finding, and selecting the best treatment approach for a given situation, can often raise questions in practice; this article aims to provide some answers for the clinician.

KEY POINTS

1. ***Giardia duodenalis*** **has a variable prevalence in the canine population; infection is often asymptomatic but can cause soft stools or watery diarrhea.**
2. **Fenbendazole and metronidazole are both recommended for treating giardiasis, and the clinician's choice will be guided by the history and circumstances of an individual patient.**
3. **An animal that has a positive *Giardia* test but has no clinical signs usually does not require treatment.**
4. **If giardiasis recurs, good environmental hygiene measures and preventing dogs from drinking surface water or eating feces can help eradicate the infection.**

Introduction

With the availability of better diagnostic methods, the single-celled parasite *Giardia duodenalis* is nowadays frequently detected in dogs and cats. However, infection can range in severity, from subclinical to causing a variety of gastrointestinal (GI) signs, and the clinician may have many questions surrounding this parasite – for example, the sensitivity and specificity of diagnostic tests, the need to treat or not, and the best options for treatment. Furthermore, clinical signs may persist after treatment, or a feces test can remain positive despite successful therapy and clinical improvement, so given that this parasite can raise so many questions, it is important that the diagnosis, treatment and management of *Giardia* infections is clear and unambiguous. Answers – sometimes confounding – can be obtained from different sources: from a parasitologist, a GI specialist, a laboratory, or the manufacturer of drugs registered for the treatment of *Giardia*. It is therefore not easy to provide general advice that is valid in all situations, but a unified approach to *Giardia* infections leads to better control and ensures that any other GI problems present can be recognized at an early stage. This article aims to provide information on which to base such an approach.

Epidemiology

The flagellate *Giardia duodenalis* (syn. *G. lamblia, G. intestinalis*) occurs worldwide as a protozoan intestinal parasite in mammals (including humans), birds, reptiles and amphibians. With genotyping, the parasite can be divided into 8 groups (known as assemblages A to H), which generally exhibit clear host specificity. Assemblages A and B occur in humans, C and D in dogs, and F in cats. Assemblages A and B are sometimes found in dogs and cats, but C, D or F have to date rarely been demonstrated in humans, (1,2).

Giardia prevalence in humans ranges from 0.4-7.5% in western countries to 8-30% in non-industrialized countries (3), and it is estimated that more than 1 billion people worldwide are infected with the parasite (4). Infection rates in humans, dogs and cats vary widely by country, living conditions and testing methods. In Europe, prevalences of 3-7% are reported in domestic dogs, but in kennels it can be as high as 46% (3,5). In non-industrialized countries, the parasite may be found in 10-30% of pet dogs (3). In a Dutch study that looked at 381 dogs without signs, hunting dogs were found to have the highest prevalence of *Giardia* (65%) while a random group of pet dogs in the same study had a prevalence of 8%. Another study reported a prevalence of 25% in fecal samples sent to a diagnostic laboratory from 192 dogs that did have clinical GI signs (6).

Life cycle

Giardia has a direct life cycle. After ingestion of infectious cysts from food, drinking water or the environment, motile trophozoites excyst in the anterior part of the small intestine and then

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attach to the mucosa with a ventral suction cup. Asexual multiplication takes place, after which the trophozoites encyst further down the small intestine and are then excreted in the feces in large numbers (sometimes intermittently) for weeks to months **(Figure 1)**. Mobile trophozoites can be seen in fresh, still-warm stools if there is accelerated intestinal passage, (*i.e.*, diarrhea) but these do not survive gastric passage and are therefore not infectious **(Figure 2)**. The immobile cysts are highly resistant (hence the persistently high environmental levels), and are immediately infectious once excreted **(Figure 3)**. Feco-oral contamination occurs by ingestion of cysts via coprophagy, or via fur, food, soil or drinking water contaminated by feces. In humans it has been shown that infection can occur with very low numbers (10-100) of cysts (7). Infection can remain active for weeks to months and be acute, chronic or subclinical. The incubation period in dogs is four to sixteen days, and the minimum time between time of infection and the first opportunity to detect the parasite in feces (the prepatent period) averages seven days. Although cysts can survive for months in the environment, they are sensitive to sunlight and dehydration and are greatly reduced in number by freeze-thaw cycles (5,8); the colder and more humid the environment, the longer the cysts remain infectious.

Asymptomatic carriers of *Giardia* (9) can infect the environment unnoticed for long periods. It is assumed that infection induces partial immunity to an individual, which reduces clinical signs, and that the infection eventually disappears, after which the host shows limited resistance to reinfection (5).

Clinical signs

Giardia infection is usually subclinical in nature and is often self-limiting, but it can cause chronic intermittent soft or slimy stools and even watery diarrhea. In addition, anorexia, vomiting, emaciation and lethargy may occur, especially in animals with reduced immunity, puppies, in the presence of concurrent infection, or working dogs. Where young puppies are infected, retarded growth and development may be observed.

At the intestinal level, little inflammation is seen in the acute stage. Maldigestion, malabsorption and malsecretion explain the clinical picture. The severity of signs is highly dependent on various factors, including the *Giardia* strain, host immunity, age and nutritional status, and the presence of any other infections. However, if a host also has a worm burden, this seems to inhibit the development of the *Giardia* population, with a lower number of cysts being found on microscopic examination (10). Treatment with anthelmintics may therefore increase susceptibility to *Giardia* infection, probably because worm-induced T-helper 2 activity ensures a good immune response against *Giardia* (11,12). Although the parasite does not invade the mucosa, changes inside and outside the GI tract have been described in humans that can lead to growth retardation and even emaciation, as well as chronic post-infectious changes, again both within the GI tract and elsewhere in the body (13).

Given that the prevalence of *Giardia* varies greatly, it can be difficult to predict how frequently it may account for clinical signs in dogs. Infection was not found to be significantly associated with loose stools in a recent study of 1,291 dogs from various backgrounds (namely, household, shelter, hunting and

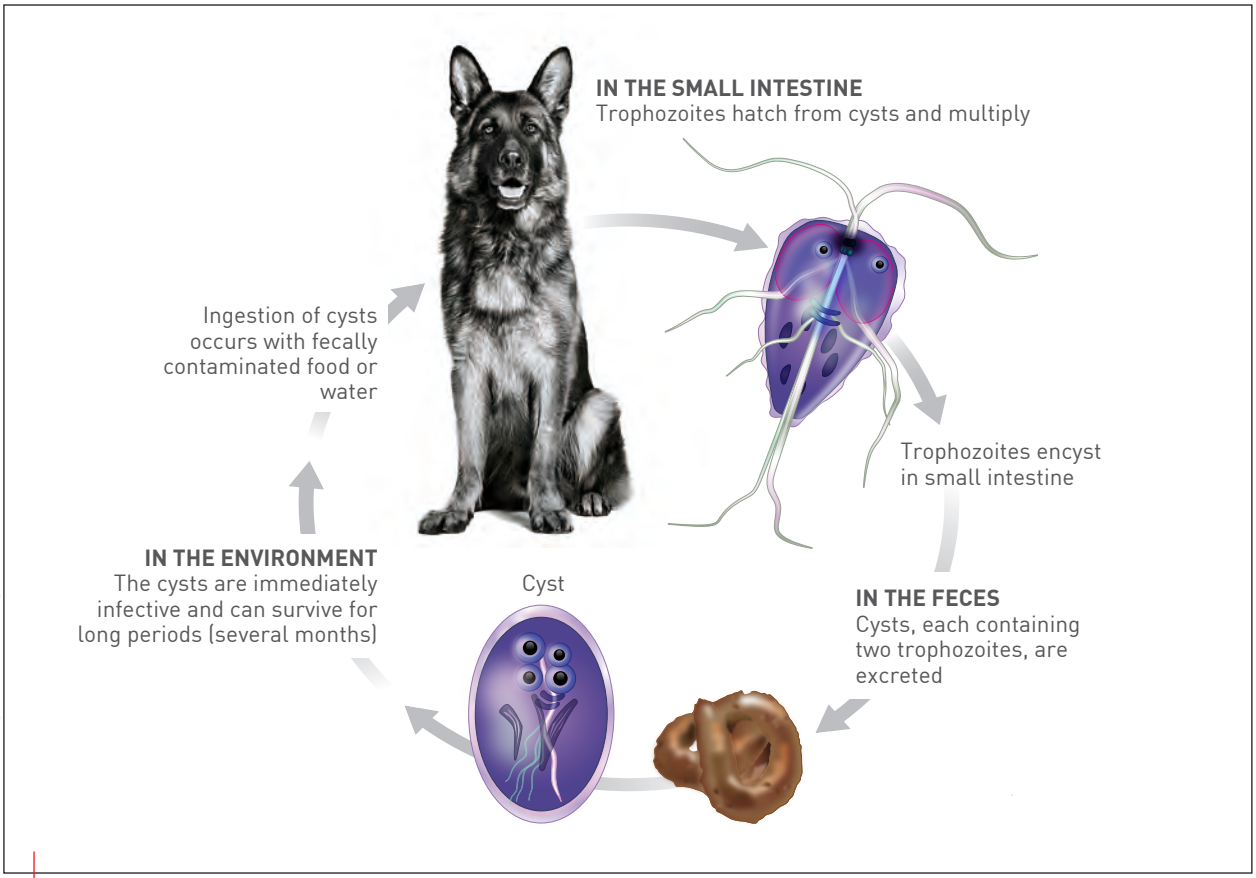

Figure 1. The life cycle of *Giardia duodenalis*.

laboratory-kept dogs), although household dogs were significantly more likely to test *Giardia*-positive if they had diarrhea. Young dogs and dogs in kennels were significantly more likely to be positive for the parasite on testing, and these associations were consistent across different diagnostic testing methods. Young dogs and dogs with clinical signs were noted to excrete the highest numbers of *Giardia* cysts (10).

Diagnostics

Several tests are available for the detection of the *Giardia* parasite (6,14); these are:

- Fecal smear (using still-warm thin stools viewed immediately for the presence or absence of moving trophozoites)
- Passive flotation technique
- Centrifuge-sedimentation flotation (CSF)
- Rapid (ELISA) point-of-care (benchtop) tests (often based on the detection of cyst wall protein in feces)
- Immunofluorescence test (IFT)/direct immunofluorescence assay (DFA)
- Polymerase chain reaction (PCR)

The relative sensitivity of each method is shown in **Figure 4**. Note that IFT and PCR tests can only be performed in specialist laboratories.

At least one study has reviewed the different tests available. Fecal samples from 573 dogs were examined using a variety of methods

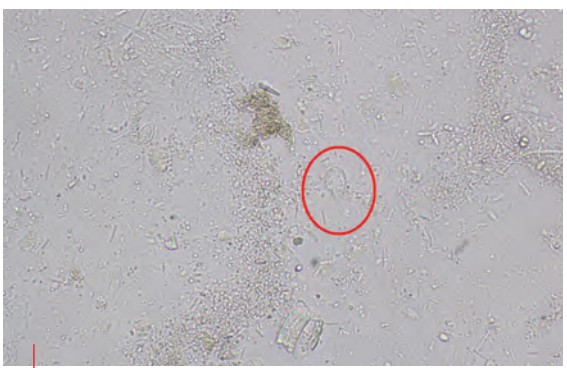

Figure 2. A *Giardia* trophozoite in the feces (red circle) (600x).

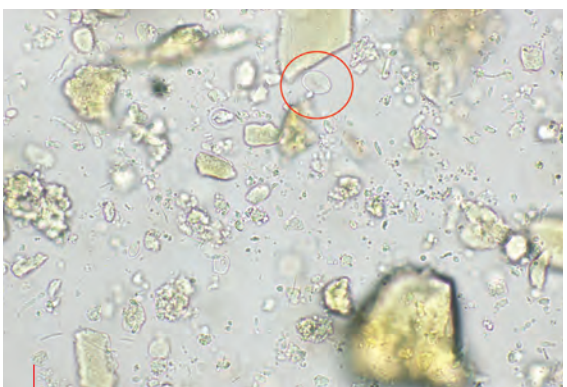

Figure 3. An intact *Giardia* cyst in the feces (red circle) (600x).

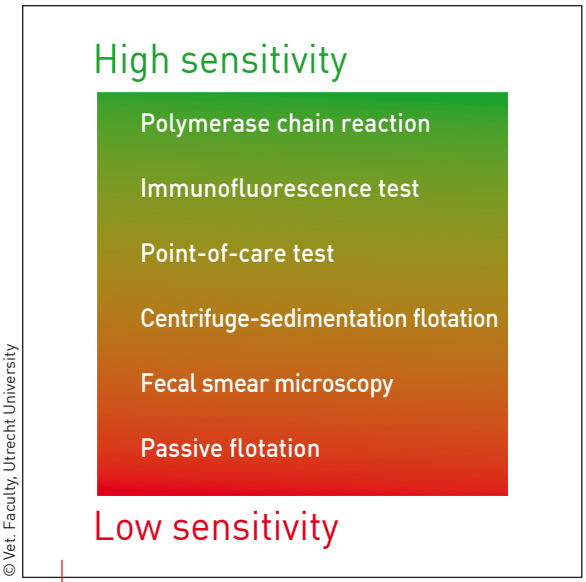

Figure 4. An overview of the sensitivity of the various *Giardia* tests.

(CSF, microscopic analysis, DFA, rapid enzyme immunochromatographic assay, and qPCR) for the presence of *G. duodenalis*. It was concluded that all tests were highly specific, with the rapid assay showed the highest relative specificity (99.6%) and qPCR the lowest (85.6%). The relative sensitivities were much more variable, with qPCR showing the highest (97.0%) and CSF the lowest (48.2%) sensitivity. DFA was more sensitive than the rapid point-of-care assay, but slightly less specific. Methods that involve microscopy for cyst identification or cyst wall detection should be used in situations where high specificity is required (6), but it is debatable if this is necessary for a diagnosis when investigating clinical cases of diarrhea.

Because the sensitivity and specificity of the various diagnostic tests are not 100%, a negative test does not completely exclude infection, and a positive result does not guarantee the presence of *Giardia* infection. Trophozoites are mainly detected when diarrhea is severe, and cysts tend to be excreted in moderate numbers and intermittently. On the other hand, a true positive test result does not always mean that *Giardia* is the cause of the clinical signs, only that

"*Giardia* infection is usually subclinical in nature and is often self-limiting, but it can cause chronic intermittent soft or slimy stools and even watery diarrhea."

Paul A.M. Overgaauw

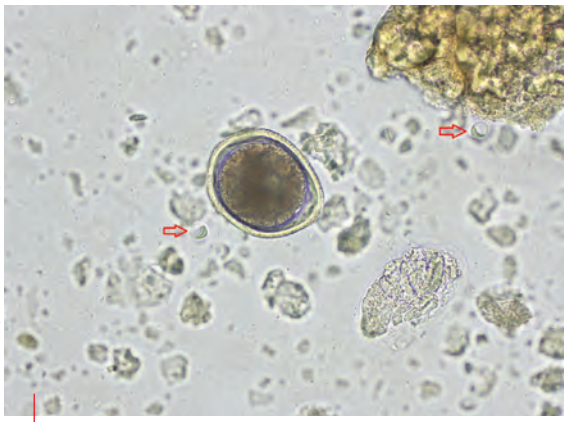

Figure 5. Mixed infection with *Giardia* cysts (red arrows) and a *Toxocara* roundworm egg (400x) in the feces.

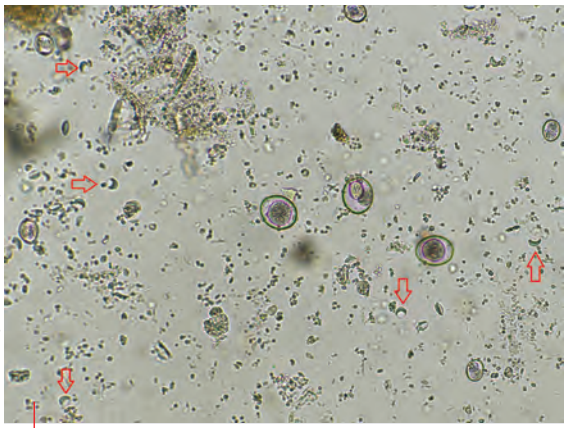

Figure 6. Mixed infection within a feces sample, showing *Giardia* (red arrows) and some *Cystoisospora* cysts (200x).

the cysts (or cyst wall proteins) are present. In a study of 152 healthy domestic dogs without clinical signs, *Giardia* cysts were found in the feces in 15% of the animals using CSF (15), whilst in a study of 8,685 dogs with diarrhea or vomiting, 24.8% of animals tested positive for *Giardia* using a rapid ELISA test (16).

Because *Giardia* cysts can be excreted intermittently, fecal examination with CSF can yield a false negative result, especially if an animal is excreting only moderate numbers of cysts. However, reliability increases when feces from three consecutive days are tested. This does not apply to the increasingly common rapid benchtop tests, where one sample is sufficient for a reliable result. An advantage of the CSF method is that it can give information about the presence of other parasites, whereas many rapid tests only detect *Giardia*. Indeed, studies have shown that mixed infections are often found in dogs with diarrhea (7), so a general fecal examination may therefore add value. In addition to worm infections **(Figure 5)**, protozoan infections such as *Cystoisospora* spp. should also be considered **(Figure 6)**. With the rapid test, a false positive result may occur if cyst wall protein is still present in the intestine even when no viable cysts remain; the proteins can still be detectable for 1 to 2 days after infection has passed (due to the transit time from

the small intestine to fecal excretion). In practice, positive rapid benchtop tests are sometimes seen in animals with no clinical signs following treatment, when other diagnostic tests return a negative result.

Because *Giardia* can also be present in dogs without signs, the clinical picture should always be the deciding factor; if trophozoites, cysts or cyst wall proteins are detected in a healthy dog that shows no clinical signs, initiating therapy is not necessary, although it is useful to monitor the animal. However, the situation may be very different if an asymptomatic animal which has tested positive is introduced into a negative population of susceptible animals.

For animals with trophozoites detected on fecal smear, or where there is a positive CSF or rapid benchtop test with matching clinical signs, therapy is a useful course of action. Dogs in shelters and kennels will often show persistent or recurrent signs suggestive of a *Giardia* infection and will frequently test positive. There is no clear correlation between the number of cysts found in feces and the severity of infection. The same applies to the presence of trophozoites in feces, and detection of such does not necessarily indicate serious infection, but does indicate accelerated transport through the intestine (*i.e.*, diarrhea), which may either be due to the presence of *Giardia* or other causes.

Treatment

Household dogs

A three-day course of fenbendazole (50 mg/kg q24H) is licensed in some countries for treating *Giardia* infections in dogs, and is the drug of first choice (17-19); however, three days of therapy can be insufficient in some cases, and there is also the risk of autoinfection/re-infection. Treatment of longer duration (*e.g.*, up to 10 days) is therefore sometimes recommended, although note this may be outside the manufacturer's recommendations in many countries (20). When dealing with clinical infections, the patient's perineum, hindquarters and hind legs can be washed (*e.g.*, with a chlorhexidine shampoo) to remove cysts from the hair. This is particularly useful if the risk of reinfection from the environment is very low and therefore the likelihood of auto-infection from an animal washing itself is relatively high. Cleaning up feces as soon as possible after toileting is always recommended.

"A true positive test result does not always mean that *Giardia* is the cause of the clinical signs, only that the cysts (or cyst wall proteins) are present."

Rolf R. Nijsse

If there is insufficient improvement after a week on treatment, and other causes such as concurrent infections have been ruled out, therapy can be repeated. If necessary, an alternative option is metronidazole (25 mg/kg q12H for five days, or as advised by the data sheet). With this drug, keep in mind that neurological side effects can sometimes occur, but there is some evidence that a dose of 25 mg/kg q24H is also effective and greatly reduces the risk of side effects (5,16). Metronidazole should be used with caution due to antibiotic resistance issues.

If multiple dogs are present in a household, it should be borne in mind that reinfection can be caused not only by the patient itself or from the environment, but also by an asymptomatic carrier in the house, and it may be prudent to test the other animals in the household as well.

In addition to medication, an easily digestible gastrointestinal diet can help support recovery, especially where metronidazole has been used, as it can have a negative impact on the intestinal flora. Some publications will recommend a low-fiber, low carbohydrate, high protein diet to prevent rapid growth and multiplication of *Giardia* and *Clostridium* spp. However, improvement is sometimes seen with a diet that has higher crude fiber content and is less digestible. The substrate change, together with the host's immunity and possible medication, can slow the growth of *Giardia* to such an extent that the immune balance reverses and the host controls the infection by itself.

The prognosis for giardiasis is usually good, but in young, dehydrated or older animals, and for those with reduced immunity, there is an increased risk of complications; for instance, attachment of the *Giardia* trophozoites may lead to breakdown of the tight junctions of the intestinal epithelium, potentially resulting in secondary bacterial infections (21). Experience shows that despite all measures, some chronic cases can persist with little or no response to therapy. If the animal has been treated and *Giardia* is no longer present, yet clinical signs persist, then further investigation is advised – for example, to look for other protozoal infections, chronic intestinal inflammation and food allergies.

Kennels

For larger groups of animals under kennel conditions with proven *Giardia* infection, it is advisable to divide the animals into smaller groups or to house them individually. In this situation it is also useful to treat asymptomatic animals which test positive for *Giardia* in order to reduce environmental contamination as much as possible. At the end of the treatment period the animals should be washed and transferred to a clean, dry and disinfected pen. Care must obviously be taken to ensure that the animals have no access to potentially contaminated natural water sources afterwards.

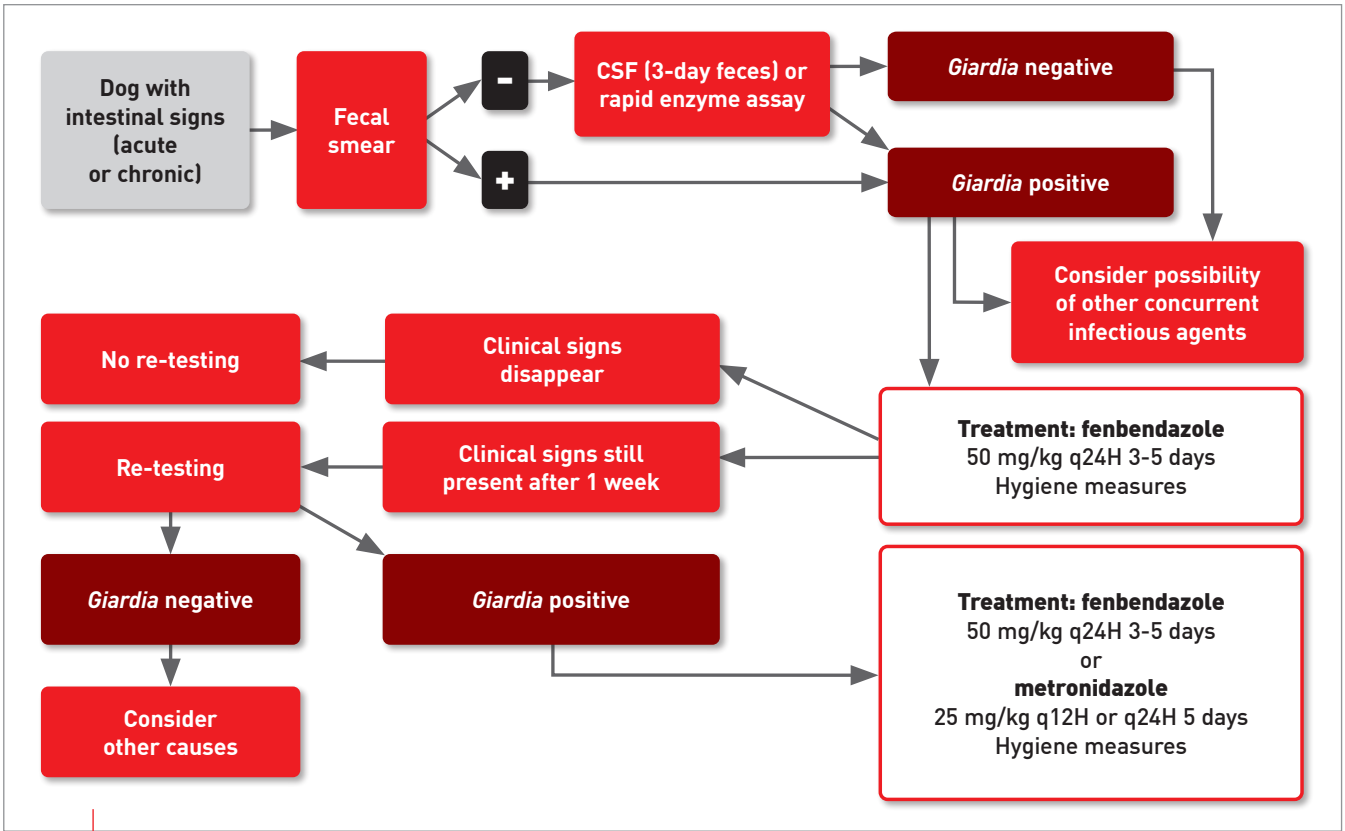

Figure 7. A decision tree for diagnosis and treatment of *Giardia* infections in dogs (modified from 25).

A study has described the control of *Giardia* in a group of test dogs (22), where individually kept beagles were treated with a combination of febantel (a precursor of fenbendazole)/praziquantel/pyrantel for three days. The pens, constructed from stainless steel with a smooth epoxy floor, were disinfected daily with quaternary ammonium compounds or sodium hypochlorite solution (bleach). The latter substance is commonly used, but an insufficient effect is regularly reported. Despite this, *Giardia* was found to be present again in several dogs after 17-24 days, and all dogs developed diarrhea again. When the dogs were washed on the last day of re-treatment and then moved to a clean pen, the problems disappeared.

Environment

When recurrences occur (and especially in kennels), attempts can be made to reduce the infection pressure by treating the environment wherever possible. Reinfection can easily occur if a dog eats feces from other animals, or drinks from an infected garden pond, or from puddles of water. The plan of action therefore depends on the situation.

After cleaning smooth surfaces within the household and allowing them to dry thoroughly, it is essential to render cysts inactive via disinfection with a quaternary ammonium compound. However, these are not widely available for private use and only work in a clean environment without soap residues. For effective disinfection, the agent must be in contact with the surface for a sufficiently long period of time, often at least five minutes, so the manufacturer's package leaflet should always be consulted. Carpets and fabric furniture can be treated with hot water or steam (5 minutes at 70°C or 1 minute at 100°C) (8), but advance testing to ensure that the surfaces can withstand these methods is recommended. Hot water (dishwashers, washing machines) can also be used to disinfect clothing, bedding, toys and food bowls, and again treatment duration depends on the temperature; water at 45°C disinfects in 20 minutes, but at 70°C only requires 5 minutes. A tumble dryer and sunlight can also contribute significantly to the disinfection process. If any cars are used to transport affected dogs (including *e.g.*, a dog-walking service), these should also be disinfected. Since *Giardia* can also cause infection via surface water, dogs should be prevented from drinking water from outside and licking the grass etc., as far as possible.

Follow-up and possible re-infection

Given the prepatent period of at least seven days, repeating fecal testing in clinical infections no sooner than eight to ten days after the end of treatment is recommended. Re-testing is really only useful if the animal still presents with clinical signs or if the animal is transferred to a closed, *Giardia*-free (susceptible) population. If signs persist, the possibility of another cause should be considered, but recurrence is a potential problem,

either by reinfection or possibly due to insufficient efficacy of the initiated therapy or lack of compliance. A summary for the various diagnostic and treatment procedures to be followed is given in **Figure 7**.

Is *Giardia* a zoonotic disease?

It is often mentioned that dog and cat *Giardia* spp. can also infect humans, but is this parasite a true zoonosis? In fact, the risk of transmission from dog or cat to humans is very low (23,24). The specific *Giardia* assemblages (C and D) from dogs and (F) from cats are rarely found in humans (3). Conversely, human assemblages can circulate in dog and cat populations, and humans can apparently be the source of infection for dogs and cats, after which these animals in turn pose a zoonotic risk. In cases where both family members and pets show symptoms suggestive of *Giardia* infection, mutual transmission of a human assemblage A or B is possible. In cases of diagnosed *Giardia* infection in a pet, the veterinarian may inquire if GI signs are present in any family member and, if the answer is positive, can advise consulting a doctor.

CONCLUSION

Fecal examination, centrifuge sedimentation flotation and rapid benchtop tests can all be used to diagnose *Giardia* in dogs presented to the clinic. If clinical signs are present and a *Giardia* test is positive, fenbendazole is the first-choice therapy, but a healthy animal that tests positive yet has no signs usually does not require treatment. Where there is recurrence, it may be useful to wash the hindquarters of the patient, and it is also important to clean and disinfect the environment, food and drinking bowls, and to prevent dogs from drinking surface water from the environment or eating feces. The risk of transmission of *Giardia* from dogs to humans is, however, very low.

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ATYPICAL CANINE HYPOADRENOCORTICISM

Romy M. Heilmann

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Professor Heilmann is an ACVIM- and ECVIM-boarded certified small animal internist, with a special interest in gastroenterology, hepatology, clinical immunology, and interventional radiology and endoscopy. After graduating in 2005 she worked in a small animal practice in Germany before returning to academia to gain her postgraduate doctoral degree. She then completed a rotating small animal internship in Switzerland before moving to Texas A&M University for a combined Small Animal Internal Medicine (ACVIM-SAIM)/Ph.D. program. She returned to Europe in 2015 as head internist at a Swiss veterinary specialist and referral center before being appointed to her current post as Professor and Head of the Small Animal Internal Medicine service at Leipzig University in 2016. Her research involves novel routes to the diagnosis and treatment of chronic gastroenteropathies in dogs and cats as well as other primary inflammatory disorders.

Addison's disease may not be the first diagnosis that comes to mind when a dog with gastrointestinal signs presents, but this possibility should not be dismissed, as Romy Heilmann describes.

KEY POINTS

1. Dogs with typical hypoadrenocorticism usually present with an obvious clinical picture and clinicopathologic findings, and may offer a straightforward diagnosis.
2. Atypical hypoadreno-corticism is often associated with nonspecific, waxing and waning chronic gastrointestinal signs, which may be triggered or exacerbated by stress and often respond to symptomatic treatment.
3. Evaluation of dogs with atypical hypoadrenocorticism requires a "detective approach" to the patient in order to arrive at the correct diagnosis.
4. Both forms of hypoadrenocorticism are generally associated with a very good long-term prognosis.

Introduction

Hypoadrenocorticism in its typical form (Addison's disease) is often a straightforward diagnosis when the classic signs and clinicopathological changes are obvious and tie in nicely with the patient's history and signalment – so it may seem odd that a gastroenterologist should need to consider this condition when doing an examination. However, the clinical picture of affected dogs – particularly those with spontaneous atypical hypoadrenocorticism – may be nonspecific. These can include chronic gastrointestinal signs that wax and wane and which can be triggered or exacerbated by stressful events, and often respond to fluid therapy and symptomatic treatment. Thus, hypoadrenocorticism – particularly its atypical form – can mimic primary gastrointestinal diseases and should not be omitted from the differential diagnosis list in dogs presenting with vague and nonspecific gastrointestinal signs.

Some background details

Terminology

Hypoadrenocorticism, or Addison's disease, develops when the adrenal cortex is unable to produce and release sufficient amounts of endogenous glucocorticoids and – particularly in typical cases – also mineralocorticoids

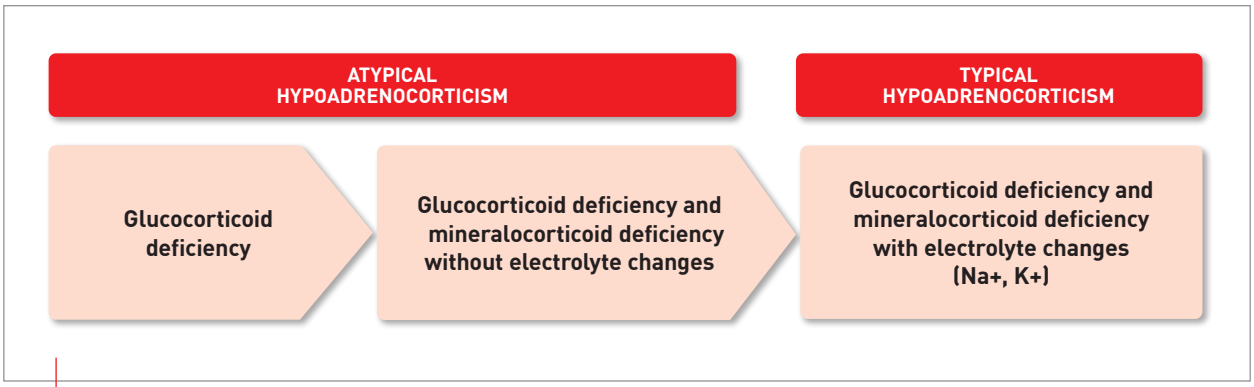

Figure 1. Current classification of spontaneous hypoadrenocorticism in dogs.

(Figure 1) (1). As opposed to the typical presentation of hypoadrenocorticism, with characteristic clinical and clinicopathological features caused by the concurrent glucocorticoid and mineralocorticoid deficiency, cases of atypical hypoadrenocorticism in dogs are more challenging to diagnose, as this form of adrenal insufficiency is not only less common but also produces a more subtle, non-specific clinical picture (1,2). A transition from atypical to typical hypoadrenocorticism is possible, for which atypical cases should be monitored over time (2). In dogs with the typical presentation, where clinical decompensation with dehydration and hypovolemic shock (Addisonian crisis) can occur, the progression from a sole glucocorticoid deficiency can merely be assumed based on the retrospective impression of a slow onset of the disease and associated clinical signs. However, this progression is difficult to prove in typical cases of hypoadrenocorticism. Breed predispositions are reported in Standard Poodles, Portuguese Water dogs, Nova Scotia Duck-tolling Retrievers, Soft-Coated Wheaten Terriers, and Bearded Collies, but dogs of any breed and age can be affected by either form of this condition (2-5). Compared to typical cases, dogs with atypical hypoadrenocorticism tend to be older.

"Dogs diagnosed with atypical hypoadrenocorticism having a normal baseline and/or ACTH-stimulated serum aldosterone concentrations require only glucocorticoid substitution, but serum electrolytes should be monitored regularly in these dogs."

Romy M. Heilmann

Etiology

Hypoadrenocorticism can be caused by any condition that decreases hormone production and release from the adrenal cortex. Most commonly it is caused by an immune-mediated process that reduces the functional mass of the hormone-producing adrenal cortex, particularly the middle-to-inner glucocorticoid-producing portion (zona fasciculata) (5-7). Other, less common or rare causes of primary hypoadrenocorticism include granulomatous conditions (*e.g.*, fungal disease), vascular causes (*e.g.*, hemorrhage, ischemia), amyloid deposits (particularly in breeds predisposed to develop amyloidosis), necrosis, or metastatic neoplasia (8-10). Secondary (central) hypoadrenocorticism can evolve from conditions affecting production and release of hypothalamic corticotropin-releasing hormone (CRH) and/or pituitary adrenocorticotropic hormone (ACTH), including inflammation, infections, trauma, and neoplasia (1,11).

Pathophysiology

In the typical form of hypoadrenocorticism, uncompensated glucocorticoid and mineralocorticoid deficiency result in the characteristic plasma electrolyte shifts (hyperkalemia, hyponatremia) (1). In contrast, in the atypical form, there is either only glucocorticoid deficiency or combined corticosteroid (glucocorticoid and mineralocorticoid) deficiency without electrolyte shifts, due to aldosterone-independent compensatory mechanisms (*e.g.*, renal compensation) (1,2).

Detecting hypoadrenocorticism – the great pretender

Clinical signs

Given the various effects of endogenously released glucocorticoids on the body **(Figure 2)**, including cardiac and gastrointestinal functions (12,13), dogs with atypical hypoadrenocorticism usually present with vague, waxing and waning nonspecific signs such as reduced activity (*e.g.*, during agility performance), lethargy, weakness, inappetence, weight loss or lean body condition **(Figure 3)**,

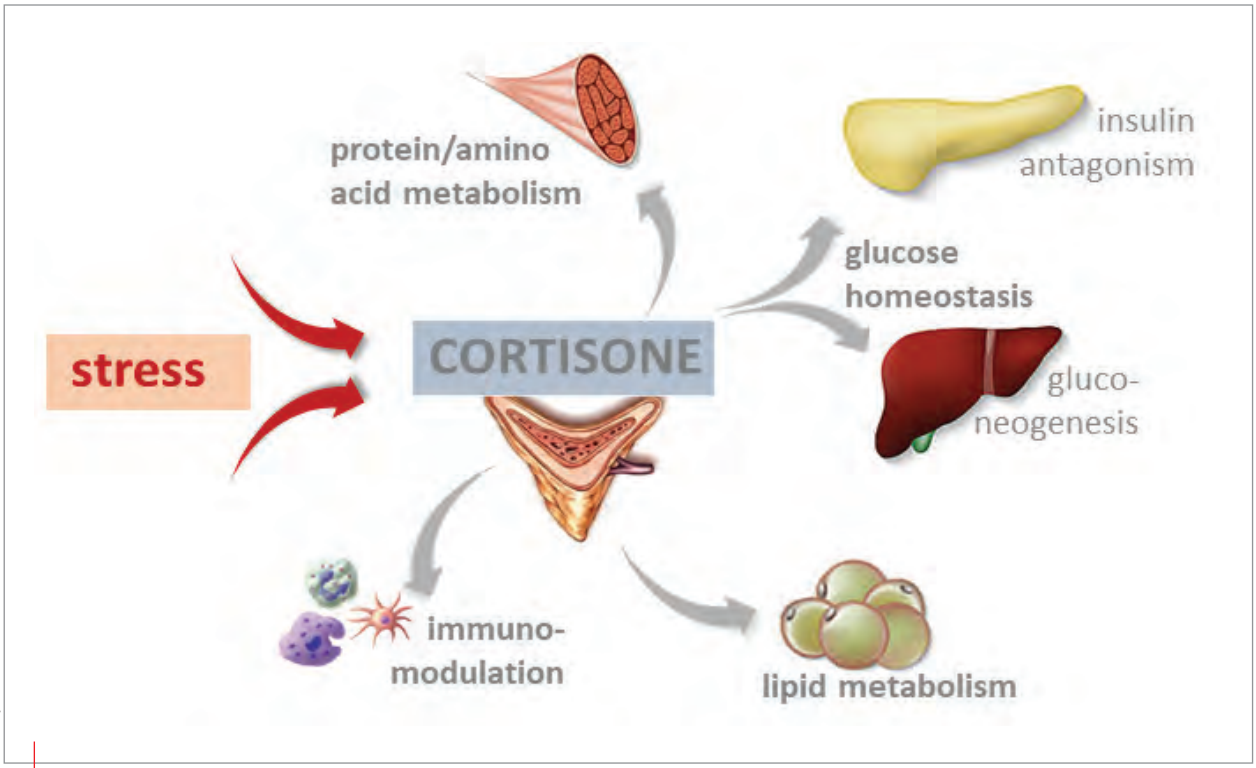

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Figure 2. Effects of endogenous glucocorticoids (cortisone) on different body tissues. With glucocorticoid deficiency (hypoadrenocorticism), these effects cannot be mounted whenever there is increased stress (indicated by red arrows), leading to an insufficient stress response (gray arrows).

vomiting (with or without hematemesis) or regurgitation, diarrhea (which may be hemorrhagic), abdominal pain, and incontinence (1,2,13,14).

Laboratory diagnostics

The minimal database should comprise a complete blood count, serum biochemistry and urinalysis (with evaluation of the urine sediment and, if indicated, bacterial culture with antimicrobial susceptibility testing and a urine protein-to-creatine ratio). These may often reveal subtle and non-specific changes in dogs with atypical hypoadrenocorticism. However, a mild non-regenerative anemia is a common finding, as cortisol increases erythropoiesis and decreases erythrocyte turnover, but the absence of an expected stress leukogram (or even opposite trends in individual cell counts, often referred to as "reverse stress leukogram") may be a subtle indicator, and can be missed if not specifically evaluated **(Box 1)**. Given the opposing effects of glucocorticoids on neutrophil and lymphocyte counts, a neutrophil-to-lymphocyte ratio of ≤2.3 should raise a suspicion of hypoadrenocorticism (15).

Hypoglycemia (or a low-normal blood glucose concentration), hypoalbuminemia, hypocholesterolemia, increased liver enzyme activities (with a hepatocellular pattern of enzyme increase – *i.e.*, serum ALT increased more than ALP increase), and mild to moderate prerenal azotemia may be detected (1).

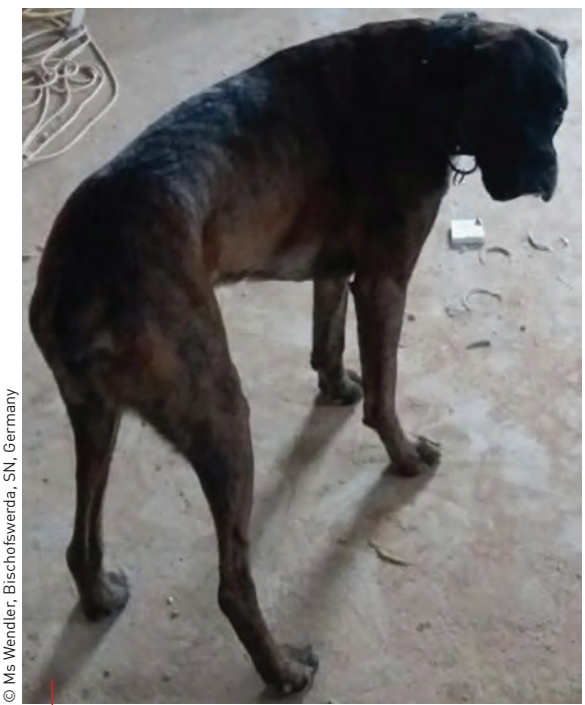

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Figure 3. Clinical appearance of a 9½-year-old male Boxer dog with atypical hypoadrenocorticism. The dog presented for further diagnostic evaluation of long-term gastrointestinal signs, with a history of chronic vomiting, hematemesis, intermittent hyporexia, diarrhea, and weight loss (14% over 3 months). Physical examination was unremarkable except for a low body condition score (BCS, 2.5/9).

However, distinction from renal azotemia can be challenging, as dogs with hypoadrenocorticism often have reduced urine-concentrating ability (urine specific gravity <1.030). At best, some or all of these clinicopathologic findings might raise the suspicion of hypoadrenocorticism, or at least should be a reason not to abandon the possibility of the condition being the underlying cause of the clinical presentation prior to evaluating other differential diagnoses (*e.g.*, protein-losing enteropathy, chronic hepatopathy) with a more invasive diagnostic approach and involving general anesthesia. This is important, because stress associated with invasive procedures could potentially place the dog in a life-threatening situation of decompensated hypoadrenocorticism if the condition remains unrecognized. Hyperkalemia and hyponatremia, which are often expressed as a decreased sodium-to-potassium ratio (Na/K <27), are characteristic findings in the typical form of hypoadrenocorticism, but are absent in the atypical form **(Box 2)** (4). Digital health tools, particularly algorithms incorporating the results of several routine findings, may help to improve the detection of atypical hypoadrenocorticism cases in the future (16).

Box 1. Relevant hematologic findings in a 6-year-old female dog with hypoadrenocorticism. Notice the presence of a "reverse stress leukogram" with mild lymphocytosis, eosinophilia, and a decreased neutrophil-to-lymphocyte ratio (N/L-R) of 1.31. Any N/L-R of ≤2.3 should raise a suspicion of hypoadrenocorticism.

N/L-R= 1.31

Parameter	Result	Unit	Reference interval
Erythrogram			
Hematocrit	33.8	%	37.3-61.7
MCV	61.2	fL	61.6-73.5
MCH	22.3	pg	21.2-25.9
Leukogram			
Neutrophil count	**7.53**	x10^9/L	2.95-11.64
Lymphocyte count	**5.75**	x10^9/L	1.05-5.10
Monocyte count	0.67	x10^9/L	0.16-1.12
Eosinophil count	**1.25**	x10^9/L	0.06-1.23
Basophil count	0.07	x10^9/L	0.00-0.10
Thrombocytes			
Platelet count	368	K/µL	148-484
MPV	9.7	fL	8.7-13.2

Box 2. Serum biochemistry panel with electrolytes from the Boxer dog in **Figure 3**. Except for mild hypoalbuminemia and low-normal serum cholesterol and glucose concentrations, this dog's serum biochemistry was unremarkable, and a protein-losing enteropathy was suspected.

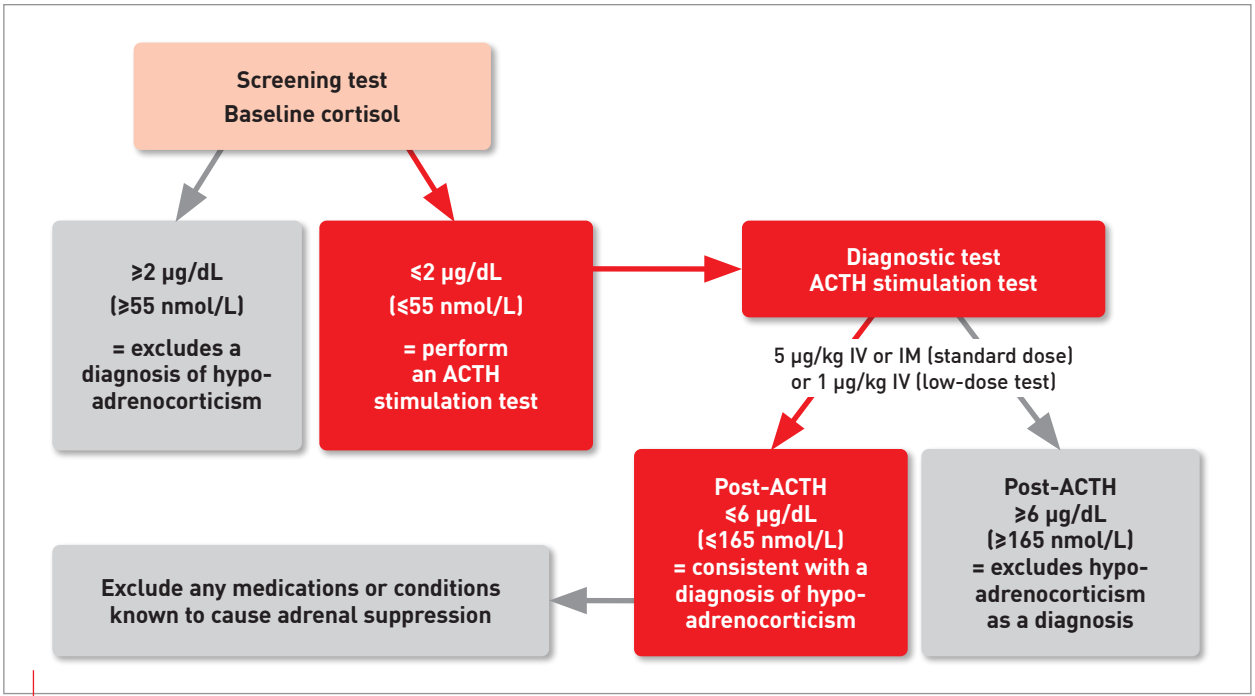
Parameter	Result	Unit	Reference interval
Glucose	97	mg/dL	57-126
Cholesterol	167	mg/dL	139-398
SDMA	11	µg/dL	0-14
Creatinine	1.1	mg/dL	0.5-1.5
BUN	21	mg/dL	9-29
Phosphate	1.1	mmol/L	0.9-1.7
Calcium	2.3	mmol/L	2.1-2.9
ALT	72	U/L	25-122
ALP	37	U/L	14-147
Total protein	5.9	g/dL	5.4-7.6
Albumin	**2.3**	g/dL	2.8-4.3
Bilirubin	0.2	mg/dL	0-0.4
Sodium	145	mmol/L	142-153
Potassium	4.2	mmol/L	3.9-5.8

Endocrine testing

Measurement of the serum baseline ***cortisol*** concentration is a useful screening test **(Box 3)**. Using a cut-off baseline of 2 µg/dL (55 nmol/L) excludes a diagnosis (100% sensitivity, 63-78% specificity) of hypoadrenocorticism **(Box 4)** (17,18). If the baseline is <2 µgdL an ACTH stimulation test should be performed to either diagnose or exclude hypoadrenocorticism (1,17,18). With this test, serum cortisol <2 µg/dL is diagnostic, whilst levels >6 µg/dL are exclusive. Low-dose ACTH-stimulation testing (using 1 µg/kg of cosyntropin IV instead of the standard dose of 5 µg/kg) is effective in diagnosing hypoadrenocorticism in dogs (19). Measurement of ***endogenous ACTH*** (eACTH) concentration can be used to confirm and further classify hypoadrenocorticism as either primary or secondary in nature **(Box 5)** (1,15). Primary hypoadrenocorticism (*i.e.*, adrenal origin) is associated with a normal or high eACTH concentration, whilst secondary hypoadrenocorticism (*i.e.*, central origin involving the hypothalamus and/or pituitary gland) is associated with an undetectable or low eACTH concentration.

Box 3. The thyroid and gastrointestinal panel from the Boxer dog with atypical hypoadrenocorticism in **Figure 3.** Low total and free thyroxine concentration, hypercobalaminemia (without prior supplementation), and hypocortisolemia (below the cut-off concentration of 55 nmol/L used for the screening for hypoadrenocorticism) are detected. These results should be followed with an ACTH stimulation test.

Parameter	Result	Unit	Reference interval
Thyroid panel			
Total T_4	**0.8**	µg/dL	1.0-4.0
Free T_4	**<0.3**	ng/dL	0.6-3.7
Gastrointestinal panel			
Spec cPL	142	µg/L	0-200
cTLI	37	µg/L	8.5-35
Cobalamin	**1,355**	pmol/L	173-599
Folate	25.9	nmol/L	21.1-54
Cortisol (baseline)	**6.5**	nmol/L	25-125



Box 4. Diagnostic algorithm for endocrine testing in dogs with suspected hypoadrenocorticism. The flow chart shows the suggested diagnostic screening for hypoadrenocorticism (left-hand panels) if the clinical suspicion for this condition is moderate or low. Correct interpretation of the confirmatory diagnostic test (right-hand panels), which is performed if the clinical suspicion for the disease is moderate to high, requires any prior treatment that could interfere with the results (*e.g.*, glucocorticoids (including topical) treatment, azole antifungal drugs) within 4 weeks of the test to be excluded. Most dogs with hypoadrenocorticism will have a baseline and post-ACTH serum cortisol concentration below 2 µg/dL (55 nmol/L). ACTH-stimulated serum cortisol concentrations >2 µg/dL (>55 nmol/L) but <6 µg/dL (<165 nmol/L) are equivocal and reflect some adrenal reserve capacity, and potential causes for adrenal suppression should be explored.

The urine cortisol-to-creatinine ratio (UCCR) has recently received attention for the diagnosis of canine hypoadrenocorticism, and a low UCCR (≤2 measured by radioimmunoassay or ≤10 by chemiluminescent immunoassay) was highly sensitive and specific to distinguish affected dogs from those with a disease mimicking hypoadrenocorticism (20).

Mineralocorticoid deficiency without hyperkalemia and/or hyponatremia, presumed to be primarily compensated via renal mechanisms, can be detected by measuring serum ***aldosterone*** pre- and post-ACTH stimulation **(Box 6)**. This test can help differentiate atypical hypoadrenocorticism cases with glucocorticoid deficiency only from dogs with combined corticosteroid deficiency but without electrolyte changes (21). Thyroid profiles in dogs with hypoadrenocorticism may reveal increased serum TSH levels and, in some cases, decreased thyroxine levels **(Box 3)**; these do not reflect true hypothyroidism and levels will normalize within weeks (up to 4 months) after starting treatment of hypoadrenocorticism (22).

Diagnostic imaging

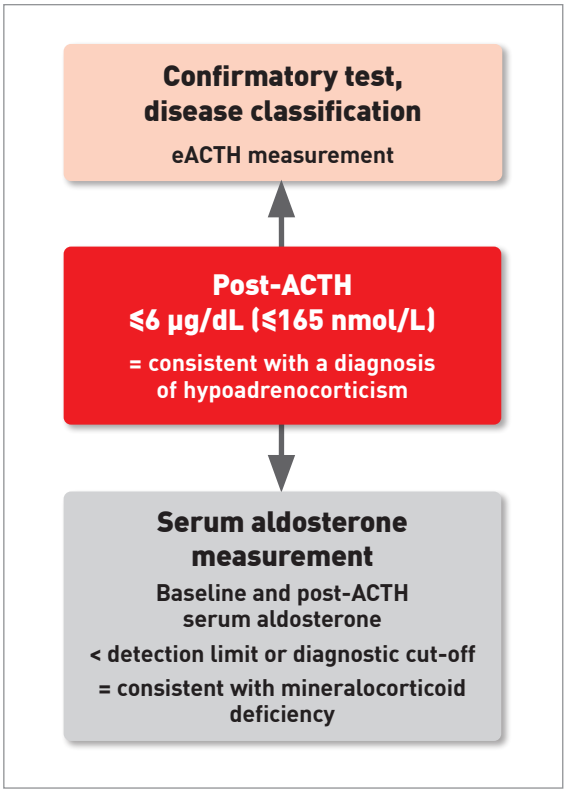
Thoracic and abdominal radiographs are usually unrewarding in dogs with hypoadrenocorticism, unless evaluating for the presence of hypoadreno-corticism-associated megaesophagus, but may be considered to rule out some differential diagnoses. Abdominal ultrasonography, including a thorough evaluation of both adrenal glands, is often also unremarkable but may suggest hypoadrenocorticism if the adrenal gland diameter is small **(Figure 4)**. Ultrasound is also recommended in suspected cases to diagnose or rule out adrenal neoplasia, infarction, or hemorrhage (1).

Treating atypical hypoadrenocorticism

Treatment initiation

Dogs with atypical hypoadrenocorticism are typically clinically stable and can be treated on an outpatient basis. However, evidence of dehydration during the physical examination warrants at least a short period of inpatient care with fluid replacement therapy (using a balanced electrolyte solution) and additional symptomatic treatment (*e.g.*, antiemetic and gastroprotective drugs) as indicated. Hypoglycemia should be corrected by IV glucose administration (dextrose solution), and blood glucose should be monitored.

Prednisolone (or prednisone) is the drug of choice to replace endogenous glucocorticoid deficiency (1-3). Fast-acting glucocorticoids (*i.e.*, dexamethasone, hydrocortisone) are more commonly used for acute glucocorticoid replacement therapy in patients with an Addisonian crisis. Prednisone or prednisolone is initially



Box 5. Diagnostic algorithm for further evaluation of the adrenal hormone status in dogs with atypical hypoadrenocorticism. If the ACTH stimulation test confirms a diagnosis of hypoadrenocorticism, particularly if the ACTH-stimulated serum cortisol concentration is <2 µg/dL, endogenous ACTH (eACTH) concentration can be measured to differentiate primary (adrenal) from secondary (central) hypoadrenocorticism. The absence of any electrolyte changes, plus pre- and post-ACTH stimulated serum aldosterone measurement, can distinguish atypical hypoadrenocorticism cases with glucocorticoid deficiency only from those dogs with concurrent (compensated) mineralocorticoid insufficiency or deficiency. Mineralocorticoid deficiency is presumed and usually not confirmed by serum aldosterone measurement in dogs with typical hypoadrenocorticism (confirmed hyperkalemia and/or hyponatremia).

Box 6. Pre- and post-ACTH stimulated serum cortisol and aldosterone levels from the Boxer dog in **Figure 3.** Neither serum cortisol nor aldosterone concentration increased after ACTH stimulation, confirming both glucocorticoid and (compensated) mineralocorticoid deficiency in this dog.

Parameter	Result	Unit	Reference interval
ACTH stimulation test (serum cortisol)			
Cortisol (baseline)	**<2.8**	nmol/L	25-125
Cortisol (post-ACTH)	**<2.8**	nmol/L	>165
ACTH stimulation test (serum aldosterone)			
Aldosterone (baseline)	**<20**	pmol/L	0-393
Aldosterone (post-ACTH)	**<20**	pmol/L	82-859

administered at a low anti-inflammatory dose (0.3-0.5 mg/kg PO q12-24h) for a few days (1,2). This short induction phase is followed by gradually reducing the dose to the lowest possible ("physiological") level that still effectively treats the endogenous glucocorticoid deficiency without causing overt side effects, and continuing it as maintenance therapy. Finding the optimal dose for an individual dog will require some time (and patience from the owner), but is usually between 0.05-0.2 mg/kg PO q24h depending on the size and age of the dog **(Box 7)**. Depending on the character and temperament of the dog, a short-term increase in the prednisone/prednisolone maintenance dose may be considered during periods of anticipated stress (1,2).

Mineralocorticoid replacement therapy is indicated in typical hypoadrenocorticism cases (*i.e.*, dogs presenting with electrolyte changes reflecting concurrent mineralocorticoid deficiency) but should be carefully considered in dogs diagnosed with atypical hypoadrenocorticism depending on the endogenous mineralocorticoid status. If serum aldosterone concentrations are low or undetectable, the serum electrolytes should be closely monitored. Alternatively, low-dose mineralocorticoid supplementation (desoxycorticosterone pivalate at an initial dose of 1.5 mg/kg SC q25-28d) (23) may be considered. While this, at least in theory, can relieve the mechanisms compensating for (measured) mineralocorticoid deficiency, long-term mineralocorticoid replacement therapy also requires careful monitoring of the patient (serum electrolytes, systemic blood pressure) and may carry the risk of potential adverse effects (24). Dogs diagnosed with atypical hypoadrenocorticism having a normal baseline and/or ACTH-stimulated serum aldosterone concentrations require only glucocorticoid substitution, but serum electrolytes should be monitored regularly in these dogs.

- **Noticeable glucocorticoid side effects**
  → dose reduction (by approx. 10-25%)
- **Recurrence of clinical signs (lethargy, anorexia, diarrhea)**
  → dose increase (by approx. 50%)

- **Anticipated significant stress (*e.g.*, agility trial, holiday fireworks, elective surgery)**
  → consider briefly increasing the dose (by approx. 100-200%) in individual dogs

Box 7. Recommended adjustments in the glucocorticoid dose based on clinical signs and suspicion of underdosing or over-supplementation.

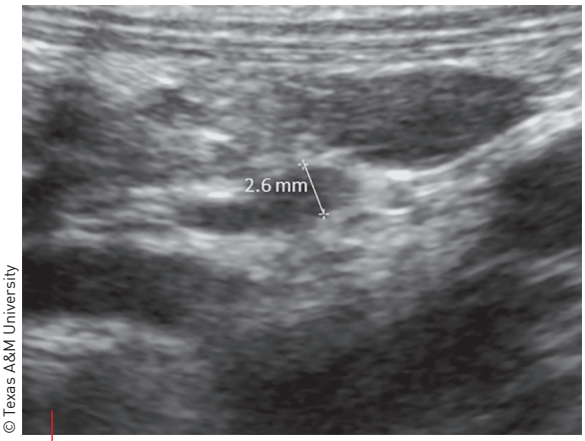


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Figure 4. A sonographic image of the left adrenal gland in a dog with hypoadrenocorticism; note the decreased adrenal size (dorsoventral diameter 2.6 mm). Generally, a maximum dorsoventral dimension (adrenal gland thickness) of <2.8 mm for the left adrenal gland suggests hypoadrenocorticism, but the dog's body weight must also be considered.

Treatment monitoring

Glucocorticoid side effects (*e.g.*, polydipsia/polyuria, polyphagia, weight gain, lean muscle loss, panting, skin and coat changes, behavioral changes) may still occur with very low prednisone/prednisolone doses, and require a dose reduction by approximately 10-15% **(Box 7)**. Whether hydrocortisone may be a good alternative choice for glucocorticoid supplementation in some dogs requires further investigation. Lethargy, weakness, hyporexia or anorexia, vomiting, and diarrhea can indicate suboptimal glucocorticoid substitution in dogs with hypoadrenocorticism and will require a dose increase of approximately 50% (1-3).

Dogs with atypical hypoadrenocorticism receiving mineralocorticoid substitution should initially be rechecked every 2-4 weeks (usually 10-14 days and again 25-28 days after starting supplementation with desoxycorticosterone pivalate) (23). If serum electrolyte (sodium and potassium) concentrations are within the target ranges, systemic blood pressure is normal, and the dose of desoxycorticosterone has not been recently adjusted, treatment monitoring is recommended to be continued every 1-3 months (depending on whether the owner can administer the mineralocorticoid injections at home) and in well-controlled dogs, every 3-6 months (unless monthly injection of desoxycorticosterone has to be performed at the veterinary clinic). Detection of hypokalemia, hypernatremia, or systemic hypertension (systolic blood pressure >140 mmHg) requires the dose of desoxycorticosterone pivalate to be reduced by approximately 10-20%, or at least temporarily discontinued (23). Careful evaluation of any potential side effects of treatment is warranted in dogs with hypoadrenocorticism. Polyuria and polydipsia, which are typically interpreted as a side effect of predniso(lo)ne (over) supplementation, can also reflect mineralocorticoid (*i.e.*, desoxycorticosterone) overdose (1,23).

"Dogs with atypical hypoadrenocorticism are typically clinically stable and can be treated on an outpatient basis. However, evidence of dehydration during the physical examination warrants at least a short period of inpatient care with fluid replacement therapy."

Romy M. Heilmann

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Figure 5. The Boxer dog with atypical hypoadrenocorticism in **Figure 3** after 6 months of glucocorticoid replacement therapy. Serum electrolyte levels remained stable, and the dog had returned to normal activity and body condition (BCS 5-6/9). Vomiting and hematemesis ceased shortly after initiation of treatment.

Prognosis for hypoadrenocorticism cases

With adequate glucocorticoid and, if indicated or elected, mineralocorticoid supplementation and follow-up evaluation of the patient at

regular intervals, atypical hypoadrenocorticism usually carries a very good long-term prognosis **(Figure 5)** (1,2,25). Monitoring for the progression to typical hypoadrenocorticism (*i.e.*, development of hyperkalemia and/or hyponatremia) is an important aspect in the long-term management of dogs with atypical hypoadrenocorticism receiving glucocorticoid monotherapy (2,21). The author recommends serum electrolyte rechecks in these cases every 3-6 months, but guidelines about the frequency of monitoring or the initiation of mineralocorticoid supplementation in dogs with aldosterone deficiency without any electrolyte changes are currently lacking.

CONCLUSION

Owners will often retrospectively recognize the slow onset of hypoadrenocorticism and its related subtle clinical changes when their pet shows a rapid improvement and better quality of life in response to treatment. The disease requires life-long therapy and management, and this is often perceived as increasing the pet-human bond, but some owners fear the development of an Addisonian crisis and are reluctant to leave the dog unsupervised. However, most owners are very comfortable managing a dog that has any form of spontaneous hypoadrenocorticism at home and know or soon learn what to observe for quality of life changes that require further veterinary care.

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FECAL MICROBIOTA TRANSPLANTATION FOR GI DISORDERS

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Dr. Toresson graduated from the Swedish University of Agricultural Science in 1995 and has worked at the Evidensia Specialist Animal Hospital in Helsingborg since 1996, serving as medical director of the unit from 2007 to 2013. She became a Swedish Specialist in diseases of dogs and cats in 2001 and a Swedish Specialist in Small Animal Internal Medicine in 2007. Between 2013-2018 she undertook a PhD in gastroenterology at Helsinki University, culminating in her thesis on oral cobalamin supplementation in dogs, and she still is affiliated with the university, with her current research focusing on fecal microbiota transplantation and bile acid diarrhea.

Fecal microbiota transplantation is starting to be seen as a viable option to treat various acute and chronic gastrointestinal problems in dogs, as Linda Toresson explains.

KEY POINTS

1. Fecal microbiota transplantation (FMT) can be used to improve an individual's intestinal microbiome, and is indicated for various gastrointestinal disorders.
2. FMT is effective as adjunctive therapy in puppies with parvovirus infection and appears to be successful in treating some dogs with chronic enteropathies that have not responded to other therapies.
3. There is currently very little experience regarding the use of FMT in cats.
4. Evidence-based protocols for FMT in veterinary medicine are lacking, but guidelines are currently being prepared by an international group.

Introduction

Fecal microbiota transplantation (FMT) is a technique that involves transferring the intestinal microbiome from a healthy donor to a diseased recipient in order to improve the latter's microbiome and decrease disease severity. Although the technique was actually mentioned in a Chinese textbook of emergency medicine in 320 A.D, it has rarely been used in traditional medicine until the start of this century, when knowledge of the intestinal microbiome and dysbiosis expanded substantially. In humans, gastrointestinal (GI) conditions are by far the most common reason to perform FMT, but multiple studies have been performed using the technique for other indications, including hepatic disorders, metabolic syndrome, treatment of antibiotic-resistant microbes, psychiatric disorders and obesity (1,2). In animals, FMT has been proven to have a beneficial effect in puppies with parvovirus enteritis (3) and also appears to be promising for dogs with chronic diarrhea (4,5), but to date there is only one feline case report available (6). There are currently no evidence-based guidelines or any consensus on donor screening, FMT dosing or the best protocol to follow for animals, but a recently formed group of international experts, the Companion Animal Fecal Bank Consortium, is working on such guidelines, with preliminary results due this year. Despite the lack of consensus, FMT is regarded as a fairly safe treatment for dogs with acute or chronic GI disorders, and has the potential to decrease disease

severity in many cases. This paper will review various reports on the use of FMT in dogs with GI disorders, present a description of the procedure, and discuss some clinical cases.

FMT for GI disorders

As noted above, the beneficial effect of FMT has been shown in various studies. One study looked at parvovirus enteritis in puppies (3), where 66 animals with parvovirus at two veterinary hospitals were treated with either "standard" measures alone or standard treatments plus FMT in a randomized controlled trial. FMT significantly reduced hospitalization periods and the time to recovery (median time 3 days versus 6 days in the control group), and survival was higher in the dogs treated with FMT (26/33, 79%) compared to the other group (21/33, 64%), but the difference was not statistically significant. In another study of 18 dogs with acute diarrhea, a single FMT at presentation improved fecal scores to the same extent as metronidazole treatment, as evaluated at day 7, and at day 28 the dogs treated with FMT had significantly better fecal consistency compared to the metronidazole treated group (7). Furthermore, FMT helped to restore the intestinal microbiome of the first group to healthy levels at day 28, whereas the metronidazole treated dogs had significant dysbiosis at this time point, when compared to both dogs treated with FMT and healthy dogs. However, in a small placebo-controlled pilot study of 8 dogs with acute hemorrhagic diarrhea, no clinical benefit was seen in dogs given FMT compared to sham-treated controls (8).

With respect to dogs with chronic diarrhea and/or chronic enteropathy, one case report and one case series on successful FMT treatment

Box 1. The CIBDAI scoring system. Six parameters are scored, each from 0-3, where 0 = normal, 1 = mild changes, 2 = moderate changes, and 3 = severe changes. The scores are added together to give the CIBDAI.

• Attitude/activity • Appetite • Vomiting	• Stool consistency • Stool frequency • Weight loss

The overall score denotes the degree of IBD present;			
0-3	4-5	6-8	9 or above
Clinically insignificant disease	Mild IBD	Moderate IBD	Severe IBD

Box 2. What are SCFAs?

Faecalibacterium, Fusobacterium, Blautia and *Turicibacter* bacteria are important producers of short chain fatty acids (SCFAs). SCFAs can exert anti-inflammatory properties in the gut, provide energy to the colonocytes, enhance epithelial barrier function and tight junctions, and contribute to normal gut motility. The levels of SCFA-producing intestinal microbes, as well as *Clostridium hiranonis* (which converts primary bile acids to secondary bile acids in the intestine), are often decreased in dogs with chronic enteropathies (12).

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Figure 1. This 5.5-year-old spayed female Norwegian Forest cat with partially refractive chronic enteropathy showed a marked improvement in fecal quality after three Fecal Microbiota Transplantations (FMT's) given with 10–14-day intervals between treatments.

have been published, as well as two scientific abstracts (4,5,9,10). In the case series, 9 dogs with refractory inflammatory bowel disease (IBD) which were unresponsive to food trials, antibiotics, corticosteroids or cyclosporine, were included (4). A significant decrease in the canine inflammatory bowel disease activity index (CIBDAI (11) – **Box 1**)) post-FMT was seen in all dogs, as well as a significant increase in fecal *Fusobacterium* spp. 7/9 dogs had lower fecal concentrations of *Fusobacterium* compared to the donor dogs prior to FMT. *Fusobacterium* is a major producer of short chain fatty acids (SCFA) and an important component of a healthy canine intestinal microbiome, whilst dysbiosis and decreased levels of SCFA-producing intestinal microbes are very common in chronic canine enteropathies **(Box 2)** (12). Dysbiosis was also present in a study of 16 dogs with chronic diarrhea which were each given one FMT, with a significant improvement in the fecal dysbiosis index* reported one week after treatment (10). The retrospective study behind the other abstracts (5,9) is discussed in more detail in the next section.

Very limited information is available on the use of FMT in cats **(Figure 1)**; there is currently only one case report, which was a cat with non-responsive ulcerative colitis that responded to FMT (6).

FMT for poorly responsive chronic enteropathies

The efficacy of FMT on chronic enteropathy (CE) cases was demonstrated by the following study. This involved a retrospective data review from a cohort of 36 dogs (aged 0.6-13 years, median 6.3) with CE that had FMT as adjunctive therapy in the

author's hospital between 2019-2021 (5). All dogs had shown either poor or no response to standard evidence-based treatments, and a follow-up period of at least 3 months post-FMT was required for inclusion. Exclusion criteria were (i) if any current maintenance therapy dose was increased during the period reviewed (ii) intestinal parasites, or (iii) starting a new immunosuppressive treatment or diet in parallel with FMT. FMT was given using a standardized protocol to all dogs, using two different donor dogs, both of which had a dysbiosis index* below -2 (normobiosis) (12).

All 36 dogs had been treated for CE for between 1-110 months (median 21) at inclusion, with the main complaints being refractory diarrhea (28/36), lethargy (15/36) and various side effects of medication (10/36). 34/36 dogs were treated with corticosteroids at inclusion, and 20/36 received second line immunosuppressive drugs, including mycophenolate, chlorambucil, cyclosporine or azathioprine. 26/36 dogs were fed a hydrolyzed diet, 8/36 a single protein diet, and 2 were fed a highly digestible "intestinal" diet.

34 dogs received between 2 and 5 FMTs, with the majority (26 dogs) receiving 3 treatments. The other 2 dogs, both non-responders, had received one FMT each. Clinical improvement based on CIBDAI was noted in 75% of dogs (27/36) after treatment, with the most common improvements being increased activity level (20/36), improved fecal scores (19/36) and weight gain and/or increased appetite (10/36). This latter group had previously shown a poor appetite and/or subnormal body condition scores. The maintenance corticosteroid dose could be tapered in 6 of the dogs to a level lower than what had been possible prior to FMT. One dog which had previously developed frequent flare-ups of diarrhea that only responded to tylosin did not need antibiotics for 21 months after the third FMT (case 2# in the next section), and another dog that was previously treated with metronidazole and immunomodulatory drugs could stop the metronidazole after FMT.

CIBDAI at inclusion was 2-17 (median 6) and this decreased significantly to 1-9 (median 2) during the first month following the last FMT. Fecal samples for analysis of the dysbiosis index* (reference interval ⩽ 0) were available from 23 dogs at inclusion. Dogs unresponsive to FMT had a significantly higher result compared to good responders at inclusion. A high dysbiosis index has been previously shown to correlate with decreased microbial diversity with fewer bacterial taxa present (In people, low microbial diversity prior to FMT is a negative prognostic factor for responding to FMT (13)). Side effects were mild and uncommon; 6/36 dogs (3 responders and 3 non-responders) had diarrhea within 48 hours post-FMT, with two of these dogs also showing clinical signs of abdominal or rectal pain within 24 hours after FMT. All side effects were, however, self-limiting.

This study has, however, several limitations. It is a retrospective study, the microbiome and metabolome were not followed over time, and there was no control group included. Nevertheless, results suggest that FMT can be used as adjunctive therapy in dogs with poorly responsive CE.

FMT procedure

As previously mentioned, there is currently no consensus or evidence-based guidelines on donor screening or the best protocol for FMT (14). The following recommendations are based on the author´s personal clinical experience and recent studies (5,7).

Donor screening

A donor animal should be an individual that is clinically healthy, with a normal body condition score and a CIBDAI score of 0-3 (*i.e.*, no clinical signs of a chronic GI disease) (11); essentially, the aim is to find a donor with plenty of beneficial microbes and no potential fecal pathogens. In addition, the animal should not be fed a raw food diet, should not be receiving any long-term medication, and must not have had any antibiotics for at least 6 months, preferably longer. For feline donors, indoor-only cats are preferred in order to avoid exposure to parasites from small rodents etc. Intestinal parasites, including *Giardia intestinalis,* should be excluded from all potential donors. To ensure high levels of beneficial microbes, such as short-chain fatty acid (SCFA)-producing bacteria and *Clostridium hiranonis*, potential donors should be screened with the canine or feline dysbiosis index* (12). The fecal canine donors at the author's hospital are also free from *Salmonella* spp., *Campylobacter jejuni, Clostridioides difficile* and *Clostridium perfringens* enterotoxinogen, including *Clostridium perfringens* netF-toxin. However, such extensive screening of donors may not be necessary – it is likely most important to exclude intestinal parasites and ensure high levels of beneficial microbes, as microbial composition and diversity of the donor transplant is vital for successful treatment of ulcerative colitis in

"FMT is regarded as a fairly safe treatment for dogs with acute or chronic GI disorders, and has the potential to decrease disease severity in many cases."

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humans (13). Furthermore, this study reported that recipients with a good response to FMT had increased fecal microbial diversity both before and after FMT compared to non-responders, as well as increased fecal levels of SCFAs and secondary bile acids post-FMT.

FMT dosing and procedure

The amount of feces used for FMT in dogs can vary considerably (14). The author currently uses 5 g of donor feces per kg bodyweight of the recipient for dogs up to 30 kg and cats; for recipient dogs over 30 kg, 2-3 g of feces per kg bodyweight is used. This is a relatively large amount, but has been associated with a good outcome in the majority of dogs with CE (5). Food should be withheld from the recipient for 6 hours prior to FMT, but water is allowed, and the recipient dog should be walked for 30-40 minutes just prior to the procedure in order to defecate. A low dose of acepromazine (0.1 mg/kg SC) can be given 15 minutes beforehand unless contraindicated; although some clinicians omit this if the recipient is calm, premedication usually makes it easier for the dog to relax and rest after the procedure, allowing a long contact time between the transplant and the colonic mucosa. In the author's experience, cats need to be fully sedated prior to FMT.

The fecal transplant can be delivered via the upper or lower GI tract. In people, the route of administration does not appear to be outcome-related for GI indications (recurrent *Clostridioides difficile* infection, ulcerative colitis and Crohn's disease) (15-17), but in published reports on FMT in dogs, the rectal route is by far the more commonly used delivery method, using a retention enema or colonoscopy.

Fresh or frozen feces can be employed; if the latter, it should first be thawed overnight in a fridge. (In people with recurrent or refractory *Clostridioides difficile*-infection, FMT using frozen feces has been shown to be as effective as fresh material

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Figure 2. Measure the rectal catheter before inserting it; the tip of the catheter should reach the level of the last rib.

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Figure 3. FMT given to a dog in a standing position. Note that the dog is not restrained, and most dogs will tolerate the procedure very well.

(18)). The feces should be blended and mixed with sterile saline (20-120 mL) until a desirable texture is achieved, before being filtered through a sieve. The filtrate is then aspirated into 60 mL sterile syringe(s) and either left at room temperature, or warmed to body temperature in a water bath prior to use, since it is highly unpleasant for the recipient to receive a large volume directly from the fridge. The transplant is administered rectally using a 12-16 FG catheter (7). The catheter should be well lubricated before insertion, with the tip placed approximately at the level of the last rib **(Figure 2)**. FMT can be given with the dog in either a standing position, sternal or lateral recumbency **(Figure 3)**. The owner is then instructed to minimize the dog´s physical exercise for 4-6 hours in order to increase the contact time between the intestinal mucosa and the transplanted feces. Food should also be withheld for the same period, since the presence of food in the stomach stimulates colonic contractions. At the author's hospital, the standard protocol **(Box 3)** is for dogs with CE to receive a series of three FMT's, with 10-20 days interval between each, as experience has shown that one treatment is often ineffective in reducing clinical

Box 3. The author's preferred FMT protocol.

1. Use fresh or frozen (thawed) feces, 5 g/kg BW for dogs up to 30 kg, dogs >30 kg 2-3 g/kg BW.
2. Remove visible grass etc., and blend with saline to a suitable texture.
3. Filter with a sieve and aspirate the mixture into 60 mL syringes.
4. The recipient should be walked for 30 minutes prior to transplantation and offered no food for 6-8 hours prior to the procedure.
5. Administer a low dose of acepromazine – optional.
6. Measure the catheter from the tip to the level of the last rib.
7. Insert the catheter after lubrication and administer the transplant.
8. Advise the owner to drive home slowly; the dog should have no walks or food for a few hours.

signs in many dogs, or not lasting long enough. However, if no beneficial effects have been noticed after two treatments, a third FMT is not given (5).

Case 1# – "Alma"

Alma **(Figure 4)** is a spayed female Golden Retriever who developed a steroid-responsive CE at 3 years of age. At the age of 5 she was on a maintenance dose of oral methylprednisolone (0.4 mg/kg EOD) and a hydrolyzed, soy-based diet. This controlled the clinical signs of CE to some extent, but she was still suffering from lethargy, signs of abdominal pain, occasional vomiting, diarrhea and a subnormal body condition score (BCS) of 3.5/9 (15% below ideal BCS), with mild to moderate muscle atrophy. Several attempts were made to decrease the methylprednisolone dose, but each time the clinical signs worsened. Treatment with mycophenolate was started as an add-on immunosuppressive, but this did not allow any reduction in the methylprednisolone dose. The owner agreed to try FMT as adjunctive therapy, and three separate FMTs were given as a rectal retention enema with 10-14 days intervals. Alma showed a very positive and rapid clinical response; she was much more active and alert, played more with other dogs, and gained 2 kg in weight, allowing a gradual tapering of methylprednisolone to 0.2 mg/kg EOD. Fecal analysis showed that Alma had a dysbiosis index* of -1.2 (normobiosis) at baseline, but she had marked alterations of fecal lipid profiles, such as sterols and fatty acids, and the most striking abnormality was a fecal coprostanol concentration 24 times that of a normal dog. Cholesterol in the gut lumen is metabolized to coprostanol by intestinal microbes, and this compound is poorly absorbed from the gut (19), so Alma had an exaggerated conversion of cholesterol to coprostanol. Two weeks after FMT 1, the fecal lipid profile was normalized, which correlated with normalization of her BCS. The positive effects of FMT lasted for 7 months, but then Alma again became lethargic and lost weight; however, a second series of FMT and a temporarily increased dose of methylprednisolone reversed the clinical signs.

Case 2# – "Moltas"

Moltas is an intact male German Shepherd that has suffered from chronic, partially refractory diarrhea all his life. He also suffers from atopic dermatitis, recurrent pyoderma and chronic otitis. At 1.5 years of age, he was clinically fairly stable on high daily doses of prednisolone, but he had a BCS of 3/9 and tapering of the prednisolone led to worsening of clinical signs. Azathioprine had no effect, and multiple dietary trials, including a highly digestible diet and two different single protein diets, were unsuccessful. During the worst flare ups of diarrhea, Moltas did respond to tylosin or metronidazole, and at this point he was referred to the author. He was started on a hydrolyzed novel protein diet and cyclosporine, which had some effect, allowing for some tapering of the prednisolone. At 2.5 years of age the cyclosporine was replaced with chlorambucil, which led to a clinical improvement and weight gain to a normal BCS. During chlorambucil treatment, prednisolone could be replaced with 3 mg budesonide every other day (EOD), which has fewer side effects. Moltas was also treated with allergen-specific immunotherapy, twice weekly medical baths with chlorhexidine, and 4 mg methylprednisolone EOD as a maintenance dose for his skin condition. During the following 2.5 years Moltas was relatively stable, but had flare-ups of diarrhea every few months. Minor exacerbations could be controlled with a temporary increase in the dose of budesonide (3 mg daily for 3-10 days). More severe flare-ups occurred roughly every six months, and these did not respond to immunosuppression, so Moltas was prescribed tylosin (25 mg/kg q24h for 7 days). At 5 years of age, the GI signs had increased, such that there were monthly flare-ups of diarrhea, regurgitation and lethargy. This increased disease activity had prompted increased polypharmacy, with more frequent use of tylosin alongside budesonide (3 mg EOD), methylprednisolone (4 mg EOD), chlorambucil (3 mg EOD) and cobalamin (1 mg orally once weekly).

Figure 4. 6-year-old spayed female Golden Retriever doing well at check-up after the second series of FMT.

On clinical examination, marked abdominal pain was obvious on palpation. Serum biochemistry revealed a mild hypoalbuminemia (28 g/L; reference interval 30-45 g/L) and mild-moderate decrease in total protein (51 g/L; reference interval 61-75 g/L). These parameters had been within the reference range at the last check-up six months previously. Serum cobalamin concentrations had also dropped significantly to 221 pmol/L (reference range 180-708 pmol/L), despite weekly maintenance therapy. Fecal samples were negative for intestinal parasites.

Moltas was treated with 1 mg of cobalamin EOD and three FMTs via rectal retention enemas at 14 day intervals. After FMT 1, the regurgitation episodes stopped, and after FMT 2 the fecal quality improved and Moltas became more playful and active **(Figure 5)**. After the third FMT, diarrhea had stopped and abdominal palpation did not induce signs of pain. Furthermore, serum albumin and total protein concentrations had increased and were back within the reference range. During the next 21 months, Moltas was much more stable, although there were mild flare-ups of diarrhea every third month, which lasted for 1-2 days and were self-limiting. After 21 months, the fecal quality became progressively worse, and a severe flare-up occurred. Increasing the dose of corticosteroids had only a limited effect, and Moltas was again treated with tylosin for a week, followed by a second series of 3 FMTs, which had the same positive effect as the first treatment.

Case 3# – "Harold"

Harold is an intact male French Bulldog **(Figure 6)** who had a persistent *Giardia intestinalis* infection as a puppy and young dog. The infection finally cleared, but diarrhea, melena and weight loss continued. The referring vet had treated Harold with metronidazole and corticosteroids, which only led to marginal improvement, and full-thickness surgical biopsies from the small intestine and the colon were taken at a year of age. The histopathologic diagnosis was granulomatous colitis and moderate lymphocytic-plasmacytic enteritis with moderate lacteal dilation. Sulfasalazine was added to the treatment without any effect, so Harold was referred to the GI-service at the author's hospital at the age of 1.5 years. At this point he was slightly lethargic and had a BCS of 3/9. He was started on a 6-week course of enrofloxacin for granulomatous colitis, which quickly led to resolution of clinical signs, including weight gain. At a check-up just after the treatment finished, Harold was asymptomatic and had a BCS of 4/9. However, 3 weeks later, diarrhea (of predominantly colitis type) and vomiting recurred. As no colonic biopsies had been sent for culture and sensitivity testing when the biopsies were collected, it was unknown if Harold was already harboring multidrug-resistant *E. coli* prior to enrofloxacin treatment. Since resistance to fluoroquinolones develops rapidly during treatment, it was very likely that multidrug-resistant *E. coli* was now part of his intestinal microbiome (20). In Boxer dogs with granulomatous colitis, it has been shown that the presence of fluoroquinolone-resistant *E. coli* is associated with failure to respond fully to enrofloxacin treatment, as well as concurrent antimicrobial resistance to chloramphenicol, rifampicin, and trimethoprim-sulfa (20), and multidrug-resistance and treatment failure often leads to euthanasia in affected dogs. Carbapenem has been reported as an alternative antibiotic in dogs with granulomatous colitis and fluoroquinolone-resistant *E. coli* (21), but it is a critically important class of antibiotics in human medicine and is prohibited for veterinary use in many countries.

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Figure 6. Granulomatous colitis is mostly seen in Boxer dogs or French Bulldogs

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Figure 5. 5-year-old intact German Shepherd with partially refractory diarrhea. After FMT 2, fecal quality improved and the dog became much more active and playful.

At this time point, the owner agreed to try FMT. The first procedure was followed by 2-3 days of flatulence, smelly feces and mild vomiting, and although the fecal quality then improved slightly, diarrhea recurred after 14 days. The second FMT 16 days after the first one was again followed by 2-3 days of similar signs, but this time the subsequent improvement of the fecal quality was more pronounced. Harold was also started on a multi-strain probiotic at this point. After FMT 3, no side effects occurred, the stool was normal and Harold was much more active and alert. He continued on the multi-strain probiotic every other day along with a hydrolyzed protein diet, and at the latest check-up (14 months after FMT 3), he was still in complete remission.

Case 4# – Ina

Ina is an intact female German Shepherd who had shown signs of CE since she was a year old, although these had responded to a hydrolyzed

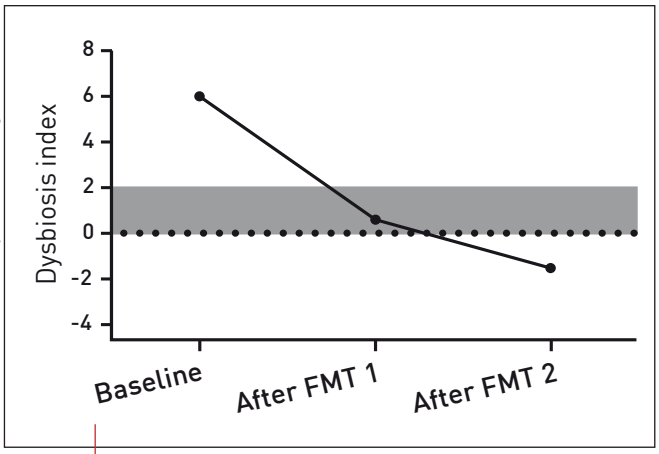

Figure 7. Dysbiosis index of a 2-year-old intact female German Shepherd dog with food-responsive enteropathy. Hyporexia, lethargy and dysbiosis occurred after treatment with antibiotics for a urinary tract infection. The grey zone is consistent with mild dysbiosis; normobiosis was restored after FMT 2.

protein diet combined with a multi-strain probiotic. At 2 years of age she developed a urinary tract infection that was treated with (unknown) antibiotics by her local veterinary clinic. After the antibiotics, Ina became markedly flatulent, lethargic and hyporectic, clinical signs similar to those she presented with during the initial work-up for CE. Intestinal dysbiosis following antibiotic treatment was suspected, and analysis of a fecal sample showed a dysbiosis index* of 6.2 **(Figure 7)**, consistent with severe dysbiosis. Ina was still lethargic and hyporectic six weeks after the antibiotics had finished, and a FMT series was scheduled. After FMT 1, Ina improved but relapsed before FMT 2; however, after two further FMT treatments she was again extremely alert with a normal appetite, and the dysbiosis index went from severe to mild classification after FMT 1, followed by normobiosis after FMT 2 **(Figure 7)**.

* The Dysbiosis Index is provided by the GI Laboratory at Texas A&M University, USA.

CONCLUSION

Fecal microbiota transplantation (FMT) is a promising treatment in companion animal gastroenterology, with published studies reporting very few unwanted side effects. At present, FMT dosage and protocol will vary somewhat among small animal clinicians, but a consensus on treatment guidelines is pending. FMT can be used in various cases, including puppies with parvovirus infection, and appears to be beneficial for the treatment of many dogs with poorly responsive chronic enteropathies. Treatment with FMT may also allow reduction in the use of antibiotics in selected cases.

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