TOPICS IN

FELINE MEDICINE

Continuous glucose monitoring in diabetic cats − Unexplained weight loss in the cat − How I approach... the vomiting cat − Feline hepatic lipidosis − Feline toxoplasmosis − House soiling in cats −

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THE LANGUAGE OF CATS?

"Curiosity killed the cat, but where human beings are concerned, the only thing a healthy curiosity can kill is ignorance." **– Harry Lorayne**

Given that cats have been an integral part of human society for at least 10,000 years, it is hardly surprising that they feature in many metaphors, similes and proverbs, although they can vary somewhat in different parts of the world. So for example, in English there is the well-known saying "to be like the cat's whiskers" – which is applied to someone who seems very pleased with themselves. Then there's the proverb "curiosity killed that cat" – which hardly needs further comment, given that the species has an uncanny knack of getting itself into tight corners and tricky situations. This may also be related to the Spanish saying "aquí hay gato encerrado" (there's a cat trapped here), meaning that something suspicious is afoot, although it's not obvious what exactly that might be. And then there's the French "être gourmand comme un chat" (to be a gourmand like a cat), an insult applied to someone who is both greedy but picky, no doubt because many cats are known to be both food-motivated yet notoriously choosy.

Other sayings may be a little more obscure in terms of their origins – such as when a French person has to prioritize their tasks, leading to the claim "avoir d'autres chats à fouetter" (to have other cats to whip). But most veterinarians can identify with the phrase "letting the cat out of the bag" – which is applied when someone inadvertently allows some private information to become widely known; whilst this hopefully never happens in the consult room, we all know that cats have an incredible ability to escape from seemingly secure carriers or cages… and the saying is particularly apt in that, once released, it is almost impossible to recapture the cat – or the secret – again.

All of which leads to the subject for this issue of *Veterinary Focus*. We will not claim that it is cat's whiskers (or indeed any other part of the animal's anatomy), but do hope that it may fulfil the *gourmand* like a cat proverb – in that we have several diverse but choice topics that should appeal to all feline-centered veterinarians, no matter how picky they might be.

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CONTINUOUS GLUCOSE MONITORING IN DIABETIC CATS

Recent technological advances now make it possible for the clinician to easily access continuous glucose monitoring in diabetic cats, as this article describes.

KEY POINTS

1 Assessment of a cat's response to insulin should include evaluation of clinical signs, measurement of urine and blood glucose, and determination of blood fructosamine levels.

2 The limitations of traditional blood glucose curves include cost, the stress of multiple venipunctures, and marked day-to-day variability in the glucose results.

3 Continuous glucose monitoring is replacing the traditional blood glucose curve for assessment of glycemic control.

4 Limitations of continuous glucose monitoring include difficulty keeping the sensors in place, sensor failure, and sensor errors.

Introduction

Diabetes mellitus (DM) is a common disorder in geriatric cats (1) and appropriate management requires careful monitoring of response to insulin treatment, and in fact good glycemic control can result in diabetic remission in many cases (2-4). The recent introduction of technology that allows continuous monitoring of interstitial glucose has led to major improvements in the veterinarian's ability to supervise and improve glycemic control in affected animals (5-9).

Type II DM is the most common type of DM in cats; this is characterized by abnormal secretion of insulin from the pancreas in combination with peripheral insulin resistance. Diagnosis is made based on the presence of clinical signs (polyuria, polydipsia, polyphagia and weight loss), and documentation of hyperglycemia and glycosuria (2,3). In cats, the diagnosis is complicated by stress hyperglycemia, so it is important not only to document persistent hyperglycemia and glycosuria, but also to rule out other diseases that may cause similar clinical signs, such as hyperthyroidism and gastrointestinal disease. Treatment of feline DM relies on insulin therapy, dietary modification, management of concurrent illness and weight management, and many type II diabetic cats will achieve remission if insulin treatment results in good glycemic control. Factors that influence the likelihood of remission include the severity of pancreatic pathology, the presence of insulin resistance caused by concurrent illness or medications, obesity, and the ability to feed a low carbohydrate diet (10,11). Progressive loss of beta-cells may ultimately result in progression to type 1 DM, therefore good glycemic control is key to a positive outcome in affected cats.

Insulin therapy

Insulin types

There are three insulin products that are appropriate for first line treatment of feline DM **(Table 1)**; protamine zinc insulin (PZI), lente (porcine insulin zinc suspension) insulin, and glargine insulin, an insulin analogue (3). Detemir (another insulin analogue) can also be used, but is not a first-line choice because of its cost. NPH (neutral protamine Hagedorn) insulin tends to have a very short duration of action in cats, and is not recommended.

The starting dose of insulin for a new feline diabetic patient is 1-3 U/cat (0.25-0.5 Unit/kg), and the author recommends the lower end of this dose. Whichever formulation is chosen, twice daily injections are more likely to result in good glycemic control than once a day therapy. If the former is not possible, once daily injections with PZI or glargine can result in effective control of clinical signs in some cats.

Table 1. Insulin products recommended for use in cats.

Lente insulin	65% crystalline and 35% amorphous
PZI insulin	insulin complexed with protamine and zinc
Glargine	insulin analogue
Detemir	insulin analogue

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Goals of insulin treatment

The primary goal of insulin therapy in affected cats is to control the clinical signs of DM while avoiding hypoglycemia. A secondary goal may include achieving diabetic remission. The plan for monitoring should take into account the owner's lifestyle, any concurrent illness, the age of the patient, and the practicality of tight glucose monitoring. The likelihood of remission in cats is higher with tighter glycemic control; however, severe hypoglycemia can be life-threatening and can lead to permanent neurologic damage. Insulin-induced hypoglycemia also causes secretion of hormones that oppose the action of insulin, such as glucagon, growth hormone, cortisol and epinephrine, which can initiate insulin resistance and worsen diabetic control.

Ideally blood glucose should be maintained between 80-200 mg/dL (4.4-11.1 mmol/L), but most diabetic cats will sometimes have levels that are above this range. However, most cats are clinically well regulated if the blood glucose concentration is maintained less than 300 mg/dL (16.7 mmol/L) for the majority of the day, because the tubular maximum for resorption of glucose from the feline kidney is approximately 270 mg/dL (15 mmol/L) (12). It is important to remember that it is difficult to assess the duration of insulin action if the glucose nadir is in the hypoglycemic range, because secretion of counter-regulatory hormones such as glucagon will prematurely increase the blood glucose. The ideal monitoring strategy for evaluating response to insulin treatment in diabetic cats should be individualized for the patient and owner.

Traditional monitoring of diabetic patients

Until recently, the primary monitoring tools at the veterinarian's disposal were assessment of clinical signs and bodyweight, and measurement of serial blood glucose concentrations, urine glucose, and glycosylated proteins.

Clinical signs

The most important treatment goal for any diabetic cat is to control the clinical signs of the disease. Cats with inadequate glycemic control will typically have persistent signs and progressive weight loss, while severe hypoglycemia may cause intermittent signs such as weakness, lethargy, and seizures.

Milder hypoglycemia is easily missed, because it may not result in obvious clinical signs, yet will still contribute to poor glycemic control.

Blood glucose curves

Traditional in-hospital or at-home blood glucose curves have been the gold standard for evaluating glycemic control in cats for many years, but this method has numerous limitations. The method is expensive and requires collection of multiple samples, which causes stress to the patient and owner. In addition, blood glucose curves exhibit marked day-to-day variability, even when performed by the owner at home **(Figure 1)** (13). Misinterpretation of the results can also lead to incorrect treatment decisions.

Glycosylated proteins

Measurement of glycosylated proteins such as fructosamine and hemoglobin A1C (HbA1c) allow assessment of longer-term glycemic control and can aid in interpretation of blood glucose curves. Glucose binds irreversibly to serum proteins and hemoglobin, and these products persist for the life of the protein; the resultant products can be measured in serum or whole blood respectively. Fructosamine indicates adequacy of glycemic

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Figure 1. Blood glucose monitoring, and blood glucose curves, can be done at home with the owner using a point of care glucometer and samples taken from the cat's pinna, but this is far from ideal.

Figure 2. There are several different interstitial glucose monitoring devices now available; this is the Freestyle Libre 14 day, which has been validated for use in cats. All of these devices are used off-label in veterinary patients.

control over the previous 1-2 weeks, while HbA1c reflects glycemic control for the previous 4-6 weeks (14-16).

Urine glucose

Measurement of urine glucose concentration can also be helpful for assessment of glycemic control, and is particularly useful in cats that are going into remission as well as detecting any relapse of diabetes after remission. Urine glucose should not be used to determine the daily dose of insulin, but glycosuria trends can be very helpful in assessing diabetic control, especially if assessed on a consistent basis and recorded in a diary or log. The presence of urinary ketones can also help indicate impending diabetic ketoacidosis.

Continuous glucose monitoring

CGM (continuous glucose monitoring) systems now allow continuous evaluation of the interstitial blood glucose concentration for up to 14 days via a small flexible catheter placed subcutaneously. The addition of CGM to the veterinarian's toolbox has improved the ability to accurately monitor insulin-treated diabetic cats, and is more sensitive than traditional glucose curves for detection of hypoglycemia. The method allows the insulin dose to be titrated in real time, and adjusted for differences between day- and night-time requirements. Validation studies in veterinary patients have shown that the interstitial glucose concentration correlates well with the blood glucose concentration in most situations, and the current CGM systems used in veterinary medicine are affordable, easy to apply and use, and well tolerated by patients. They allow an integrated analysis of changes in interstitial glucose in the patient over a 14-day period. The most common

device currently in use is the Freestyle Libre (FSL) 14 day interstitial glucose monitor **(Figure 2)**, which has been validated in cats. The Freestyle Libre 2 and 3 models have also been used in cats, but their accuracy has yet to be fully reported in peer-reviewed literature. There are other continuous glucose monitors on the market, including the Dexcom-CGM™ and Eversense CGM™, but again these systems have not yet been evaluated in cats.

In terms of indications for use, the FSL is now an important tool for treating patients with diabetic ketoacidosis, in patients with newly diagnosed DM, and in unstable diabetic patients, where it can be used continuously until better glycemic control is achieved. It is also very useful for routine intermittent monitoring of stable patients.

Accuracy of the FSL monitor

Several studies have investigated the accuracy of the 14-day FSL device in cats (5-8). In these studies, interstitial glucose measured by the sensor correlated well with both peripheral blood glucose measured by a point-of-care (POC) glucometer and an automated biochemistry analyzer. Most studies indicate that the FSL slightly underestimates the blood glucose compared to the actual value, but evaluation using a surveillance error grid analysis indicates good clinical accuracy **(Figure 3)** (5). It is important to recognize that there is a lag of up to 30 minutes between changes in the blood glucose and changes in the interstitial glucose, so measurements may differ somewhat (8), and the difference between the two measures is most marked when blood glucose is changing quickly. Most studies have shown a slightly poorer correlation between blood glucose and interstitial glucose in the hypoglycemic range, but this may be due to the smaller number of hypoglycemic samples in published studies, as well as the effect of rapid changes in the blood glucose.

Assessment of the Libre 2 sensor has to date only been published as a single abstract (17), which noted that the sensor slightly underestimated

"The addition of continuous glucose monitoring to the veterinarian's toolbox has improved the ability to accurately monitor insulin-treated diabetic cats."

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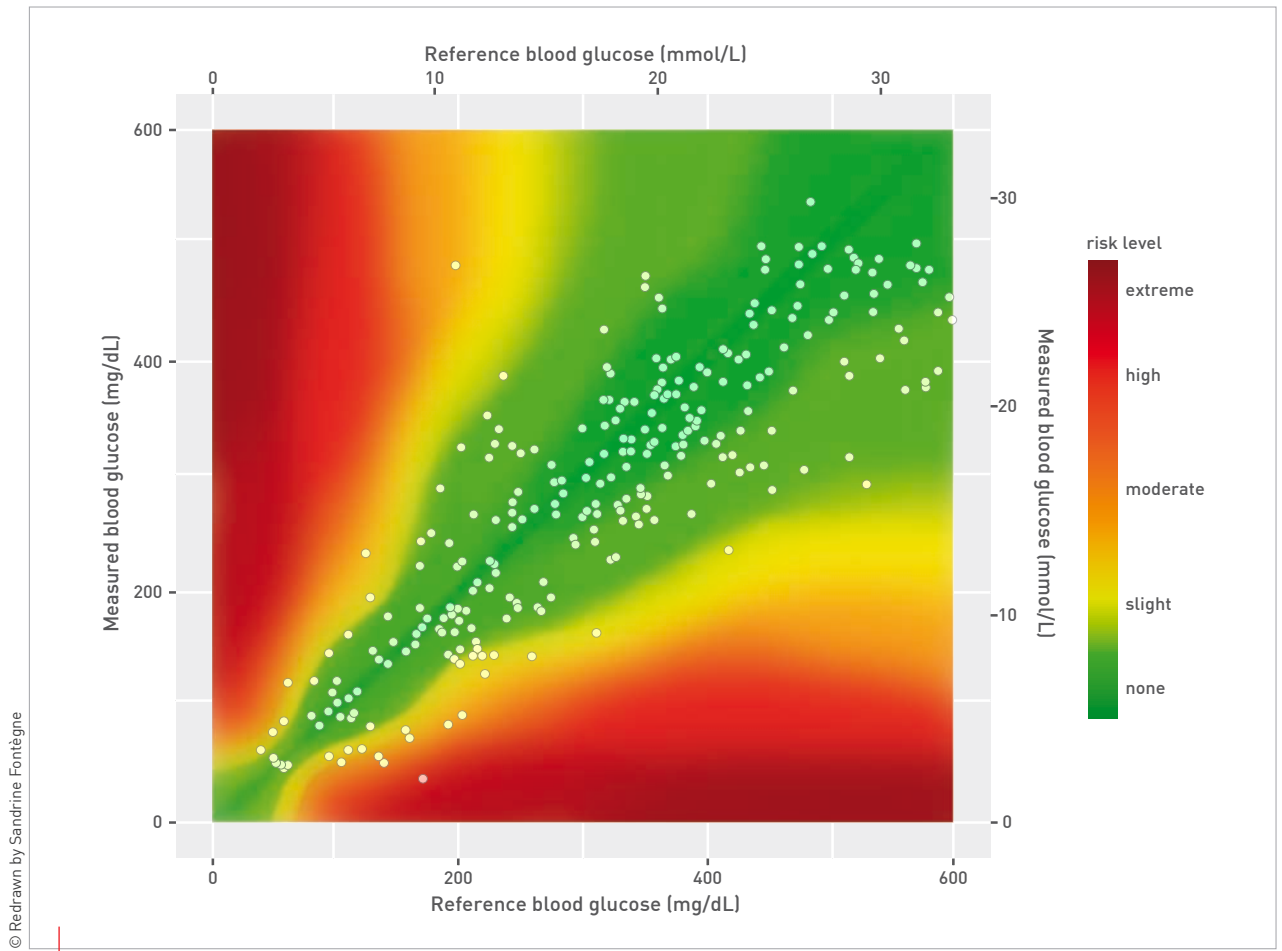
Figure 3. An example of a typical surveillance error grid analysis of an interstitial glucose sensor. The reference blood glucose concentrations are on the x-axis and plotted against the interstitial glucose measurement; the different zones indicate the magnitude of risk from green (no risk) to dark red (high risk).

the blood glucose in the mildly hypoglycemic and euglycemic ranges, while it overestimated levels at very low glucose concentrations (< 49 mg/dL/2.7 mmol/L).

Overall, studies suggest that for most diabetic cats, the difference between the interstitial glucose and the blood glucose has little or no impact on clinical decision-making, and that the FSL is sufficiently accurate for monitoring affected cats. The device has not yet been evaluated in cats with diabetic ketoacidosis (DKA), but in the author's hospital it is very helpful for cats in this category, and it is known that in dogs the device's performance is not affected by ketosis; however, there is lower accuracy in dehydrated animals (18,19). Skin thickness has also been shown to influence the accuracy of the device in dogs (20), but this has not been evaluated in cats.

Using the FSL monitor

The FSL 14 day sensor is a single use disposable device with a diameter of 35 mm and a thickness of 5 mm **(Figure 4)**, allowing interstitial glucose measurements to be accessed in real time by swiping a scanner over the sensor. A dedicated reader can be purchased and used multiple times with sequential sensors, which is advantageous for hospitalized patients, or there are free apps

Figure 4. Close-up views of the Freestyle Libre 14 day sensor.

Figure 5. A sensor loaded into the applicator and ready to deploy.

Figure 6. An example of typical sensor placement in a cat.

for most Android or iPhones that can be used to scan the sensor. With either option the data can then be uploaded to a computer or the LibreView website using free software. For the Freestyle Libre 14 day sensor, the reader and the app can be used together as long as the reader is initially used to set up the sensor. Note that this is not true for the Libre 2 sensor, where the reader and phone app cannot be used interchangeably. Purchase of the sensor and reader from a retail pharmacy requires a prescription in the United States, but not in most other parts of the world.

To prepare for sensor placement, an area of skin (approximately 5 cm x 5 cm) slightly bigger than the sensor should be shaved and cleaned with an alcohol swab. The sensor pack is loaded into the applicator **(Figure 5)**, and 4-8 drops of tissue adhesive are placed in a clock pattern on the underside of the disc. The applicator is then deployed, making sure that it is held at right angles to the skin surface and avoids bony prominences. As the sensor is deployed, the needle deposits the sensor subcutaneously, leaving the disc adhered to the skin surface. A reader or phone is then used to start the sensor, which is ready to use 60 minutes later. There are numerous possible sites on an animal that can be used, but the best location is typically the dorso-lateral chest wall or between the shoulders **(Figure 6)**. It is important to avoid

any contact with collars or harnesses that may rub on the sensor. A video demonstrating how to place a sensor can be accessed using the QR code opposite.
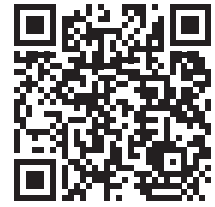
Depending upon the individual patient, the sensor can be left uncovered, or protected by an adhesive patch, a T-shirt, pet sweater, or similar **(Figure 7)**. A covering should certainly be used in active patients or where there are housemates that might attempt to remove the sensor; there is no need to remove any covering in order to download data from the reader. Although the sensor is waterproof, it is not recommended to bathe the pet or allow it to swim while the sensor is in place. Once the sensor has expired it can easily be removed by gently peeling it from the skin, if necessary using alcohol or baby oil to remove the glue.

The FSL measures the interstitial glucose every minute and stores this data every 15 minutes on the sensor disc for up to 14 days. The disc can store up to 8 hours of data, but every time the sensor is scanned the data is downloaded onto the reader or mobile phone. The sensor can be scanned at any time, but in order to obtain continuous readings it should be scanned at least every 8 hours to prevent the data from being over-written. The data can then be uploaded to a computer or the LibreView website and viewed on-line or as a pdf file any time during the life of the sensor. The LibreView website allows data from multiple patients to be stored in the cloud, and can be accessed by both the owner and the veterinary care team. The free software allows the user to generate a summary report, which can be viewed on-line or downloaded as a pdf.

Complications of CGM

Although in general there is good correlation between blood glucose and interstitial glucose, problems can arise with the use of the sensor. These include error messages, delays in reporting

Figure 7. The sensor may be protected after placement by a pet sweater or similar.
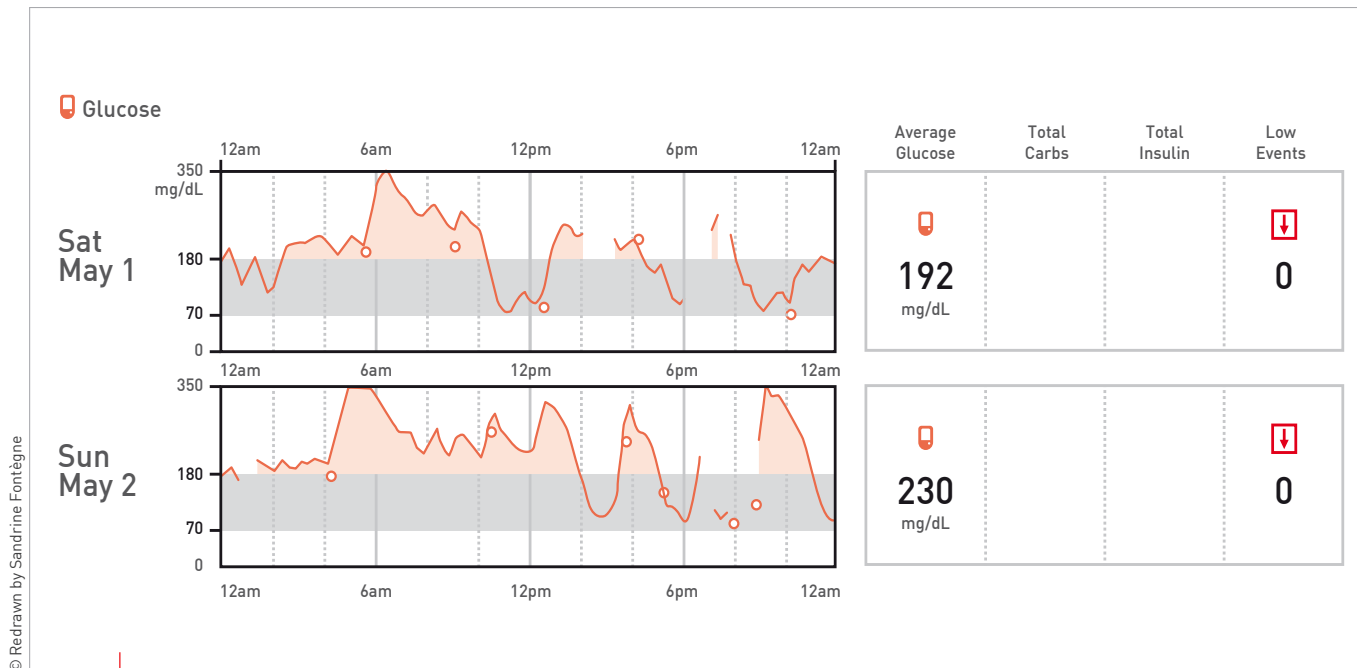
Figure 8. Indications of sensor error include rapid fluctuations in the reported interstitial glucose, delays in reporting the measured glucose, persistently high or low readings that do not correlate with the clinical picture, error messages, and gaps in the data. Here a section of the weekly summary shows rapid fluctuations in the glucose concentration unassociated with insulin administration (Note all glucose values are in mg/dL.).

the measured glucose, persistently high or low readings that do not correlate with the clinical picture, gaps in the data, and rapid fluctuations in the reported interstitial glucose **(Figure 8)**. Total sensor failure may also occasionally occur. Another small point is that although the device measures glucose concentrations between 40 and 500 mg/dL, the graphs generated in the reports do not display glucose concentrations greater than 350 mg/dL (19.4 mmol/L). If there is any doubt about the accuracy of the readings, blood glucose should be checked with either a validated POC glucometer or an automated biochemistry analyzer. Complications with the patient can also sometimes develop; these include erythema at the placement site, and (rarely) abscess formation, so if sequential sensors are to be used in an individual patient, the placement site should be varied to avoid using the same location twice. Note also that although the FSL can measure interstitial glucose for up to 14 days, early detachment occurs in many patients; in cats the average sensor life is approximately 8 days.

Interpretation of data

The FSL summary report, which can be viewed on the manufacturer's website or via free downloadable software, has a number of different viewing options. The *Daily Log* and *Weekly Summary* show curves from individual days, while the *Glucose Patterns Insights* and *Ambulatory Glucose Report* display the data averaged over time. This allows assessment of both day-to-day variability and weekly trends. The reports allow the veterinarian to evaluate the insulin dose and duration, and to determine whether there are differences in insulin requirements during the day versus overnight. This

also enables accurate assessment of glycemic control in cats given once daily insulin. Another major advantage is the ability to evaluate day-to-day variability in insulin response and to determine the frequency of hypo- and hyperglycemia events.

Interpretation of individual curves is similar to interpretation of a traditional blood glucose curve, but with the ability to better appreciate day-to-day variability. The glucose nadir, duration of insulin effect and average glucose levels can be easily determined. Ideally, the glucose nadir should fall between 80-150 mg/dL (4.4 to 8.3 mmol/L) and the glucose concentration should remain below 300 mg/dL (16.6 mmol/L) for the majority of the day. Problems that can be detected using the FSL reports include inadequate insulin dose, inadequate duration of insulin action (rapid metabolism), insulin-induced hypoglycemia **(Figure 9)**, and lack of response to insulin; this latter problem suggests either poor client compliance or insulin resistance. Based on the assessment of the curve, a change in insulin dose or formulation can be made if needed, and the response assessed while the sensor is still in place. Because the glucose measurements are available in real time, clinically relevant hypoglycemia can also be spotted and treated immediately, and the insulin dose decreased. When using the FSL to adjust the insulin dose, it is important to wait 5-7 days between alterations, and since the sensor has a 14 day lifespan it is usually possible to make two adjustments to the dose during this period; of course, the dose can be decreased multiple times if necessary.

Although the correlation between the FSL and POC glucometers is usually good, sensor failure or errors can and do occur. If the FSL glucose
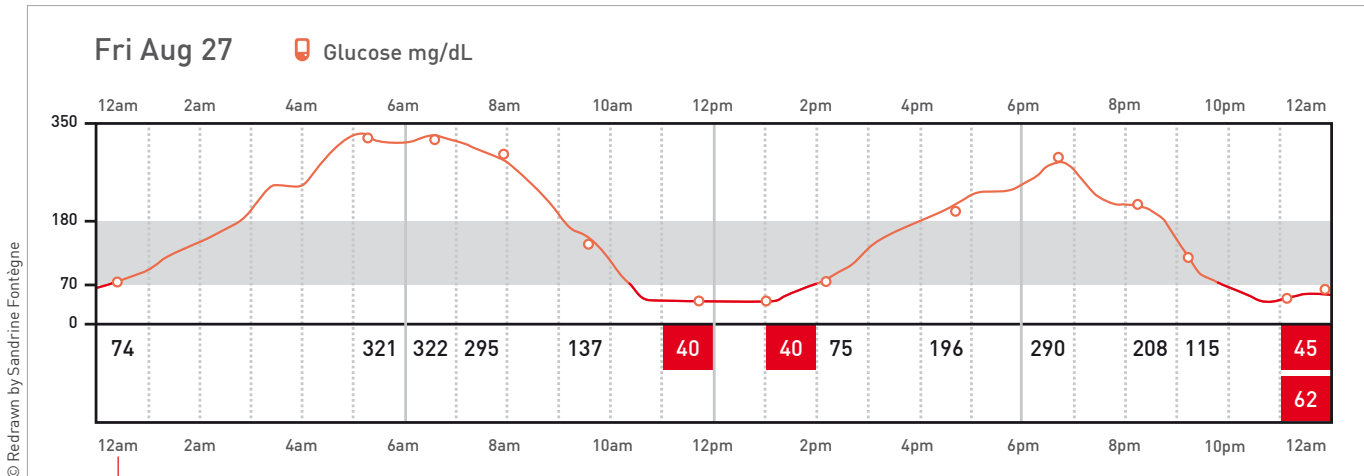
Figure 9. Problems that can be detected using the FSL include insulin-induced hypoglycemia, inadequate duration of insulin action (rapid metabolism), and marked day-to-day variability in response to insulin. Here the daily log shows insulin-induced hypoglycemia in a diabetic cat. (Note all glucose values are in mg/dL.).

measurements do not fit with the clinical picture, the blood glucose should be assessed using a POC glucometer or another trusted method. Indications of sensor failure include an error message, a message indicating that the sensor should be scanned again at a later time, gaps in data, and unexpectedly wide swings in the blood glucose that do not fit with clinical signs. In these situations, if the results of the FSL do not correlate with a POC device, the sensor should be replaced.

CONCLUSION

In summary, continuous glucose monitoring devices can be very valuable in assessment of glycemic control in cats, but having a good understanding of the technology of the chosen sensor (and its limitations and potential errors) allows maximum utilization of the technology. The devices now enable the clinician to undertake more accurate monitoring of diabetic patients, and thus potentially increase the likelihood of diabetic remission, and can now be used in most first-opinion clinics whenever necessary.

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UNEXPLAINED WEIGHT LOSS IN THE CAT

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The "Shrinking Kitty" is a common presentation in the small animal clinic; this article offers a logical approach to the cat with unexplained weight loss.

KEY POINTS

1 Unexplained weight loss should be investigated promptly, as it usually indicates a significant change in the cat's health.

2 Subtle changes in the routine laboratory data may hold key clues regarding the cause of unexplained weight loss.

3 Gastrointestinal disease is a common cause of weight loss in cats but may not be accompanied by overt signs of digestive tract dysfunction such as vomiting or diarrhea.

4 The cat's nutritional needs must be evaluated and addressed pending the determination of the underlying cause of weight loss.

Introduction

A cat with unexplained weight loss is a familiar scenario within the small animal consult room, and such cases can be both challenging and frustrating for the clinician. This article will outline a logical approach to the situation where no obvious diagnosis is apparent, with an emphasis on a cost-conscious, stepwise approach; a typical scenario is shown in **Box 1**.

Step 1: revisit the history

Owners can become accustomed to abnormal behaviors and may discount the significance of clinical signs such as vomiting. It is not unusual for an owner to say "Fluffy seems fine" when talking about a cat that vomits on a weekly basis. Similarly, an owner may fail to recognize the importance of a subtle change in stool consistency or an increase in urine output. Occasional coughing may be attributed to hairballs and not reported to the veterinary care team. A careful review of the patient's history, using open-ended questions to encourage more detailed responses, may highlight issues that could explain the weight loss and merit further investigation.

Step 2: revisit the physical examination

It can often be very useful to repeat the physical examination in a cat with unexplained weight loss, as subtle abnormalities may be initially overlooked or discounted. If the muscle condition score was not initially noted, this should be established and recorded. It can be difficult to examine the oral cavity in an awake cat, but inspection of the teeth and gum line may reveal significant pathology. It is however important to bear in mind that a cursory visual examination does not rule out significant

and impactful dental disease; the extent of painful conditions such as tooth resorption may only be determined with radiographic studies **(Figure 1)** (1). A thorough ophthalmologic examination should be performed, looking for signs of uveitis or chorioretinitis. These are non-specific findings, but are often seen in cats with fungal or protozoal infections **(Figure 2)** (2). Any skin or subcutaneous nodules should be carefully examined, particularly if noted in proximity to the mammary chain. It is also prudent to watch the cat ambulate to look for signs of joint, spinal, or neurological disease; many of us examine our feline patients on the table and may therefore fail to notice changes in gait, coordination, or muscle strength.

Step 3: collect a thorough nutritional history

Detailed information should be collected regarding the amount and type of food offered and consumed daily, with the goal of establishing the cat's actual caloric intake. Unfortunately, collecting this piece of information can be difficult, as many cats are offered *ad libitum* dry food and the owner can have a limited understanding of how much is actually consumed. Under these circumstances, the owner
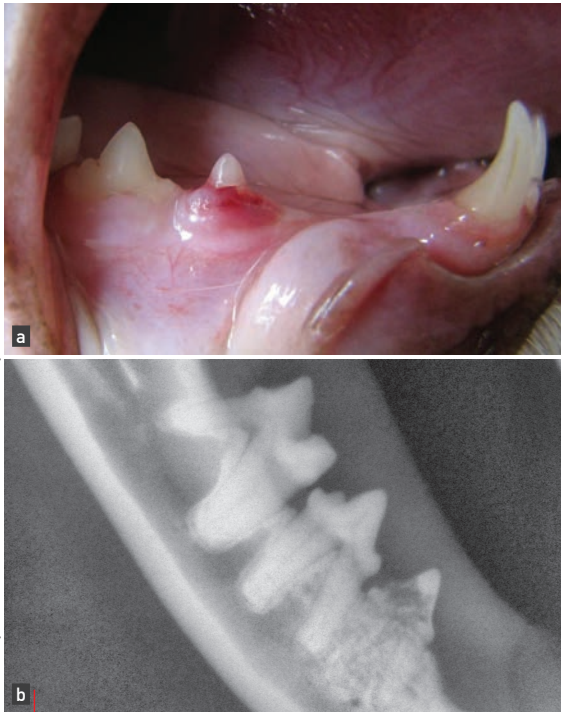
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Figure 1. (a) The right mandible of an 8-year-old cat with unexplained weight loss. Note the area of hyperemia and erosion on the rostral side of tooth 407. **(b)** Radiographic image of the same patient. Note the lucent lesion in the caudal portion of tooth 407, and the loss of root structures; these changes are consistent with type 2 tooth resorption.

Box 1. The cat with unexplained weight loss – a typical presentation.

Presentation
It is 10 am on a busy Monday morning, and Mrs. Smith arrives at the clinic with her 8-year-old, male (castrated) cat, Freddie, for his annual wellness visit. Freddie's physical examination is unremarkable except for grade 2 periodontal disease. Findings on routine lab work* are within reference ranges, but he has lost 0.5 kg since his last visit.

*Complete blood count; serum biochemical profile; urinalysis with sediment examination; fecal flotation; total thyroxine concentration; FeLV and FIV testing

Follow-up on Freddie
On further questioning, it was established that Freddie was maintained on a dry, senior diet, offered *ad libitum*. The owner was unaware of any changes in intake, but was unable to specify the amount consumed. No vomiting or changes in stool consistency had been noted. However, the cat's serum albumin had decreased from 3.6 g/dL a year ago to 3.1 g/dL (reference interval: 2.8-3.6 g/dL).

Due to concerns about underlying GI disease, serum folate, cobalamin and PLI were measured. All values were within the reference interval, but cobalamin was judged to be questionable at 388 µg/dL (normal serum cobalamin levels will vary depending on the reference laboratory used). Findings on abdominal ultrasonography were unremarkable; the overall appearance and thickness of the small intestinal wall were normal.

After a thorough discussion with the owner, the decision was made to anesthetize Freddie for dental prophylaxis with intraoral radiographs, along with upper and lower GI endoscopic examination and biopsy of the stomach, duodenum, ileum, and colon.

The dental procedure confirmed and addressed mild periodontal disease. Histopathology of the stomach and duodenum identified a mild lymphoplasmacytic infiltrate; a histiocytic infiltrate with intralesional yeast (appearance consistent with *Histoplasma capsulatum*) was reported in the ileal and colonic biopsies.

The diagnosis of histoplasmosis was subsequently confirmed with an enzymatic immunoassay performed on a urine sample, and Freddie was treated successfully with itraconazole.

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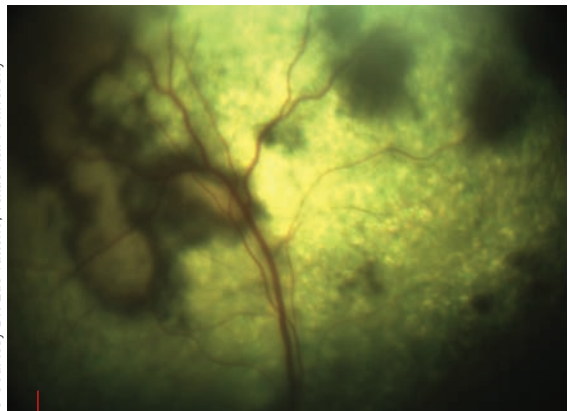
Figure 2. All senior cats should be given a full ophthalmology assessment in the consult room, as this can reveal signs of systemic disease. This cat with systemic histoplasmosis had an active retinitis visible on ophthalmoscopic examination.

should be asked to carefully measure or weigh out a daily allowance and determine the amount that remains uneaten, over several 24-hour periods.

It is also important to ask questions about changes in food preferences or feeding behaviors. Owners will sometimes describe their cat as "hungrier than usual" or "having a good appetite" if the cat exhibits food-seeking behaviors such as rubbing against the owner's legs or vocalizing at established mealtimes. Although these activities suggest an interest in eating, it is still important to find out how much the cat takes in. Some cats will continue to "ask" for (and consume) treats or canned food but decrease their intake of kibble-based diets. Inattentive owners may think their cat's intake is robust, when in fact the total calories consumed are inadequate.

It can be particularly difficult to determine a specific cat's intake in multiple cat households. Under these circumstances, the owner should pay

Table 1. Diagnostic considerations in cats with unexplained weight loss despite adequate or excessive caloric intake.

Disorder	Initial diagnostic considerations
Hyperthyroidism	Measure free thyroxine +/- feline thyroid stimulating hormone
Exocrine pancreatic insufficiency	Measure fasted trypsin-like immunoreactivity
Inflammatory/infiltrative bowel disease	Measure serum folate and cobalamin (B_{12})
Cachectic disorders (less likely)	Thoracic radiographs; abdominal ultrasonography

Table 2. Diagnostic considerations in cats with unexplained weight loss and inadequate caloric intake.

Disorder	Initial diagnostic considerations
Prehension disorders/ oral discomfort	Observe feeding behaviors; sedated oral examination
Psychological stress	Assess environment, feeding practices, overall husbandry
Chronic kidney disease	Measure SDMA*; check blood pressure; quantify proteinuria; ultrasonography
Pancreatitis	Measure pancreas-specific lipase activity; ultrasonography
Inflammatory/infiltrative bowel disease	Measure serum folate and cobalamin (B_{12}); ultrasonography
Idiopathic hypercalcemia	Measure ionized calcium; measure parathyroid hormone and parathyroid-related protein
Cachectic disorders (e.g., neoplasia; chronic infection).	Thoracic radiography; abdominal ultrasonography

*SDMA = symmetric dimethylarginine

close attention to the group dynamics, as a more assertive cat may make it more difficult for a timid individual to get adequate access to food (3). Cats are thought to prefer to eat small, frequent meals when alone and unobserved; even in the absence of overt inter-cat aggression, the presence of other animals may limit food intake. Consideration should also be given to the location of the cat's food; if this is up on a counter and the cat has orthopedic disease, it may take in less calories simply because accessing the food causes discomfort or requires significant effort. Food bowls placed next to noisy machinery, such as the washing machine, may also be problematic.

The actual calories needed to maintain a stable body weight vary from cat to cat, and will depend on age, sexual status, and activity level. For a sedentary, neutered adult cat, 40-66 kcal/kg body weight/day is a useful starting point, but this number should be regarded as a rough guide. Basal/resting energy requirement (RER) may also be calculated using a non-linear formula: body weight $(kg)^{0.75}$ x 70. For the average middle-aged cat, the RER should be multiplied by a factor of 1.2 to 1.4 to determine the actual daily (or maintenance) energy requirement (4). If the cat is underweight, the ideal body weight should be used to determine the true daily energy requirement.

In the author's experience, unexplained weight loss (*i.e.*, weight loss in a cat with essentially unremarkable routine labwork) accompanied by adequate or robust caloric intake is uncommon. Diagnoses to consider under these circumstances include early hyperthyroidism, inflammatory bowel disease (IBD) and exocrine pancreatic insufficiency **(Table 1)**. Additionally, some cats with cachexia related to cancer or chronic infection will experience weight loss despite an adequate food intake; however, hyporexia is more commonly noted under these circumstances (5). Patients with cachectic disorders may be recognized by the loss of muscle rather than adipose tissue; this pattern suggests changes in metabolism that are driven in part by increases in inflammatory cytokines such as tumor necrosis factor-alpha, and interleukins 1 and 6. The diagnostic possibilities for cats with unexplained weight loss and decreased intake are broader, and a more extensive list of differentials should be considered for these patients **(Table 2)**.

Step 4: scrutinize the available laboratory data

The "minimum database" for a feline patient with weight loss should include a complete blood count, serum biochemical profile with electrolytes, and urinalysis. A fecal floatation should be performed in the cat that has access to the outdoors. If the patient is 7 years or older, total thyroxine concentration should also be measured. As per recommendations from the American Association of

Table 3. Key laboratory parameters to trend in cats with unexplained weight loss and normal laboratory data.

Parameter	Diagnostic considerations
Albumin	A decrease from baseline suggests GI disease. Consider measurement of serum folate and cobalamin concentrations.
Creatinine	An increase from baseline suggests CKD (in a euvolemic patient). Consider measurement of systolic blood pressure and renal ultrasonography.
Thyroxine	An increase from baseline or a value within the upper half of the reference range suggests hyperthyroidism. Consider measurement of free T_4 +/- feline-specific thyroid stimulating hormone.
Calcium	A robust total calcium suggests hypercalcemia. Consider measurement of ionized calcium.
Eosinophil count	A robust count is suggestive of lymphoma, mast cell tumor, protozoal or fungal infection, eosinophilic IBD. Consider abdominal ultrasonography +/- infectious disease testing

Feline Practitioners, cats with evidence of systemic disease should also be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV).

Although this is a very comprehensive approach, patients with significant organic disease may have "normal" bloodwork. It is therefore important to closely evaluate the available data and compare – whenever possible – with historical findings (see **Table 3**). Some analytes, such as creatinine and albumin, will remain remarkably consistent over many years in healthy cats; looking for trends rather than simply focusing on "abnormal" values can therefore be very helpful. For example:

- A decrease in serum albumin (even if still within the reference range) may indicate gastrointestinal (GI) disease such as IBD or small cell lymphoma (SCL) [6]. It is important to bear in mind that many cats with significant GI dysfunction continue to produce well-formed feces; normal stools do not discount the possibility of IBD or similar conditions in this species. Serum folate and cobalamin concentrations should be measured as appropriate; subnormal levels of either analyte support a suspicion of GI disease (see next section for more details).

- Serum creatinine concentrations are within the reference interval for cats with stage 1 chronic kidney disease (CKD) and may still be "normal" for some with stage 2 disease. However, even early-stage CKD reflects substantial loss of renal function, and affected cats may experience significant weight loss [7]. The reasons for this are complex, but likely reflect the wide-ranging metabolic changes that accompany CKD and the

impact of inflammatory cytokines on food intake. An increase in serum creatinine concentration >26 µmol/L (0.3 mg/dL) when compared to a previous value in a euvolemic cat suggests a significant loss of renal function. This possibility is supported when urine specific gravity is < 1.035, or there is a concurrent proteinuria [8]. Renal status should be further investigated under these circumstances, with measurement of systolic blood pressure and ultrasonography of the renal system.

- An apparently "normal" total thyroxine (T_4) concentration should also be considered carefully. As cats age, the total T_4 will gradually drift towards the lower end of the reference interval. A robust or increasing value in a cat with weight loss is therefore suggestive of early hyperthyroidism and merits further investigation [9]. As a general rule, a total T_4 within the upper half of the reference interval in a senior cat with weight loss should prompt the measurement of free T_4. Feline-specific thyroid stimulating hormone concentrations may also provide useful information, as values will be subnormal in cats with hyperthyroidism [10].

- Serum total calcium concentrations are poorly correlated with ionized levels in cats, potentially impactful increases in ionized calcium may be overlooked if the total value is within the reference interval. If the total calcium is close to the upper end of the reference range, measurement of ionized calcium may be warranted [11]. Hypercalcemia for any reason is routinely associated with hyporexia, and almost 20% of cats with a final diagnosis of idiopathic hypercalcemia were reported to have experienced weight loss [12].

- Findings on a "normal" complete blood count are less likely to suggest a specific cause of weight loss, but an eosinophil count approaching the upper end of the reference range may be meaningful. Neoplastic processes such as lymphoma and mast cell tumor release chemokines that attract eosinophils, as do fungal and protozoal infections [13]. A robust eosinophil count may also be noted in cats with eosinophilic IBD.

●●● Step 5: additional laboratory testing
○○

If the minimum data base does not provide any useful clues, the author will prioritize the investigation of GI tract function, and measure serum folate and cobalamin concentrations. Hypofolatemia indicates absorptive dysfunction in the duodenum, but this finding is a relatively insensitive indicator of disease, and a normal value does not discount inflammatory or neoplastic changes in this segment of the bowel [14]. Serum cobalamin (B_{12}) concentrations appear to be more useful, and subnormal values indicate ileal

disease, intestinal dysbiosis, or exocrine pancreatic insufficiency. In the author's practice, a concentration < 400 ng/L (reference range: 290-1,500 ng/L) is considered significant. Cobalamin deficiency may in turn impact appetite, so prompt recognition and management of hypocobalaminemia is important (15).

Another useful consideration is chronic pancreatitis. Affected cats may not vomit or exhibit overt signs of abdominal discomfort; instead, food intake is variably decreased. Although a definitive diagnosis requires pancreatic histopathology, a presumptive clinical diagnosis is usually based on a combination of signs (which may be limited to hyporexia), along with findings on abdominal ultrasonography and/or measurement of pancreas-specific lipase immunoreactivity. An increase in this parameter is strongly indicative of active pancreatic acinar cell damage; however, this may not be the only cause of a patient's weight loss, and the possibility of concurrent GI tract disease or other systemic disorders should be considered (16). Additionally, pancreatic inflammation may wax and wane, so a result within the reference range does not exclude the possibility of cyclical bouts of inflammation; repeated measurement of pancreas-specific lipase may be helpful under these circumstances.

In canine patients, C-reactive protein is recognized as emerging biomarker for inflammatory conditions, and increased concentrations have been associated with numerous disorders (17). This is a positive acute phase protein, and concentrations increase substantially (often > 20-fold) in response to inflammation, injury or neoplasia in dogs. Unfortunately, C-reactive protein does not seem to be useful in cats and it is not regarded as a reliable indicator of underlying inflammatory or neoplastic disease in this species. In one study, serum concentrations did not differentiate clinically normal cats from post-operative patients (18).

"If food intake is clearly suboptimal, efforts must be made to increase caloric intake while diagnostics are completed; appropriate approaches include offering alternative foods and administering appetite stimulants."

Audrey K. Cook

Step 6: imaging studies

In the author's opinion, an ultrasonographic examination of the abdomen is often a high yield diagnostic test in a cat with unexplained weight loss. Particular attention should be paid to the GI tract, and both the overall thickness of the various sections of the bowel, and the ratio of the thickness of the mucosal versus the muscularis layer, should be determined. As a general rule, any segment of the small intestine with wall thickness > 3 mm is a concern; similarly, a prominent muscularis can be indicative of pathology (19). Diffuse thickening of the muscularis is sometimes seen in clinically normal cats, but is more often associated with IBD or infiltrative GI conditions such as small cell
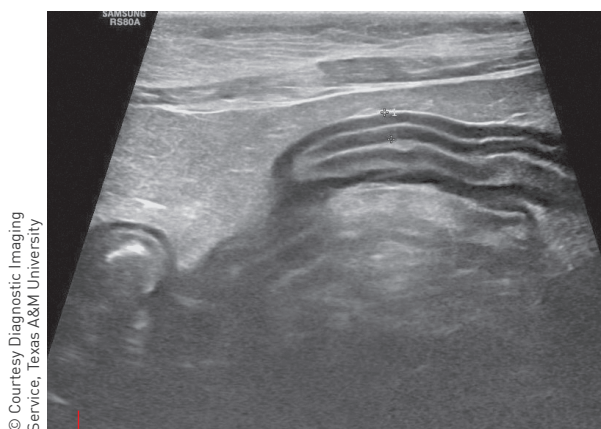
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Figure 3. Ultrasonographic image of the jejunum in a cat with unexplained weight loss and subnormal serum cobalamin concentrations. Although the overall thickness of the bowel is within normal limits, the muscularis layer is more prominent than expected. This cat was subsequently diagnosed with small cell lymphoma via endoscopic biopsies.
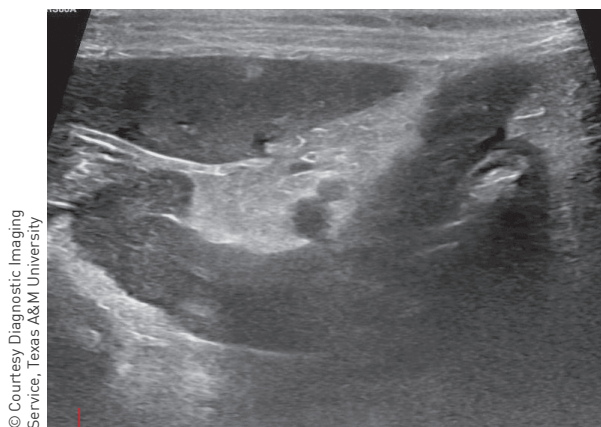
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Figure 4. Ultrasonographic image of the left limb of the pancreas in a cat with unexplained weight loss and intermittently increased pancreas-specific lipase immunoreactivity. The pancreas is enlarged and hypoechoic, and the surrounding mesentery is hyperechoic.
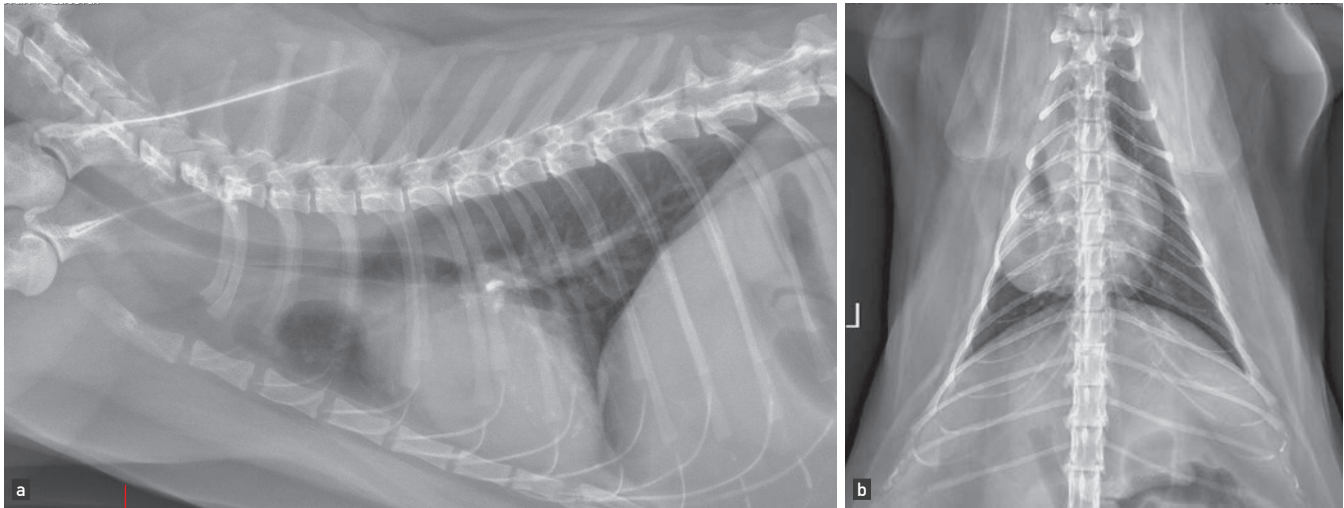
Figure 5. **(a)** Right lateral thoracic radiograph of an 11-year-old cat with unexplained weight loss. A mineralized density is noted just caudal to the carina. **(b)** Ventrodorsal thoracic radiograph of the same cat. A soft tissue mass is evident in the left thorax, which effaces the cardiac silhouette and the lateral body wall. There are multifocal angular mineral opacities throughout the mass, which are most numerous dorsally, and there is a large, rounded, gas opacity within the mass. There is a mild rightward mediastinal shift. Cytologic findings were consistent with carcinoma.

lymphoma and histoplasmosis **(Figure 3)**. Other intra-abdominal conditions causing low grade discomfort and secondary hyporexia such as chronic pancreatitis may be identified with ultrasonography, although subtle changes in echogenicity may be difficult to appreciate without a high-end machine or substantial experience **(Figure 4)** (16). Problems affecting the kidneys (*e.g.*, a ureteral obstruction or hydronephrosis) can be easily identified with ultrasonography and may well cause enough chronic discomfort to impact food intake (20). Bear in mind that if the contralateral kidney is unaffected, serum creatinine and urine specific gravity will be within the reference ranges.

If appropriate, changes in size or echogenicity of organs such as liver, spleen, and lymph nodes should prompt the collection of cytologic specimens by fine-needle aspiration.

Thoracic radiographs are an appropriate next step if abdominal ultrasonography does not provide additional direction. The fact that clinical signs of respiratory disease are lacking should not be used to discount the possibility of conditions such as pulmonary neoplasia that could account for weight loss (21). A three-view study (left and right lateral images and a ventrodorsal image) should be performed, and interpretation by a board-certified radiologist may be helpful **(Figure 5)**.

Step 7: supportive care

If food intake is clearly suboptimal, efforts must be made to increase caloric intake while diagnostics are completed; appropriate approaches include offering alternative foods and administering appetite stimulants. New foods should ideally be energy dense and highly palatable; digestibility may also be important if there are concerns about underlying GI dysfunction.

Cats have complex behaviors regarding food preferences and are often reluctant to consume an unfamiliar diet. For example, switching a cat accustomed to an exclusively dry diet to a feeding plan based on canned food can be difficult; the cat may nibble at the new food but fail to consume adequate amounts. Simply changing the shape or flavor of a kibbled diet can also be problematic if the cat is not used to novel foods. As a general rule, the old diet should be offered alongside one or two new options, with each new food served on a separate dish and tested for 24 hours before any decision is made. It is very important that the amount of food eaten is carefully measured, so that caloric intake can be monitored appropriately.

Increasing the palatability of a familiar or novel food by adding a small amount of a highly flavored protein (*e.g.*, tuna or salmon) may encourage intake. In the short term (2-3 weeks), feeding a home-cooked diet is unlikely to be harmful. However, prolonged dependence on an unbalanced diet may have significant consequences; input from a nutritionist is warranted under these circumstances.

Over the last decade, various medications have been used off-label to encourage food intake in cats. Many of these had questionable safety and efficacy. Fortunately, there are now two products licensed in many countries to specifically address weight loss in cats. Mirtazapine can be administered transdermally on the inner side of the pinna q24H at a dose of 2 mg/cat (22). This drug is thought to improve appetite by increasing central norepinephrine levels, along with antagonism of specific serotonin receptor subtypes. In a study looking at its effect in cats with ≥ 5% unintended weight loss, the treated group gained an average of 3.9% body weight in 2 weeks, while those in the placebo group gained just 0.4% (22). Transdermal mirtazapine is generally well tolerated, although skin irritation at the site of application has been reported. Overdose can result in vocalization,

agitation, and vomiting, and the recommended dose or frequency should be decreased in any cat with significant hepatic or renal disease.

Capromorelin is a ghrelin receptor agonist, and a liquid oral formulation is licensed in the USA for use in cats, at a dose of 2 mg/kg q24H (23). Ghrelin is a peptide hormone secreted by the gastric mucosa; serum levels increase during the interprandial interval and stimulate food seeking behaviors. This product is specifically approved for use in feline CKD and has been shown to promote weight gain in cats with this condition. In an eight-week study, treated cats averaged a weight gain of > 5%; animals in the placebo group lost an average of 1.6% of body weight (24). Ghrelin has significant anti-inflammatory properties, and additionally stimulates growth hormone secretion. Side effects include salivation, and occasional cats may experience a temporary decrease in heart rate and blood pressure following administration of the first few doses.

CONCLUSION

Even small decreases in the weight of a feline patient can signal a significant underlying disorder; cats (much like people) tend to maintain a stable weight or slowly gain over time unless caloric intake is deliberately restricted, or disease arises. Unexplained weight loss therefore requires a logical and thorough evaluation. Supportive care to encourage adequate intake should be instituted while diagnostics are pursued.

If adequate food intake cannot be maintained with these simple interventions, more aggressive steps (*e.g.*, placement of an esophageal feeding tube) should be considered.

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HOW I APPROACH... THE VOMITING CAT

Vomiting, alone or in combination with other clinical signs, is a common presenting complaint in cats; in this paper the authors share their recommendations for a systematic clinical approach for both acute and chronic vomiting cases.

KEY POINTS

1 Signalment, a detailed history, and clinical findings must all be considered before formulating likely differential diagnoses and a diagnostic plan for vomiting in cats.

2 The acute vomiting cat should firstly be triaged to determine if immediate stabilization measures are required before any diagnostics are performed.

3 Therapeutic or dietary trials can be considered before diagnostic investigations in clinically stable cases, but any inadequate nutrition should be promptly recognized and addressed.

4 Differentiation of inflammation from neoplasia is particularly important in the feline gut, as inflammatory bowel disease and lymphoma have a differing prognosis and treatments.

An introduction to the vomiting cat

Both acute and chronic vomiting can be the manifestations of primary gastrointestinal (GI) disease or extra-GI conditions in the cat. The list of potential differential diagnoses for vomiting is extensive, and other criteria from both the history and physical examination, followed by appropriate laboratory and diagnostic imaging tests, can often help to narrow those down. For acute vomiting, the two most important decisions to be made following initial triage are to decide if relatively swift supportive care (particularly replacement of fluid losses and correction of electrolyte or acid-base imbalances) is needed, and if surgical intervention may be necessary (which could be diagnostic, therapeutic or both) when stabilization is achieved. Once the patient is cardiovascularly stable and there is no immediate indication for surgery, a more complete list of differential diagnoses for acute vomiting can be considered **(Table 1)**.

For chronic vomiting, consideration of possible causes and diagnostic tests can usually be at a slower pace, and can depend on any additional presenting complaints, physical examination findings, and (not uncommonly) an owner's preferences. It seems reasonable to assess more common conditions first and to proceed from there in a stepwise manner. For a cat with chronic GI signs and no evidence of extra-GI or infectious

disease, the two most common remaining differential diagnoses are idiopathic Inflammatory Bowel Disease (IBD) and Low-Grade Alimentary Lymphoma (LGAL), and more invasive tests (*e.g.*, biopsies) are commonly performed relatively early in the diagnostic workup compared to dogs. This article will describe a stepwise diagnostic approach for cats presented with either acute or chronic vomiting, and discuss management of the more common underlying conditions.

Key aspects – signalment and clinical history

A complete clinical history is extremely useful to refine the list of differential diagnoses. It is particularly important to establish that the owner does not describe regurgitation, retching or even coughing instead of vomiting, as these can be difficult to distinguish from one another in cats. Once it is established to be vomiting, the respective signalment and the presence or absence of additional clinical signs can help prioritizing some conditions over others. Therefore, the clinician should consider:

Age and breed

Cats with dietary indiscretions, food hypersensitivities or food-responsive chronic enteropathies (FRE) tend to be younger than those

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with other conditions, especially other forms of chronic enteropathies (CE) (1). Conversely, hyperthyroidism is a common cause of chronic vomiting, as is neoplasia, with both being more likely in older cats. Siamese cats are at an increased risk of GI adenocarcinoma (2), whilst longhair breeds are more likely to have trichobezoars, which can lead to partial or complete GI obstruction.

Feeding habits and environment

Any recent food changes increase the likelihood of intolerances. Hunting behavior raises the possibility of an infectious disease (especially in conjunction with diarrhea and/or pyrexia), and the clinician should ask if the cat is free-roaming, with possible access to toxins.

Timeline of clinical signs

The differential diagnoses, diagnostic approach and therefore management of acute (< 1 week) vs. chronic (> 3 weeks) are considerably different. Intermittent vomiting can be "physiological" in some cases, but some cats with IBD or food-responsive enteropathy (FRE) can have mild and intermittent GI signs for months to years without significant clinical deterioration (1). Progressive, or more frequent chronic intermittent vomiting might warrant more prompt investigations, especially in adult/older cats.

Other clinical signs

The presence or absence of diarrhea can help narrow differential diagnoses down to potential infectious or obstructive disease (especially in acute vomiting), or to diseases of the GI tract and adjacent organs (pancreas, liver) when chronic, especially in the absence of other signs. Some cats with chronic enteropathies (CE) or IBD will not present with diarrhea, but only with vomiting +/- weight loss (1). Concurrent polyuria/polydipsia (PUPD)

Table 1. Differential diagnoses for acute vomiting in cats.

Extra-gastrointestinal diseases
- AKI (toxins, drugs, UTI/pyelonephritis), ureteral or urethral obstruction
- Hepatobiliary diseases:
  - Neutrophilic cholangitis
  - Acute liver failure (drugs, toxins)
  - Toxoplasmosis
  - Neoplasia
  - Gallbladder stones
- Acute pancreatitis
- Diabetic ketoacidosis
- Drugs/toxins: heavy metals, ethylene glycol, NSAIDs, chemotherapy
- Electrolyte and acid-based disturbances
- Vestibular disease

Gastrointestinal diseases
- Alimentary indiscretion
- Infectious (virus, parasites, bacteria)
- Foreign bodies
- Gastritis/gastroenteritis
- Ulceration
- Solitary neoplasia (adenocarcinoma, mast cell tumor, leiomyosarcoma, GIST), especially if suddenly obstructive can appear acute in onset
- Constipation

AKI = acute kidney injury, GIST = gastrointestinal stromal tumor, NSAIDs = non-steroidal anti-inflammatory drugs, UTI = urinary tract infection

in chronic vomiting might raise a suspicion of chronic kidney disease (CKD) or diabetes mellitus. The presence of jaundice suggests hepatobiliary disease or pancreatitis (although pre-hepatic causes (*i.e.*, hemolysis) have to be ruled out). Weight loss and anorexia are non-specific signs, but when chronic (especially in the absence of other specific signs or abnormalities) can be an indicator of primary GI disease, including lymphoma.

Key aspects – physical exam

During physical examination special attention should be paid to the following aspects:

1. triaging for signs that indicate immediate supportive treatment is required,
2. identifying aspects that may raise suspicion for a condition requiring prompt surgical intervention, and
3. identifying abnormalities suggestive of a potential cause and/or comorbidities.

Triage should be targeted to identify weak pulses, dehydration (which can be difficult to gauge in cats with moderate to severe weight loss), hypo- or hyperthermia, prolonged capillary refill time, or marked lethargy. In contrast to dogs, cats with shock do not generally compensate and can present with either tachycardia, a normal heart rate or even bradycardia (which would be a major concern in an ill animal). Such indicators of severe disease warrant supportive treatment before a more thorough evaluation.

Cats that are otherwise well, still eating and have a normal hydration status should be considered as having mild disease. Abdominal palpation in cats with vomiting is mandatory and can be very rewarding, as is usually easy to evaluate intra-abdominal structures such as liver, kidneys, bladder, and intestines. Intestinal wall thickening, masses (intestinal, lymph nodes or others), intussusceptions and sometimes even intestinal foreign bodies (FB) can be palpated, unless the patient is obese or difficult to handle. However, normal palpation does not exclude abdominal pathology, especially chronic conditions like pancreatitis, IBD or a FB. The most common type of FB in cats are linear ones such as sewing thread (3), which cannot usually be palpated directly. As one end of the thread can remain attached to the base of the tongue (3), careful examination of the oral cavity should be performed where there is acute onset of vomiting, particularly if dysphagia or hypersalivation are present concurrently.

In the authors' experience it can be challenging to assess cats for abdominal pain or discomfort, as it seems to be an infrequent finding with feline intra-abdominal conditions. For example, only 10-30% of cats with acute pancreatitis have been reported to show apparent abdominal pain (4), and neither is it commonly reported with chronic small bowel disease, lymphoma (1), or even intestinal foreign bodies.

Finding jaundice in a feline patient with vomiting is significant; not only because it can indicate primary hepatobiliary disease, but because it could suggest hepatic lipidosis and the need for nutritional support.

Finally, any cat with vomiting could be at risk of developing aspiration pneumonia, thus the respiratory system should be carefully assessed by auscultation and/or thoracic imaging (either via radiography or point of care ultrasound [POCUS]) as indicated.

Diagnostic tests – acute vomiting

A minimalistic approach is often sufficient for cats with acute vomiting and unremarkable clinical examination (*i.e.*, mild disease). The term "non-specific gastroenteritis" refers to self-limiting vomiting ± diarrhea of unknown origin, often presumed to be secondary to infection or dietary indiscretion. Here symptomatic treatment is often sufficient, but cats failing to respond to this need a more thorough evaluation.

The absence of abnormalities on abdominal palpation does not fully exclude the presence of a pathology; therefore, abdominal radiography can be considered – even with mild disease – in case surgical treatment is required. If a FB is not directly visible (*e.g.*, not radiopaque), the clinician should be mindful of typical imaging findings that are indirect indicators of obstruction, such as central "bunching" of the intestines **(Figure 1)**, or abnormal "crescent" or "teardrop" shaped intestinal gas bubbles (5). The presence of a so-called "gravel sign" is indicative of chronic intestinal obstruction **(Figure 2)**. While other types of intestinal FBs tend to produce complete obstruction, with dilation of small bowel loops cranial to the foreign material, it does not seem to be the case for linear foreign bodies (5). Likewise, some cats with chronic GI disease (especially young patients) may present with chronic/dynamic intussusception with no obvious dilation of intestinal loops. It is very important to take two, if not three abdominal radiographic views (left and right lateral and an orthogonal image), as key abnormalities may be evident only in one view **(Figure 3)**.

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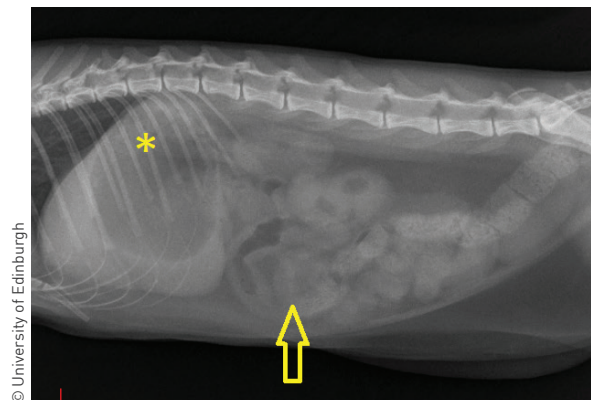
Figure 1. Right lateral abdominal radiograph of an adult cat presented with acute onset of vomiting due to presence of intestinal foreign body. Bunching of small intestinal loops (arrow) is observed with associated stomach distension (asterisk), although the foreign body cannot be visualized directly.

Figure 2. Right lateral abdominal radiograph of an adult cat with chronic history of vomiting and intestinal granulomas leading to partial intestinal obstruction. There is marked distension of small intestinal loops (asterisks) with a gravel sign (presence of small mineral opacities) in ventral aspects of small intestinal loops (arrow).

Figure 4. Ultrasonographic image of a small intestinal loop from an adult cat showing marked small intestinal plication (arrows). The cat was diagnosed with a linear foreign body.

Figure 3. Left **(a)** and right **(b)** lateral abdominal radiographs from an adult cat presented with acute vomiting and diagnosed with intestinal intussusception. The intussusception is only visible in the left lateral projection as an intestinal loop with a "sausage-like" homogenous soft-tissue appearance (arrow).

Figure 5. Ultrasonographic image of a small intestinal segment from an adult cat presented with acute onset vomiting and diarrhea diagnosed with pancreatitis. The picture shows intestinal corrugation (arrows indicate the intestinal lining).

Abdominal ultrasound can be a useful complementary tool in investigating causes of vomiting. For example, evidence of intestinal plication raises suspicion for a linear FB **(Figure 4)**, although this can be misinterpreted as corrugation **(Figure 5)** which is a non-specific finding reported in cats with enteritis, pancreatitis, peritonitis or neoplasia (5). Architectural changes such as loss of layering or GI thickening can also be assessed.

Overall, loss of layering raise suspicion for neoplasia, but severe inflammation can also lead to this. While ulcers are usually not detected by ultrasonography, a circumscribed thickening of the GI wall with an echogenic center (trapped gas) can be seen in some cases.

Exploratory laparotomy can be considered if there is a high suspicion of obstruction (*e.g.*, marked segmental intestinal dilatation on radiographs or ultrasound) even if a specific etiology (intussusception/FB) is not identified. The presence of peritoneal gas on an abdominal radiograph (suggestive of GI perforation) is another indication for emergency exploratory surgery.

For cats that are systemically unwell, or clinically stable cats who have failed symptomatic treatment, establishing a laboratory minimum data base (MDB) or a comprehensive complete blood count (CBC) and serum biochemistry (SB) is indicated. The MDB should include packed cell volume (PCV) and total solids (TS), electrolytes (with or

without venous blood gases if available), and basic biochemistry parameters (glucose, creatinine, blood urea nitrogen (BUN), liver enzymes, albumin and total bilirubin).

Findings such as sudden onset azotemia that are consistent with acute kidney injury (AKI) warrant investigations to identify specific treatable conditions, *e.g.*, urinary tract infection (UTI)/pyelonephritis (by urine culture and sensitivity (C&S) testing before antibiotic administration) or urolithiasis. However, in a large proportion of cats the cause of AKI is never identified.

Antemortem diagnosis of acute pancreatitis in cats is challenging and abdominal ultrasound seems to be insensitive to confirm the diagnosis, even in the presence of clinical signs (4,6). Specific feline pancreatic lipase immunoreactivity (fPLI) may aid in the diagnosis, and a combination of both techniques increases both sensitivity and specificity (4). Similarly, some cats with cholecystitis or cholangitis do not have abnormalities of the hepatobiliary system on ultrasound (7), while others show changes of the gall bladder wall or content, or extrahepatic bile duct obstruction (EHBDO). Aspiration of bile (for cytology and C&S) is strongly recommended when cholecystitis or cholangitis is suspected before antibiotics are administered, but this can risk gall bladder rupture in cases of severe edema or inflammation of the wall. Generally, the rate of complications associated with cholecystocentesis is low when performed under adequate sedation and appropriate technique; the gallbladder must be emptied as much as possible to minimize the risk of leakage. However, if deemed too risky, fine needle aspiration (FNA) from the hepatic parenchyma just adjacent to the gall bladder (again for both cytology and C&S) is an appropriate alternative.

> "A complete clinical history is extremely useful to refine the list of differential diagnoses. It is particularly important to establish that the owner does not describe regurgitation, retching or even coughing instead of vomiting, as these can be difficult to distinguish from one another in cats."

Ivan Montanes-Sancho

Table 2. Differential diagnoses for chronic vomiting in cats.

Extra-gastrointestinal diseases
- Chronic (azotemic) kidney disease
- Hepatobiliary diseases with or without EHBDO:
  - Neutrophilic cholangitis
  - Lymphoplasmacytic cholangitis
  - FIP
- Chronic pancreatitis
- Triaditis
- Hyperthyroidism

Gastrointestinal diseases
- Food-responsive chronic enteropathy
- Inflammatory Bowel Disease
- Chronic infection (*e.g.*, FCoV enteritis/FIP, *Physaloptera* spp.)
- Chronic foreign body
- GI granulomas (*e.g.*, mycobacterial disease)
- FGESF
- Gastric neoplasia (*e.g.*, adenocarcinoma, MCT, leiomyosarcoma, polyp)
- GI lymphoma (LGAL or large cellular lymphoma)

EHBDO = extrahepatic bile duct obstruction, FCoV = feline Coronavirus, FIP = feline infectious peritonitis, GI = gastrointestinal, FGESF = feline gastrointestinal eosinophilic sclerosing fibroplasia, LGAL = low-grade alimentary lymphoma, MCT = mast cell tumor.

Diagnostic tests – chronic vomiting

In cats with chronic vomiting ± diarrhea but are otherwise systemically well, an elimination dietary trial and minimal diagnostic tests (for example fecal parasitology) should be considered before a more comprehensive workup. Conversely, cats with additional significant weight loss or that are systemically unwell need a more thorough evaluation (see below).

As for acute vomiting, differential diagnoses for chronic vomiting include various GI and extra-GI conditions **(Table 2)**. Comprehensive laboratory work (CBC, SB, total thyroxin, urinalysis, fecal parasitology and other fecal pathogen testing [*e.g.*, via PCR]) are considered initial relatively non-invasive diagnostic steps that can help exclude common extra-GI disorders. In most cases it is advisable to take extra serum samples that can be used later for additional laboratory examinations if required, based on the initial findings. For example, these can include tests for pancreatic and/or intestinal function (fPLI, fTLI, serum cobalamin), infectious diseases (*e.g.*, toxoplasma titers, feline coronavirus (FCoV) titers), and hepatic function tests (baseline bile acids). The diagnosis of chronic feline pancreatitis can be especially challenging, because clinical signs are usually non-specific, and fPLI may be normal or borderline elevated. Depending on other clinical findings, the clinician may also consider further laboratory investigations (*e.g.*, citrated blood to check clotting times in cases of hepatobiliary disease, or ionized calcium where neoplasia might be suspected).

Table 3. Advantages and disadvantages of endoscopic and surgical gastrointestinal biopsies.

Endoscopic mucosal biopsies		Full-thickness surgical biopsies	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
• Minimally invasive • Mucosa can be directly visualized • More biopsies available and larger area of GI tract visible • Treatment (*e.g.*, immunosuppression) can be started immediately after biopsy collection	• Only mucosa and submucosa layers sampled • Jejunum cannot be reached • Access to equipment and special training required • Histopathological interpretation of biopsies is harder (crush artefact, lack of orientation) • Hepatic biopsies can be achieved simultaneously by ultrasound guided tru-cut, but pancreas cannot be accessed without surgery	• All layers of the GI wall included • Other abdominal organs (liver, pancreas, lymph nodes) can be assessed and sampled at the same time. • Easier histopathological assessment of biopsies for the pathologist • Special equipment not needed	• More invasive and risk of dehiscence • No direct visualization of the mucosa • Usually smaller number of samples, so lesions can be missed • Treatment (especially with immunosuppressive medication) is usually delayed due to time for healing

Ultrasonography is the preferred diagnostic imaging modality, particularly in skilled hands, as it provides useful detail on the size and structure of intra-abdominal organs. Initial survey abdominal radiographs can be considered, but they are insensitive for the diagnosis of pancreatitis, cholecystitis/cholangitis, and assessment of changes in the GI wall consistent with inflammation/IBD (or triaditis, the three conditions combined) or diffuse GI neoplasia. Abdominal masses can only be identified on radiographs beyond a certain size, and their origin is rarely identified. Only ultrasound can provide a finer assessment of changes within the GI wall (*i.e.*, thickness and structure, where the loss of layering raises suspicion for neoplasia), as well as assessment of abdominal lymph nodes (for size and echogenicity). Increased echogenicity of specific gut layers (*e.g.*, mucosa) can be a sign of inflammatory or neoplastic changes, or (rarely) lymphangiectasia. Thickening of the muscularis layer is often observed in IBD, but can also be found in healthy cats. Skilled operators can reliably assess the pancreas with ultrasound, but sensitivity for chronic pancreatitis is poor and it may appear completely normal (4). The origin and inner architecture of any mass can also be characterized, but remember that in some cats with diffuse primary GI conditions such as FRE, IBD or even LGAL, imaging findings can be completely normal – so a "normal" ultrasound does not rule out primary GI disease.

Minimally invasive sampling of abnormal structures (*e.g.,* FNA) should be considered, often in conjunction with an ultrasound scan, and hence ideally discussed with owners beforehand. The main indication for FNA is differentiation between inflammatory and neoplastic conditions, and whilst not always diagnostic, they are easy to perform, do not require specialist equipment, can be done under sedation, and are associated with extremely low morbidity. As for cases with acute hepatobiliary disease, cholecystocentesis should also be considered in suspected chronic hepatobiliary conditions, where changes on ultrasound might be more subtle. If cytology findings are not diagnostic,

they can be repeated (apart from bile samples), or a biopsy of the relevant organ taken, *e.g.*, a tru-cut biopsy for the liver, or laparoscopic, surgical or GI mucosal pinch biopsies.

Especially where there is a single abdominal mass (+/- enlarged lymph nodes), ultrasound and biopsy can help differentiate neoplasia from other possible diagnoses; these include granulomas of fungal or feline infectious peritonitis (FIP) origin, mycobacterial disease, or (if located in the gut) feline gastrointestinal eosinophilic sclerosing fibroplasia (FGESF) (8). FNAs are also useful in the characterization of neoplasia within or outside the GI tract, although some tumors (lymphoma, adenocarcinoma, mast cell tumors) exfoliate better than others (gastrointestinal stromal tumors (GIST), leiomyoma or -sarcoma). For some of the more common cancers, FNAs can also be a tool for full staging (assessing metastasis to liver, spleen, lymph nodes, or other organs).

Finally, computed tomography (CT) is very rarely needed to aid in the diagnosis of primary abdominal disease leading to (chronic) vomiting. It can however be helpful for mesenteric torsions (extremely rare in cats), vascular abnormalities (portosystemic shunts), or assessing large abdominal masses before surgical removal (for invasion of surrounding structures including vessels, thrombus formation etc.).

GI biopsy

The two main differential diagnosis for cats with chronic vomiting, ± diarrhea, ± weight loss but otherwise no specific findings on diagnostic investigation are IBD and LGAL (1,9), which can unfortunately look identical. Hence biopsies are often the only way to differentiate between these conditions with any level of confidence; these can be obtained either during endoscopy as mucosal pinch biopsies, or as surgical full-thickness biopsies. Both methods have advantages and disadvantages **(Table 3)**, but diagnostic accuracy

may also be dependent on sampling technique. For example, it has been suggested that full-thickness biopsies from the duodenum are more accurate than endoscopic biopsies in differentiating IBD from LGAL (10).

When performing endoscopic mucosal pinch biopsies, current guidelines recommend a minimum of six samples from each section of the feline GI tract (11), although most clinicians collect at least 8-15 biopsies from each segment as some are expected to be of suboptimal quality. The submission and processing of samples are also important (12), which can be subject to the methods of a particular laboratory/pathologist. A recent study showed that mounted and orientated GI specimens were superior to biopsies floating free in formalin (12).

Decisions about the biopsy method should therefore be made for each case depending on the index of suspicion for a specific condition or combination of diseases. For example, if hepatobiliary and/or pancreatic disease along with a chronic enteropathy is suspected, it might be both medically and practically favorable to take biopsies from all three organs surgically, rather than endoscopic gut biopsies only. Ultimately, cost, invasiveness, potential risks and owner preferences also have to play a role.

While histopathology remains the gold standard to differentiate IBD from LGAL, it has its limitations, particularly in the context of sensitivity and specificity (1,9). This is likely due to the fact that – as opposed to most dogs with lymphoma – LGAL is a continuation from long-standing IBD in cats, hence there is variation from inflammation to neoplasia on a sliding scale, sometimes making diagnosis difficult. In addition, despite the availability of histopathological templates (11), there seems to be difficulty in differentiating both IBD and LGAL from healthy tissue. In a recent blinded study, 12/20 duodenal biopsies from supposedly healthy cats were classified as LGAL, but only 3 cats developed GI signs after a median follow-up time of 709 days (13). If clinical observations and histopathological diagnosis

"It can be challenging to assess cats for abdominal pain or discomfort, as it seems to be an infrequent finding with feline intra-abdominal conditions."

Silke Salavati

do not seem to match, the authors strongly recommend seeking a dialogue with the pathologist involved to discuss what more can be done to further the diagnosis. This can include advanced immunohistochemistry or clonality testing, but even these have limitations (9,14); for example, one study found 40% of cats with IBD to feature monoclonality in their GI biopsies (14).

Establishing a diagnosis of IBD or LGAL therefore remains a challenge, as clinical signs, laboratory results, imaging findings, histology, immunohistochemistry and clonality features may overlap between these conditions (1,9,14). There are other types of alimentary lymphoma, including intermediate/high-grade, large granular or epitheliotropic lymphomas, that more frequently present as focal intestinal mass lesion(s) characterized by a B or T cell immunophenotype (15,16). These can be usually diagnosed with less invasive tests such as assessment of cytology or flow cytometry performed from FNAs (15,16).

Therapeutic management

Clinically stable cats with acute vomiting usually have self-limiting gastroenteritis, especially if a foreign body has been ruled out. Here treatment can be limited to feeding a commercial "gastrointestinal" diet for few days, probiotics (*e.g.*, *Enterococcus faecium*) and anti-emetics depending on the severity of the vomiting. Various anti-emetics are available (some off-license for cats) but the most frequently used is maropitant (a neurokinin-1 receptor antagonist with both central and peripheral action). It has been associated with bone marrow hypoplasia in kittens and should not be used in cats < 16 weeks of age. Metoclopramide is less effective as an anti-emetic in cats compared to dogs, especially with regards to central effects, because it is a dopamine (D_2) receptor antagonist, yet α_2-adrenergic receptors are much more important in controlling vomiting in the feline vomiting center. Ondansetron is also very effective (both centrally and peripherally) but is quite expensive and is unlicensed, so should be used as a last resort and only in very sick animals where other anti-emetics have failed. Phenothiazines (α_2-agonists) such as chlorpromazine or prochlorperazine can also be very effective anti-emetics in cats, and are often more cost-effective.

Lack of adequate nutrition should always be a concern in vomiting cats. This is often due to the duration of inappetence or anorexia, as well as their propensity to develop hepatic lipidosis and associated problems, and additional supportive treatment should be considered. This can be in the form of increased medical treatment in mild cases, *e.g.*, appetite stimulants as well as anti-emetics. Available options (not always licensed for cats) include oral or transdermal mirtazapine, capromorelin or cyproheptadine. In more severe or prolonged cases, or when appetite stimulation with drugs is unsuccessful, nutritional support should be provided via a feeding tube once the

vomiting is adequately addressed. This can either be a naso-esophageal tube (for short-term usage and very liquid food) or an esophagostomy tube (O-tube), when tube-feeding is likely to carry on for more than a few days. An O-tube can also easily be placed during a pre-planned procedure (*e.g.*, endoscopy, surgical biopsies).

Extra-GI disorders need to be treated specifically according to the underlying etiology, and it is beyond the scope of this article to provide specific details about treatment for these disorders.

In cats with suspected food-responsive CE or IBD, an elimination diet trial should be performed using a commercial hydrolyzed diet or a novel protein diet. In contrast to dogs, cats with FRE usually respond very rapidly (2-3 weeks) to a food change, although it can take up to 6-8 weeks to see a full response. A short course of either anti-emetics or appetite stimulants can be considered to improve compliance with a new diet. In cats with partial response to diet change, a second dietary trial with a different type of appropriate food can be attempted.

Additional sequential treatments for IBD if elimination diet(s) are not successful include administration of probiotics or glucocorticoids. Ideally, GI biopsies should be obtained before administration of the latter if a diagnosis is desired (especially if lymphomas other than LGAL have not been excluded, as they may require alternative treatment). However, not only are feline IBD and LGAL treated similarly with glucocorticoids, they also have nearly the same prognosis and outcome – hence even if a final differentiation has not been made based on biopsy, it is often a pragmatic step to treat these cases the same. If glucocorticoids and diet alone do not improve the situation, a sensible additional immunosuppressive drug is chlorambucil; this will not only be beneficial in

severe IBD, but is also standard treatment for LGAL. Cyclosporine or other immunosuppressants are not used as often for (suspected) IBD in cats compared to dogs. However, chlorambucil is not effective for the treatment of alimentary intermediate to high grade or large granular lymphomas, which is why differentiating these is important – these require either intravenous chemotherapy (COP or CHOP protocols) or oral lomustine (CCNU).

CONCLUSION

Vomiting can be the presenting sign of many different problems in cats, so signalment, history and clinical examination should all be taken into account before formulating a diagnostic plan. Initial assessment of acute vomiting should focus on identifying unstable patients requiring emergency treatment and and/or immediate surgical intervention, and (for both acute and chronic vomiting) should also consider the need for nutritional support before more extensive diagnostic tests are performed. In cats with chronic vomiting, diagnosis can usually be at a slower pace, and diet or symptomatic drug trials can be performed before advanced diagnostic testing. Supportive treatment is part of managing most etiologies that cause vomiting, but clinicians must make an effort to identify specific causes to be able to perform the appropriate diagnostic tests in order to construct a targeted and effective treatment plan.

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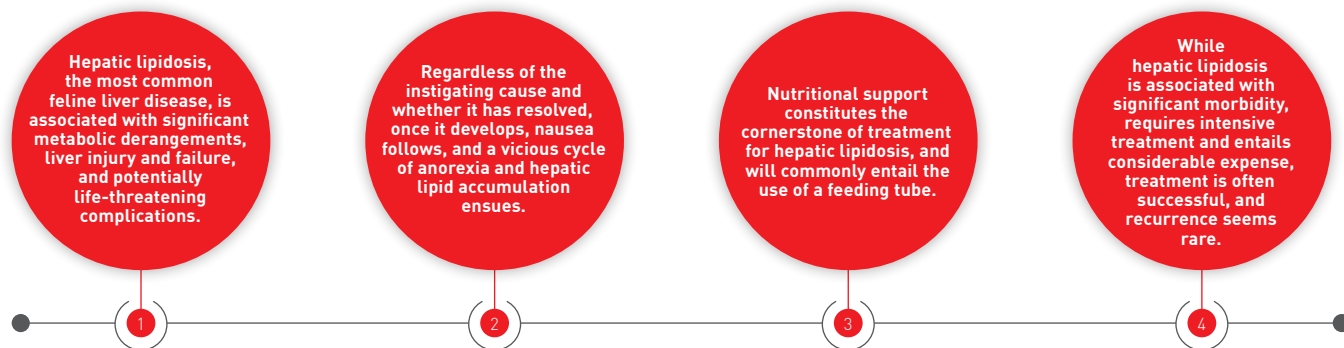
FELINE HEPATIC LIPIDOSIS

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Hepatic lipidosis in the cat is a common and life-threatening condition, but a considered approach can often result in a positive outcome.

KEY POINTS

1 — Hepatic lipidosis, the most common feline liver disease, is associated with significant metabolic derangements, liver injury and failure, and potentially life-threatening complications.

2 — Regardless of the instigating cause and whether it has resolved, once it develops, nausea follows, and a vicious cycle of anorexia and hepatic lipid accumulation ensues.

3 — Nutritional support constitutes the cornerstone of treatment for hepatic lipidosis, and will commonly entail the use of a feeding tube.

4 — While hepatic lipidosis is associated with significant morbidity, requires intensive treatment and entails considerable expense, treatment is often successful, and recurrence seems rare.

Introduction

First described in 1977, hepatic lipidosis (HL) has since emerged as the most commonly diagnosed hepatobiliary disease in cats (1,2). Accumulation of triglycerides within hepatocytes engenders hepatocyte swelling and intrahepatic cholestasis, oxidative damage, secondary inflammation, and ultimately hepatic dysfunction (1,2). Metabolic complications and systemic ramifications of HL are diverse, and include electrolyte imbalances, insulin resistance, pancreatitis, hyperammonemia, hepatic encephalopathy and coagulopathies. Therefore, feline hepatic lipidosis (FHL) is associated with significant morbidity and often requires hospitalization for initial stabilization, with the possibility of several weeks of intensive treatment for complete recovery, and it carries a guarded-to-favorable prognosis overall.

Pathophysiology

Feline HL is defined by abnormal accumulation of lipid-filled vacuoles within hepatocytes. In severe cases, fat accounts for over 30% of the total liver weight, in striking contrast to normal cats where hepatic fat content rarely exceeds 1-5% (3,4). The predominant fat type in FHL is adipose tissue-derived triglycerides, from enhanced lipolysis during catabolic states of starvation, rather than *de novo* synthesis of triglycerides in the liver (2,3). Furthermore, impaired oxidation and utilization of fat within hepatocytes, diminished redistribution of fat from the liver to peripheral tissues, and altered lipoprotein metabolism all contribute to the development of FHL (4,5). Whether an individual propensity to develop FHL exists is debatable; a female predisposition is infrequently reported (1,6,7), but there is no obvious gender or breed predilection. The most salient risk factor for FHL is probably obesity, owing to pre-existing abnormalities in lipid and carbohydrate metabolism

and higher fat reserves (2). Nonetheless, HL has been shown to develop irrespective of the body condition score (8), and FHL should always be suspected when compatible history, clinical findings and laboratory abnormalities exist.

Experimentally, HL develops after several weeks of restricted caloric intake, but in the clinical setting periods of anorexia as short as two days have been reported to precede the diagnosis (1,6,7,9). These reports, however, are subjective, relying on owner perception of food intake by their cat, and must therefore be cautiously interpreted. Maintenance energy requirements should be reduced by more than 50% for HL to develop, but the composition of the diet, rather than its caloric density alone, is also important (2). A diet deficient in essential amino acids (AA) might predispose to hepatic lipid accumulation, while L-carnitine supplementation can protect against FHL even in face of severe caloric restriction (2,10).

Cats are obligate carnivores, whose capacity to endogenously synthetize many essential fatty acids and AA has been greatly diminished or lost over time. Furthermore, feline carbohydrate metabolism is different from omnivorous species, with cats having a lower overall requirement for carbohydrates, a propensity to utilize fats and proteins over carbohydrates for energy, and a tendency to favor AA-dependent pathways of gluconeogenesis to maintain normoglycemia (1,2). These peculiarities are reflected in their diet, which is primarily protein and fat-based, and might also account for their proclivity to accumulate fat in the liver in states of food deprivation. For example, compared to dogs and humans, endogenous production of several long-chain polyunsaturated fatty acids is reduced in cats. These fatty acids protect against HL by promoting triglyceride oxidation and glycogen synthesis rather than lipogenesis, but these protective properties are lost when dietary intake is reduced, which may contribute to the development of FHL (1). Cats also have limited capacity to synthesize enough arginine, methionine, cysteine and taurine. Depletion of these essential AA interferes with beta-oxidation of non-esterified fatty acids (NEFA), diminishes the production of very-low density lipoprotein particles which transport triglycerides from the liver to the body, and reduces endogenous L-carnitine production, thereby preventing transportation of NEFA to mitochondria (1,2). Lastly, impaired insulin secretion and responsiveness in peripheral tissues are common in obese cats and in cats with FHL (4), and this promotes lipolysis and mobilization of NEFA from peripheral tissues. Collectively, these dietary deficiencies, metabolic derangements and hormonal changes culminate in the development of FHL.

History and clinical findings

Protracted periods of hyporexia/anorexia always precede the development of FHL (6,7,9), which in turn may result from inadvertent food deprivation, decreased palatability of new diets, or stressful environmental situations (*e.g.*, boarding, change of

Table 1. Classification of feline hepatic lipidosis (FHL) and selected etiologies.

Primary FHL (5-51%)	
Decreased food intake	• Stressful events • Decreased palatability of new diets • Food restriction/unavailability • Idiopathic (no identifiable cause)
Secondary FHL (49-95%)	
Oral diseases	• Periodontal and dental disease • Ulcers (infectious/chemical or traumatic injuries) • Neoplasia • Calicivirus
Decreased food intake (pathological)	• Altered mentation • Dysphagia • Esophageal and gastric pathologies
Endocrino-pathies	• Diabetes mellitus • Hyperthyroidism
Hepato-biliary diseases	• Cholangiohepatitis • Hepatic neoplasia • Obstructive biliary diseases • Portosystemic shunts
Pancreatic diseases	• Acute/chronic pancreatitis • Exocrine pancreatic insufficiency • Neoplasia
Urogenital diseases	• Chronic or acute kidney injury • Ureteral or urethral obstructive diseases • Idiopathic inflammatory or infectious urinary tract diseases • Pyometra • Urogenital neoplasia
Gastro-intestinal	• Inflammatory bowel disease • Ulceration • Obstructive diseases • Neoplasia (*e.g.*, small-cell lymphoma)
Neurological diseases	• Vestibular diseases • CNS problems (*e.g.*, neoplasia; inflammatory pathologies)
Miscellaneous	• Cardiomyopathy • Infection (*e.g.*, FIP; upper respiratory tract infections; virulent calicivirus; FeLV) • Severe anemia

ownership, moving to a new house). Secondary FHL implies the presence of an identifiable underlying disease and occurs in 50-95% of cats (1,6,7,9). Therefore, a thorough questioning and diagnostic work-up is warranted to identify and address any possible underlying cause **(Table 1)**.

Weight loss is invariably present, as the result of decreased caloric intake. Even in cats with an ostensibly normal bodyweight, a more careful physical examination often reveals a decreased body condition score and sarcopenia, especially in the hindlimbs and epaxial muscles. Lethargy, weakness, clinical signs referable to the gastrointestinal tract (*e.g.*, vomiting, diarrhea, constipation), dehydration and hepatomegaly are frequent complaints

Figure 1. Jaundice in a 4-year-old, castrated male cat with idiopathic hepatic lipidosis. Jaundice is more readily discernible in the third eyelid **(a)** and sclera, compared to the gingival mucosa **(b)** in non-anemic cats. Jaundice can also be observed in the pinna **(c)** and other non-furred skin surfaces.

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and findings. Jaundice is common, and is best appreciated in the sclera or pinnae, in addition to mucosal surfaces (6,7,9) **(Figure 1)**. Ptyalism, albeit a non-specific sign, might be the only clinical manifestation of hepatic encephalopathy (HE) in FHL, and occurs in a minority of cases. Furthermore, ptyalism at presentation has been associated with a worse outcome (9). Other etiologies of ptyalism include oral diseases, nausea, and idiosyncratic reactions to orally administered medications.

Additional, less frequent clinical signs can arise secondary to FHL-associated complications (*e.g.*, bleeding diathesis; HE; skin fragility syndrome) or the underlying etiology (*e.g.*, fever with infections or inflammatory diseases such as pancreatitis; polyuria and polydipsia in cats with kidney disease or diabetes, etc.).

Clinicopathological findings

The biochemical hallmark of FHL is increased alkaline phosphatase activity (ALP), which occurs in > 80% of affected cats (7,9,11). Experimentally, increased ALP levels precede the development of hyperbilirubinemia (8), and this is considered a highly sensitive and rather specific marker of FHL. Conversely, gamma-glutamyl transpeptidase (GGT) activity is seldom increased, unless a concurrent cholestatic/biliary pathology coexists (11). A disparate increase in ALP activity in face of a normal or slightly increased GGT activity is therefore suggestive of FHL. Nonetheless, additional differential diagnoses for increased ALP activity do exist, including hepatobiliary (*e.g.*, cholangiohepatitis; biliary obstruction) and hormonal (*i.e.*, hyperthyroidism) diseases.

Hyperbilirubinemia and increased alanine (ALT)/aspartate (AST) aminotransferase activities are common, non-specific findings (7,9). Hepatic fat accumulation, irrespective of etiology, causes cellular swelling and intrahepatic cholestasis, as well as oxidative damage and secondary inflammation, which result in increased transaminase activities – therefore, abnormal hepatic transaminase levels do not necessarily imply an additional underlying hepatic pathology. A

higher-fold increase in ALT/AST activities (relative to their respective reference intervals) compared to that of ALP activity, might suggest an additional underlying disease (7).

Low urea concentration can result from decreased protein intake, and malfunction of the urea cycle. The latter is aggravated by arginine and vitamin B_{12} deficiencies, which commonly occur in FHL. Similarly, hyperammonemia can develop secondary to hepatic failure, vitamin B_{12} deficiency and inadequate dietary intake of arginine, and has clinical and therapeutic implications (1,2). Additional, infrequently observed derangements are non-specific and include hypoalbuminemia/hypoproteinemia from protein losing enteropathy and/or hepatic synthetic failure, hypocholesterolemia and cholestasis-associated hypercholesterolemia (7,9). Hypertriglyceridemia is common in obese cats in general, and during FHL in particular (12). Hyperglycemia can develop secondary to insulin resistance, pancreatitis or overt diabetes mellitus (7,9). Hypoglycemia, on the other hand, is seldom observed (9), but might arise secondary to hepatic failure, sepsis or pancreatitis, and constitutes a negative prognostic factor (13).

In terms of electrolyte derangement, hypokalemia is perhaps the most common and clinically significant finding in cats with FHL (1). Common complications include muscular weakness, inability to adequately concentrate urine with development of polyuria/polydipsia, gastric and intestinal ileus, exacerbation of HE, and cardiac dysfunction in more severe cases. The true magnitude of potassium depletion is often masked by dehydration upon admission, and instituting enteral and parenteral feeding can exacerbate hypokalemia (14,15). Therefore, close monitoring and correction of blood potassium concentration is crucial. Additional, less frequent electrolyte abnormalities include hypomagnesemia and hypophosphatemia (1,14,15). These may be present upon admission (secondary to intestinal and urinary loss), but often develop later in the course of disease following rehydration and commencement of parenteral or enteral feeding. Development thereof has deleterious ramifications, including muscular/cardiac and neurological manifestations (hypophosphatemia

and hypomagnesemia), hemolytic anemia and thrombocytopenia (hypophosphatemia) and the development of refractory hypokalemia and hypocalcemia (hypomagnesemia).

Changes in the complete blood count are diverse and non-specific, and can develop secondary to the underlying disease or as a complication of FHL. Changes in erythrocyte morphology include poikilocytosis, microcytosis and Heinz bodies (1,6,7). The last is the result of increased oxidative stress and hypophosphatemia and might contribute to the development of anemia. Alternatively, severe hypophosphatemia can directly result in hemolytic anemia (14). Microcytosis, when severe, is suggestive of iron deficiency or hepatic vascular diseases (*e.g.*, porto-systemic shunts).

Coagulopathies are common in cats with HL (1,7) and in one report more than 90% of cases had abnormally prolonged prothrombin time (PT) and/ or activated partial thromboplastin time (aPTT) (9). When comparing the proteins-induced by vitamin K absence test (PIVKA) to PT/aPTT tests, the sensitivity of the former is significantly higher in detecting vitamin-K associated coagulopathies in cats with hepatic and intestinal diseases (16). However, since PIVKA measurement is currently commercially unavailable, and given the high prevalence of coagulopathies and vitamin K deficiency in FHL, vitamin K supplementation is advised **(Table 2)**.

Diagnostic work-up

Definitive diagnosis of FHL can often be achieved by ultrasound-guided fine needle aspiration (FNA) of the liver (17), typically using a long, 22/23G hypodermic or spinal needle. Lipid vacuoles appear as sharply demarcated, clear vesicles within the cytosol, unlike the irregular, feathery glycogen-filled hepatic vacuoles **(Figure 2)**. Special stains can help differentiate between the two but are rarely indicated. The presence of microvesicular and macrovesicular, distinct cytosolic vacuoles within hepatocytes from cytological specimens is often sufficient to establish diagnosis of FHL, and FNA is associated with a lower prevalence of significant complications (most notably bleeding) when compared to hepatic biopsies. Rarely, a liver FNA will reveal an underlying or concurrent hepatic pathology, but agreement between liver biopsies and FNA is poor (18,19) and cytological interpretation of inflammatory infiltrates in the liver is hindered by blood contamination. Furthermore, infectious hepatic diseases are seldom diagnosed cytologically in FNA samples, but conversely, neoplastic infiltrates, particularly round-cell tumors, can easily be diagnosed cytologically. Thus, the shortcomings of hepatic FNA must be recognized, and additional diagnostic procedures might be considered under specific circumstances.

Table 2. Frequently used medications for feline hepatic lipidosis.

Treatment	Dose		Comments
Vitamin supplementation			
Cyanocobalamin (B_{12})	250 mcg/cat once a week SC/IM or 250 mcg/cat q24h PO; both for 6w-8 weeks		Vitamin B complex preparations for IV or SC/IM injections might be considered, but the quantities of individual vitamins might be insufficient in some products
Vitamin K	1-1.5 mg/kg q12-24h SC/IM, (x3 injections)		
Thiamine	100 mg/cat q24h SC/IM or 100-200 mg/cat q24h PO		
Vitamin E	50-100 IU/cat q24h PO		As an antioxidant
Anti-oxidants and nutraceuticals			
Ursodeoxycholic acid	10-15 mg/kg q12h PO		Minimal side effects (diarrhea, nausea); taurine depletion
L-carnitine	200-250 mg/cat q24h, PO		
S-adenosyl-methionine (SAMe)	20 mg/kg q24h PO on an empty stomach		Minimal side effects (inappetence, vomiting)
Silymarin	5-10 mg/kg q24h PO		Phosphatidylcholine conjugates are preferable owing to improved absorption
N-acetylcysteine	70 mg/kg (diluted with saline/D5W) over 15-30 mins, q8-12h IV		Vomiting with rapid administration; use until oral treatment with SAMe/silymarin is feasible
Taurine	250-500 mg/kg/cat q24 PO		Most commercial diets provide sufficient taurine
Potassium supplementation			
KCL	Serum concentration (mEq/L)	KCL added (mEq/100 mL)	The final dose changes with the fluid rate; do not exceed 0.5 mEq/kg/h. If hypophosphatemia coexists, KPO_4 can be used with KCl in varying combinations to achieve the same final potassium concentration in the fluid solution; often a KPO_4:KCl ratio of 1:1 is used, unless severe phosphate deficits exist; avoid calcium-containing fluids with KPO_4
	< 2	8	
	2.1-2.5	6	
	2.6-3	4	
	3.1-3.5	3	
	3.6-5	2	

Apart from its utility in guiding FNA sampling, abdominal ultrasound is a useful imaging modality to rule out concurrent or underlying diseases that might have precipitated FHL (17). Sonography of the liver in general is a non-specific, non-sensitive diagnostic tool (20); parenchymal changes in echogenicity have many disparate differentials, while hepatic masses and nodules might be overlooked. In FHL, hepatomegaly and increased hepatic echogenicity (compared to the falciform fat), with resultant decreased visibility of intrahepatic portal vein walls, are commonly documented, but alternative pathologies (*e.g.*, infiltrative diseases) might also account for such changes or coexist (20).

The initial diagnostic work-up of a cat with FHL will include a complete blood count, biochemistry panel, PT/aPTT measurement and abdominal ultrasound with FNA of the liver. These tests provide a robust minimum database which will allow the diagnosis of FHL, complications thereof, and many underlying or concomitant diseases. Otherwise, further diagnosis is often halted at this stage, and initial treatment is instituted. When warranted, additional tests, directly related to FHL, might include the measurement of blood ammonia and B_{12} (cobalamin) concentrations. The former is indicated in cats that are severely depressed or have neurological signs, while the latter is indicated in any cat with FHL, since B_{12} reserves are rapidly depleted in anorectic cats. If a concurrent bacterial biliary infection is suspected, gallbladder cystocentesis can be performed for cytological and bacteriological evaluation of bile fluid. This procedure is considered safe, with minimal risk of gallbladder perforation/leakage or vagally mediated hypotension (21). Lastly, if laboratory and clinical improvement are not seen with treatment over the course of several weeks, a liver biopsy might be considered to rule out an underlying hepatic pathology.

Figure 2. Liver cytology from a cat with hepatic lipidosis. Notice the distinct fat vacuoles of varying sizes within the hepatocytes, which displace the nucleus peripherally in more severe cases **(a, b)**. Not uncommonly, free fat vesicles and adipocytes are also found in liver aspirates, especially when the adjacent adipose tissue is inadvertently sampled.

Treatment

Malnutrition is a hallmark of FHL. Regardless of the instigating cause and whether it has resolved, once HL develops, nausea follows, and a vicious cycle of anorexia and hepatic lipid accumulation ensues. The cornerstones of treatment therefore include nutritional support and anti-nausea treatment. Secondary oxidative damage, inflammation and intrahepatic cholestasis are common sequelae of FHL, and additional medications are used to promote fat-utilization, choleresis and antioxidant activity.

Nutritional management

Nutritional management must address several factors, namely:
1. Caloric requirements.
2. The nutritional peculiarities of cats.

3. The provision of essential AA which are pivotal for proper functioning of the urea cycle, lipoprotein assembly and synthesis of antioxidant molecules such as s-adenosylmethionine (SAMe) and glutathione.
4. Provision of fat- and water-soluble vitamins that are depleted in FHL.
5. Correction of electrolyte imbalances (often achieved intravenously, with some electrolytes also supplemented in the food).

Cats with FHL rarely consume enough food during the initial stages of hospitalization, but force-feeding might result in food aversion and postpone resumption of voluntary feeding. Since recovery can take several weeks, and to facilitate the administration of medications, treatment of FHL often entails the use of a feeding tube. Nutritional support should be instituted as early as possible, but the presence of severe dehydration, electrolyte changes, acute kidney injury, hypotension or severe neurological deficits might delay the procedure. Partial parenteral nutrition (PPN) can be used in

the first days of hospitalization until the cat is stable enough to undergo general anesthesia. Unlike total parenteral nutrition, PPN does not require central vein access, and has fewer complications. Amino-acid solutions may be used alone as a constant rate infusion if premixed PPN solutions are unavailable.

Once the cat is stable, a feeding tube can be placed under general anesthesia. Esophageal tubes are often the first-choice for several reasons: they are easy to insert and use; both liquid and blended food and medications can be administered; they are associated with a lower prevalence of significant complications (other than dislodgement or stoma site infection) and are easily managed by owners; feeding can be instituted shortly after recovery from anesthesia; and no complications arise with inadvertent, premature tube removal (22) **(Box 1)**. Naso-esophageal and nasogastric tubes can be used until a longer general anesthesia is feasible, but are not suitable long-term: only liquids can be passed through them, and they entail significant discomfort to the cat. Lastly, a percutaneous endoscopically assisted feeding tube is rarely indicated, unless the esophagus must be bypassed owing to an esophageal pathology.

Commercially available, calorie-dense, protein-rich recovery diets often suffice to provide the nutritional needs of the cat in terms of essential AA and fats. Protein restriction is rarely indicated unless severe HE is present. The calculated daily caloric intake (resting energy requirement: 30 x (body weight) +70 or (body weight)$^{0.75}$ x70), is divided into 4-6 meals. The volume of each meal, including the water used at the end to flush the feeding tube, must not exceed 10-15 mL/kg/meal. A gradual upward titration of the food volume and the overall caloric intake is advised, usually over the course of 3 days. This is meant to ensure a gradual adaptation of the gastrointestinal tract to food, to monitor the development of gastric ileus which might preclude further feeding, and to reduce the risk of refeeding syndrome (see "complications" section below).

"Since recovery can take several weeks, treatment of FHL often entails the use of a feeding tube."

Ran Nivy

Both fat-soluble (*e.g.*, vitamin D, vitamin K) and water-soluble (*e.g.*, thiamine, cobalamin) vitamins are depleted in cats with FHL (2). Deficiencies are associated with a plethora of complications, including coagulopathies, villous atrophy, hyperammonemia, anemia and neurological deficits, rendering vitamin supplementation an integral part of treatment **(Table 2)**.

Fluid therapy and anti-nausea treatment

Hydration status, maintenance needs, and sensible (*e.g.*, vomiting/diarrhea) and insensible fluid losses are considered when calculating the daily fluid requirement. However, the potential for concurrent cardiac disease, and the amount of enterally-administered water via the feeding tube, must also be considered. Potassium supplementation is often indicated, either as potassium chloride (KCl) or potassium phosphate (KPO$_4$) when hypophosphatemia coexists **(Table 2)**. If measurement of blood magnesium concentration is unavailable, a conservative approach might be to supplement the fluid with magnesium sulphate at 0.5 mEq/kg q24h for 2 days.

Antinausea and antiemetic therapy is indicated in all cats, with metoclopramide, maropitant and ondansetron being used in various combinations. Mirtazapine is often added owing to its antinausea and appetite-stimulating properties, especially to anorectic cats after hospital discharge. Metoclopramide has the added benefit of promoting gastrointestinal motility. If ileus develops despite metoclopramide treatment and resolution of hypokalemia, cisapride treatment (0.5 mg/kg q8h PO) should be considered.

Cytoprotective therapy

Oxidative damage and decreased glutathione concentration are known complications of FHL, and antioxidant therapy is commonly prescribed to affected cats; these include SAMe and silymarin. SAMe is a ubiquitous molecule involved in a myriad of biochemical pathways (23,24), whilst silymarin (which contains several compounds, of which silibinin is the most abundant and active ingredient) exerts anti-inflammatory and choleretic activities, as well as antioxidant activity (23). Several veterinary products now provide a combination of silymarin and SAMe, but if oral or enteral supplementation is not feasible, n-acetylcysteine can be used intravenously to replenish hepatic cysteine concentration and subsequently glutathione levels. However, it does not possess the additional benefits of silymarin and SAMe, and can induce vomiting if administered rapidly (23). Lastly, vitamin E might be supplemented, as it is a free radical scavenger which protects against phospholipid oxidation in the cell membrane; it has minimal side effects, but there are no reported clinical benefits either (23) **(Table 2)**.

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Box 1. Insertion of an esophageal tube in a 7-year-old, male cat with acute pancreatitis and secondary hepatic lipidosis. Cats with hepatic lipidosis are prone to anesthetic complications, and some drugs might be contraindicated owing to liver dysfunction, so an opioid will often be used for premedication, and etomidate, propofol or a low dose of ketamine for induction. Esophageal tubes are inserted only in intubated cats, using inhalation anesthesia, while fluid support (as well as colloids and/or vasopressor therapy, when indicated) is used to maintain blood pressure.

The cat is placed in right lateral recumbency, and the left cervical area clipped and scrubbed. The 14-G feeding tube is pre-measured from the mid-cervical point of entry to the 7th-9th intercostal space **(a)**. However, any location caudal to the heart and cranial to the diaphragm might be tolerable to the cat. Curved, blunt-tipped forceps (*e.g.*, Carmalt forceps) are inserted through the mouth, to the mid-cervical area, laterally and away from the adjacent jugular vein. A small cut is made over the bulge created by the tip of the forceps **(b)**. The feeding tube is grabbed and retracted out of the mouth **(c)**. The tip of the tube is then guided manually into the esophagus, until the outer part of the tube is flipped. After inserting the tube to its premeasured location, it is secured using a Chinese-finger trap technique **(d)**. Using a purse string suture is discouraged, as it can interfere with proper drainage of secretions in case of stoma site infection. Location of the tube must always be ascertained by a thoracic radiograph at the end of the procedure.

Miscellaneous medications

Ursodeoxycholic acid, a hydrophilic bile acid, might prove beneficial in FHL owing to its choleretic, anti-apoptotic, anti-inflammatory properties, and rarity of side-effects (23) **(Table 2)**. L-carnitine transports long-chain fatty acids into the mitochondria, thereby facilitating their utilization for energy production, and in obese cats undergoing food restriction it attenuates hepatic triglyceride accumulation, with clinical observations indicating a potential beneficial effect in FHL (10). Even though carnitine levels are increased in cats with FHL (25), a relative deficiency thereof might still exist, and supplementation is recommended **(Table 2)**. Taurine deficiency is associated with various cardiac, neurological, reproductive and developmental pathologies, and contributes to hepatic fat accumulation. Commercial diets will provide adequate amounts of this amino acid, but enteral supplementation is occasionally advocated, especially when ursodeoxycholic acid

is used, as it exacerbates biliary loss of taurine (1). Lastly, lactulose might be considered when severe signs of HE and hyperammonemia exist, or in constipated cats, while pantoprazole/omeprazole are used when gastric ulceration or reflux esophagitis are suspected.

Complications

A myriad of complications can arise secondary to FHL and following treatment. Refeeding syndrome, a constellation of metabolic changes which develop after reinstitution of feeding following protracted malnutrition, is a frequently mentioned but poorly documented complication in cats. It is associated with severe hypophosphatemia, and occasionally hypokalemia, hypomagnesemia, and thiamine deficiency. A gradual increase in caloric intake, with carbohydrate restriction, pre-emptive

electrolyte supplementation and close monitoring will help avoid the deleterious consequences of this syndrome (1,14,15).

Diffuse villous atrophy is another complication which develops with prolonged anorexia, resulting in malabsorption and diarrhea following reinstitution of enteral feeding. Gradual introduction of enteral feeding, and the use of highly digestible diets, can alleviate diarrhea. Concurrent pathologies are common in cats with FHL, and include pancreatitis, kidney injury, cardiomyopathies, bleeding/thrombotic complications, and insulin resistance. Additionally, cavitary effusions might develop secondary to hypoalbuminemia, cardiac disease, or pancreatitis, and these constitute a negative prognostic factor (9).

Finally, immunosuppression from malnutrition can predispose to secondary bacterial infections, and antibiotic treatment is indicated if an infection is documented (*e.g.*, cholecystitis). Under specific circumstances antibacterial therapy might also be considered when severe neutropenia/neutrophilia, and/or hypoglycemia occur, even if there is no cytological or bacteriological proof of infection.

CONCLUSION

Feline hepatic lipidosis is the most common liver disease in cats, and can have a highly variable outcome because of the prognostic implications of different underlying diseases and comorbidities. Whilst overall survival rates range from 50-85%, acute pancreatitis, ptyalism, cavitary effusions, hypoalbuminemia, and an older age at onset are but few of the reported negative prognostic markers. Nevertheless, whilst the condition is associated with significant morbidity, requires intensive treatment, and entails considerable financial expenditure, treatment is often successful, and recurrence seems rare.

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FELINE TOXOPLASMOSIS

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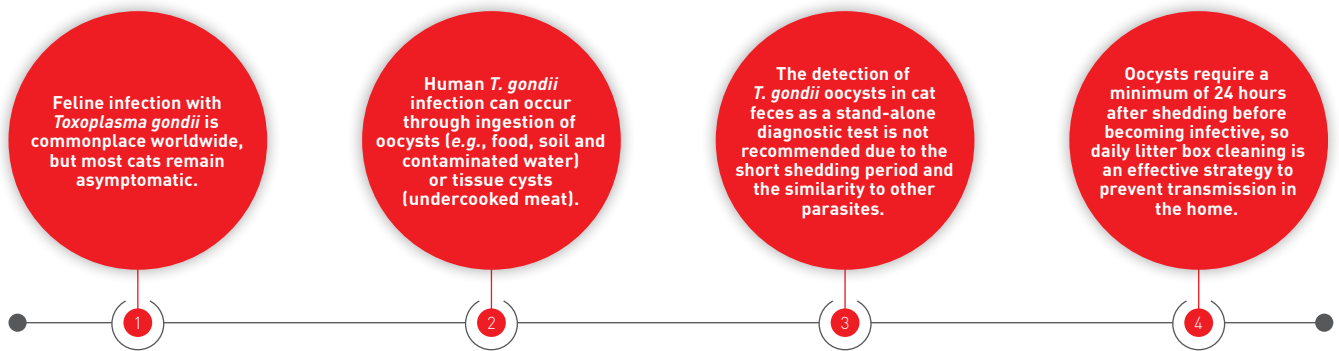
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> Toxoplasmosis is now known to have a worldwide distribution, and although the cat is the sole definitive host, the parasite can have significant implications for both human and animal health.

KEY POINTS

1. Feline infection with *Toxoplasma gondii* is commonplace worldwide, but most cats remain asymptomatic.

2. Human *T. gondii* infection can occur through ingestion of oocysts (*e.g.*, food, soil and contaminated water) or tissue cysts (undercooked meat).

3. The detection of *T. gondii* oocysts in cat feces as a stand-alone diagnostic test is not recommended due to the short shedding period and the similarity to other parasites.

4. Oocysts require a minimum of 24 hours after shedding before becoming infective, so daily litter box cleaning is an effective strategy to prevent transmission in the home.

Introduction

The intracellular protozoan parasite *Toxoplasma gondii* can infect the majority of vertebrate animal species, and although felids serve as its sole definitive host, it is being increasingly recognized as a major threat in many ecosystems. Ingestion of the parasite by either the definitive or an intermediate host will typically culminate in either a chronic subclinical or asymptomatic infection; in susceptible or non-immunocompetent subjects, however, toxoplasmosis may lead to abortion and reproductive failure, or even organ failure and death (1). Nowadays toxoplasmosis is found worldwide; the prevalence of oocyst shedding varies from 0.7-41% of cats at any given time, depending on the country in question. In the USA the prevalence of positive *T. gondii* antibody titers in cats ranges from 14-100% (2). Whilst many humans are also infected (for example, approximately 40 million in the USA), most are asymptomatic, but some, especially those that are immunocompromised, may suffer from associated ocular or neurological problems (3).
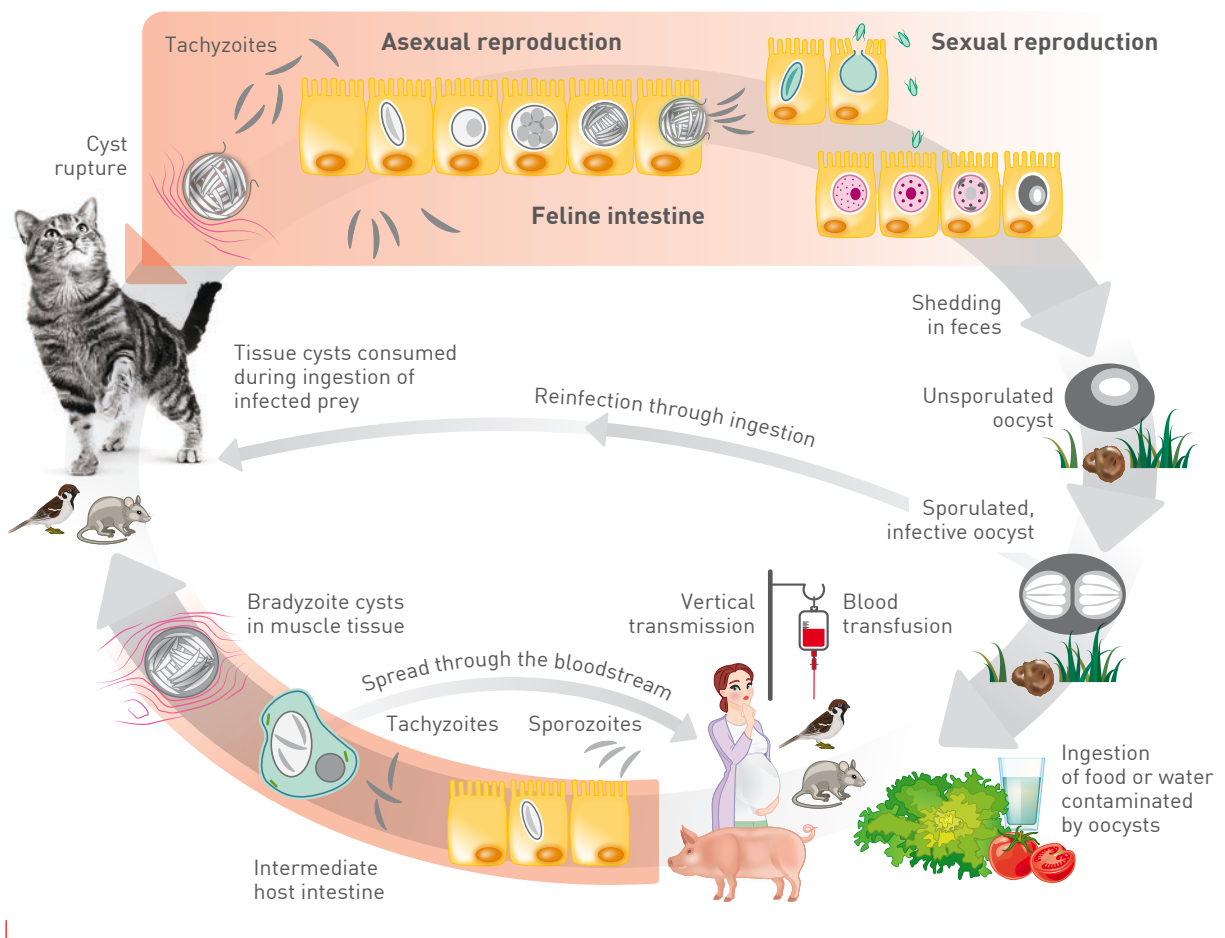
Figure 1. Life cycle of *Toxoplasma gondii*. Unsporulated oocysts are shed in the cat's feces, which then take 1-5 days to sporulate in the environment before becoming infective. Intermediate hosts in nature (including mammals and birds) become infected after ingesting soil, water or plant material contaminated with oocysts. Cats become infected after consuming intermediate hosts (*e.g.*, birds and rodents) harboring tissue cysts, or by direct ingestion of sporulated oocysts. Oocysts transform into tachyzoites shortly after ingestion; these localize in neural and muscle tissue and develop into tissue cyst bradyzoites. Humans become infected by ingesting undercooked meat containing tissue cysts or food, water, soil and other materials contaminated with oocysts from cat feces. Vertical transmission from mother to fetus and transmission through blood transfusion is also possible.

Toxoplasma gondii life cycle

Toxoplasma gondii has a complex lifecycle, requiring a definitive host and an intermediate host to complete sexual and asexual cycles respectively **(Figure 1)**. The parasite exists in 3 distinct forms – tachyzoite, bradyzoite, and sporozoite (in oocyst), all of which can be infectious to humans. Tachyzoites constitute the rapidly-dividing asexual stage of the parasite, and may be found in the tissues of any vertebrate host. Bradyzoites are also ubiquitous and will also be found in host tissues, but this life stage divides slowly and is encysted.

Cats, the definitive host of *T. gondii*, become infected through ingestion of tissue cysts, for example when hunting and eating prey **(Figure 2)** or sporulated or infective oocysts (from soil, water, or plants contaminated with feline feces). The parasite can reproduce sexually in this species, and cats infected by bradyzoites or oocysts will begin to shed oocysts in their own feces 3-10 or 19-48 days following ingestion,

Figure 2. Cats can become infected by eating prey that carry the parasitic cysts; there is a theory (the behavior manipulation hypothesis) that the toxoplasma organism in the brain of small mammals alters their behavior, such that they are less wary of predators and more likely to be caught – and hence increasing the likelihood that the parasite can continue its life cycle.
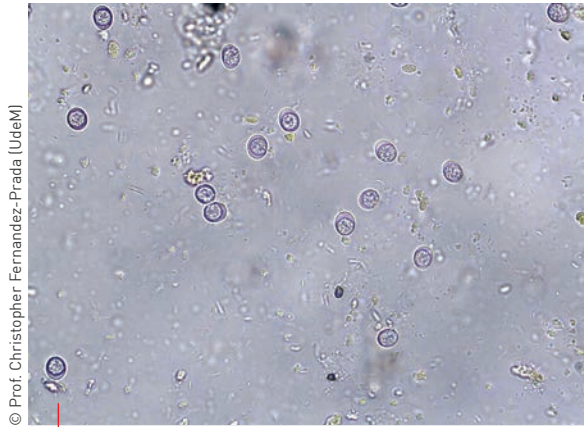
Figure 3. *Toxoplasma gondii* oocysts in a fecal flotation from a feline patient (x40 magnification).

respectively, and may continue to shed for up to 2 weeks **(Figure 3)** (2,4). Oocysts sporulate and become infective 1-5 days following excretion, and are extremely resistant in the environment.

The main methods through which humans are infected with *T. gondii* include ingestion of undercooked meat containing parasitic cysts, or ingestion of oocysts through fecal contamination of food, hands, etc. (4,5).

Clinical signs of feline toxoplasmosis

Toxoplasmosis can be difficult to identify in cats, as most infections are asymptomatic; if clinical signs are present, fever, anorexia, and lethargy are most frequently seen. Intracellular growth of the organism results in direct cytopathic effects, with cellular inflammation and necrosis, so other more specific signs depend on the location of tachyzoites in the body **(Figures 4-6)**; these may include ocular changes, neurological signs, pneumonia, and jaundice (4). Feline leukemia virus, feline immunodeficiency virus, neoplasia, and administration of immunosuppressive drugs (especially cyclosporin) are all risk factors for the development of clinical disease. Acute infections, especially in kittens, are usually fatal (6).

Diagnosis

Reliable diagnosis of toxoplasmosis can be problematic. Hematological abnormalities noted in affected cats may include non-regenerative anemia, leukocytosis, lymphocytosis, monocytosis, and eosinophilia. Severe infections can also cause leukopenia; in particular, neutropenia with a degenerative left shift. Changes in serum biochemistry and urinary values will depend on the organs involved (6).

As a diagnostic tool, detection of *T. gondii* oocysts in the feces as a stand-alone test is not recommended due to the short shedding period of feline hosts, as well as the microscopic similarity of *T. gondii* oocysts to other parasites (4,7). Furthermore, identification
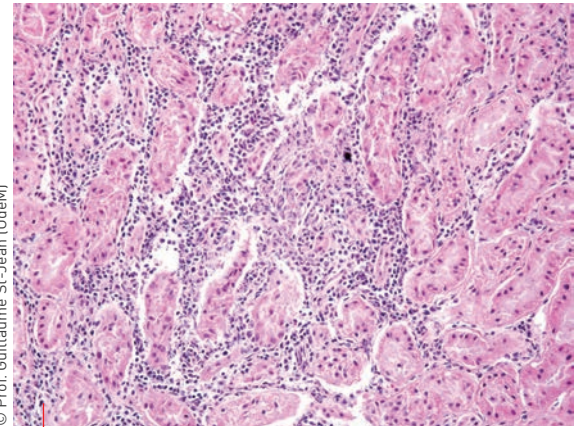
Figure 4. Histopathological images from the kidneys of a kitten that had *Toxoplasma gondii* infection; there is mild lymphohistiocytic interstitial nephritis, and (not shown here) rare forms of zoites were observed (x20 magnification).
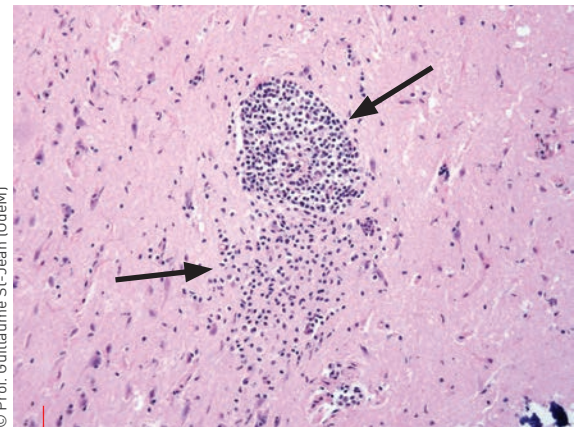
Figure 5. Samples taken from the brain of the kitten in **Figure 4**, showing a moderate, non-suppurative encephalitis, with the formation of perivascular lymphohistiocytic cuffs (small arrow). The inflammation extends slightly into the adjacent neuropil (arrowhead) with mild glial reaction. (x20 magnification).
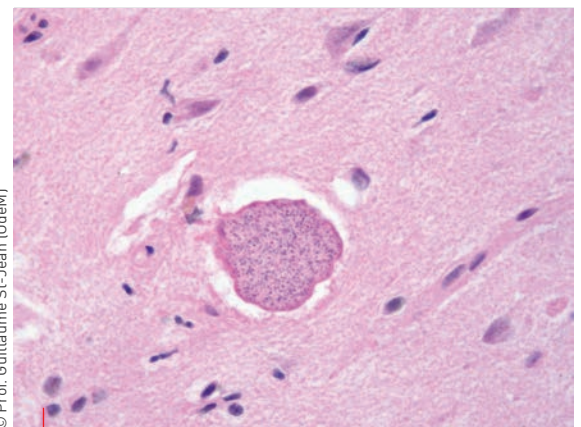
Figure 6. A protozoal cyst in the brain of the kitten in **Figure 4**, containing numerous small (1-2 μm in diameter) round structures (bradyzoites). The cysts later tested positive for *Toxoplasma gondii* by immunohistochemistry (x63 magnification).

of oocysts in the feces does not correlate with development of clinical disease in cats (2). Instead, serologic testing is recommended for definitive ante-mortem diagnosis, and high IgM titers (> 1:256) are generally compatible with recent *T. gondii* infection. Alternatively, paired IgG titers (taken 2-4 weeks apart) can be used, although interpretation of results can be complex **(Table 1)** (1,2). Some cats may also suffer from chronic *T. gondii* infection, whereby tissue cysts rupture and re-release bradyzoites into the circulation; such episodes may or may not be associated with excretion of oocysts, depending on the immune status of the animal in question (8).

Testing healthy cats for *T. gondii* antibodies is not recommended (6), as serologic testing is not an accurate predictor of oocyst shedding in cats, and most cats when actively shedding oocysts are actually seronegative at the time (2).

Treatment and prognosis

There is no licensed treatment for feline toxoplasmosis, but for acute or disseminated cases clindamycin is the drug of choice (10-12.5 mg/kg PO q12h for up to 4 weeks), accompanied by appropriate supportive care (6). For reduction of oocyst shedding, pyrimethamine (0.25-0.5 mg/kg PO q12h for up to 4 weeks) or sulfonamides (15-30 mg/kg PO q12h for up to 4 weeks) can be administered, and will generally prove beneficial during the acute phase of infection, but are rarely effective at clearing infection. Trimethoprim-sulfonamide combination treatments are an alternative option (15 mg/kg PO q12h for 4 weeks) (2), and anti-coccidial drugs (*e.g.*, toltrazuril, ponazuril) may also be considered. Of note, no treatments have proven significantly effective during the bradyzoite stage of infection (1).

A number of factors affect the prognosis for cats that display clinical signs of toxoplasmosis; these include the systems/organs affected **(Figures 7 and 8)**, and the time between infection

Table 1. Interpretation of *T. gondii* IgG serology results (6).

Serology result	Interpretation/analysis
≥ 4-fold increase in titer in paired serum samples	True positive (recent/active infection)
< 4-fold increase in titer in paired serum samples	True negative (no recent/active infection) OR false negative (recrudescent infection)
Single high positive result (*e.g.*, 1:1000)	Presence of bradyzoite tissue cysts

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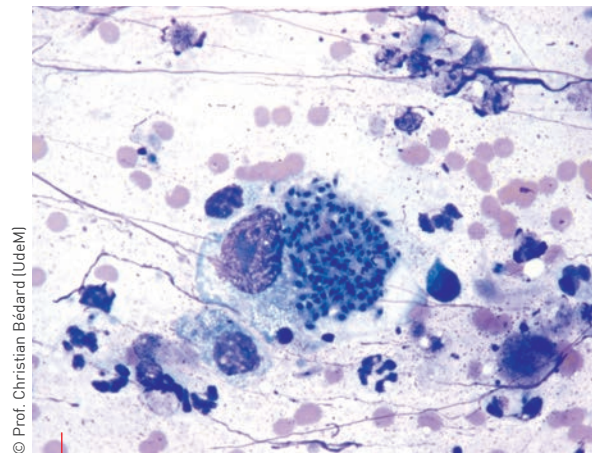
Figure 7. Cytology of a bronchoalveolar lavage from an infected cat. There is mixed inflammation associated with the presence of numerous crescent-shaped *Toxoplasma* tachyzoites (x500 magnification).

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Figure 8. Cytology of an enlarged lymph node in a cat, characterized by reactive hyperplasia and macrophagic inflammation. Two intracellular *Toxoplasma* tachyzoites can be seen (x500 magnification).


"Toxoplasmosis can be difficult to identify in cats, as most infections are asymptomatic; if clinical signs are present, fever, anorexia and lethargy are most frequently seen."
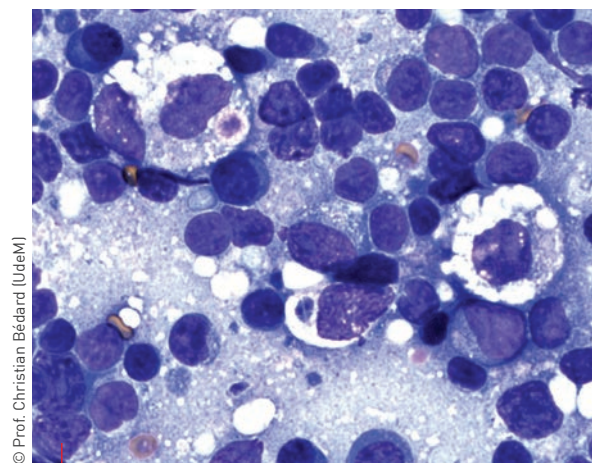
Christopher Fernandez-Prada

Figure 9. Daily cleaning of a cat's litter tray will help reduce the risk of toxoplasmosis cysts being passed to humans.

and the beginning of treatment. Generally, if clinical signs improve within 2-3 days after starting therapy, prognosis is more favorable, but toxoplasmosis infection affecting the lungs or liver carries a poor prognosis (4).

Zoonotic implications

Humans are at risk for *T. gondii* infection through ingestion of oocyst-contaminated food or water, tissue cysts in contaminated undercooked meat, or from blood transfusions, organ transplantation, or congenital infection. Most infections are asymptomatic, although occasional cases of fever, lymphadenopathy, and malaise have been reported. However, *T. gondii* represents a serious risk for the

fetus during human pregnancy; congenital toxoplasmosis can cause severe ocular and/or neurological damage when tachyzoites migrate transplacentally to reach the fetus (1). Although generally born without symptoms, these individuals can suffer from severe vision impairment, seizures, or other neurological issues later in life (9). Furthermore, immunocompromised individuals of any age are at risk of developing symptomatic toxoplasmosis, involving the brain, lungs, and/or other vital organs (5).

It is being increasingly reported that *Toxoplasma* oocysts are contaminating soil and groundwater worldwide. A review of 22 studies concluded that this is a serious cause for concern, with run-off from infected cat feces polluting bodies of water

Table 2. Strategies to mitigate zoonotic risk from *T. gondii* infection (1-4).

General strategies	Feline-specific strategies
Wash hands thoroughly after handling raw meat, gardening, or other at-risk activities (*e.g.*, emptying/cleaning a litter box)	Keep pet cats indoors
Wash kitchen knives and cutting boards carefully after preparing raw meat, fruits, or vegetables	Feed cats only commercially prepared dry canned or cooked food
Cook meat thoroughly before consumption	Clean the litter box daily, and dispose of litter responsibly (*e.g.*, sealed rubbish bags)
Wash or peel fruits and vegetables before consumption	Avoid pregnant or immunocompromised individuals cleaning the litter box
Wear gloves when gardening	Cover sandboxes and loose soil in play areas outdoors to prevent cats defecating

"Testing healthy cats for *T. gondii* antibodies is not recommended; serologic testing is not an accurate predictor of oocyst excretion, and most cats when actively shedding oocysts are actually seronegative at the time."

Victoria Wagner

to a considerable degree (3). Contamination of the ocean has led to infection and death of various marine mammals, including seals, whales, dolphins, and sea otters (10,11). Drinking water is also at risk; cat litter being flushed down toilets has contributed to a number of outbreaks of human toxoplasmosis in various countries (12,13).

Oocysts are remarkably robust, and are able to survive and remain infective for years, even in suboptimal conditions (14). Furthermore, it is likely that very few oocysts are required to successfully infect a human; studies in pigs demonstrated that one oocyst was sufficient to induce infection (15). As such, taking steps to responsibly dispose of cat feces is crucial.

Contrary to popular belief, it has been determined that direct contact with cats is not a significant risk factor for human infection with *Toxoplasma gondii* (16). However, daily litter box cleaning in and of itself is an easy strategy to prevent infection **(Figure 9)** – oocysts require at least 24 hours to become infective (4), and (where possible) keeping cats indoors will also help. Veterinarians must play a critical role in educating clients on steps to take to mitigate the risks related to *T. gondii* infection, both in cats and in general **(Table 2)**.

💬 **CONCLUSION**

Toxoplasma gondii is a common parasitic infection in cats but is often asymptomatic, although acute or disseminated infections may affect the eyes, brain or other systems, with clindamycin being the preferred treatment. Conclusive diagnosis requires either IgM or paired IgG titer serology. As a zoonotic disease, toxoplasmosis is especially dangerous for pregnant or immunocompromised individuals, but cat ownership is not a significant risk for human infection; rather, ingestion of oocyst-contaminated food or water, or tissue cysts in undercooked meat are a much more real threat. Fecal contamination of soil and water also presents a serious health risk. Simple hygiene strategies can prevent transmission of *T. gondii* and, for cat owners, keeping their pets indoors (if possible) and daily cleaning of the litter box greatly mitigates the zoonotic risk.

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10 IDEAS TO PREVENT TOXOPLASMOSIS AT HOME

1 Wash hands thoroughly after handling raw meat, gardening, or performing other high-risk activities (*e.g.*, emptying/cleaning a litter box).
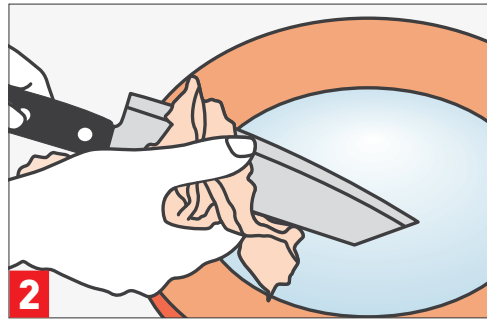
2 Wash kitchen knives and cutting boards thoroughly after preparing raw meat, fruits, or vegetables.

3 Cook the meat well before eating it.
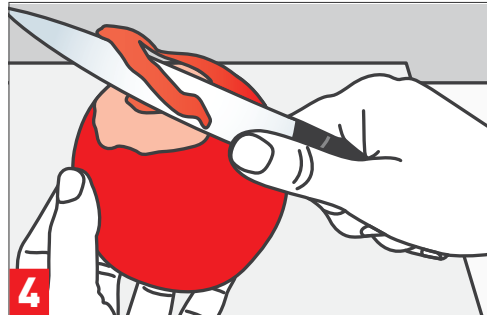
4 Wash or peel fruit and vegetables before eating them.

5 Wear gloves while gardening.

6 Keep pet cats indoors.

7 Feed cats only commercially prepared dry, canned or cooked foods.

8 Clean the litter box daily and dispose of litter responsibly (*e.g.*, in sealed garbage bags).

9 Prevent pregnant or immuno-compromised individuals from cleaning the litter box.
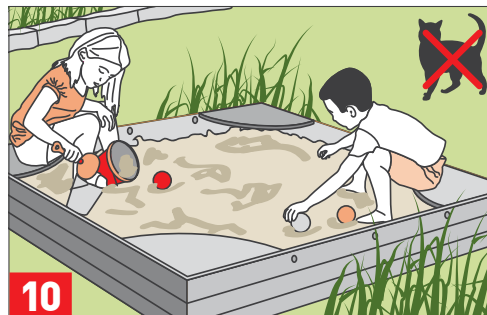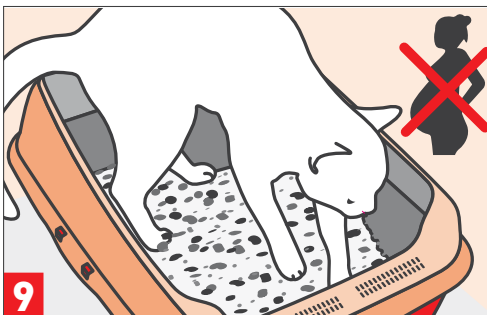
10 Cover sandboxes and loose soil in outdoor play areas to prevent cats from defecating.

ROYAL CANIN®

HOUSE SOILING IN CATS

Kelly A. St. Denis
MSc, DVM, Dip. ABVP (feline practice), Powassan, Ontario, Canada

Dr. St. Denis is a practicing feline medicine specialist, board certified with the American Board of Veterinary Practitioners in the specialty of feline practice. In her early career she trained in molecular biology and immunology before going on graduate from the Ontario Veterinary College in 1999. She owned and operated the Charing Cross Cat Clinic from 2007 to 2020, and has co-authored a number of practice feline guidelines, as well as being co-editor of both the *AAFP Feline Practitioner Magazine* and the *Journal of Feline Medicine and Surgery*. Dr. St. Denis is a consultant on the Veterinary Information Network in feline internal medicine, and lectures internationally on all things feline. She is past president of the American Association of Feline Practitioners.

House soiling in cats is an all-too-common problem for many owners; this paper offers a holistic approach to help clinicians advise their clients.

KEY POINTS

1 House soiling is voiding or defecating in a location that is appropriate to the cat at the time, based on their physical, emotional and cognitive needs.

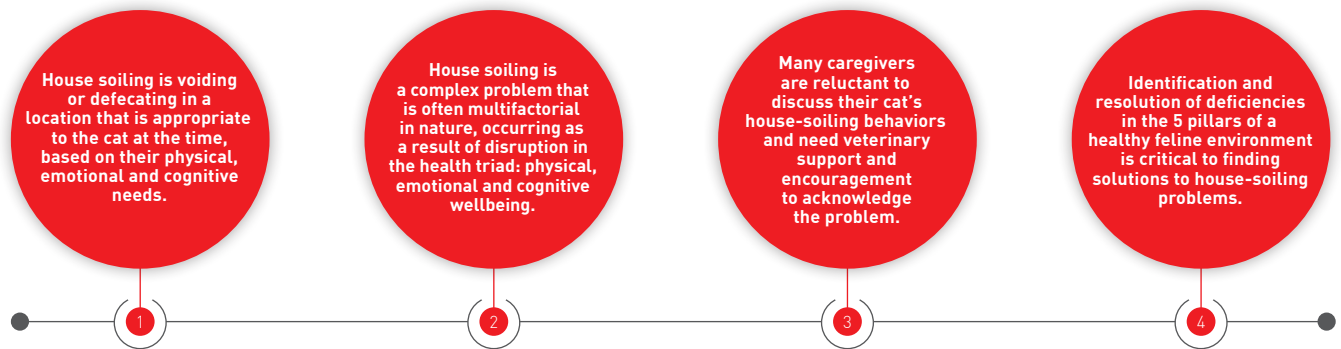**2** House soiling is a complex problem that is often multifactorial in nature, occurring as a result of disruption in the health triad: physical, emotional and cognitive wellbeing.

3 Many caregivers are reluctant to discuss their cat's house-soiling behaviors and need veterinary support and encouragement to acknowledge the problem.

4 Identification and resolution of deficiencies in the 5 pillars of a healthy feline environment is critical to finding solutions to house-soiling problems.

House soiling – an introduction

Cats have long been assumed to be an independent species requiring minimal care – but this assumption can often result in deficiencies in their environment and a failure to meet a cat's basic needs. As a result, the cat's health, a triad comprised of physical, emotional, and cognitive wellbeing **(Figure 1)** is likely to be negatively impacted. Caregivers have nearly complete control over their cat's life, making decisions about diet, feeding schedules, other cats and other pets, toys, resting spaces and litter boxes. In spite of having minimal or no control, as long as the cat is able to, they will remain cooperative with human expectations. However, when deficiencies in the environment exist and the health triad is disturbed, their ability to conform diminishes. For litter box use, this can mean that alternative latrining locations become the appropriate place for the cat to void urine and/or defecate. House soiling is therefore the act of depositing urine or feces outside of a toileting area that the caregiver has designated as acceptable **(Box 1)**.

Cognitive

Emotional

Physical

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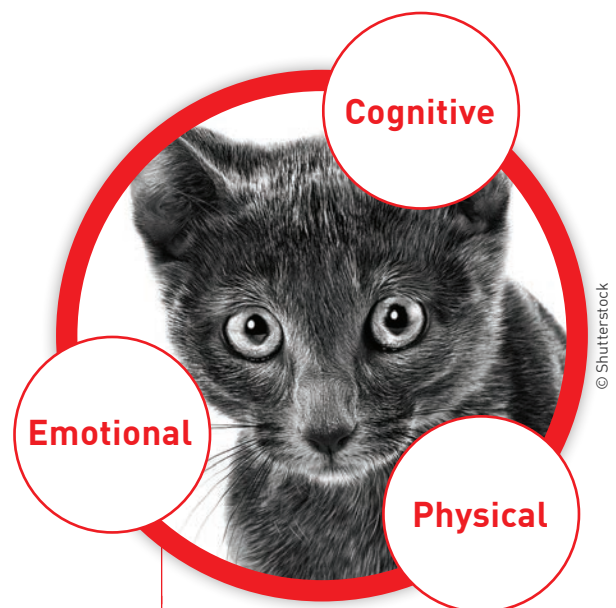
Figure 1. The Triad of health for the domestic cat: physical, cognitive and emotional wellbeing.

Box 1. House-soiling terminology.

Voiding	The conscious process of passing urine from the distal urethra.
Defecation	The conscious process of passing feces from the rectum.
House soiling	The conscious or unconscious process of depositing urine or feces outside the litter box onto horizontal, and sometimes vertical, surfaces; full or partial volumes may be deposited.
Urine spraying	The conscious process of depositing urine outside the litter box typically on vertical surfaces and typically associated with territorial marking behavior. This is most commonly observed in intact males, but can also occur in late-neutered males, intact females and neutered males and females.
Periuria	Urine house soiling or spraying
Perichezia	Feces house soiling
Middening	The conscious process of depositing feces in distinct locations usually as a form of territorial marking

House soiling – changing the perspective and language

Some of the terminology used in reference to house soiling can have a misleading impact on the perceived cause(s), and specifically on the cat's behavior and intentions. For example, the word "inappropriate" (urination, defecation, latrining) is often used, but it is erroneous to consider the behavior as being inappropriate, and erroneous to consider that the cat is aware of this and acting with malicious intent. Lacking self-reflection and internal dialogue, cats do not avoid the litter box for revenge or other vindictive reasons (1). When they defecate or urinate, they are making the decision to do so in a location that is appropriate to them at the time and for their needs, much as they would out of doors. By applying the correct language and avoiding terms like "inappropriate", we can correctly direct caregivers away from the concept of *misbehavior* and turn the focus to what the cat's essential needs are, with the goal of resolving the problem. Of equal or greater importance is that by educating all caregivers about the cat's essential needs before problems occur, we can actively prevent house-soiling issues from ever arising.

Causes of house soiling

House soiling is a multifactorial problem that signals there are derangements in the cat's physical, emotional or cognitive wellbeing. The main medical differential diagnoses for feline urine house soiling include lower urinary tract disease (FLUTD), constipation, dehydration, neurologic disease and/or neoplasia. FLUTD describes a group of diseases of the lower urinary tract which may have overlapping clinical signs and are not necessarily mutually exclusive. These include feline idiopathic cystitis (FIC), urolithiasis, crystalluria, infection and/or bladder neoplasia. The main medical differential diagnoses for house soiling with feces include structural abnormalities, constipation, neurologic conditions, urinary tract disease, intestinal disease, dehydration and/or neoplasia. Additionally, any condition that causes pain may contribute to inconsistent litter box use and aversion. Deficiencies in the environmental needs of the cat that can lead to house soiling include insufficient availability, or incorrect distribution or management of resources such as litter boxes, feeding and/or water stations, scratching surfaces, and sleeping locations. Inter-cat issues may also lead to litter box avoidance. Cats in multicat households may have reduced access if insufficient boxes are available, or if a cat is blocking access. Intact males or males neutered after the onset of puberty, and even some neutered males and females, may engage in house soiling in the form of territorial urine marking (spraying) or marking with feces (middening). A presumed territorial nature for certain types of house soiling does not rule out the need for a full medical evaluation (2).

Barriers to identification and resolution

Caregivers may not be aware that their cat is house soiling, or only become aware of the problem after it has been going on for a long period. They may draw mistaken conclusions about the cause(s), attempting to resolve the concern on their own. They may also fail to report the problem, either because they are unaware of the potential for sickness and pain associated with house soiling, or due to an unwillingness to pursue what they misconceive to be a potentially expensive and doomed process. In a 2016 telephone survey conducted of 281 households owning 455 cats, 26% of all cats in the study were reported to have urinated or defecated outside the litter box at some point in their lives (3), but only 31.7% of these cats were evaluated by a veterinarian for this condition. For 56.7% of cats the behavior resolved, but for the remainder the behavior persisted. This supports the experience in clinical practice, whereby caregivers allow house soiling to continue, making little to no consistent effort to determine a path to resolution, sometimes for months or years. It may sometimes be mentioned in passing at a preventive care visit, and at times caregivers may dismiss house soiling as "revengeful" behavior. Litter box use and urination and defecation should be included as part of every history taking. Close-ended questions with "yes" or "no" answers do not give the caregiver the appropriate opportunity to evaluate and report accurately on their cat's activities. Open-ended questions will increase information disclosure by providing some degree of acceptability to the activity we are asking about and allowing the caregiver to frame the information in their own words. For example, a close-ended question such as "Does

"By educating all cat caregivers about a cat's essential needs we can actively prevent house-soiling issues from ever arising."

Kelly A. St. Denis

your cat use the litter box?" should be replaced with "How often does your cat urinate or defecate outside the litter box?" or "Where does your cat urinate or defecate outside the litter box?" For the cat that intermittently soils outside the litter box, the answer to the closed question is likely to be "yes", but the answers to the open-ended questions are likely to be much more revealing.

Getting a good history

When it has been determined that a cat is house soiling, signalment and a detailed history of the problem require special consideration **(Box 2)**. Signalment may suggest or eliminate certain differential diagnoses – for example, neutered male cats are at increased risk of FLUTD. The history information should include diet (brand, canned or dry, treats), appetite (actual intake amounts), perceived weight loss or gain, water intake, and characteristics of the cat's urine and feces. A

Box 2. Important historical information for assessing house soiling in cats.

General health & care history	Appetite (actual daily intake), diet (brand, canned or dry, treats) drinking habits, perceived weight loss or gain, vomiting, diarrhea, coughing, sneezing, activity level, medications and supplements
Characteristics of the urine	Frequency, (changes in) urine clump diameter/size, color, odor, evidence of distress during voiding
Characteristics of the feces	Size, odor, volume, frequency, color, presence of frank or altered blood, presence of mucus, fecal score, any evidence of distress during defecation
House-soiling information	Duration of the problem, when and where the problem is occurring, under what circumstances or triggers, details on litter box care, under what conditions the cat uses the litter box (if at all), other pets in the home, inter-pet relationships
Other behavior changes	Increased sleeping, reduced play, increased/decreased interaction with caregiver, increased/decreased grooming (specific to one body location or generalized), hiding, changes in mobility (jumping up and down, walking, movement up and down stairs)

healthy adult cat urinates approximately 30 to 40 mL/kg per day, although large variations exist depending on diet, water consumption and health status. Caregivers should be asked about changes in urine clump diameter or size and encouraged to have increased awareness of urine volumes for each cat in the household. This can be easier to track than it might be assumed, particularly if specific cats have preferred litter boxes that they use, and it may be possible to set up cameras to gather more information. Defecation is typically once or twice daily, although a less frequent but regular pattern (ex. q48hrs) may be observed in some cats. Fecal characteristics including consistency should be evaluated using a specific fecal score chart **(Figure 2)** which will provide significant detail about the stool, even if the caregiver believes it to be "normal". The clinician should collect information on the duration of the problem, other behavior changes, when and where the problem is occurring, under what apparent circumstances, litter box care, and under what conditions the cat uses the litter box (if at all). A census of other pets in the home should include an evaluation of inter-pet relationships, particularly in multi-cat households, as this is a known risk factor for house soiling (4).

Assessment of physical wellbeing

A thorough physical examination is critical to identifying physical changes secondary to illness or which predispose to litter box issues. For example, obese cats may have mobility issues, but may also be diabetic, which causes polyuria and predisposes to lower urinary infection, all potential causes of house soiling. All affected cats require a basic urinalysis (including macroscopic assessment, specific gravity, biochemistry analysis, and sediment microscopy). This includes cases with fecal house soiling, as some of these patients may have painful urination, leading them to defecate away from the pain-associated litter box. Cystocentesis is the gold standard for urine collection, reducing the risk of false positive sediment or culture results (5), with samples ideally assessed immediately to reduce the risk of struvite formation in a stored sample, which can result in a false diagnosis of crystalluria (6). Urine culture and sensitivity should be carried out for any cat with an active sediment (white blood cells, bacteria), low urine specific gravity (USG) and/or glucosuria (5). Hematuria in the absence of any other changes may be iatrogenic, but is also characteristic of cats with FLUTD, particularly those experiencing an episode of FIC (7,8). It may be possible to monitor for microscopic hematuria at home by using a commercial litter additive product that is highly sensitive for detection of blood. Another important part of the minimum database required to rule out systemic disease is blood testing, especially in cats that are middle age (7-10 years) and older (9). Relevant tests include clinical chemistry panels, electrolytes, total T_4, a complete blood count and retroviral testing. Blood pressure assessments will

FECAL SCORING SYSTEM
FOR CATS

GASTROINTESTINAL TRACT

DIRECTIONS FOR USE	Score stools individually **from 1 (formed and dry) to 5 (liquid)**. When consistency of the stools is not homogenous, record the higher score.	**TOO HARD/ TOO SOFT**	**ACCEPTABLE**	**OPTIMAL**

1

HARD, DRY, CRUMBLY STOOL (crumbs)
Crushing the stool with a fork leaves no mark on it.
It tends to split apart rather than being crushed.
Looks like crumble topping.

2

FORMED, HARD STOOL
This stool has very clearly defined cracks. The outside is very dry and the inside is almost dry (unlike the *score 2.5* stool, which is softer).
When you press down on it with a fork, separate little pieces break off along the cracks. Leaves no residue on the ground when picked up.

2.5

FORMED, FIRM STOOL
This stool has a clearly defined shape with visible cracks.
Its surface may be slightly damp but is still well formed.
When you press down on it with a fork, the stool is crushed, although you will feel some resistance, unlike the *score 3* stool.
It leaves very little residue on the ground when picked up.

3

UNFORMED STOOL, SOFT BUT WITH SOME SHAPE
A moist stool with no cracks.
It still has a distinct shape when compared to the *score 4* stool.
This stool's different "components" stick to one another.
Leaves residue on the ground when picked up.

4

VERY SOFT STOOL
Very wet, but not liquid stool. When compared to the *score 5* stool, this stool retains the water that is nevertheless visible between its different constituent parts.

5

LIQUID STOOL
Entirely liquid stool (no texture)
or liquid stool with minimal consistency.

Figure 2. Fecal scoring charts provide a standardized guide by which caregivers and veterinary team members can gauge the status of the cat's feces. Utilizing a chart improves initial historical information on the cat's feces and facilitates future communication in particular as pertains to any response to treatment.

also be critical in cats over 8 years of age, as hypertension can cause behavioral changes including house soiling. Other investigations include imaging of the abdomen by plain or contrast radiography, ultrasound, or other modalities (10,11).

The environmental impact on feline health

The 5 essential pillars of a healthy feline environment

Given that house soiling is a multifactorial issue, it is critical that medical concerns be identified and addressed, but it is equally important to evaluate the cat's environment. Cats are a unique species, being obligate carnivores that are predator but also prey, so they need a territory in which they can hunt safely, and which provides them with their essential resources with minimal threat of predation or competition. Their overall needs are described in the five pillars of a healthy feline environment **(Figure 3)** (12). Deficiencies in one or more pillars can predispose to disturbances in the health triad, potentially leading to issues such as house soiling. When evaluating the cat's home environment, it is ideal to provide the caregiver with detailed information about these five pillars, and work with them to evaluate what deficiencies might exist. Adjustments to the environment and resource management can then be considered. Caregivers can also be encouraged to monitor the cat's environment for disruptions in the five pillars in the future, which can facilitate prompt corrections, avoiding further issues.

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Figure 4. Pillar 1 – Provide a safe space. Cats need to feel safe within their own home territory; spaces are needed throughout the home where the cat can hide and increase perceived safety.

PILLAR 1. Provide a safe place

Cats need to feel safe within their own home territory, with the sense of safety from their own perspective, not that of the caregiver (as many people assume that their cat is and should feel safe within their home). They may not be aware of potential outdoor threats and might erroneously expect the cat to understand that those threats cannot enter the home. For example, neighboring outdoor cats may not have access to the home, but their sight, sound and/or smell can lead the indoor cat to perceive a threat to its own safety and resources. Within the home, there may also be smells, noises, or other animals or humans that make the cat feel unsafe. Since caregivers do not have complete control over this at all times, spaces are needed throughout the home where the cat can hide and thus increase its perceived safety **(Figure 4)**.

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Figure 3. The overall needs of cats are described in the five essential pillars of a healthy feline environment. Deficiencies in any of these pillars can predispose disturbances in the health triad, potentially leading to issues such as house soiling.

Figure 5. Pillar 2 – Provide multiple and separated key environmental resources. Within the cat's territory, key environmental resources include resting places at different vertical heights with some that only fit one individual cat.

PILLAR 2. Provide multiple and separated key environmental resources

Within the cat's territory, key environmental resources include separated food and water sources; appropriately managed litter trays; resting places at different vertical heights with some that only fit one individual cat; and multiple scratching resources **(Figure 5)**. As solo hunters, it is recommended that cats be fed singly in separate rooms, or with visual barriers between them and a minimum of 6 feet/2 meters apart (13). While definitive research is lacking, feline experts recommend that water bowls be placed away from feeding stations, as the cat's natural preference is to keep food away from water sources. All resources should be provided in multiples and distributed to various areas throughout the home; this allows the cat the option to choose a resource in a particular location if another location does not feel safe or cannot be easily accessed at that moment. For example, if another cat is blocking access to a specific litter box, a second litter box in a different location may prevent a house-soiling event.

PILLAR 3. Provide opportunities for play and predatory behavior

The cat's natural hunting instincts require an outlet, even in an indoor setting where food is available. Puzzle feeders can promote predatory behavior and maintain mental acuity. Interactive play with caregivers for short periods once or more each day will also help to fulfill the cat's predatory drive. Caregivers may need to try multiple different puzzle feeders and toy styles to determine what their cat prefers, switching these as the cat's preferences change. Play and predatory behavior enhance physical fitness and mental acuity.

PILLAR 4. Provide positive, consistent & predictable human-cat social interaction

Cats are naturally solitary by nature, and while they engage socially with humans, they prefer to interact on their own terms and at their own initiation. As a social species, humans would prefer more physical interactions with their cat, and may want to do so spontaneously and at times that do not fit with the cat's desires. Further, not all humans understand how to interact respectfully with cats. A person may be physical in a way that cats do not like, such as rubbing or petting them vigorously and/or on parts of their body they don't want touched; holding them against their will; or picking the cat up when they don't wish to be. "Hand play" is also problematic for cats, potentially leading to injury (bites, scratches etc.) and other repulsive behaviors; this is not play and will increase the cat's anxiety. Human social interactions which cause the cat to experience fear or anxiety will increase the likelihood of unwanted behaviors, including house soiling.

PILLAR 5. Provide an environment that respects the cat's sense of smell.

Cats have a sense of smell that is significantly more heightened than that of humans. The many fragrances and scents that humans like in their homes, including scented cat litter, can reduce the cat's ability to survey the territory for predators, potentially making them feel unsafe. These smells are also potentially irritating to the cat's senses.

Litter boxes require special attention

Litter boxes are a critical Pillar 2 key resource that require particular attention when assessing house-soiling cases. Cats are expected to urinate and defecate within prescribed containers which typically contain a substrate that is hopefully conducive to digging a hole and burying of feces or urine. The humans living with the cat(s) make decisions about how many of these containers there will be, how many cats there will be to share them with, how large or small they will be, where they will be located, what they will contain and how often they will be cleaned out. Out of doors, domestic cats make all of these decisions based on their own needs including a sense of safety, their preferences, and the defining borders of their home territory. While cats usually accept what is available, a house-soiling cat has likely developed some aversion or objection to the litter box that may be related to the box itself. During the initial house-soiling consult, it is helpful to provide caregivers with a list of cats' preferred litter box criteria **(Box 3)**. Caregivers may indicate that their cat has never had any concerns with the litter box situation, but it is important to emphasize that acceptance of certain litter standards depends on good physical, emotional and cognitive wellbeing. Where there is reduced health, it is unlikely that the cat will be as willing or able to tolerate litter boxes that fail to meet these criteria. House soiling will sometimes reduce in frequency or stop altogether once litter box criteria have been met.

Number of boxes	• Provide multiple boxes with a minimum of one box per cat plus one extra • Boxes side by side are viewed as one box by the cat
Box location in the home	• Distribute boxes throughout the home • Avoid moving boxes around; instead add a new box in a newly desired location
Litter box size	• Minimum size should be 1.5 times the length of the cat; bigger is better • Cats with arthritis pain do best using transparent, high-walled boxes with large, easy to access doors
Litter type	• Unscented litter is best; scented litters are too strong for the cat's sensitive sense of smell • Cats most commonly prefer play sand or clumping litter
Litter depth	• Most cats prefer litter to be 2.5-4 cm/1-1½ in deep • Use a second box to experiment with different depths
Clean litter regularly	• Scoop the box 1-2 times daily; more often is better. • Empty litter box every 1 to 4 weeks, clean with a mild soap, rinse well and dry before adding new litter
Keep litter boxes away from food	• Cats prefer not to void or defecate near where they eat or drink • Separate rooms are best or a minimum of 152 cm (5 ft) away
Avoid negative associations	• Keep litter box locations away from noisy appliances and busy, loud areas of the home • Avoid medicating or any other potentially unpleasant experience while cat is at or in the litter box
Covered litter boxes	• Are not ideal, as cats may feel trapped inside with only one route of escape which can be blocked • Covered litter boxes should have two entry/exit points

Inter-cat relationships

It is frequently assumed that cats need another feline companion in the home, and will be lonely without one; however the inherent solitary nature of the cat means that in most situations they prefer not to share their territory or resources. This is not to say that cats cannot form positive relationships with other cats in the home, but being solitary is a cat's preferred default social behavior. Cats may develop social attachments to other cats in the household and become friends – but more often they become foes, existing in the same household with the other cat either in apparent indifference or with repeated inter-cat tensions **(Box 4)**. These tensions often go unnoticed by the caregiver, yet these can be a major cause of stress and subsequent house soiling in the multi-cat household. The ability of caregivers to recognize whether cats are friends or foes is very limited, due to their lack of understanding of the

five pillars, cat body language and cat interactions. Cohabitating cats that are friends will express affiliative behaviors including allogrooming (grooming one another), co-sleeping (in physical contact or close proximity), and other physically interactive behaviors such as nose touching, tail wrapping, facial or body rubbing and play. Foes rarely or never express affiliative behaviors, but rather will avoid one another to minimize conflict and possibly express agonistic behaviors. Foes may time-share resources, or one cat may block access to resources, and the cats may exchange vocal repulsive messages (hissing or growling) and fight. Discerning the difference between play and fighting is also difficult in some instances (14), making the identification of friend or foe more challenging. Cats that are playing will take turns initiating the activity, with rest periods throughout, and there is little to no growling or hissing. Fighting can look like play at times, as cats engage in wrestling and chasing, but these activities are often initiated by the same cat, sometimes with stalking behavior; in addition, rest periods are not taken, there is frequent growling and hissing, and physical fighting will ensue. Foe-related behaviors do not stem from a dominance hierarchy, which is not part of the cat's social structures (15), but rather from the need to protect the territory and resources, which appear limited. To meet the needs of each cat within the house, each individual must have free access to its own key resources, ideally positioned out of sight of the other cats. This provides cats the opportunity to develop their own territory within the home, avoiding others as much as they choose to.

Management & resolution of house-soiling behaviors

As a multifactorial problem, treatment of house soiling is best approached from a holistic perspective. This means addressing the physical, emotional, and cognitive well-being of the cat, rather than focusing on one dimensional solutions. Issues between cats in multicat households can often be addressed by examining deficiencies in the five pillars, including meeting all litter box criteria if possible, whilst cats diagnosed with specific medical conditions will require targeted therapy in addition to environmental adjustments.

Friends	Foes
• Facial rubbing or body rubbing between cats • Tail wrapping • Nose touching • Resting or sleeping in physical contact or close proximity • Allogrooming • Playing together	• Live in separate areas of house • Hissing/growling • Fighting • Confrontational stares • Time-share resources • Resource-blocking • Monopoling resources

Box 5. Psychotropic medications which may be needed to supplement other treatment approaches for house soiling. Drug interventions will not work in the absence of other management strategies and should be used as a last resort, with the intention of discontinuing their use over time. Drug selection will be based on the individual patient and washout periods between drugs may be required (*e.g.*, transitioning from a TCA or SSRI to an MAOI requires a 5-week washout. Note TCA or SSRIs should never be used with MAOI-B (from 20).

Drug name	Dosage	Indications	Side effects	Comments
Anticonvulsant				
Gabapentin	5-20 mg/kg PO q8-12h	Anxiolytic, analgesia	Sedation, ataxia	Decrease dose for frail cats and cats with CKD
Benzodiazepine				
Alprazolam	0.02-0.1 mg/kg PO q8h	Anxiety, urine marking, FLUTD	Sedation, ataxia, disinhibition of undesirable behaviors	Start with lowest dosage
Selective serotonin reuptake inhibitor (SSRI)				
Fluoxetine	0.5-1.0 mg/kg PO q24h	Anxiety, house soiling	Agitation, anxiety, sedation, inappetence	4-6 weeks to effect
Tricyclic antidepressant (TCA)				
Amitriptylline	0.5-2.0 mg/kg PO q24h	Anxiety, marking behavior, compulsive behaviors	Sedation, appetite changes, vomiting, urinary retention, constipation, diarrhea, tachycardia	> 1 week to effect Bitter tasting Taper dose to discontinue
Clomipramine	0.25-0.5 mg/kg PO q24h			> 1 week to effect
Monoamine oxidase B-inhibitor (MAOI-B)				
Selegeline	0.25-1.0 mg/kg PO 24h	Cognitive dysfunction	Restlessness, agitation, vomiting, diarrhea, disorientation, hearing loss	Dosage can be split q12h
Azapirones				
Buspirone	0.5-1.0 mg/kg PO q8-24h	Anxiety, urine marking, toileting problems	Bradycardia or tachycardia, nervousness, GI disturbances, stereotypic behaviors	~ 1 week to effect

Dietary modifications

A change in diet can be helpful in the long-term management of cats with house-soiling issues. Prescription diets targeted to specific medical conditions are important, but a change in formulation (*e.g.*, dry to canned) may be recommended. For example, cats with FLUTD will not only benefit from a targeted therapeutic diet, but they will also benefit from a transition to a wet food as a means of promoting a more dilute urine. Overweight cats that develop litter box issues should be started on a progressive weight loss program. Where cases of house soiling include increased anxiety, or a decreased ability to handle stressors, such as for cats with FIC, foods containing calming supplements can be incorporated into the treatment plan (16), but these must be the cat's sole source of nutrition and used consistently in the long term. Nutraceutical products which assist in reduction of anxiety or alter inflammation are of potential benefit; products which contain L-theanine, alpha-S1 tryptic casein, milk hydrolysate alpha-casozepine, whey protein and/or omega-3 fatty acids (OFA-3) are all available commercially for cats (17).

Pharmacologic interventions

Analgesics are often overlooked in cases of house soiling, yet pain can play a direct role in litter box avoidance for numerous reasons. For example, mature cats are at increased risk of degenerative joint disease (DJD) (18) which can decrease mobility, reduce ease of access to litter boxes, and predispose to house soiling. Analgesia should be a major component of most therapeutic plans for cats with house soiling whenever clinical illness has been diagnosed.

A variety of behavioral modification drugs have been used empirically in cats with house-soiling concerns, but their efficacy will vary with each situation. Treatment of house soiling will be most successful when an accurate diagnosis is made and patient needs are addressed, and all medical, dietary, environmental and resource concerns must be addressed prior to or in conjunction with the use of pharmacologic agents. Anxiety will improve with environmental adjustments (19), but in some cases anxiolytic or anti-anxiety medications (selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants

(TCAs) etc.) or other behavioral modifying pharmacologic drugs may be needed **(Box 5)**. Caregivers will need to understand that these latter medications may take days or weeks to take effect and that they will not work without other management strategies. Behavioral modification pharmacologic drugs should be used as a last resort, and should be considered as one component of the holistic approach, with the intention of being able to discontinue medications over time. Selection of drugs will be based on the identified areas of concern, whether these are anxiety based, or secondary to inter-cat issues in a multicat household.

CONCLUSION

Resolution of house-soiling issues requires a dedicated team approach including caregiver and the veterinary staff. Caregivers need to be made aware of the multifactorial nature of the issue from the outset, which will facilitate development of a treatment plan that can be successful over time and avoid the misconception that the problem is a "one and done" matter. There are rarely simple solutions, but the sooner an issue is identified, the clearer the pathway to resolution will be. At times house soiling may have been occurring for an extended period, and this may increase the challenges associated with untangling the problem; the veterinary team must commit to providing caregivers with ongoing assistance throughout the process, promoting good communication throughout.

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