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Issues in Endocrinology

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The Diagnosis of Canine Hyperadrenocorticism

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Hyperadrenocorticism (HAC or Cushing's syndrome) describes the clinical manifestations of chronic exposure to excessive glucocorticoids. Spontaneous HAC is often caused by inappropriate secretion of adrenocorticotropic hormone (ACTH) by a pituitary tumor (i.e., pituitary-dependent HAC [PDH]) or may reflect the autonomous production of cortisol by an adrenal tumor (AT).[1]

There are occasional reports of dogs with HAC due to an aberrant response to a digestive hormone (i.e., food-dependent HAC) or from ectopic ACTH secretion, but these are extremely rare.

CLINICAL PRESENTATION

Spontaneous HAC is usually diagnosed in older dogs, particularly Boston terriers, dachshunds, miniature poodles, and beagles.[1] It is uncommon in dogs younger than 5 years of age. Onset is often insidious, and owners frequently attribute changes to aging. A strong understanding of the clinical manifestations of HAC is essential because it helps us identify suitable candidates for further testing. A dog with Cushing's syndrome must have some (usually many) of the classic signs (**BOX 1**).

More than 95% of dogs are polyuric/polydipsic; a normal water intake makes HAC less likely. Additionally, most manifest dermatologic changes;[2] in my experience, a good hair coat

BOX 1 Clinical Signs Commonly Associated With Canine HAC

- Polyuria and polydipsia
- Polyphagia
- Panting
- Abdominal distention
- Hepatomegaly
- Muscle weakness
- Dermatologic changes
  - Symmetric truncal alopecia
  - Hyperpigmentation
  - Comedones
  - Thin skin (**FIGURE 2**)
  - Poor hair regrowth

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BOX 2 Indications to Pursue Diagnostics for HAC

- Client concern (you ***hear*** something)
  - Increased thirst or urination
  - Hunger, food stealing
  - Panting
  - Difficulty jumping
- Physical examination (you ***see*** something)
  - Endocrine alopecia
  - Thin skin, comedones
  - Hepatomegaly/abdominal distention
- Comorbid condition (you are ***fighting*** something)
  - Recurrent urinary tract infection
  - Frequent otitis externa; pyoderma
  - Hypertension

(particularly if shaved hair grows back promptly) essentially rules out HAC. Although calcinosis cutis is pathognomonic for HAC, it is uncommon. A "pot-bellied" appearance with palpable hepatomegaly is expected, along with poor forelimb and hindlimb musculature (**FIGURE 1**). A small number of dogs with PDH will present with signs referable to a large pituitary tumor, such as personality change, vision loss, and poor appetite.[3] Retinal changes may be noted in dogs with concurrent hypertension.

FIGURE 1. Dog with PDH. Note the abdominal distention and hepatomegaly.

A careful history is always important in a cushingoid patient because exogenous steroid administration may otherwise be overlooked.

DIAGNOSTIC PROCESS

HAC can often be considered an "exam room" diagnosis, meaning that the owner's concern or the dog's physical appearance suggests HAC. Less frequently, a comorbid condition suggests the possibility (**BOX 2**). I do not advise pursuing a diagnostic workup for HAC without a strong clinical index of suspicion. Chasing a diagnosis based on biochemical changes alone often results in substantial frustration for both client and veterinarian. There are essentially 3 steps to the HAC diagnostic workup (**BOX 3**).

Step 1: Scrutinize Routine Laboratory Findings

Most dogs manifest many (or all) of the expected patterns on routine laboratory tests.[1]

Urine is usually dilute, with specific gravity less than 1.020. Hyposthenuria may be documented: In fact, HAC is one of the most common causes of a urine specific gravity less than 1.008. Proteinuria may be

FIGURE 2. Dog with PDH. Note the thin skin with alopecia and loss of elasticity.

noted and should be quantified with a urine protein-to-creatinine ratio. Urinary tract infection is also common and may not be accompanied by significant pyuria or overt clinical signs. A urine culture is often recommended in dogs with evidence of HAC.

On the biochemistry panel, the most consistent finding is increased alkaline phosphatase (ALP) activity. This is often substantially elevated (>1000 U/L; reference range, 24 to 147 U/L) and routinely accompanied by an increase in γ-glutamyl transferase activity. However, increased ALP activity is common in older and obese dogs, dogs with various physiologic stressors, and dogs with primary hepatobiliary disease. High ALP activity in the absence of clinical signs of Cushing's syndrome should not prompt a hunt for HAC. Cholesterol and triglyceride concentrations are consistently elevated; a normal value is unusual in a cushingoid dog. Other common biochemical changes are an increased phosphorus concentration (seen in <50% of cases but still a useful marker[4]), mild hyperglycemia, and (variably) a modest decrease in blood urea nitrogen. Some dogs have mild increases in alanine aminotransferase activity, but this is usually less than 3 times the upper limit of normal.

The complete blood count shows a stress leukogram (neutrophilia, lymphopenia, monocytosis, and eosinopenia). The hematocrit should be robustly normal or even mildly high (>50% is not uncommon); anemia is not consistent with HAC and should prompt further investigation. Platelets are often increased and may cause spurious hyperkalemia.

Step 2: Screen for HAC

There is limited consensus about the "best" screening test, although sensitivity and specificity data support the routine use of the low-dose dexamethsone suppression test (LDDST).[1] However, a clinician's confidence in a positive (or negative) result is determined by population characteristics, meaning that a result supporting HAC is inherently more believable in a geriatric dog with polydipsia and truncal alopecia than in an apparently normal juvenile (same test, different patient population).

Serum/plasma assays for "cortisol" cross-react with many synthetic glucocorticoids (apart from dexamethasone); exogenous steroids should therefore be withheld for at least 72 hours before adrenal function tests are performed. In addition, prolonged administration of exogenous steroids of any type will suppress adrenal gland function after 2 to 3 weeks.

BOX 3 Stepwise Diagnostic Approach for HAC

Step 1: Scrutinize routine laboratory findings for evidence of HAC

- Urinalysis
  - Specific gravity < 1.020
  - Proteinuria
- Chemistry panel
  - Increased ALP activity and cholesterol
  - +/- Increased phosphorus
  - +/- Hyperglycemia (mild; <150 mg/dL)
  - +/- Low BUN
  - +/- Increased alanine aminotransferase or γ-glutamyl transferase activity
- Complete blood count
  - Stress leukogram
  - Robust hematocrit
  - +/- Increased platelet count

Step 2: Screen for HAC (see text for details)

- LDDST
- ACTH stimulation test
- Urine cortisol-to-creatinine ratio (low specificity; a positive result is not adequate evidence to establish this diagnosis)

Step 3: Differentiate PDH from AT (necessary only if adrenalectomy is an option)

- Abdominal ultrasonography
- Endogenous ACTH measurement
- HDDST (limited reliability; failure to suppress does not differentiate PDH from AT)

LDDST

The LDDST is an elegant way to interrogate the pituitary-adrenal axis, with reported sensitivities of 85% to 100%.[1] In addition, it is more reliable in dogs with AT than the ACTH stimulation test.[5]

First, collect a baseline cortisol sample; serum is generally preferred, although some laboratories will accept heparinized plasma. Next, administer 0.01 mg/kg of dexamethasone IV. This dose is slightly

About 85% of dogs with HAC have PDH, particularly small dogs.

supraphysiologic and will suppress the release of ACTH (and therefore cortisol) in a normal dog for more than 12 hours. If the sodium phosphate formulation is used ("Dex SP"), the dose should be adjusted to reflect that 1.3 mg of this formulation contains 1.0 mg of dexamethasone.[1] The product used should be diluted for accurate dosing in small dogs (**BOX 4**). Subsequent blood samples are collected at 4 and 8 hours.

Cortisol concentrations indicating "suppression" vary, with some laboratories using a value of less than 0.7 mcg/dL and others defining suppression as anything less than 1.4 mcg/dL.[1] Lower values increase test sensitivity but may produce more false-positive results. Nonadrenal issues, such as fear and pain, affect cortisol release and cause false-positive results. Chronic illness may also affect results because long-term endogenous hypercortisolemia may shorten the half-life of exogenous glucocorticoids;[6] the suppressive effects of dexamethasone therefore abate within 8 hours.

One advantage of the LDDST over other screening tests is its ability to differentiate PDH from AT. PDH can be diagnosed with confidence if the 4-hour cortisol level is less than 50% of baseline or below the level established by the laboratory. The LDDST can cause confusion, so always look at the 8-hour result first and see if this value indicates HAC. If the answer is "yes," then look at the 4-hour result; suppression at this point indicates PDH. Failure to suppress at the 4-hour mark is not diagnostically useful; it is seen in many dogs with PDH and all those with AT.

BOX 4 Protocols for the Dilution of Dexamethasone for LDDST

- **Dexamethasone 2 mg/mL:**
  0.5 mL + 9.5 mL of saline = dexamethasone 0.1 mg/mL
  Administer 0.1 mL/kg (=0.01 mg/kg of dexamethasone)

- **Dexamethasone sodium phosphate 4 mg/mL:**
  0.32 mL + 9.68 mL of saline = dexamethasone 0.1 mg/mL
  Administer 0.1 mL/kg (=0.01 mg/kg of dexamethasone)

ACTH Stimulation Test

This test is convenient—it takes just over an hour. First, collect a baseline cortisol sample. Then inject cosyntropin (5 mcg/kg IM or IV; maximum, 250 mcg per dog) and collect a second serum sample 1 hour later. Compounded ACTH gel products are best avoided because their biological effect is uncertain. To save costs, reconstituted cosyntropin can be divided into aliquots in plastic syringes and kept frozen for up to 6 months.[7]

This test is based on the premise that the response to exogenous ACTH is proportional to functional adrenocortical tissue; this is increased in dogs with PDH or AT. Most labs use a cutoff serum concentration of 17 to 20 mcg/dL; a serum concentration above this level supports HAC.[1] The disadvantages to this test include poor specificity in dogs with chronic disease, meaning that false-positive results are likely. It also has poor sensitivity in dogs with AT; many dogs with this condition have normal results or findings suggesting hypoadrenocorticism,[8] likely due to limited ACTH receptor expression by neoplastic cortical cells. A "flat-line" or addisonian response is also seen in dogs with iatrogenic HAC; chronic exposure to exogenous glucocorticoids results in adrenocortical atrophy and a blunted response to exogenous ACTH.

Urine Cortisol-to-Creatinine Ratio

This test is overly sensitive and not very specific, meaning that false-positive results are common, particularly in dogs with other polyuric disorders.[9] However, a negative result is highly reliable and can be used to exclude HAC when there is a low index of suspicion. Test reliability is optimized by having the owner collect morning urine at home. Stress or fear can quickly increase cortisol concentrations in normal dogs, so it is unwise to collect this sample in the clinic environment.

Step 3: Differentiate PDH From AT

About 85% of dogs with HAC have PDH, particularly small dogs. HAC due to AT is most often reported in dogs that weigh more than 20 kg.

Differentiating the 2 forms is important because the diagnosis affects therapy and prognosis, but it is not necessary if the dog is a poor candidate for surgery or the owner is unwilling to consider adrenalectomy (the treatment of choice for AT).

Abdominal ultrasonography can readily differentiate PHD from AT but is operator and machine dependent. Normal adrenal gland width (at the caudal pole) is 3 to 5 mm, although it is not unusual to find 7-mm adrenals in large dogs with nonadrenal illness.[10] Bilateral, symmetric adrenomegaly indicates PDH in a dog with a positive result on a confirmatory test for HAC. A solitary mass in 1 gland suggests AT; contralateral atrophy (<4 to 5 mm) is expected. Dogs can develop PDH and have a concurrent pheochromocytoma or adrenal tumor.[11]

Abdominal radiography is a backup option if ultrasonography is not available. About 50% of ATs become calcified and can be seen on a plain lateral abdominal study. Calcification does not indicate malignancy.

Many reference laboratories offer highly sensitive assays for endogenous ACTH concentrations, which can be used to reliably differentiate the 2 forms of HAC. Dogs with AT have essentially undetectable levels, whereas those with PDH have normal or increased levels.[12] Endogenous ACTH is a fragile hormone, so careful sample handling is essential. Contact your laboratory to clarify requirements for sample submission.

The high-dose dexamethasone suppression test (which uses 0.1 mg/kg IV of dexamethasone) is rarely performed these days because its role has been supplanted by ultrasonography and measurement of endogenous ACTH. Suppression of cortisol production for the 8-hour test period is diagnostic for PDH, but a lack of suppression is inconclusive.[1]

SUMMARY

- The clinical recognition of dogs with HAC is a key part of the diagnostic process.
- Do not chase this diagnosis without overt clinical manifestations of HAC.
- The confirmatory tests have limitations; more than 1 may be needed to establish a diagnosis.
- If adrenalectomy is not an option, client resources may be directed toward treatment rather than differentiating PDH from AT. However, life expectancy for dogs with AT will be affected by the biological behavior of the tumor (benign vs malignant). TVP

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Canine Hypothyroidism: Diagnosis and Treatment

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Hypothyroidism is a common endocrine disease of dogs. It occurs when the thyroid glands fail to produce adequate amounts of the hormones thyroxine (T4) and triiodothyronine (T3). Primary hypothyroidism resulting from idiopathic thyroid gland atrophy or immune-mediated lymphocytic thyroiditis is the most common diagnosis. Uncommon causes of canine hypothyroidism include congenital disease resulting from dyshormonogenesis of thyroid hormone, abnormal thyroid-stimulating hormone (TSH) production, or abnormal thyroid gland development.[1]

Thyroid hormones are involved in a wide variety of metabolic processes, and low thyroid hormone levels result in a constellation of clinical signs and laboratory abnormalities that characterize hypothyroidism. Multiple hormone tests are required to make a diagnosis. The diagnosis should never be based on low T4 concentration as a sole finding.

CLINICAL PRESENTATION

Hypothyroidism typically affects middle-aged dogs, although it has been reported in younger and older dogs. Any breed can be affected.

Clinical signs (**BOX 1**) may be nonspecific, which can result in overdiagnosis of this disorder; lethargy and weight gain are common.[2,3] Clinical signs may have an insidious onset and may not be noticed by the owner. Hypothyroidism often causes hair coat changes, including bilaterally symmetric, nonpruritic alopecia over the trunk or areas of wear, post-clipping alopecia, and a dull, lusterless hair coat (**FIGURE 1**). Skin changes may include scaling, seborrhea, hyperpigmentation, and recurrent infections (pyoderma or otitis externa).[2,3]

FIGURE 1. Dog with hypothyroidism—note the excessive body weight, dull hair coat, and scaling.

From the top: taro911 Photographer/shutterstock.com. Opposite: Courtesy of David Panciera, Virginia-Maryland College of Veterinary Medicine, Blacksburg, VA.

Rare clinical signs and syndromes that have been associated with hypothyroidism include megaesophagus, vestibular dysfunction, facial nerve paralysis, and atherosclerosis.[4,5,8]

BOX 1 Clinical Signs Commonly Associated With Canine Hypothyroidism[2-7]

- Signs related to decreased metabolic rate
  - Lethargy or dull mentation
  - Inactivity or unwillingness to exercise
  - Weight gain
  - Cold intolerance or heat seeking
- Dermatologic changes
  - Symmetric, nonpruritic hair loss
  - Post-clipping alopecia
  - Dry, dull hair coat
  - Scaling
  - Hyperpigmentation
  - Recurrent pyoderma or otitis externa

Uncommon

- Incoordination
- Ocular signs
  - Lipid corneal deposits
- Peripheral nervous system signs
  - Facial nerve paralysis
  - Laryngeal paralysis
  - Polyneuropathy
  - Other
- Vestibular signs
- Megaesophagus or esophageal dysmotility
- Cardiovascular abnormalities
  - Bradycardia
  - Exacerbation of other cardiac signs
  - Atherosclerosis
- Reproductive effects
  - Periparturient mortality
  - Lower birth weights
- Myxedema coma
  - Depressed mental status
  - Altered thermoregulation
  - Bradycardia
  - Hypoventilation
  - Thickened skin

DIAGNOSTIC PROCESS

Dogs should be tested for hypothyroidism only when the disease is strongly suspected based on the patient's history and physical examination findings (**BOX 1**). Complete blood count and serum biochemistry panel results may heighten clinical suspicion for hypothyroidism. Hypothyroidism can be misdiagnosed when testing is performed only because a dog is overweight or because a T4 concentration is included with a standard biochemistry panel.

A stepwise approach is helpful in accurately diagnosing canine hypothyroidism (**FIGURE 2**).

Step 1: Evaluate Minimum Database Results for Supportive Findings

Results from a complete blood count, serum biochemistry panel, and urinalysis are helpful to rule out concurrent disorders that could affect thyroid test results. However, none of the abnormal results that may be seen on these tests are specific for hypothyroidism.

Approximately 75% of hypothyroid dogs have elevated cholesterol levels.[2,3] While mild hypercholesterolemia alone should not prompt testing for hypothyroidism, it supports a suspicion of hypothyroidism. Liver enzymes may be mildly elevated. A mild, nonregenerative anemia is present in about 30% to 40% of hypothyroid dogs.[2,3] The urinalysis typically shows no abnormalities. Dilute urine, if present, should prompt investigation for concurrent illness or another cause of clinical signs.

Step 2: Screen With a T4 Concentration

Total T4 concentration is a useful screening test for hypothyroidism. The sensitivity of this test for the diagnosis of canine hypothyroidism is reported to be 89% to 100%.[9-12] If the T4 concentration is well within reference range, it is very likely the dog is euthyroid and further thyroid testing is not required. Free T4 (fT4) and thyroid-stimulating hormone (TSH) are evaluated only if the T4 concentration is low (**FIGURE 2**). Combined T4, fT4, and TSH testing is not recommended at this stage and may add unnecessary expense since a normal T4 concentration effectively rules out hypothyroidism.

However, a T4 concentration below reference range is not diagnostic for hypothyroidism. In addition to normal daily fluctuations, several medications have

BOX 2 Drugs That Alter Canine Thyroid Hormone Function or Test Results[13–20]

- Prednisone (high dose)
- Phenobarbital
- Trimethoprim–sulfamethoxazole
- Aspirin (high dose)
- Clomipramine
- Thyroxine supplementation

BOX 3 Euthyroid Sick Syndrome

This syndrome refers to a condition in which nonthyroidal illness suppresses the concentration of circulating thyroid hormones. The mechanism is complex and likely involves changes in hormone distribution and metabolism and altered binding of hormones to proteins.

been demonstrated to lower the serum T4 concentration of dogs (**BOX 2**), and some also affect fT4 and TSH concentrations. Certain drugs, such as trimethoprim–sulfamethoxazole, can have direct effects on the pituitary–thyroid axis and result in hypothyroidism.[13] Furthermore, nonthyroidal illnesses can alter thyroid hormone metabolism and result in the euthyroid sick syndrome (**BOX 3**). Concentrations of fT4 are less likely to be affected by concurrent illness, but if the illness is severe enough, fT4 can also be low.[21,22] Therefore, thyroid testing should not be performed in dogs that are systemically ill. If a dog with a concurrent illness is tested for hypothyroidism, test results should be interpreted with caution.

Because diagnosing hypothyroidism is not an emergency, sending samples out to a reference laboratory is advisable. Since additional confirmatory tests are required, it is helpful to collect and hold extra serum when collecting for the T4 test.

It is important to remember that "normal" reference ranges for T4 do not apply to sighthounds, as healthy dogs of these breeds have lower T4 concentrations than other breeds.[23,24]

FIGURE 2. Approach to canine thyroid testing.

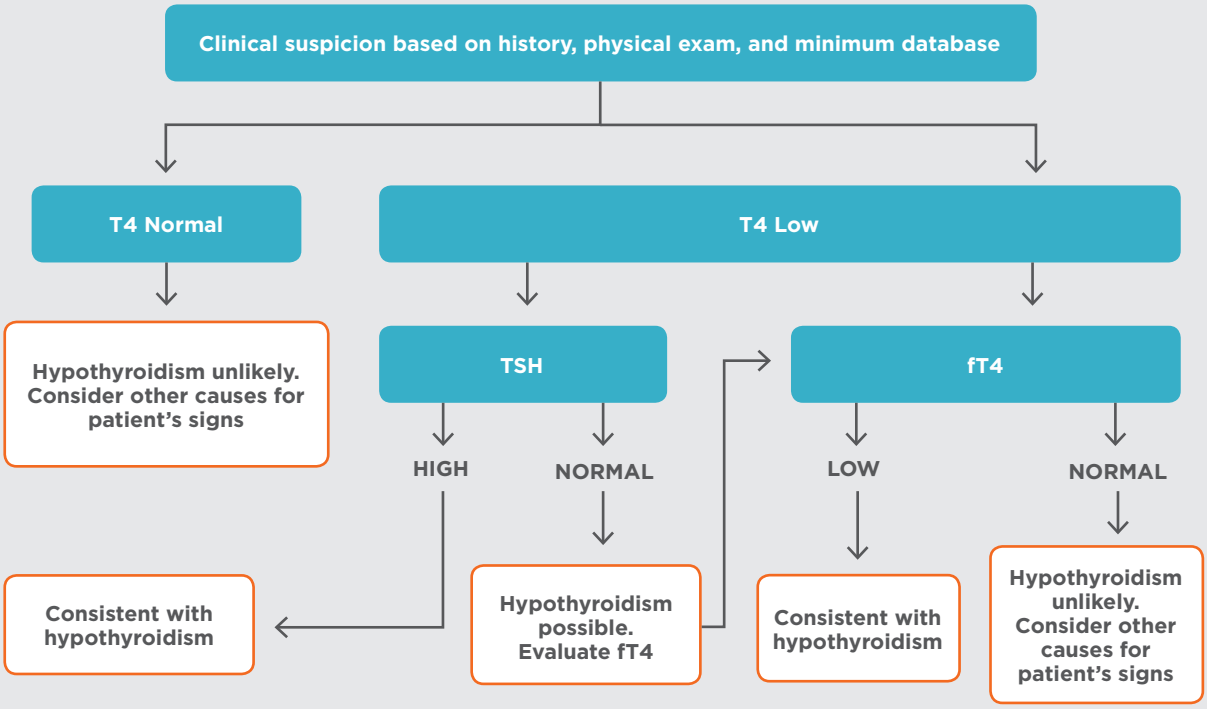

TABLE 1 Test Results for Diagnosis of Canine Hypothyroidism[a]

HORMONE	CONCENTRATION
Total T4	Low
Free T4	Low
TSH	High or normal

[a]To confirm the diagnosis, all 3 results must be obtained.

Step 3: Confirm With an fT4 or TSH Concentration

When a dog suspected to have hypothyroidism has a low total T4 concentration, fT4 and/or TSH concentrations must be evaluated to help confirm or refute the diagnosis (**TABLE 1**). If the TSH concentration is high, hypothyroidism can be diagnosed. However, 13% to 38% of hypothyroid dogs have normal TSH concentrations,[10-12,25] so a normal TSH concentration does not exclude the diagnosis. Because of this limitation, it is often helpful to evaluate fT4 and TSH simultaneously as confirmatory tests. If the fT4 is low, a diagnosis of hypothyroidism can be made.

If T4 is low and fT4 is within reference range, hypothyroidism cannot be diagnosed, and the clinician should consider other differentials for the dog's clinical signs.

T3 concentrations vary widely and are not diagnostically useful.

Approximately 75% of hypothyroid dogs have elevated cholesterol levels.[2,3] While mild hypercholesterolemia alone should not prompt testing for hypothyroidism, it supports a suspicion of hypothyroidism.

TREATMENT

Initiating Therapy

Studies have shown that most dogs can be regulated with once-daily levothyroxine,[26,27] usually initiated at 0.02 mg/kg PO q24h. Some clinicians begin with twice-daily administration of levothyroxine (0.02 mg/kg PO q12h) and attempt to reduce the dosing to once daily, once clinical signs are well controlled. Lethargy often improves after a few weeks. Most clinical signs improve within 4 to 6 weeks, although dermatologic changes take months to resolve.

Monitoring and Adjusting Therapy

After 4 weeks of therapy, blood is collected 4 to 6 hours post-pill for T4 measurement. (T4 can be measured as early as 2 weeks after starting or adjusting therapy,[26] but waiting until 4 weeks allows for assessment of improvement in clinical signs at the same visit.) The post-pill T4 concentration should be at the upper end of the reference range or slightly above (<6 mcg/dL). Laboratory reference ranges for "initial" T4 concentrations and "post-pill" concentrations may be different, so careful sample labeling and interpretation are important.

If the post-pill T4 concentration is below the target concentration, the dose of levothyroxine should be increased by 25%. The T4 concentration is then rechecked in 2 to 4 weeks. The dose is gradually increased until the post-pill T4 concentration is within the target range. Similarly, if the post-pill T4 concentration is too high, the dose should be decreased by 25% and the concentration rechecked. Once an effective dose has been established, the interval between monitoring visits is increased to every 6 months.

Treatment Failure and Adverse Effects

Treatment failure is uncommon. Possible reasons for failure to achieve the targeted T4 concentration include owner noncompliance in administering medication or patient refusal to swallow the pills. Variable gastrointestinal absorption of levothyroxine is also considered to be a possible cause.[28] If a target post-pill T4 concentration has been achieved and clinical signs are not controlled, the dosing frequency should be increased to twice daily. Additionally, the diagnosis of hypothyroidism should be reconsidered. If the diagnosis of hypothyroidism is definitive and the dog's

T4 concentration is well controlled, consider whether a concurrent disorder could be causing clinical signs.

Dogs are generally resistant to the effects of excessive levothyroxine supplementation. However, clinical signs such as polyuria/polydipsia and hyperactivity may develop.[26]

SUMMARY

Thyroid testing should be carried out only when patients are suspected of having thyroid disease. Measurement of T4 concentration is helpful to rule out hypothyroidism but should not be solely relied on to confirm the diagnosis. Combined testing that includes the serum T4 concentration along with fT4 and/or TSH levels is needed for definitive diagnosis and will help decrease the possibility for misdiagnosis of hypothyroidism. Since lifelong therapy is required, it is appropriate to achieve a definitive diagnosis before starting therapy. TVP

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Managing Feline Diabetes Mellitus

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Diabetes mellitus (DM) is a common endocrinopathy in cats, with reported prevalence rates ranging from 0.4% to 1.2%.[1-4] The vast majority of cats with experimentally induced diabetes developed an initial period of insulin resistance, with the associated persistent hyperglycemia directly reducing functional pancreatic beta cell mass.[5] Though an oversimplified explanation, this "glucotoxicity," paired with damage stemming from progressive islet amyloid deposition, generation of reactive oxygen species, and local inflammation, leads to permanent insulin dependence if left uncorrected.[6] Factors related to the patient's diet and adiposity and the presence of comorbid conditions (e.g., acromegaly, pancreatitis) likely contribute to the pathogenesis of feline DM as well as influence response to therapy and chances for achieving remission.

DIAGNOSIS

Overt DM is diagnosed by documenting persistent hyperglycemia with glycosuria in a patient with appropriate clinical signs (polyphagia, polydipsia, polyuria, and/or weight loss).[7] To rule out stress hyperglycemia, additional testing such as blood or urinary glucose monitoring in a nonstressful environment or assessing a serum fructosamine concentration to gauge mean blood glucose (BG) over the preceding 1 to 2 weeks may be required.[8] Some cats may present with a plantigrade stance from diabetic neuropathy (**FIGURE 1**).

A "preclinical" diabetic state is likely to exist in cats before the onset of overt DM, similar to the

FIGURE 1. Cat with plantigrade stance caused by diabetic neuropathy.

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pathogenesis in people. During this time, modest or intermittent hyperglycemia suggesting glucose intolerance may contribute to only mild clinical signs that go unrecognized by the owner. While no standardized method currently exists to identify these prediabetic patients, the finding of repeated mild hyperglycemia on routine diagnostic screenings of a healthy patient should not always be written off to stress. Serial glucose monitoring, fructosamine assessment, or a glucose tolerance test may be warranted if a prediabetic state is suspected.

MANAGEMENT

The general goals of treatment are to mitigate clinical signs through improvement of hyperglycemia and avoidance of diabetic complications (e.g., hypoglycemia, ketosis). These goals are most reliably met using a combination of insulin administration and carbohydrate-restricted dietary modification. A subset of newly diagnosed or insulin-naïve cats in which DM is quickly well controlled may go on to achieve diabetic remission, loosely defined as normoglycemia independent of insulin therapy for more than 4 weeks.[9]

Reported remission rates range from 0% to 100% using various insulin or dietary protocols.[9-11] A survey of 282 cats managed by diplomates of the American Board of Veterinary Practitioners across the United States reported remission rates of 8% to 42% with an average rate of 26% for all cats evaluated.[12] The authors feel this average rate is a realistic figure to discuss with owners in regard to the likelihood of a newly diagnosed diabetic cat achieving remission. Approximately 30% of cats that achieve remission relapse, so maintenance of an appropriate diet and diligent monitoring for recurrence of clinical signs of diabetes are worthwhile.[13]

Insulin Therapy

Most available insulin preparations (**TABLE 1**) contain human insulin or insulin analogues engineered through recombinant DNA technology using bacteria or yeast; the exception is porcine zinc insulin suspension. Most preparations use amino acid modifications to the insulin molecule and/or added zinc or protamine for the purpose of slowing absorption and/or increasing the duration of insulin action. The authors recommend either protamine zinc insulin (PZI) or glargine as first-choice insulin selection and initiation of all insulin preparations at a starting dose of 1 to 2 units per cat, given subcutaneously twice daily.[7,21]

Unlike dogs, most cats do not experience a profound postprandial hyperglycemia.[22] So while meal feeding immediately before insulin injection is ideal, diabetic cats can "graze" over the course of the day if necessary. Owners should monitor for any cessation of food or water intake, as well as signs of gastrointestinal upset (i.e., vomiting or diarrhea), which may require a temporary insulin dose reduction to prevent inadvertent hypoglycemia.

Assessment of glycemic response immediately after starting insulin is not recommended; instead, assessment is typically delayed until 7 to 14 days after treatment initiation. However, spot-checking a glucose reading daily after starting insulin therapy to identify lower than

Potential Complements or Future Alternatives to Insulin Therapy

Glucagon-like peptide 1 (GLP-1) analogues have received attention as a possible alternative or complement to insulin therapy. While still injectable, these products would allow a reduction in the frequency of injections to once weekly instead of once to twice daily. The GLP-1 analogue exenatide-ER (Bydureon, AstraZeneca) was evaluated in a population of 30 diabetic cats concurrently treated with glargine insulin and dietary modification.[1] The drug was proven safe; however, diabetic control and remission outcomes were not statistically different from placebo. Larger studies are warranted to determine if GLP-1 analogue use provides any advantage over standard management protocols.

Oral hypoglycemics, such as the sulfonylurea glipizide, have historically been reserved only for patients in which insulin therapy is vehemently declined or cannot be administered by the owner.[2] The authors do not recommend using glipizide, as the medication is only temporarily effective in some cats in combination with dietary modification and delays appropriate treatment with insulin, thereby possibly predisposing patients to diabetic complications.[3] Novel oral hypoglycemic therapies, such as renal sodium-glucose linked transporter 2 (SGLT2) inhibitors, which induce urinary glucose wasting, may provide future alternatives to insulin injections for management of feline DM, but prospective studies are needed.

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desired glucose values (typically <100 mg/dL), which might prompt a dose reduction, would be acceptable.

Dietary Therapy

The goals of dietary therapy are to complement insulin in controlling hyperglycemia through limiting carbohydrate availability as well as to assist in achieving or maintaining an ideal body weight (BW). Diets containing a high-protein (≥40% metabolizable energy), low-carbohydrate (≤12% metabolizable energy) nutrient profile are preferred.[23-25] Obese cats should be fed a total daily caloric requirement calculated using their ideal BW, with regular monitoring to ensure gradual (<2% BW reduction per week) weight loss.[7] Achieving effective control of hyperglycemia with a combination of glargine insulin and dietary therapy within 6 months of the initial DM diagnosis increases diabetic remission potential.[24]

MONITORING

No gold-standard diagnostic exists for monitoring diabetic patients or directing therapeutic decision-

TABLE 1 Commercially Available Insulin Products

INSULIN	BRAND NAME (MANUFACTURER)	CONCENTRATION (U/ML)	FDA APPROVED FOR CATS?	MECHANISM OF PROLONGED DURATION	NOTES
Protamine zinc insulin (PZI)[14,15]	ProZinc (Boehringer Ingelheim)	U40	Yes	Added protamine sulfate and zinc oxide components promote crystallization in tissues.	—
Glargine[16]	Lantus (Sanofi)	U100	No	Amino acid alterations promote solubility at an acidic pH of 4.0 (in vial) and precipitation around a physiologic pH of 7.0. This tissue precipitation delays absorption and extends the duration of insulin action.	As pH plays an essential role in the action of glargine, glargine should never be diluted without using the proper diluent to prevent action interference.
	Basaglar (Eli Lilly & Boehringer Ingelheim)	U100			
	Toujeo (Sanofi)	U300			
Detemir[17,18]	Levemir (Novo Nordisk)	U100	No	A fatty acid added to insulin's molecular structure enables strong but reversible binding to albumin, which slows absorption and extends the duration of action.	Detemir has a higher molar concentration of insulin than other preparations, which can increase the hypoglycemic effect in some species, such as dogs, potentially requiring lower starting doses. Cats do not appear to be as susceptible to this concentration difference.
Porcine zinc[19]	Vetsulin and Caninsulin (Merck Animal Health)	U40	Yes	The amorphous and crystalline zinc insulin content is manipulated.	The currently available product has unique handling instructions.
Degludec[15]	Tresiba (Novo Nordisk)	U100	No	A single amino acid substitution causes multi-hexamers to form in the subcutaneous tissues, delaying insulin absorption.	—
Neutral protamine Hagedorn (NPH)[20,a]	Humulin-N (Eli Lilly)	U100	No	Added protamine sulfate and zinc oxide or chloride components promote crystallization in tissues.	—
	Novolin-N & ReliOn-N (Novo Nordisk)	U100			

[a]NPH insulin formulations are not currently recommended in cats due to their inconsistent effect and short duration of action.[20] The authors typically reserve them only for rare circumstances when all other insulin options have failed to control the cat's DM.

Most patients with clinically well-controlled diabetes (serum glucose between 100 and 300 mg/dL over the course of the day) are expected to have glucosuria.

making. Additionally, management decisions are complicated by factors unique to veterinary medicine, such as owner compliance and finances and patient stress hyperglycemia. In the authors' opinion, individualizing a monitoring plan for each patient using a combination of owner-reported clinical signs and biochemical data maximizes the accuracy of assessments used to direct treatment recommendations.

Most diabetic monitoring tools are used to gauge the general level of glycemic regulation. These tests alert the veterinarian that DM control is present or absent; however, they should not be used alone in directing changes to insulin therapy. Ideally, cats with abnormal monitoring results should have their insulin response evaluated through the generation of a BG curve.

Owner-Reported Clinical Signs

Clinical signs reported by the owner have been shown to provide information that often reflects the patient's true state of glycemic control better than most biochemical analyses.[26] Clinical signs of DM are most pronounced when the BG concentration is above the renal threshold for reabsorption (~250-300 mg/dL). When concentrations are above this threshold, glucose spills into the urine, creating an osmotic gradient that pulls in excess body water. This contributes to the development of an obligatory polyuria that stimulates a compensatory polydipsia in an attempt to maintain adequate hydration. Additionally, when the insulin concentration is insufficient, nutrient uptake by tissues is impaired and insulin does not function in its physiologic role as a central regulator of satiety. Therefore, client-provided information about the presence or absence of polyuria, polydipsia, polyphagia, and weight loss is an essential component of each diabetic evaluation.

It should be determined at each visit whether the owner has noted signs of hypoglycemia (weakness, lethargy, tremors, collapse episodes, and/or seizures). Persistence of signs at home suggests the patient is unregulated, but the presence of these abnormalities does not provide insight as to the source of the glycemic dysregulation (i.e., excessive or insufficient insulin dose or inappropriate duration of action). Therefore, persistent clinical signs should be a catalyst for an assessment of the patient's insulin response before making changes to insulin therapy.

Serial Evaluation of Body Weight

An accurate BW should be recorded at each patient evaluation. Ideally, the BW would be obtained in a similar fashion (i.e., timing following meals, urination, or defecation) and on the same scale to maximize the accuracy of observed trends. Fluctuations in BW can provide useful insight into the patient's relative state of glycemic regulation, with weight gain suggesting glycemic control and unexpected weight loss suggesting unregulated DM.

Changes in BW need to be considered along with additional systemic factors such as the patient's daily caloric intake, active attempts at weight loss, and/or concurrent disease processes (e.g., hyperthyroidism or renal disease). An unintentional downward trend in BW should prompt further assessment of the patient's insulin response, especially when clinical signs are present. Weight gain in the face of otherwise poor clinical DM control may suggest the presence of acromegaly, especially if consistent clinical findings are present (e.g., organomegaly, changes to facial features).

Glycosylated Serum Proteins

Proteins in the bloodstream normally undergo nonenzymatic and permanent binding reactions with circulating carbohydrates. Therefore, glycosylated serum proteins are expected during euglycemia and established reference ranges exist for cats.

Fructosamine is the most commonly used glycosylated serum protein test, with normal concentrations in cats reported between approximately 150 to 350 µmol/L.[27] Serum fructosamine concentration has been correlated with the mean BG concentration during the 1 to 2 weeks before measurement.[28] An elevated serum fructosamine concentration suggests the patient has been persistently hyperglycemic, while low

concentrations imply prolonged periods of hypoglycemia (**TABLE 2**).

Factors affecting serum protein concentrations and protein turnover can affect fructosamine. In cats, conditions associated with reduced protein intake, protein-losing disorders, and hyperthyroidism have been shown to reduce measured fructosamine concentrations.[27,29] While the fructosamine concentration is often used initially to diagnose persistent hyperglycemia, in the monitoring phase of diabetic management it is simply another tool used to judge relative glycemic control.[28] It is important to remember that the measured result represents an average glucose level over time; therefore, short periods of hypoglycemia can occur without detection if there are prolonged bouts of hyperglycemia.

Urine Glucose Evaluation

Glucose appears in the urine once the threshold for renal tubular reabsorption is exceeded. The average renal tubular threshold for glucose is around 250 to 290 mg/dL in cats.[30] The urine glucose concentration reflects the total amount of glucose excreted into the urine since the previous micturition event. Therefore, periods of hypoglycemia are masked by bouts of hyperglycemia and excess urinary glucose spillage.

Most patients with clinically well-controlled diabetes (serum glucose between 100 and 300 mg/dL over the course of the day) are expected to have glucosuria. Therefore, urine monitoring may be most helpful in identifying persistent hypoglycemia or diabetic remission, as the cat should consistently test negative for urine glucose. Additionally, urine dipstick strips that detect ketones are useful for monitoring hyperglycemic patients at risk for developing ketoacidosis.

Table 2 General Interpretive Criteria for Fructosamine Concentrations (µmol/L)[a]

>450	Poor diabetic control
400-450	Fair diabetic control
300-400	Good diabetic control
<300	Tightly controlled, diabetic remission onset, or prolonged hypoglycemia

[a]The reference range of the individual laboratory should be used when interpreting patient results.

ASSESSMENT OF INSULIN RESPONSE

BG curve monitoring is typically initiated 7 to 14 days after starting insulin or adjusting the insulin dose. This allows a consistent glycemic response to the insulin dose to develop and optimizes the accuracy of assessment. Once the appropriate insulin dose is found and DM controlled, the frequency of glucose monitoring is typically extended to intervals ranging from 1 to 6 months.

In the authors' experience, most diabetic cats tend to fluctuate within a narrowed glycemic range over the course of the day, unlike dogs. However, the general aim of hyperglycemic treatment is to have a BG nadir of ~100 mg/dL, with an overall range during the curve period between 100 and 300 mg/dL. Treatment decisions are ideally made using a BG curve interpretation in conjunction with other factors such as the presence of clinical signs, changes in BW, or a fructosamine concentration.

Standard Blood Glucose Curve

Evaluating the glycemic response to a prescribed insulin dose involves obtaining serial BG readings before and then every 2 to 4 hours after insulin administration using a veterinary-calibrated handheld glucometer. Variables assessed by a BG curve include the pre-insulin BG concentration, onset of insulin action, maximum insulin response (BG nadir), duration of insulin action, and range of BG over the dosing interval. Since all aspects of a patient's insulin response are represented, this is the ideal monitoring tool to direct changes to insulin therapy. However, information should be interpreted in light of the factors discussed above.

Sampling Considerations

A veterinary-specific glucometer should be used, as those calibrated for people often underestimate veterinary patient BG concentrations.[31] A skin prick to obtain a capillary whole blood bleb is most commonly performed; however, the use of serum or plasma samples has been reported to result in less variability.[32] Peripheral body sites sampled in cats include the lateral aspect of the pinna, the pisiform pad, and the metacarpal/tarsal pads (**FIGURES 2 AND 3**).[33-36] The authors typically compare a BG reading from the selected sample site with a jugular venous BG reading to ensure relative accuracy before proceeding with long-term monitoring.

Consideration should be given to the pricking device (needle or spring-loaded lancet) used in cats, as lancets were less likely to be associated with causing a pain response in dogs (unpublished data).[a] Additionally, while warming a cat's ear before pricking may increase the likelihood of getting a sufficiently sized bleb, squeezing pricked sites increased the chance of obtaining an erroneous result compared with a simultaneously obtained jugular venous BG in dogs (unpublished data).

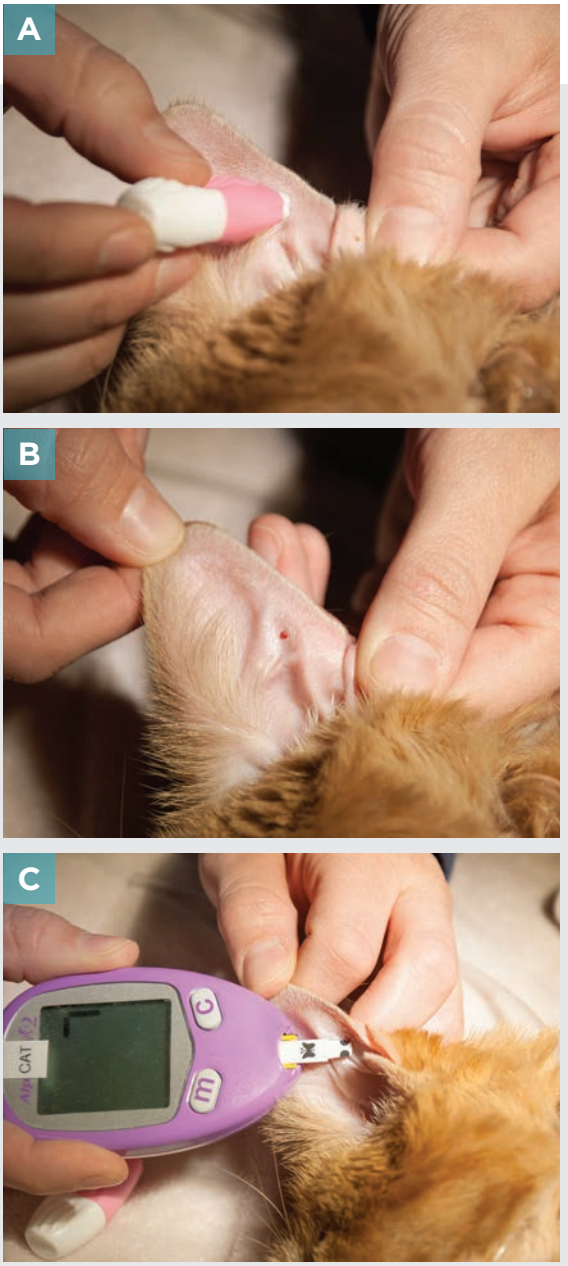

FIGURE 2. Glucose measurement using ear prick in a cat.

Home Monitoring

In-hospital BG curves have inherent flaws that can affect how results are interpreted. The stress associated with travel to the hospital, lack of acclimatization to a new environment, handling for repeated sampling, and/or disruption of normal daily activities can all affect glycemic regulation and curve results. This has led to most consensus recommendations suggesting the use of home monitoring in cats, where owners generate BG curves for veterinary interpretation.[7,37]

Although home monitoring minimizes the influence of some stressors, it can contribute to client anxiety and a strained human-animal bond if owners unnecessarily oversample their pet's BG.[38] Owners can also develop a false sense of confidence over time and may begin adjusting insulin doses without the direction of a veterinarian. So while at-home curves can be useful when done appropriately, a successful home monitoring program requires careful client-patient selection and exceptional client-veterinarian communication.

With a clearly defined monitoring protocol, clients are typically capable of performing curves and are overall satisfied with the home monitoring process.[38,39] Clear expectations and guidelines should be set for clients to follow and report back the necessary information required to manage their pet. Home monitoring does not mitigate the need for regular in-hospital evaluations, and clients have been shown to maintain continuity of in-hospital care for their cat while performing home monitoring.[39]

Role in Patient Management

Several studies have documented large day-to-day variability in BG curve results obtained in both hospital and home environments.[40,41] This highlights the fact that BG curves are only one tool in comprehensive diabetic patient assessment and should be interpreted concurrently with other clinical data (such as presence of clinical signs) to maximize accuracy of treatment recommendations. For most diabetic cats, the authors recommend intermittent glucose curve assessment and prefers home monitoring when appropriate. However,

[a]Bugbee A, Ward C. (2013). Validation of pediatric spring-loaded lancets to obtain capillary glucose readings at various body sites in healthy dogs.

glucose monitoring of any kind may be impractical in some cats (i.e., those that are fractious in-hospital and at home). Therefore, serial glucose monitoring may have to be replaced by a combination of other monitoring tools, such as clinical signs and fructosamine concentrations, to obtain information to guide therapeutic decision-making.

Continuous Interstitial Glucose Monitoring

The continuous interstitial glucose monitoring (CIGM) process involves implantation of a subcutaneous catheter (sensor) that facilitates measurement of the interstitial fluid (ISF) glucose concentration. The device uses glucose oxidase to produce an enzymatic reaction, which is converted into an electrical signal for measurement. The ISF glucose concentration has been shown to correlate with the BG concentration, although there is a 5- to 12-minute delay before acute changes in the BG are reflected in the ISF.[42,43] The device validated for use in cats (iPro2, Medtronics) samples ISF glucose every few seconds, and an external transmitter records readings every 5 minutes (equating to 288 readings per 24 hours). Thus, the greatest advantage of CIGM is in providing a huge amount of glycemic data obtained over 3 to 5 days with the patient in its home environment. The major disadvantages of the validated CIGM system are the requirement to obtain a minimum of 2 glucometer-derived BG readings per day for calibration purposes and a manufacturer-reported working range of only 40 to 400 mg/dL.

A novel flash glucose monitoring system (FreeStyle Libre, Abbot) uses a disposable sensor that can be worn for up to 14 days and measures ISF glucose every minute.[44] The reported working range is between 20 and 500 mg/dL, and the device is factory calibrated, thereby mitigating the need for any glucometer-derived calibrations. An external handheld reader containing a built-in glucometer system (FreeStyle Precision, Abbot) can be held up to the implanted sensor to digitally display a real-time glucose reading as well as trend historical results within a 15-minute period.[45] The accuracy and performance of this device have been validated for use in dogs, but there are only anecdotal reports of successful use in cats.[44] TVP

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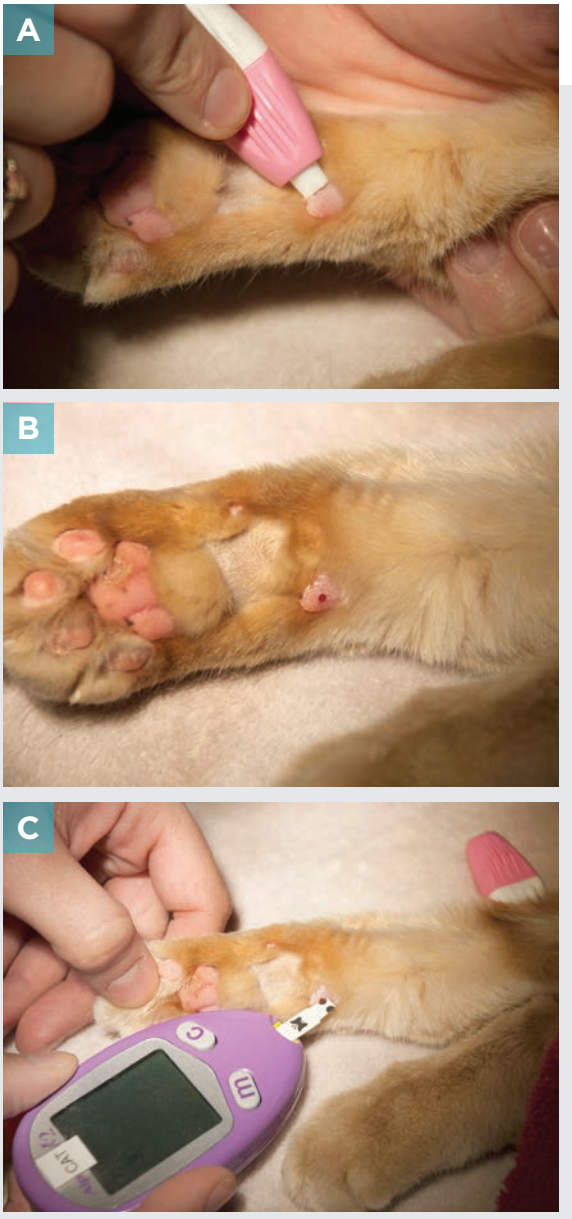

FIGURE 3. Glucose measurement using paw prick in a cat.

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Diagnosis and Management of Hypoadrenocorticism in Dogs

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Primary hypoadrenocorticism, also known as Addison's disease, is a syndrome caused by bilateral dysfunction of the adrenal cortices. The adrenal glands are located in the abdomen medial to the kidneys and are composed of the cortex (outer portion) and medulla (inner portion). Within the adrenal cortex are 3 distinct layers, which are responsible for production of different hormones. From the outermost to the innermost, these layers are the zona glomerulosa, zona fasciculata, and zona reticularis. Cells in these layers produce aldosterone, cortisol, and adrenal androgens, respectively.

Hypoadrenocorticism is primarily a disease of dogs and occurs only rarely in cats. This condition is heritable and most commonly affects dogs of 4 breeds: standard poodles,[1] Portuguese water dogs,[2] Nova Scotia duck tolling retrievers,[3] and bearded collies. Other commonly affected breeds include West Highland white terriers,[4,5] Great Pyrenees,[6] and wheaten terriers.[4,5] Although the most common cause is thought to be immune-mediated adrenalitis,[7] in the absence of a definitive diagnosis, most hypoadrenocorticism is classified as idiopathic. However, it can also occur secondary to other disorders that result in bilateral adrenal gland destruction (e.g., amyloidosis, hemorrhage, and neoplasia).[4] A recent report described hypoadrenocorticism secondary to intravascular lymphoma in a 2-year-old German shepherd.[8]

Most cases of hypoadrenocorticism represent a deficiency of glucocorticoids (primarily cortisol) and mineralocorticoids (primarily aldosterone), but other manifestations can occur. Atypical Addison's disease causes signs of isolated glucocorticoid deficiency. Some affected dogs are in very poor condition and considered to be experiencing an addisonian crisis. In addition to the more commonly reported gastrointestinal signs that may be evident from a thorough history, dogs experiencing an addisonian crisis are in hypovolemic shock and may have collapsed. In this article, we describe the diagnosis and management of these manifestations of hypoadrenocorticism.

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PRESENTATION

The clinical signs of hypoadrenocorticism can vary along a continuum of severity and chronicity (**BOX 1**). Because glucocorticoids help counteract the effects of stress and maintain normal gastrointestinal mucosal integrity and function, many dogs with glucocorticoid deficiency initially display waxing and waning nonspecific signs such as episodic vomiting, diarrhea, melena (**FIGURE 1**), lethargy, and dehydration. These dogs may respond well to supportive care;[9] thus, underlying hypoadrenocorticism can initially go undiagnosed.

However, when mineralocorticoid deficiency accompanies glucocorticoid deficiency, clinical signs can become more severe. Aldosterone stimulates sodium, chloride, and water retention along with potassium excretion in the distal renal tubules; therefore, lack of aldosterone results in hypochloremia, hypovolemia, acidosis, and hyperkalemia.[10]

In patients with atypical Addison's disease, clinical signs result from cortisol deficiency alone.

Among patients experiencing addisonian crisis, some have previously received treatment for nonspecific signs; others have not because they displayed no clinical signs.

DIAGNOSTICS

For any dog suspected to have hypoadrenocorticism, an excellent screening test is resting cortisol levels. This test is sensitive in that if the resting cortisol level is greater than 2.0 mcg/dL, for almost all dogs you can rule out hypoadrenocorticism. However, a low resting cortisol level alone can be normal for some dogs and thus a definitive diagnosis requires further testing. Classic bloodwork abnormalities associated with hypoadrenocorticism are hyperkalemia, hyponatremia, and lack of a stress leukogram.[4]

BOX 1 Classic and Potential Clinical Signs of Hypoadrenocorticism

- Decreased appetite
- Vomiting, hematemesis
- Diarrhea, melena
- Lethargy or decreased willingness to exercise

FIGURE 1. Melena is common in dogs with hypoadrenocorticism, although because of ileus, it may not be obvious until after the dog has been hospitalized for 2 to 3 days. It is often present when packed cell volume drops precipitously after an addisonian crisis but no other cause for the drop can be found.

Serum Chemistry

In a dog with compatible history and clinical signs, a sodium:potassium ratio of less than 27 should prompt definitive testing. Be aware that low sodium:potassium ratios can occur in dogs with other conditions (e.g., renal failure,[11] trichuriasis,[12] pregnancy,[13] and body cavity effusions[11]) (**BOX 2**).

Additional abnormalities on serum biochemistry panels can include azotemia, hypoalbuminemia, hypocholesteremia, hypoglycemia, hypercalcemia, and elevated liver enzyme levels (**BOX 3**). Most patients do not have all of these abnormalities but instead may have a few that are severe (e.g., hypoglycemia and/or azotemia). Most dogs with hypoadrenocorticism show

BOX 2 Differential Diagnoses Other Than Hypoadrenocorticism for Low Sodium:Potassium Ratio

Digestive system

- Acute kidney injury (anuria or oliguria)
- Trichuriasis
- Cavitary effusions (e.g., chylothorax)
- Pregnancy and periparturient illness
- Receipt of angiotensin-converting enzyme drug

vague symptoms that can prompt investigation of other body systems, including the gastrointestinal tract and kidneys. The laboratory findings for dogs with hypoadrenocorticism are similar to those of acute kidney injury (e.g., azotemia, electrolyte changes, and isosthenuria); thus, hypoadrenocorticism should always be a major differential diagnosis for dogs with these laboratory findings.

In dogs with atypical Addison's disease, electrolyte derangements are absent; hence, we rely on the signs of hypocortisolism (e.g., vomiting, diarrhea, melena, lethargy) to raise suspicion and prompt testing. One study suggested that aldosterone levels in patients with atypical Addison's disease are low;[14] it is unclear as to why patients with atypical Addison's disease do not have electrolyte abnormalities.

Complete Blood Count

Along with clues from the serum biochemistry, a normal lymphocyte count may further raise suspicion for hypoadrenocorticism because a dog ill from another cause should have lymphopenia secondary to cortisol release (stress leukogram).[4] One study found that for all dogs with hypoadrenocorticism, lymphocyte counts were greater than 750/mcL; thus, for dogs with fewer than 750 lymphocytes/mcL (and no previous receipt of glucocorticoids), hypoadrenocorticism is unlikely.[15]

BOX 3 Common Clinicopathologic Abnormalities in Dogs With Hypoadrenocorticism

- Hyperkalemia
- Hyponatremia
- Hypochloremia
- Acidosis
- Azotemia
- Hypoglycemia
- Increased alanine and aspartate aminotransferase levels
- Hypercalcemia
- Hypoalbuminemia
- Hypocholesterolemia
- Anemia
- Eosinophilia
- Lack of stress leukogram

BOX 4 Procedure for Performing ACTH Stimulation Test[18]

1. Collect a blood sample into a red top tube.
2. Administer 5 mcg/kg of synthetic ACTH IV (up to a maximum of 250 mcg/dog). Avoid use of compounded formulations.
3. After 60 minutes, collect a second blood sample.
4. Submit both serum samples for cortisol measurement.

In addition to not showing a stress leukogram, dogs with hypoadrenocorticism can be mildly to severely anemic. Severe anemia is often accompanied by melena and/or hematochezia, caused by gastrointestinal bleeding resulting from increased vascular permeability in the absence of cortisol. The packed cell volume (PCV) in patients in addisonian crisis may initially be within reference range or mildly decreased but 1 to 2 days later severely decreased after rehydration and further blood loss. Because of ileus, which is common in dogs with hypoadrenocorticism, melena may not be apparent for 2 to 3 days.

Imaging

Diagnostic imaging is not typically required for the diagnosis of hypoadrenocorticism. However, because of the nonspecific signs of this disease, thoracic and abdominal imaging are often included in the diagnostic workup of these patients. Some ultrasonographic and radiographic signs can be helpful. As you might expect, ultrasonography has shown that the adrenal glands are shorter and thinner in affected dogs than in those of their unaffected counterparts.[16] Radiographs may indicate hypovolemia (e.g., small heart and liver and decreased diameter of the cranial lobar pulmonary artery and caudal vena cava).[17]

Definitive Diagnosis

To confirm hypoadrenocorticism, an adrenocorticotropic hormone (ACTH) stimulation test (**BOX 4**) must be performed. This test is performed by

measuring serum cortisol concentrations before and 1 hour after administration of synthetic ACTH. Use of synthetic cosyntropin at 5 mcg/kg, compared with the previously used dose of 250 mcg/dog, helps reduce the costs associated with testing.[18] In addition, reconstituted cosyntropin can be stored in plastic (not glass) syringes and frozen for up to 6 months without affecting efficacy,[19] making it more cost-effective for practitioners who would otherwise not use an entire vial before effectiveness is affected. A definitive diagnosis of hypoadrenocorticism can be made when post-ACTH cortisol levels are less than or equal to 2 mcg/dL. A recent study evaluated dogs that were suspected of having hypoadrenocorticism but had higher cortisol concentrations (up to 10 mcg/dL) after ACTH stimulation testing.[20] For these dogs, hypoadrenocorticism was ruled out for the following reasons: another disease (inflammatory bowel disease) was diagnosed, they did not respond to glucocorticoid administration, or signs of hypoadrenocorticism did not return after discontinuation of glucocorticoids. In our experience, rare patients with confirmed hypoadrenocorticism may have post-ACTH stimulation cortisol results of 2 to 3 mcg/dL.

TREATMENT

Some patients exhibit chronic clinical signs only; others, however, experience a life-threatening addisonian crisis, requiring acute stabilization and intensive therapy. The rest of the patients lie somewhere in between; although their condition is not immediately life-threatening, they may require fluid therapy and other supportive care in addition to steroid supplementation.

Chronic Disease

For most hypoadrenocorticism patients who are clinically stable, treatment consists of supplementation with a mineralocorticoid and a glucocorticoid.

Mineralocorticoids

Mineralocorticoid supplementation is available in 2 forms: daily oral (fludrocortisone) and monthly injection (desoxycorticosterone pivalate [DOCP]).

Fludrocortisone: Fludrocortisone acetate (0.01 mg/kg PO q12h) possesses both glucocorticoid and mineralocorticoid activity.[21] Although the dual functions may seem like a benefit, they can make it more difficult to titrate the drug to an acceptable dosage. For example, an increase in fludrocortisone dose may be necessary to keep sodium and potassium within normal parameters, but this increased dose may result in a higher than necessary glucocorticoid effect and precipitate undesirable consequences of hypercortisolemia.

DOCP: Because DOCP has only mineralocorticoid activity, concurrent glucocorticoid (e.g., prednisone) supplementation is always necessary. However, many clinicians prefer DOCP because of its efficacy and the ability to adjust glucocorticoid supplementation independently. In addition, DOCP is more likely than fludrocortisone to normalize renin activity, suggesting that DOCP is a more effective mineralocorticoid supplement for dogs with hypoadrenocorticism.[16] Two formulations of DOCP are available: Percorten-V (Elanco, elanco.com) and Zycortal (Dechra Pharmaceuticals, dechra.com). The U.S. Food and Drug Administration–approved label for each formulation recommends an initial dose of 2.2 mg/kg[22,23] every 25 days. However, 1 publication documents using lower doses,[24] and we often begin treatment with a dose of 1.5 mg/kg. Zycortal is labeled for SC administration; Percorten-V is labeled for IM administration only but can also be given SC[25] off-label.

After the initial dose of DOCP is given, electrolytes should be checked at 14 days to assess the dosage and at 25 days to assess the dosing interval. At 14 days, if hyponatremia or hyperkalemia is present, increase the next dose (at 25 to 28 days) by 10% to 15%; if hypernatremia or hypokalemia is present, decrease the next dose by 10% to 15%. At 25 days, if hyponatremia or hyperkalemia is present, decrease the dosing interval by 1 to 2 days. If electrolytes are within reference range, to make the dosing interval more convenient for the client we often extend the dosing interval to 28 days, at which time we confirm that the electrolytes are within reference range. One study demonstrated that the dosing interval can be extended as long as 90 days, but this study used a dose of 2.2 mg/kg and initially required up to weekly electrolyte assessments to determine the optimal dosing interval.[26] We prefer to adjust the dose rather than extend the dosing interval beyond 28 to 30 days, and we do not recommend adjusting both dose and dosing interval. After the optimal dose and interval are determined, most clients can be taught to give DOCP at home.

Glucocorticoids

All patients receiving DOCP must receive supplemental glucocorticoids. Some patients receiving fludrocortisone do not require additional prednisone long-term, but these patients seem to stabilize more quickly when additional glucocorticoid is given initially and then tapered after stabilization.[27]

For glucocorticoid replacement, oral prednisone at a starting dose of 0.5 to 1.0 mg/kg/day is usually recommended. This dose should be gradually lowered (over several weeks) to an optimal dose that controls signs of hypoadrenocorticism and avoids side effects (e.g., polyuria, polydipsia, polyphagia, panting). Larger dogs seem to be more sensitive to the side effects of glucocorticoids. Although published maintenance doses are usually 0.1 to 0.22 mg/kg/day,[4] we have managed a number of patients with lower doses (as low as 0.03 mg/kg/day). Dosage adjustments should be based on clinical signs only; for dogs with confirmed naturally occurring hypoadrenocorticism, an ACTH stimulation test should not be repeated for monitoring purposes.

Atypical Addison's Disease

Because dogs with atypical Addison's disease have signs of glucocorticoid deficiency only, they require glucocorticoid supplementation only, administered according to the guidelines described above. For some of these dogs, electrolyte abnormalities may eventually develop and require mineralocorticoid supplementation. Rechecking electrolytes is recommended 2 weeks after diagnosis, then every month for 3 months, then every 3 months for 1 year.

FIGURE 2. Administration of IV fluids is imperative for a dog experiencing an addisonian crisis. ECG and blood pressure are monitored to look for indications of hyperkalemia and to determine response to therapy.

Addisonian Crisis

Dogs experiencing addisonian crisis may have arrhythmias and/or bradycardia as a result of hyperkalemia and require treatment specifically targeted at correcting the hyperkalemia. Hypoglycemia has been reported in up to 38% of dogs with hypoadrenocorticism,[9] so insulin therapy for treatment of hyperkalemia should be withheld until normal blood glucose levels are confirmed. If severe enough, hypoglycemia may lead to seizures.[2] Dogs experiencing addisonian crisis often have moderate to severe prerenal azotemia.

Prompt recognition or suspicion of an addisonian crisis and subsequent treatment (**BOX 5**) are paramount to a successful outcome. Fluid resuscitation (**FIGURE 2**) is of utmost importance and will address hypovolemia, hypotension, metabolic acidosis, and hyperkalemia.[31] The latest recommendation is to give a balanced crystalloid solution (e.g., Plasmalyte 148, lactated Ringer's, or Normosol-R).[32] The previous recommendation was to give 0.9% sodium chloride. However, neurologic signs in dogs receiving treatment for addisonian crises are thought to be the result of myelinolysis secondary to rapid correction of hyponatremia;[33,34] this concern, however, is valid only if the hyponatremia is chronic. When the patient's sodium concentration is less than 120 mEq/L, we monitor sodium concentrations more often and may use a fluid with a lower sodium concentration than lactated Ringer's solution. Sodium concentration should not be increased by more than 12 mEq/L every 24 hours.[34] In addition, balanced crystalloids are more alkalinizing than sodium chloride. Fluid resuscitation should be performed with boluses of 20 to 30 mL/kg over 15 to 20 minutes; after administration of each bolus, vital signs (heart rate, pulse quality, and blood pressure) should be reassessed. Fluid resuscitation is considered complete when vital signs have returned to reference range. Lactate levels can also be used as an objective measure.

After the patient has received appropriate fluid resuscitation, IV dexamethasone can be administered. Dexamethasone does not interfere with results of a subsequent ACTH stimulation test because it is not detected by the cortisol assay, whereas prednisone, prednisolone, and methylprednisolone are. The patient should remain hospitalized and receiving IV fluids until electrolyte abnormalities are stabilized and any clinical abnormalities are controlled with oral medications. Among these oral medications will be prednisone. In the acute phase immediately after recovery from crisis,

BOX 5 Treatment of Addisonian Crisis

Correct the following:

- **Hypovolemia and hypotension**
  - Balanced crystalloids, 20 to 30 mL/kg; reassess and repeat if necessary.
- **Acidosis**
  - IV fluid therapy is almost always adequate.
- **Hyperkalemia**
  - Fluids are usually adequate unless severe (>8.5 to 9.0 mEq/L) or ECG derangements (bradycardia, spiked T waves, flattened to absent P wave, widened QRS complexes) are present.

  ECG derangements/severe hyperkalemia
  - Calcium gluconate, 10% solution: 0.5 to 1.5 mL/kg over 10 to 15 minutes. Watch ECG for worsening bradycardia as a side effect. Will stabilize the heart but does not treat hyperkalemia directly.
  - Dextrose, 1 mL/kg 50% dextrose, diluted 1:3 with balanced crystalloids[28]
  - R insulin, 0.2 U/kg, followed by a bolus of 1 to 2 g dextrose/unit of insulin, then dextrose added to balanced crystalloids to make a 2.5% to 5.0% solution of dextrose
  - Dogs with life-threatening arrhythmias should receive insulin. Dextrose alone will help decrease the potassium concentration by causing endogenous insulin release, but this takes more time.
  - Alpha-2 agonists (e.g., inhaled albuterol or IV terbutaline at 0.01 mg/kg[29])
- **Hypoglycemia**
  - 1 mL/kg 50% dextrose, diluted 1:2 with balanced crystalloid
- **Severe anemia from gastrointestinal blood loss**
  - Packed red blood cell transfusion
- **Glucocorticoid deficiency**
  - Dexamethasone, 0.2 mg/kg IV initially, then 0.1 mg/kg q12h until oral prednisone is tolerated. CAN be given before obtaining samples for ACTH stimulation test

  OR

  - Hydrocortisone sodium succinate, 0.5 to 0.625 mg/kg/hr.[30] CANNOT be given before obtaining samples for ACTH stimulation test.
- **Supportive therapy**
  - Warming measures if patient is hypothermic
  - Anti-emetics
  - Gastroprotectants
  - Pain management
  - Nutrition (patients are usually eating within 24 hours)

we usually give 0.5 to 1.0 mg/kg/day. As the dog transitions to at-home care, the dose should be gradually lowered over a few weeks. Mineralocorticoid supplementation with DOCP or fludrocortisone is usually postponed until the diagnosis of hypoadrenocorticism is confirmed. Future dosing will need to be based on laboratory results, particularly electrolyte concentrations, and clinical signs.

PROGNOSIS

For dogs with properly diagnosed hypoadrenocorticism, the prognosis and quality of life are good (**FIGURE 3**); most of these dogs die of something unrelated to hypoadrenocorticism. One study encompassing 205 dogs revealed a median survival time of 4.7 years with no significant effect resulting from factors such as age, breed, sex, or weight.[35] However, clients must be well aware of subtle signs of illness and committed to daily medication and regular rechecks for the rest of the dog's life. With proper treatment and regular veterinary follow-up, dogs with hypoadrenocorticism can lead a long and healthy life. TVP

FIGURE 3. This golden retriever exhibited nonspecific lethargy and gastrointestinal signs after a new (human) baby joined the household. He was 2 years old at the time of diagnosis and is thriving 8 years later. He receives 1.3 mg/kg of DOCP q30d and 0.03 mg/kg prednisone/day. Dogs with hypoadrenocorticism typically have a great quality of life as long as the clients are diligent about maintaining an appropriate medication and monitoring schedule.

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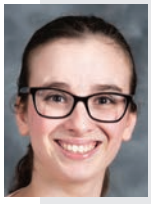

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Treatment of Pituitary-Dependent Hyperadrenocorticism

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Pituitary-dependent hyperadrenocorticism (PDH) is the most common cause of spontaneous Cushing's syndrome in dogs. It is the result of the inappropriate secretion of adrenocorticotropic hormone (ACTH) by a pituitary adenoma.

Currently, the vast majority of dogs with PDH are managed medically. This approach does not address the underlying pathology (i.e., the pituitary tumor), but it mitigates the clinical manifestations of the disease and reduces patient morbidity from complications associated with hyperadrenocorticism (HAC). Lifelong therapy is necessary to maintain wellness, and owners need to commit to regular monitoring and diligent follow-up. Although medical therapy for PDH has not been consistently shown to improve longevity, most practitioners feel that quality of life for both patient and owner is substantially improved when the disease is successfully managed.[1]

TREATMENT OPTIONS

In people, PDH is routinely cured by excision of the adenoma using a minimally invasive endoscopic approach through the nose. This methodology is not technically possible in dogs, but a small number of institutions now offer hypophysectomy using a transsphenoidal approach. Long-term outcomes are positive, with a greater than 75% survival at 2 years, although the cost of surgery is substantial and treated dogs need lifelong hormone supplementation (prednisone, thyroxine, +/– desmopressin).[2]

Radiotherapy is also an option for canine patients, but it may require multiple anesthetic events (depending on the method and protocol selected) and complete reversal of hypercortisolemia is unusual. It is hard to compare survival rates between hypophysectomy and radiation therapy, as patient selection criteria likely bias the results. In addition, outcomes with radiation appear to be influenced by the method selected. A cohort of 12 dogs with PDH receiving 10 fractions of 3.8 Gy over 4 weeks achieved a median survival

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time of 961 days (range, 28 to 1328 days)[3]; in contrast, 29 dogs receiving stereotactic radiotherapy (one 15-Gy fraction or three 8-Gy fractions) had a median survival time of just 245 days.[4]

Several medical therapies have been used in dogs with PDH, including mitotane (o,p'-DDD; Lysodren®; bms.com), L-deprenyl (selegiline; Anipryl®; zoetisus.com), ketoconazole, and trilostane (Vetoryl®; dechra-us.com). Many clinicians feel that L-deprenyl and ketoconazole have limited impact on adrenal function, and these drugs are not widely used. Mitotane is a chemotherapeutic agent and is directly toxic to adrenal tissue; the dose must therefore be carefully titrated to avoid complete adrenal necrosis. Although mitotane can provide excellent control of HAC, practitioners should familiarize themselves with published protocols or consult with an internist when using this drug. It is not licensed for use in dogs, and owners should be provided with appropriate written guidelines regarding handling and use. Trilostane was FDA approved for treatment of both pituitary- and adrenal-dependent HAC in dogs in 2008 and is now the first choice of most practitioners.

TRILOSTANE

Background

Trilostane is a synthetic steroid analogue. It is a competitive inhibitor of 3-β hydroxysteroid dehydrogenase (3-β HSD), which plays a crucial role in the production of several adrenal cortical hormones. Therapeutic concentrations of trilostane therefore limit the production of cortisol. Although the production pathway for aldosterone also depends on 3-β HSD,

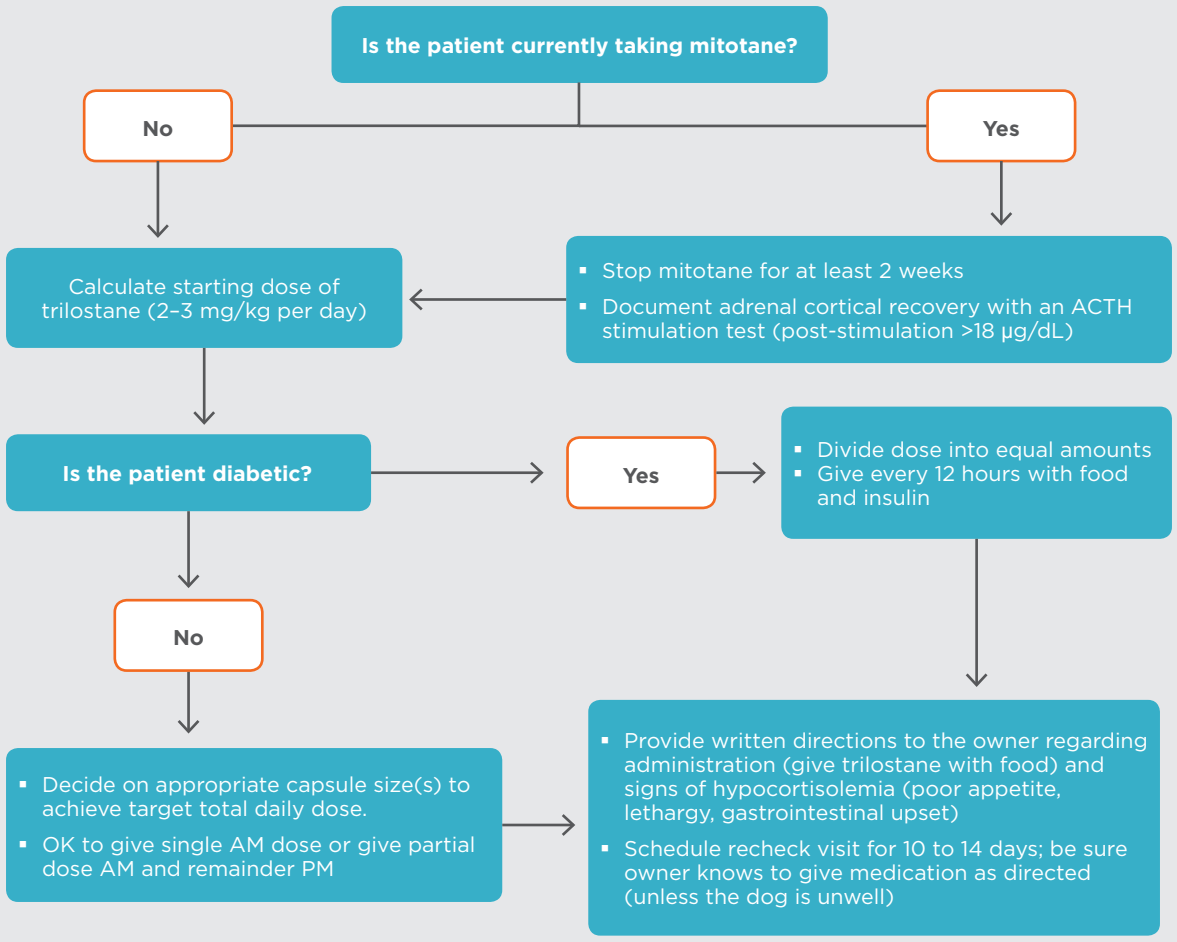

FIGURE 1. Algorithm for starting trilostane.

trilostane's effects on aldosterone are usually modest.[5] Evidence indicates that trilostane also promotes the intracellular conversion of cortisol to cortisone, which has no biologic activity.[6] This limits activation of the glucocorticoid receptor and its downstream effects. Because of trilostane's mechanism of action, its effects are reversible and dose dependent.

Trilostane is administered orally. Peak plasma levels occur about 2 hours after ingestion. Absorption appears to be somewhat erratic, and administration with food is recommended. The drug undergoes hepatic metabolism; clearance time varies, but is generally within 18 hours.[7]

The manufacturer states that trilostane should not be used in dogs with renal or hepatic compromise and should be avoided in animals intended for breeding.[8] The caveats regarding renal and hepatic disease reflect the fact that trilostane has not been specifically evaluated in these patient populations; however, the author routinely uses trilostane in dogs with stage 1 or 2 chronic kidney disease or stable hepatic disease. The drug should be used with caution in anemic patients. Dogs with a history of congestive heart failure and those on drugs such as spironolactone and angiotensin-converting enzyme inhibitors may be prone to hyperkalemia. Trilostane should therefore be used cautiously in these patients, with close monitoring of serum electrolytes.

Starting Therapy

The package insert for the FDA-approved product Vetoryl® recommends a starting dose of 2.2 to 6.7 mg/kg, given once daily. However, most practitioners start with a lower dose and many routinely recommend twice-daily therapy. Giving trilostane every 12 hours may hasten the achievement of target post-ACTH stimulation results (2 weeks versus 12 weeks) but has not been shown to improve clinical responses.[9] In the author's practice, most patients are started on a total daily dose of 2 to 3 mg/kg, given with food in the morning (**FIGURE 1**). In dogs with diabetes mellitus, the dose is divided evenly for twice-daily administration so that day- and nighttime cortisol levels and insulin responsiveness are well balanced. It is acceptable to round down to the nearest appropriate capsule size. There is no urgency to reverse HAC, and a cautious approach is usually appropriate.

Although mitotane can provide excellent control of HAC, practitioners should familiarize themselves with published protocols or consult with an internist when using this drug.

Owners need to understand the signs of hypocortisolemia, namely hyporexia, weakness, lethargy, vomiting, and diarrhea. If any of these are noted, they should withhold trilostane and seek veterinary advice. Particularly anxious owners can be dispensed a small supply of prednisone (0.5 mg/kg); this will reverse signs related to low cortisol within an hour. If signs of hypocortisolism do not improve rapidly following prednisone administration, the dog should be promptly evaluated by a veterinarian.

Conditions related to HAC such as clinically significant hypertension, infection, and substantial proteinuria should be addressed concurrently; it is not appropriate to simply wait and see what effect trilostane may have on these comorbidities. If a dog with evidence of HAC is found to be diabetic, insulin therapy should be initiated immediately to prevent diabetic ketoacidosis. Managing dogs with concurrent diabetes mellitus and HAC can be challenging, and consultation with a specialist may be helpful.

Monitoring Therapy

As the response to trilostane is variable, the dose needs to be adjusted on a case-by-case basis. The patient needs just enough cortisol to maintain wellbeing, but enough adrenal suppression to minimize clinical signs (e.g., thirst, urination, hunger) and complications (infection, thromboembolism, proteinuria) associated with uncontrolled HAC.

Frequency and Parameters

Dogs should be evaluated 10 to 14 days after starting trilostane, 1 month later, and then every 4 to 6 months. In addition, an evaluation is indicated any time the dog is not feeling well or if the owner notices signs of HAC.

BOX 1 Questionnaire: Owner Perception of the Effectiveness of Trilostane Therapy[a,b]

Please rate your dog's behavior/appearance for the past 4 weeks in the following categories.

QUESTION	SCORE
1. Drinking. Do you think your dog has drunk:	
Less than normal	PI
Normal	1
More than is normal (e.g., 1 or 2 times normal)	3
Very much more than is normal	4
2. Urinating. Do you think that the volume or frequency of urination is:	
Less than normal	PI
Normal	1
More than is normal (e.g., 1 or 2 times normal)	3
Very much more than is normal	4
3. Appetite. Would you describe your dog's appetite as:	
Very poor (not eating at all or hardly eating)	PI
Poor (does eat some food but requires encouragement)	PI
Normal	1
Increased (eats all food quickly and will look for more)	3
Greatly increased (seems ravenously hungry all the time)	4
4. Vomiting and diarrhea. How often has your dog had sickness and diarrhea?	
Never had sickness or diarrhea	0
Has had sickness or diarrhea once	0
Has had sickness or diarrhea more than once but not every day	PI
Has had sickness or diarrhea every day	PI
5. Exercise. How active is your dog?	
Lies in one place nearly all of the time	4/PI
Goes for walks and will also play on occasions	3
Very active, happy to run off-leash but does get tired	2
I cannot tire my dog out!	1
6. Skin and coat. How would you describe your dog's coat and skin condition?	
Very poor (e.g., thin coat, bald patches, very dull)	4
Poor (e.g., slightly thin coat, hairs dull)	3
Reasonable (e.g., no bald patches, slightly dull)	2
Very good (e.g., thick coat, shiny, no dandruff)	1
7. Other problems. Does your dog have any of the following?	
Trembling/shaking/muscle twitches more than once a week	PI
Persistent panting even at rest	3
Pain (anywhere)	PI
Difficulty moving	PI
Mental depression	PI
8. General. How do you feel your pet enjoys life?	
Miserable most of the time	PI
Has more bad days than good days	0
Happy most of the time; occasional bad days	0
Happy all of the time	0
9. Overall. How good do you feel your dog's current treatment for Cushing's is?	
My dog has more clinical signs than before treatment	5/PI
There is no difference now than before treatment	4
There is some improvement since starting treatment	3
My dog is nearly back to his/her normal self	2
If I did not know, I would think there was nothing wrong with my dog now	1

PI=possible illness.
[a] Dog is classified as unwell and is NOT scored if PI is selected 3 or more times.
[b] Adapted from: Macfarlane L, Parkin T, Ramsey I. Pre-trilostane and 3-hour post-trilostane cortisol to monitor trilostane therapy in dogs. Vet Rec *2016;179(23):597.*

Unless the dog is feeling unwell, trilostane should be given the morning of the appointment, which should be timed so that an ACTH stimulation test (if indicated) can be started 4 hours after dosing. Some sources suggest starting the stimulation test 3 hours post dose; the package insert recommends 4 to 6 hours. The objective is to assess adrenal functional capacity at the time the trilostane is likely to be maximally effective.

Each recheck visit should include a detailed history, as this information is key to making appropriate dose adjustments. A team from the United Kingdom recently created a "score sheet" for dogs on trilostane (**BOX 1**); this sheet is routinely used in the author's practice.[10] A thorough physical examination, paying close attention to the haircoat, condition of the skin, and liver size, is also important. It may take up to 6 months to see a resolution of the changes associated with HAC, but some improvement should be noted within 6 to 8 weeks. Persistent physical examination findings suggesting continued hypercortisolemia support a dose increase.

Ideally, every recheck visit would include a blood chemistry panel with electrolytes. This can be omitted if the dose of trilostane has not changed and the dog is doing well clinically. However, a blood chemistry and serum electrolyte concentration analysis is essential after a dose increase and any time the dog is ill, to identify evidence of hypoaldosteronism (hyperkalemia, hyponatremia, azotemia).

Assessing Response to Therapy

Consensus about how best to assess the effect of the current dose of trilostane is limited. The manufacturer recommends that dose adjustments be made on the basis of post-ACTH stimulation cortisol concentrations, measured 4 to 6 hours after trilostane administration, with a target range of 1.45 to 5.4 µg/dL (40 to 150 nmol/L). A post-ACTH cortisol concentration between 5.4 and 9.1 µg/dL (150 to 250 nmol/L) is acceptable if the clinical signs are controlled, but otherwise merits a dose increase.

It is clear that a markedly blunted response to exogenous ACTH indicates profound suppression of cortisol production, and ACTH stimulation is the diagnostic test of choice if clinical signs of hypoadrenocorticism are noted. What is less clear is how well post-ACTH cortisol values reflect control of HAC in dogs without signs of hypocortisolemia and what the ideal post-ACTH cortisol concentration should be. A 2015 report described 13 dogs with PDH on twice-daily trilostane; all were clinically normal despite post-ACTH cortisol concentrations <2 µg/dL (55 nmol/L) obtained 4 hours after trilostane administration. These dogs had substantially higher cortisol concentrations when retested 9 to 12 hours after trilostane administration (mean, 5.3 µg/dL [146 nmol/L]) and were successfully maintained on the same dose for extended periods.[11]

Other reports have evaluated a single baseline cortisol measurement, collected at a fixed time after trilostane administration or immediately before a dose. Monitoring methods that do not rely on an ACTH stimulation test would be advantageous, given issues with the cost and availability of synthetic ACTH.

In a report published in 2010, the author looked at repeated ACTH stimulation tests in 103 dogs on once-daily trilostane; these findings suggested that measuring baseline cortisol concentration in a sample collected 4 to 6 hours post dose could be used to monitor response to therapy.[12] It is important to note that "response to therapy" was determined by post-ACTH cortisol concentrations; clinical signs were not evaluated in this study. A resting cortisol value ≥1.3 µg/dL (35 nmol/L) was used to reliably exclude excessive suppression (defined by a post-ACTH cortisol concentration of <1.5 µg/dL [40 nmol/L]), and a value ≤2.9 µg/dL (80 nmol/L) excluded grossly inadequate control (defined by post-ACTH cortisol concentration >9.1 µg/dL [250 nmol/L]). However, a 2013 study of 40 dogs on once-daily trilostane therapy found substantial overlap between baseline cortisol concentrations in dogs with excessive, adequate, and inadequate (defined by post-ACTH stimulation of >5.4 µg/dL [150 nmol/L]) control of HAC and concluded that the baseline value had limited clinical use.[13]

In a 2016 study, owner perceptions of control (determined using the score sheet in **BOX 1**) were correlated with various objective measurements of adrenal function. Interestingly, 3-hour post-trilostane cortisol concentrations were better correlated to owner scores than ACTH stimulation results.[10] Most of the 67 dogs in this study were on once-daily therapy, and a 3-hour post-trilostane cortisol concentration <2.3 µg/dL (62 nmol/L) was predictive of excellent control. This study also looked at pre-trilostane cortisol concentrations and found that a value of 1.5 to 5 µg/dL (40 to 140 nmol/L) correlated well with owner perceptions of effective control.[10] This novel

monitoring tool may prove to be very useful moving forward, although further studies looking at larger cohorts of dogs on both once-daily and twice-daily therapy are needed. A monitoring approach based on a single cortisol measurement (either before or 4 hours after trilostane administration) is outlined in **FIGURE 2**.

Owner Observations

It is interesting to note the disconnect between owners' reports on the efficacy of trilostane and patients' ACTH stimulation test results described in various studies.[10,13] Trilostane has complex effects on the intracellular handling of cortisol, so circulating levels

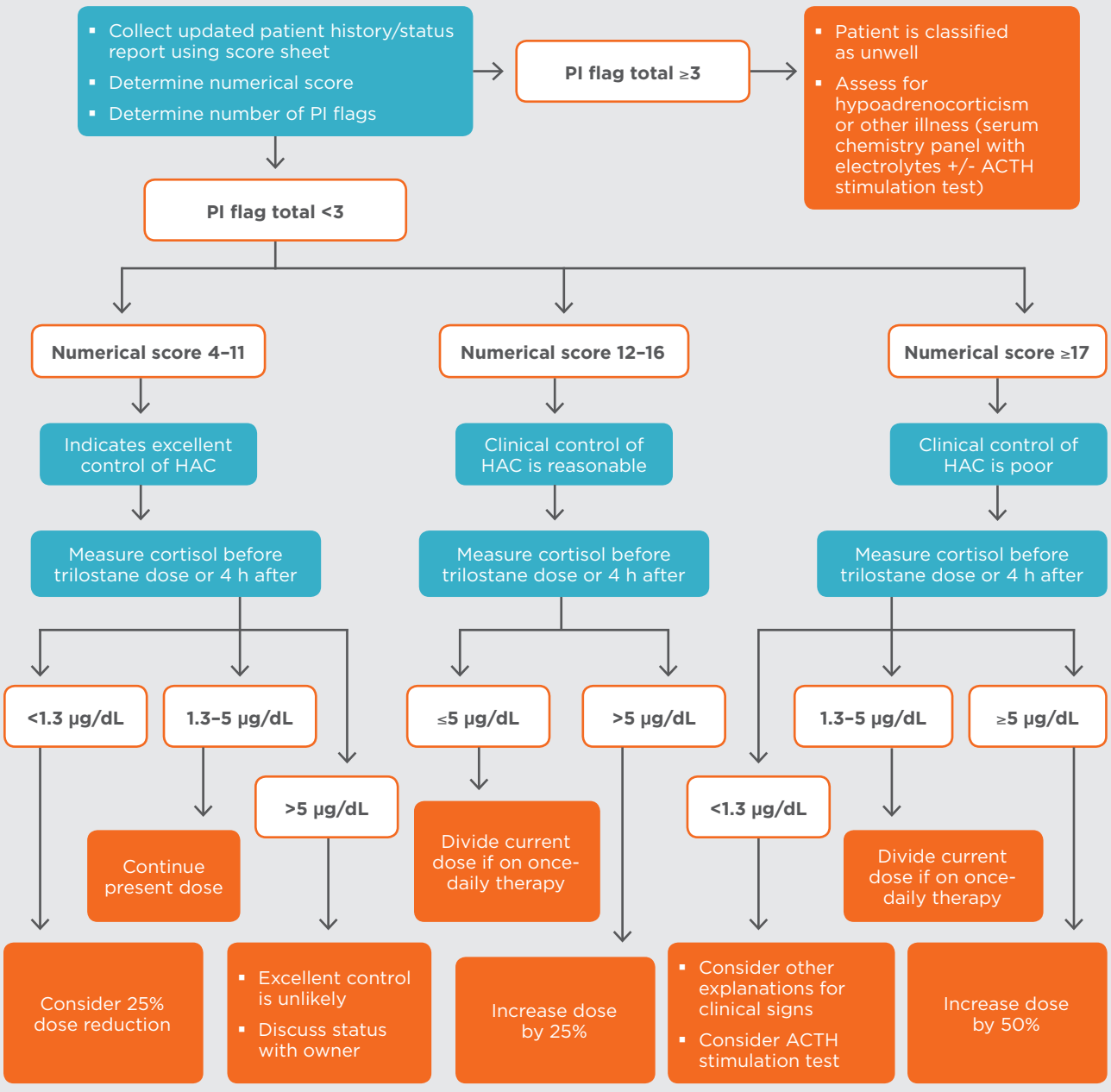

FIGURE 2. Algorithm for monitoring patients on trilostane. Numerical scores are calculated using the owner questionnaire in **BOX 1**. Note that cutoff values for cortisol are based on measurements made before or 4 hours after trilostane administration, not after ACTH stimulation.
PI=possible illness.

do not always reflect the clinical status of the patient. Dogs with either cortisol excess or cortisol deficiency are easily identified based on appetite, thirst, energy levels, and physical appearance; therefore, one of the most useful aspects of a recheck visit for a dog on trilostane is the conversation with the owner. How is the dog doing at home? Does it seem well? Is the owner satisfied with the dog's quality of life? Treatment decisions should be primarily based on this information, with cortisol concentrations (with or without results of ACTH stimulation tests) used to guide dose adjustments as necessary.

In the author's practice, the standard is to simply measure a baseline cortisol concentration (collected 4 hours post dose) in dogs that are clinically well, to be sure that adrenal function is not excessively suppressed. If the baseline is ≥1.3 µg/dL (35 nmol/L), the dog can be left on the same dose. If there are any concerns about the patient, an ACTH stimulation test is performed and the results used to adjust the treatment plan.

Dose Adjustments

The most reliable indicator of efficacy is the patient's behavior at home and the clinical examination. Information obtained from the owner regarding the dog's thirst, urination, appetite, energy levels, and overall status is key when making decisions about dose adjustment. It may take several months for the physical changes associated with HAC to reverse, but consistent improvement in haircoat, skin, musculature, and hepatomegaly should be noted.

In the author's practice, because trilostane simply reverses the clinical manifestations of HAC, if the dog looks good and the owner is satisfied, the dose is usually not increased based solely on test results. If the dog is showing clinical signs of HAC and the post-ACTH cortisol concentration is >7 µg/dL (190 nmol/L), the trilostane dose is increased by 25% to 50%. If the post-ACTH stimulation cortisol concentration is <7 µg/dL but the dog is clinically cushingoid, the current dose is divided into two and given every 12 hours, under the assumption that the duration of effect is too short. If no acceptable response is seen, the dose is slowly increased.

Complications

Transient oversuppression of adrenal cortical function and subsequent hypocortisolemia is the most common complication seen in dogs on trilostane. Owners may report that the dog is lethargic or dull; appetite may be decreased. Affected dogs improve within 2 hours of administration of a single dose of prednisone (0.5 mg/kg PO). Trilostane should be briefly withheld and then restarted at 50% to 75% of the previous dose when signs of HAC recur (usually 1 or 2 days).

A recent report described hypoadrenocorticism in 15% of 156 dogs treated with trilostane for up to 24 months.[14] This was generally transient (75% of instances), but irreversible adrenal necrosis has been reported in dogs after various periods of trilostane therapy. Affected dogs are systemically ill with hyperkalemia and hyponatremia. Owners should be informed of this (rare) complication but be reassured that it is easily recognized (baseline and post-ACTH stimulation cortisol concentration <1 µg/dL [28 nmol/L]) and effectively treated with short-term supportive care and long-term prednisone and desoxycorticosterone pivalate. It seems likely (based on rodent studies) that adrenal necrosis is the result of markedly elevated endogenous ACTH concentrations in dogs with tightly controlled HAC.[15]

KEY POINTS

- Trilostane is widely regarded as the treatment of choice for dogs with PDH and is the only product approved by the FDA for use in dogs with both forms of spontaneous HAC. L-deprenyl is approved for use in dogs with PDH only; ketoconazole and mitotane are not approved for the treatment of dogs with HAC.
- Most clinicians use a starting trilostane dose of 2 to 3 mg/kg daily (may be divided q12h), but dose adjustments are often necessary and clients must be prepared to return for routine reassessments.
- Patient status with respect to signs of hypo- or hypercortisolemia plays a key role in making appropriate dose adjustments. Various assessments of adrenal cortical function (including pre-trilostane, 3 to 4 hours post trilostane, or post-ACTH stimulation cortisol concentrations) may be used to guide dose adjustments.
- Adrenal necrosis is an uncommon consequence of trilostane administration but is readily identified by hyponatremia and hyperkalemia and confirmed on an ACTH stimulation test. Affected dogs need cortisol and aldosterone replacement therapy. TVP

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Treating and Managing Diabetes Mellitus in Dogs

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Diabetes mellitus (DM) is a common endocrine disease in dogs; the reported worldwide prevalence ranges from 0.3% to 1.3%.[1-4] This disease results from an absolute or relative lack of the hormone insulin. Most commonly, dogs get insulin-dependent DM, similar to type 1 DM in people. This type of DM results from a presumed immune-mediated attack on the pancreatic beta cells, which are responsible for synthesizing and secreting insulin, although it can also result from vacuolar degeneration of the pancreas or pancreatitis.[5-7] The loss of pancreatic beta cells results in an absolute decrease in circulating insulin. Other risk factors for DM in dogs include concomitant diseases such as hypothyroidism, hyperadrenocorticism, and obesity, or other hormonal or iatrogenic insulin-resistance triggers (e.g., diestrus or medications such as steroids or progestins).[8,9]

SIGNALMENT AND CLINICAL SIGNS

DM usually affects middle-aged dogs, especially Samoyeds, poodles, schnauzers, and bichon frises.[10,11] Common clinical signs include polyuria/polydipsia, polyphagia, weight loss, persistent or recurrent urinary tract infections, decreased muscle mass, cataracts, and, rarely, peripheral neuropathy. If the disease is not treated, signs can progress to inappetence, lethargy, and vomiting. Because pancreatitis is often associated with DM (as a causative or resultant factor), clinical signs of abdominal pain may also be present.

DIAGNOSIS

DM is relatively easy to diagnose by recognition of clinical signs and persistent fasting hyperglycemia and glucosuria. However, one factor that may confound diagnosis is stress. Stress alone can cause hyperglycemia, and if sufficiently elevated in the serum, glucose can spill over into the urine. In dogs, the renal glucose threshold at which glucose will spill into the urine is approximately 180 mg/dL. Should the practitioner have any doubt as to whether hyperglycemia and glucosuria are the result of DM or stress, checking the serum fructosamine

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level can be helpful. Fructosamine is a compound formed by a nonenzymatic covalent bond between a sugar (fructose or glucose) and a protein (largely albumin). The measurement represents the average of the blood glucose over the preceding 2 to 3 weeks and is not affected by rapid increases and decreases of blood sugar, such as those caused by a stressful event.[12] If the serum fructosamine level is elevated, then a diagnosis of DM is appropriate; if not elevated, then stress is probably the cause of the hyperglycemia/glucosuria.

Initial evaluation of the patient should include a complete physical examination, complete blood count, chemistry profile, and urinalysis. Even if urinalysis and sediment parameters are within normal limits, consider culturing the urine since up to 35% of urinary tract infections can be microscopically silent (no bacteruria or white blood cells) in animals with DM, hyperadrenocorticism, or both, probably the result of the dilute urine and immunosuppression.[13] Abdominal imaging may be pursued if clinically indicated.

Coexisting medical conditions should be addressed early and aggressively so that the DM can be easier to regulate; clients may become frustrated and give up if the DM is not easily controlled. Any concurrent disease can cause insulin resistance by causing release of inflammatory mediators, which interfere with the action of insulin, or by release of adrenal hormones.[14] The most common concurrent diseases in dogs with DM include urinary tract infections, pancreatitis, and endocrinopathies (e.g., Cushing's disease and hypothyroidism).[8]

TREATMENT

Initial evaluation will determine how intensively the patient should be managed. If the dog is eating and drinking normally and is well hydrated, there is no reason to hospitalize it while insulin therapy is initiated. If the dog is dehydrated, acidotic, or hyperosmolar, it should be hospitalized and stabilized before institution of long-term insulin therapy.

Insulin

The definitive therapy for DM in dogs is insulin, to replace the deficiency caused by lack of functional pancreatic beta cells.[9] A short-acting insulin such as regular insulin has a rapid onset of action; is degraded quickly; and may be given by the intravenous, intramuscular, or subcutaneous routes. It is used to treat diabetic animals in unstable condition, such as those who are dehydrated, ketotic, or hyperosmolar. For dogs in stable condition, the practitioner can start with intermediate or long-acting insulins that generally require subcutaneous administration and thus are not appropriate for dehydrated animals. The many types of insulin on the market differ according to the pharmacologic mechanism by which they are made into a repository form. Dogs may have a differential response to a singular insulin. In the United States, the insulins most commonly used in dogs are porcine lente (Vetsulin, merck-animal-health-usa.com) and isophane insulin (also known as NPH) (Novolin-N, novonordisk-us.com; Humulin-N, lilly.com/products), which are optimally given twice daily.[9] The human basal insulins glargine (Lantus, sanofi.us) and detemir (Levemir, novonordisk-us.com) have also been used in dogs and may be longer-lasting, although current recommendations are to initiate therapy twice daily. Human recombinant protamine zinc insulin (ProZinc, bi-vetmedica.com) has recently been licensed for use in dogs; in a field trial, it was shown to be effective in 72% of over 200 dogs given the drug once daily. Factors to consider when choosing insulin are price (NPH is the least expensive), U.S. Food and Drug Administration approval for veterinary use (the U-40 insulins Vetsulin and ProZinc), availability of dosing pens (Lantus, Levemir, Vetsulin), and possible once-daily dosing (Lantus, Levemir, ProZinc). Regardless of insulin type, the initial dose for dogs is 0.5 U/kg q12h, except for determir, which should initially be given at 0.25 U/kg q12h.

For most diabetic dogs, insulin therapy will improve clinical signs soon after initiation. However, it may take several weeks for the animal to fully adjust to insulin therapy. Because the average time for initial DM control is 4 to 6 weeks (C.R. Ward, unpublished data), remind clients to be patient.

Feeding

Dogs receiving insulin should be fed twice daily. The optimal diet for diabetic dogs is high in insoluble fiber.[15] This diet slows glucose absorption from the gut and reduces postprandial hyperglycemia. Many clients give insulin while the dog is eating; doing so associates the insulin injection with a pleasant experience for the dog, which makes it easier for clients to administer. To avoid obesity in the dog, clients should ensure that the dogs are not receiving more than their caloric needs. The daily caloric intake should be divided into 2 equal

meals. A small snack calculated into the daily caloric requirements may be given at peak insulin activity time, usually 4 to 8 hours after insulin administration. If the dog does not eat its meal, insulin should be given at half the normal dose. If the dog misses another meal, the client should contact the veterinarian.

Exercise

Exercise is beneficial for diabetic dogs; it helps lower insulin requirements and provide better glycemic control. Daily walking or play exercise for dogs with DM can be an effective ancillary treatment to help achieve glucose control at a lower dose of insulin.

Treatment of DM in dogs can be frustrating, expensive, and time-consuming for clients. In a recent worldwide study, 10% of dogs with DM were euthanized at or within the first year of diagnosis.[16] The reason for 32% of euthanasia cases was cited as the effect on the client's lifestyle; therefore, be flexible when establishing a treatment plan. The long-lasting sequelae of DM in people (e.g., glomerlular disease, retinal degeneration, and hypertension) are not problematic for veterinary patients.[9] Perhaps our patients do not live long enough for these problems to surface, or perhaps they are protected in some way. Regardless, the veterinarian and client should not strive for perfect blood glucose control; rather, the goal should be good clinical control. Good rapport with clients with diabetic dogs is helpful because clients will be asked to provide invasive (injections) and time-consuming (glucose monitoring) care for their dog. It is beneficial to have an in-depth discussion with clients as to the time, effort, and financial resources they can realistically commit to treatment for their diabetic dog.

Remember that the goals for DM therapy should be correction of clinical signs, restoration of normal musculature and energy level, control of concurrent diseases, and avoidance of emergency situations (e.g., hypoglycemia, ketosis, and hyperosmolality).

MONITORING

After insulin therapy has been started, wait 7 to 14 days to monitor any effects since it takes that long for the dog to adjust to the therapy. During that period, clients can measure urine glucose and ketones with Keto-Diastix (pharma.bayer.com). These strips can be put on any area that contains urine moisture, such as grass or gravel; as long as the strip is wet, it will provide ketone and glucose readings. Clients should notify the veterinarian if more than 2 urine glucose readings are negative, especially if the dog shows clinical signs of hypoglycemia or if the ketone readings are positive. If urine glucose is negative, hypoglycemia may be present since the strip will only show glucose if the blood glucose is greater than 180 mg/dL (the renal threshold).

Because DM is so common among people, many veterinary clients may be familiar with glucometer use. For those willing to obtain spot blood glucose measurements at home, the Alpha-Trak2 glucose monitor (zoetisus.com) may be helpful. It is specially calibrated for use in dogs and requires substantially less blood to obtain a reading, therefore making it more convenient to use than human glucometers. Although glucose measurements using serum chemistry analyzers are more accurate, glucometer measurements are easily obtained in the home environment with rapidly available results. Trends in glucose measurements can

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HEART-TO-HEART TALK
Though most cases of canine diabetes mellitus are uncomplicated and can be treated at home, pet owners can be overwhelmed by the diagnosis. When talking to these clients, it is important to explain that dogs with DM—even those with other complicating diseases—can live a full and healthy life.

To capture the optimal glucose lowering effects, clients should optimally check blood glucose levels 4 to 8 hours after injecting insulin.

be followed. Blood samples can be obtained by pricking the ear pinna, gum, paw pad, or elbow areas.

During the initial insulin acclimation period, insulin doses should not be changed as a result of glucose readings, but clients should notify the veterinarian if the animal is ketotic or hypoglycemic. To capture the optimal glucose lowering effects, clients should optimally check blood glucose levels 4 to 8 hours after injecting insulin.

At the initial recheck after insulin therapy has been initiated, ask the client about resolution of clinical signs and perform a physical examination, weight measurement, and determination of body condition score. Examine muscle mass and record a muscle condition score. These parameters measure the most important goal of DM therapy in dogs: resolution of clinical signs and normalization of physical examination parameters. For many patients, these factors are more predictive of diabetic control than glucose measurements.[17]

Another useful aid for monitoring response to therapy is serum fructosamine.[12] For fructosamine values to be interpretable, the dog should have received a stable insulin dose for at least 3 weeks before the serum fructosamine level is measured. Although fructosamine levels can be useful for monitoring long-term response to insulin therapy, they are inappropriate for use in animals in unstable condition or those in which a hypoglycemia-induced hyperglycemic (Somogyi) response is suspected. For these patients, a glucose curve must be completed.

A glucose curve is the only way to truly evaluate the body's response to insulin. Serum glucose levels directly reflect insulin activity. Information obtained from glucose curves includes insulin onset of action, duration of action, time of peak activity, and lowest glucose level (nadir). The first 3 parameters indicate whether the right type of insulin is being used; the last parameter provides information about the appropriate dose of insulin.

Obtaining a traditional in-hospital glucose curve requires measuring blood glucose levels, usually by glucometer, every 2 hours over a 9- to 12-hour period. These curves have many limitations, including disruption of the patient's normal activity and eating routine, introduction of stress-related hyperglycemia, and labor intensiveness of the procedure. Furthermore, diabetic dogs experience significant variations in day-to-day glycemic control.[18] Intermittent blood sampling over a 12-hour period only may grossly overestimate or underestimate a patient's glycemic control, and glucose peaks and nadirs may be missed if they occur between samplings. Some clients can complete glucose curves at home and send the data to the veterinarian. Although such home-generated curves minimize the change in the dog's normal routine, the daily variance in data can lead the clinician to make different insulin recommendations, depending on the curve examined.[19]

Continuous glucose monitoring and flash glucose monitoring systems provide minimally invasive ways to continuously evaluate glycemic control for up to 14 days.[20] They measure interstitial glucose and record an average value every 5 minutes. The systems comprise an external sensor with a flexible electrode that is inserted into the subcutaneous tissue. The electrode emits a small electrical current proportional to the amount of glucose in the interstitium. The electrical charge is then calibrated to a glucose measurement that is read on a monitor.

Two systems that have been validated for use in veterinary patients—the MiniMed iPro2 (continuous, professional.medtronicdiabetes.com) and the Abbott Freestyle Libre (flash, freestylelibre.us/index.html) systems—have been used successfully and can be sent home with the patients.[21,22] The iPro2 sends data continuously from the disposable sensor to a recorder attached to the end of the sensor. Clients are blinded to the glucose results until the device is removed and downloaded onto the MiniMed website. The iPro2 requires calibration by blood glucose measurement every 8 to 12 hours. The Abbott Freestyle Libre consists of a disposable sensor and recorder attached to the skin of the patient. The interstitial glucose data are stored in

the recorder until a reader is passed over it, which will show the glucose level and download updated information to the reader. The glucose information can be shared with the practitioner via a website. The Freestyle Libre is factory calibrated and does not require blood sample calibration at home.

Both of these systems have the advantage of being able to evaluate the response to insulin therapy in the patient's home environment and during its usual routine. The stress of frequent blood sampling is avoided and glucose data can be captured at all times during the day. Flash glucose monitoring has the advantage of allowing clients to see glucose measurements, thereby relieving concerns of extreme hyper- or hypoglycemia. This monitoring can make it easier to manage diabetic dogs with concurrent diseases, such as hyperadrenocorticism, for which insulin therapy needs to be tailored to adrenolytic therapy.

PROGNOSIS

Because veterinary patients do not experience the detrimental long-term effects of DM-associated hyperglycemia experienced by people, target blood glucose ranges can be more relaxed than those necessary for managing DM in human patients. However, veterinary practitioners should be vigilant in monitoring for urinary tract infections, pancreatitis, and other endocrinopathies, such as hyperadrencorticism.

With client commitment and appropriate veterinary care, dogs with DM—even those with other complicating diseases—can live a full and healthy life. **TVP**

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MANAGEMENT STRATEGIES

Chronic Pancreatitis in Cats

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Pancreatitis is common among cats, although its exact incidence is unknown. The disease can take several forms—acute, chronic (**FIGURE 1**), and acute on chronic (an episode of acute pancreatitis in a patient with chronic pancreatitis)—and differentiating among the forms clinically and making an antemortem diagnosis in cats remain challenging.[1] According to one study, the prevalence of pancreatitis in cats that had died or had been euthanized for a variety of reasons was more than 50%.[2] This article focuses on the management of chronic pancreatitis in cats: minimizing risk factors, nutritional management, treating symptoms, treating concurrent conditions, identifying and treating autoimmune components, and monitoring.

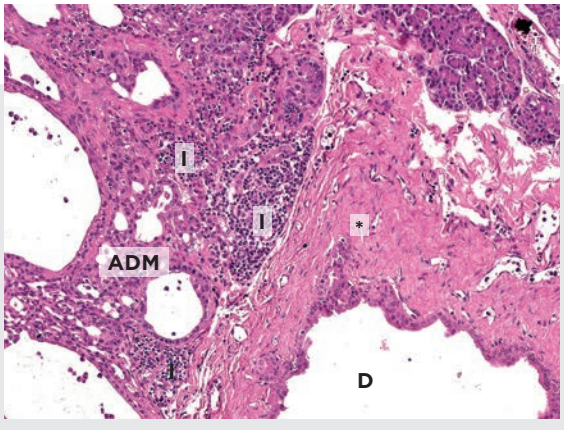

FIGURE 1. Histopathologic image of pancreatic tissue from cat with chronic pancreatitis, showing fibrosis **(*)** around a duct **(D)**, inter- and intralobular lympho-plasmacellular infiltration **(I)**, and acinar to ductal metaplasia **(ADM)**. Hematoxylin and eosin staining; original magnification ×20.

RISK REDUCTION

Although the underlying cause of chronic pancreatitis in cats often cannot be determined, possible risk factors should be eliminated. In our experience, factors that have been associated with the development of chronic pancreatitis in cats include high-fat diets, infections (i.e., feline parvovirus, *Toxoplasma gondii*, feline calicivirus, feline herpesvirus, and feline coronavirus), hypercalcemia, some drugs, and potentially autoimmune disease. However, most cases are idiopathic. Thus, as a first step, we recommend the following (depending on the patient): consider a diet change; test for specific infectious diseases, if suspected; identify and treat the underlying causes of hypercalcemia, if present; take a thorough drug history and discontinue any nonessential drugs or replace essential drugs with alternative medications, if possible; and consider immunosuppressants for autoimmune disease, if suspected.

From top: Natata/shutterstock.com. Courtesy of Dr. Katja Steiger, Technical University of Munich, Germany.

NUTRITIONAL MANAGEMENT

By the time cats with chronic pancreatitis are taken to the veterinarian, most have already been hyporexic or anorexic for days to weeks.[1] Prolonged undernutrition in cats can lead to weight loss or even hepatic lipidosis.

Although appetite stimulants may encourage food intake in hyporexic cats, they rarely result in attainment of caloric requirements. The only Food and Drug Administration (FDA)-approved drug that can be used as an appetite stimulant in cats is mirtazapine transdermal ointment (2 mg/cat transdermally every 14 days) (**FIGURE 2**), although the drug has actually been approved for management of undesired weight loss. However, take caution when administering appetite stimulants to cats with hepatic lipidosis.[3] Another drug, capromorelin (a ghrelin-receptor agonist) has been FDA-approved as an appetite stimulant for use in dogs. Also, initial studies have shown that its daily administration was well tolerated by healthy laboratory cats; mild side effects (e.g., vomiting, hypersalivation, lethargy, head shaking, and lip smacking) were associated with its administration.[4] Further studies are needed before the routine use of this drug in cats can be recommended.

In contrast to its effect in dogs, the effect of dietary fat content on pancreatitis in cats is still controversial. However, anecdotal evidence suggests that chronic pancreatitis does develop in some cats that are fed high-fat diets (e.g., diets for the management of chronic kidney disease or low-carbohydrate diets). Thus, if a cat with chronic pancreatitis is being fed a high-fat diet, the cat should be transitioned to a lower-fat diet. However, commercial ultra–low-fat diets are not available for cats and are probably unnecessary for this species.

To prevent food aversion in cats, forced oral feeding is strongly discouraged. For cats with chronic pancreatitis that do not consume adequate amounts of food despite antinausea therapy and appetite stimulants, consider tube feeding. For short-term caloric support, a nasogastric tube (5- to 8-French flexible polyurethane feeding tube) can be placed. However, these tubes can be very disturbing to cats, who are obligate nasal breathers, and an Elizabethan collar will probably be needed to keep the cat from removing the tube. Persistently anorexic patients who need longer periods of supplemental nutrition may do better with an esophageal or gastric tube. These tubes also facilitate administration of oral medications, which can be challenging in any cat. The initial goal of nutritional management is to provide 25% to 50% of target caloric intake. Over the next 2 to 4 days, gradually increase the volume to reach the target caloric intake.

By the time cats with chronic pancreatitis are taken to the veterinarian, most have already been hyporexic or anorexic for days to weeks.[1]

The selection of diet should take into account concurrent conditions. Cats with secondary hepatic lipidosis require a high-protein (30% to 40% of metabolizable energy, while taking caution not to feed excessive amounts of fat), calorie-dense diet. Cats with concurrent inflammatory bowel disease (IBD) may benefit from a novel or hydrolyzed protein diet.

SYMPTOMATIC THERAPY

Antiemetic/Antinausea Drugs

Although not all cats with pancreatitis vomit, it is suspected that they often experience nausea. Cats >4 months of age can be given maropitant at 1 mg/kg SC or PO q24h. Maropitant is a neurokinin-1 receptor

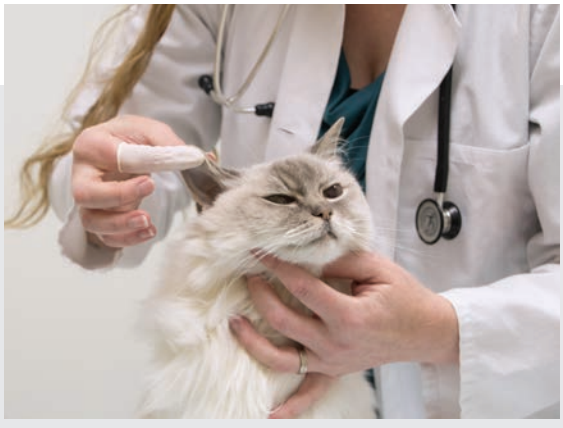

FIGURE 2. Transdermal application of mirtazapine ointment (being used as an appetite stimulant) on the inside pinna of the ear of a cat.

Courtesy of Dr. Jessica Quimby, The Ohio State University, Columbus, Ohio.

antagonist that has both central and peripheral effects. It has been speculated that maropitant may provide analgesia through inhibition of visceral neurokinin-1 receptors. There is evidence that ondansetron (a serotonin [5-HT_3] antagonist) has poor oral bioavailability and a short half-life; therefore, the preferred route of administration for this drug may be subcutaneous.[5] Another 5-HT_3 antagonist that can be given either subcutaneously or orally and may decrease nausea, and in turn increase appetite, is dolasetron.

Chronic pancreatitis can be associated with concurrent cholangitis and IBD, sometimes referred to as triaditis.[8]

Pain Management

Cats are extremely good at hiding pain. Cats with chronic pancreatitis rarely display signs of abdominal pain.[1] Outpatient analgesia can be provided by buprenorphine at 0.01 to 0.03 mg/kg sublingually q4h to q12h or butorphanol at 0.5 to 1.0 mg/kg PO q6h to q8h. For more severe pain, the only feasible modality is a transdermal fentanyl patch q72h to q120h (12 µg/hour for small cats and 25 µg/hour for large cats).[6] For cats with chronic pancreatitis, nonsteroidal anti-inflammatory drugs are contraindicated because of the risk for nephrotoxicity, gastroduodenal erosion and ulceration, and because they are considered risk factors for pancreatitis in humans.

Antimicrobial Drugs

Chronic pancreatitis in cats is usually sterile.[2] One study suggested that bacterial DNA was present in pancreatic biopsy samples from cats with pancreatitis, but it is unclear whether these findings have any clinical relevance.[7] Therefore, antimicrobial therapy is rarely indicated unless patients have evidence of a concurrent bacterial infection (i.e, septic fluid within the pancreas [sometimes referred to as a pancreatic abscess], neutrophilic cholangitis, or severe neutropenia).

Gastrointestinal Protectants

Gastrointestinal protectants (e.g., H_2 antagonists, proton-pump inhibitors, or sucralfate) are sometimes given to cats with chronic pancreatitis, but they are rarely, if ever, indicated. Even in cats with severe acute pancreatitis, gastric ulceration is extremely rare. Gastroprotectants may dramatically shift the gastrointestinal microbiota, which may have detrimental effects on the patient.

CONCURRENT CONDITIONS

Diagnosis and management of concurrent conditions are paramount for the care of cats with chronic pancreatitis. Chronic pancreatitis can be associated with concurrent cholangitis and IBD, sometimes referred to as triaditis.[8] According to one prospective study of cats, concurrent pancreatic, hepatic, and/or intestinal inflammation was more common (27/47) than isolated pancreatic inflammation (1/47).[9] Also, chronic pancreatitis is often associated with diabetes mellitus. However, some evidence also indicates that hyperglycemia may lead to pancreatic inflammation in cats.[10]

Cholangitis

Cholangitis is a common liver disease in cats and can take on several forms: neutrophilic, lymphocytic, mixed, or liver fluke associated. Studies have led to different conclusions about the prevalence of each form of cholangitis, resulting in discrepancies regarding which is most common.[9,11] Because the clinical presentations of cats with these different forms may be similar, it is important to determine which kind of cholangitis is present before instituting treatment.

The most common route for development of neutrophilic cholangitis is thought to be an enteric bacterial infection ascending via the biliary tree. Cytology and bacterial culture (aerobic and anaerobic) and sensitivity testing should be performed on bile and/or liver biopsy samples.[12] If neither of these samples can be safely obtained, culture can be attempted from a fine-needle aspirate of the liver or gall bladder. If infection is established, antibiotics should be administered. Antibiotics can be selected before culture susceptibility results are available; appropriate choices for gram-positive and gram-negative aerobes and anaerobes include fluoroquinolones, penicillin and metronidazole, or a fluoroquinolone and a potentiated penicillin.[12-14] Given the difficulty of achieving adequate concentrations of the antibiotic in hepatic

and biliary tissue, prolonged courses of treatment are recommended. Although duration of treatment should be guided by follow-up sampling, collecting the samples can be risky and costly. If no culture and sensitivity testing can be obtained, empiric antibiotic therapy for 4 to 6 weeks is suggested.[13]

Lymphocytic cholangitis is thought to be immune mediated. Given this assumption, treatment usually involves the administration of prednisolone (1 to 2 mg/kg q12h starting dose).[15] However, prednisolone should not be initiated until active bacterial infections have been ruled out or treated with empiric administration of antibiotics.[6]

Inflammatory Bowel Disease

Cats with pancreatitis often have concurrent inflammatory infiltrates (e.g., lymphocytes, plasma cells) of the intestines.[9] With better understanding of chronic enteropathies in cats, therapeutic options have become more refined. Most of these cats will respond to dietary therapy (e.g., food-responsive enteropathy); some may respond to modification of the intestinal microbiota (suggesting an underlying dysbiosis), but others may require immunosuppressive therapy (i.e, they have idiopathic IBD).[16] Many cats with idiopathic IBD are deficient in cobalamin and require oral or parenteral supplementation with cyanocobalamin.

Diabetes Mellitus

Many cats with chronic pancreatitis have concurrent diabetes mellitus. Some of these cats are undergoing dietary management with a low-carbohydrate diet. We believe that these patients may benefit from being switched to a diet with a lower fat content.

IMMUNOSUPPRESSIVE THERAPY

Although immune-mediated chronic pancreatitis is well described for humans, it has not been definitively proven whether this condition occurs in cats. Anecdotally, however, cats with chronic pancreatitis may respond to treatment with prednisolone (the dosing varies, but we use 2 mg/kg q12h for 10 days, then 1 mg/kg q12h for 6 weeks, followed by a decreasing dose at 6-week intervals) or cyclosporine (5 mg/kg q12h to q24h for 6 weeks followed by a decreasing dose at 6-week intervals). To determine whether treatment is effective, re-evaluate the patient after the first 2 to 3 weeks of therapy. Therapeutic trials are under way to study the efficacy of these drugs in cats with chronic pancreatitis (vetmed.tamu.edu/gilab/research/feline-chronic-pancreatitis).

MONITORING

With appropriate management and symptomatic care, cats with pancreatitis should show clinical improvement (e.g., increased activity, appetite, and body condition score). It is imperative to educate clients about the potential long-term sequelae of chronic pancreatitis, such as diabetes mellitus, exocrine pancreatic insufficiency, or acute exacerbation of this chronic disease. The management of cats with concurrent chronic pancreatitis and diabetes mellitus is more complex.

Long-term follow-up of cats with pancreatitis is indicated. Based on clinical experience, we recommend monitoring feline pancreatic lipase (fPL) immunoreactivity (fPLI), as measured by a Spec fPL test (IDEXX Laboratories Inc., idexx.com) every 2 to 3 weeks until the level reaches a plateau, at which point the monitoring interval can be decreased. Although the goal of management is amelioration of clinical signs and normalization of the spec fPL concentration, some cats will improve clinically but maintain a mildly increased spec fPL serum concentration.

CONCLUSIONS

Chronic pancreatitis is a common, yet complex, disease in cats, and its management is nonspecific and multifaceted. The successful management of these patients involves management of risk factors (switching to a diet with a lower fat content, addressing hypercalcemia, minimizing exposure to unnecessary drugs), managing nutrition, symptomatic care (antinausea and analgesic therapy), diagnosing and managing concurrent conditions, administering immunosuppressive drugs, and monitoring fPLI concentration. TVP

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Dr. Lim graduated with a DVM degree from Universiti Putra Malaysia in 2009 and continued her studies at Hokkaido University, Japan. She earned her PhD degree in 2014 researching on the application of contrast-enhanced ultrasound in diagnosing canine pancreatitis. Her current research at Texas A&M's GI Laboratory is focused on pancreatic lipases.