UNIQUE SEMINAR DESTINATIONS

Royalton, St. George's, Grenada 2023 (February 11 - 18)

INTERNAL MEDICINE TOPICS (10 hour CE)

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Session 1 & 2 - Diabetes Mellitus

Session 3 - Feline Hyperthyroidism

Session 4 - Hypothyroidism

Session 5 - Hyperadrenocorticism (Cushing's syndrome)

Session 6 - Hypoadrenocoroticism (Addison's disease)

Session 7 - Chronic Kidney Disease - Early Diagnosis & Treatment

Session 8 - Chronic Kidney Disease - Advanced Treatment & QOL Considerations

Session 9 & 10 - Bacterial Urinary Tract Infection -
Treatment and Prevention of Sporadic & Recurrent Infections

Management of Canine and Feline Diabetes Mellitus
"Lessons learned in 35 years of medical practice"

Introduction
Persistent hyperglycemia and glucosuria associated with Diabetes mellitus (DM) results in polyuria, polydipsia, polyphagia, weight loss and cataracts (dogs) commonly present. The diagnosis is generally straight forward but there are factors that make successful management difficult in some patients. Substantial differences exist between canine and feline diabetes. A thorough understanding of the disease in dogs vs. cats, proper diet principles, insulin therapy and other treatment selections, treatment monitoring and realistic treatment goals will help veterinarians and owners obtain satisfactory diabetic control.

Diabetes Mellitus Etiopathogenesis
Dogs develop Type I DM (insulin-dependent) with an inability to produce sufficient insulin due to extensive pancreatic islet cell atrophy or tissue destruction. The majority of affected cats are Type II DM (non-insulin dependent) when diagnosed. Obesity, indoor confinement, cereal-based diets (higher CHO, lower protein) and prior glucocorticoid therapy are risk factors in feline patients as they promote persistently higher blood glucose values necessitating chronically increased insulin production. "Glucose toxicity" causes pancreatic islet cell down-regulation with impaired insulin secretion resulting in persistent hyperglycemia and clinical diabetes mellitus. Early down-regulation in pancreatic islet cells is functional and maybe reversible; however, amyloid deposition occurs over time destroying islets resulting in irreversible Type I DM (insulin-dependent).

Diagnosis
The diagnosis of DM is based on classic clinical signs (polydipsia, polyuria, polyphasic and weight loss) associated with persistent hyperglycemia and glucosuria. Ketonuria and acidemia are associated with complicated ketotic/ketoacidotic DM (DKA). Even with good diabetic regulation, dogs frequently develop bilateral mature cataracts (50% within 6 months of DM diagnosis, 80% within 16 months). Approximately 10% of poorly regulated DM cats will develop rear limb weakness due to diabetic polyneuropathy. The importance of recognizing a "prediabetic" state has recently been introduced, especially in type II diabetic cats, which may allow for newer non-insulin treatments.

Treatment
Newly diagnosed DM patients have a fair to good prognosis. Successful management is not defined as achieving perfect glycemic control but rather minimizing clinical signs, improving life quality and preventing complications.
Type 1 diabetic dogs require life long insulin therapy. Type 2 diabetic cats may achieve diabetic remission after starting glucose-lowering therapy. Diet therapy alone is unlikely to reverse glucose toxicity in cats so insulin therapy or other drugs that lower blood glucose should be started promptly following diagnosis. Cats most likely to achieve remission are first time diabetics, have no concurrent medical disease, and have an owner that is able to administer therapy and monitor glycemic control. Treatments that

may result in feline DM remission include low carbohydrate diet, long-acting basal insulin therapy, incretin therapy (GLP-1), and oral sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy. Remission is most likely to occur within 2-6 months of treatment initiation. Remission lapses occur in 25-30% of cases, associated with impaired glucose tolerance, necessitating resumption of insulin therapy in some cats.

Selecting an appropriate insulin type -

INSULIN	Brand	Formulation	Duration
SHORT ACTING			
Regular	Humulin R	U100 recombinant human	1-4 hr cats 1-4 hr dogs
Aspart	Novalog	U100 recombinant human	3-4 hr cats 3-4 hr dogs
Lispro	Humalog	U100 recombinant human	3-4 hr cats 3-4 hr dogs
INTERMEDIATE			
NPH	Humulin N Novolin	U100 recombinant human	4-10 hr dogs < 10 hr cats
Lente	Vetsulin Caninsulin	U40 porcine insulin zinc	8-14 hr cats 8-24 hr dogs
LONGER ACTING			
Protamine Zinc	ProZinc	U40 recombinant human	9-24 hr cats 16-24 hr dogs
Glargine	Lantus	U100 recombinant human	9-24 hr cats 12-20 dogs
Glargine	Toujeo^{R}	U300 recombinant human	14 hr cats 16 hr dogs
Detemir	Levemir	U100 recombinant human	10-17 hr cats 10-24 hr dogs
Degludec	Tresiba^{R}	U100 U200	10 hr cats 20 hr dogs

The initial choice of a specific insulin is based on reported effectiveness, prior clinician experience, availability, and owner cost. Any given insulin type may work well in an individual patient and it is impossible to predict in advance which insulin product is best for any individual patient. Veterinary compounded insulin formulations should be avoided in my opinion as variability in formulation can lead to serious regulation issues.

Mammalian insulins are structurally similar, with small differences in amino acid sequences present between species. Pork insulin is identical to dog insulin in amino acid structure. **Pork lente insulin (Vetsulin, Caninsulin)** is an intermediate duration insulin containing 35% amorphous insulin for rapid onset of activity and 65% crystalline insulin for slower absorption. Prior to syringe use it is critical to vigorously shake the Vetsulin vial until the insulin is uniformly milky. Vetsulin is FDA licensed for use in dogs and cats. Beef insulin is most similar to cat insulin, differing by only one amino acid, but is not commercially available.
Genetically engineered recombinant insulins, which reduce hypersensitivity reactions and antibody formation, have replaced animal-source insulins in human medicine. Human recombinant insulins are readily available and commonly used in animals. **NPH formulations (Humulin, Novalin),** while often less expensive, have a shorter duration limiting their effective use in dogs and cats. **Recombinant PZI insulin (ProZinc)** is FDA approved for feline and canine use. PZI allows for prolonged release of insulin monomers and dimers from subcutaneous tissue extending insulin duration. ProZinc is administered every 12 hours in cats; it may provide 24 hour activity following once daily administration in some canine patients. Longer-acting basal (peakless) insulins, such as **Insulin glargine and detemir,** have proven to be effective with twice daily administration in cats and dogs. Insulin glargine 300 (IGlar300) and degludec (IDeg) are new basal peakless forms of insulin that generate soluble multihexamers following subcutaneous injection, resulting in longer duration of action in humans. IGla300 and IDeg provide less variation in insulin activity and are associated with lower risk of hypoglycemia. A novel ultra-long-acting insulin construct (AKS-218d) intended for once-weekly administration is currently being investigated in diabetic dogs.

Insulin concentration and syringes - Insulin is commercially available in 40 (U-40) and 100 (U-100) unit/ml concentrations, respectively. Owners should purchase appropriate syringe for the prescribed insulin concentration to be certain of appropriate dosing. There are four different types of insulin syringes available: U-100 syringes (0.3 ml, 0.5 ml and 1 ml capacities); U-40 syringes are only available as 1 ml capacity. In cats and smaller dogs, a low-dose (0.3 ml) syringe with ½ unit markings is recommended as it is easier to visualize and deliver appropriate small doses.
Insulin pens are available which provide more accurate dosing in smaller patients and for clients that have difficulty with vial and syringe administration. Insulin pens minimize variability and maximize precision. Pens are available for Vetsulin, Glargine (Lantus and Trujeo), Detemir and Degludec.

Insulin dosage - Initial insulin therapy should be designed to mimic physiologic insulin concentrations without induction of hypoglycemia. Initial insulin therapy should be

conservative and given at the time of feeding, followed by incremental dose adjustments based on observation of clinical signs and serial blood glucose monitoring.
In dogs, the starting insulin dose for intermediate-acting insulins (Vetsulin or NPH) is 0.25 - 0.5 U/kg BID. Detemir is a very potent insulin in dogs and is initiated at 0.0625 – 0.125 U/kg BID. ProZinc insulin dose is initiated at 0.2 - 0.7 U/kg once to twice daily. All types of insulin should be started on a BID schedule (intermediate-acting or longer-acting basal insulins) and later reduced to QD only if appropriate based on clinical signs and blood glucose monitoring. A starting dose of 1-2 units is appropriate for most cats. Detemir is a very potent insulin and is always started at 1 unit per cat BID. The insulin glargine compounds have a similar duration of action that is < 24 hours in healthy cats, but the metabolic effect of Trujeo (IGla U300) is more evenly distributed over the 24 hour period making it a better consideration for once-daily injection in diabetics when compared with Lantus (IGla U100).

Injection site - The site of insulin injection is an important consideration. An appropriate location must be chosen, as absorption of insulin from various sites in the body differs. In dogs and cats, the dorsal neck or scruff has commonly been used, but this site may not be ideal due to low blood flow, dead space and fibrosis caused by repeated injections. A better option is to administer the insulin at sites along the lateral abdomen and thorax. The chosen area should be rotated daily in order to prevent fibrosis at an injection site. A good practice is to make the injections part of a positive experience. For diabetics that are meal fed and are very into their food, inject them as they are eating. For others, you can give the injections when doing a pleasurable activity.

Dietary management -
Dogs - There is no 'one-diet-fits-all' approach for canine diabetes. Patient body condition, diet preferences, and other concurrent diseases or medical conditions are considered to determine the best diet for each individual diabetic dog. However, there are some guiding principles that should be consistent for each dog to maximize diabetic regulation – use the same food, same treats, feed and give insulin at the same time every day and provide consistent regular exercise to reduce insulin needs. Dogs should be fed a diet with moderate to elevated protein content (> 75 grams/1000kcal) to maintain/improve lean muscle mass, and moderate insoluble fiber content. Fat content should be reduced (< 30 grams/1000kcal, < 10% DMB) especially in patients with concurrent pancreatitc or lipidemia issues. Dietary fiber slows intestinal nutrient absorption reducing fluctuations and producing less variation over time in blood glucose levels following a meal. Daily caloric need should be calculated and intake should be based on patient body condition and the need to lose or gain weight over time. While being overweight isn't a risk factor for the development of diabetes in dogs, it can contribute to difficulty controlling diabetes once it develops. Excess body fat can cause insulin resistance so all overweight diabetic dogs should be encouraged to slowly lose weight. Higher calorie diets will be best for underweight dogs to encourage restoration of normal body condition.
Cats - cats have a higher dietary protein and lower carbohydrate requirements due to their obligate carnivore ancestry. Feeding a higher protein/lower CHO diet formulation will produce a lower and less fluctuant blood glucose value. These diets also aid in

weight loss and establishment of a leaner body mass, are helpful in diabetic regulation and may aid in reversal of hyperglycemia and islet cell glucose toxicity.

Non-Insulin Therapies
Various drugs are available to reduce blood glucose. Mechanisms of action include inhibition of intestinal glucose absorption, promotion of insulin release from the pancreas, inhibition of hepatic glucose output, improvement of peripheral insulin sensitivity and decrease renal glucose absorption.

Alpha-glucosidase inhibitors, such as acarbose, inhibit intestinal glucose absorption and reduce postprandial hyperglycemia. Acarbose has been used in cats and dogs along with insulin and diet to improve glycemic control and decrease the dose of exogenous insulin administration. Diarrhea is a possible side effect.

Sulfonylureas, such as glipizide, promote insulin secretion from the pancreas and can be considered for use in cats; clinical benefit is reported in approximately 40% of cats. Glipizide use in cats is generally reserved for owners who refuse insulin therapy, and should be used with concurrent dietary therapy. An initial dose is 2.5 mg/cat orally q 12 hr; dose can be increased to 5 mg/cat q 12 hr if an inadequate response is seen after 2 weeks. If no response is seen after 4–6 weeks, insulin therapy should be instituted. Glipizide is not used in dogs as they no longer have functional pancreatic B cells.

Incretins are gastrointestinal metabolic hormones secreted by enteroendocrine cells. The amount of insulin secreted in response to an oral meal is higher than the amount secreted in response to the same IV glucose load. The difference in insulin amount is called “the incretin effect”. Incretin hormones increase insulin secretion, decreases glucagon secretion, stimulates beta-cell differentiation, delays gastric emptying and induce satiety. Glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the major incretins. They are broken down by the enzyme dipeptidyl peptidase-4 (DPP-4). GLP-1 mimetics (Exenitide, Liraglutide) or DPP-4 inhibitors are available as pharmaceutical drug formulations. Reports in cats and dogs suggest they are safe and may be most helpful in early Type II diabetic cats that retain insulin secretory ability. Exenatide improved the remission rate and percentage of cats that achieved good diabetic control. In Type I diabetic dogs, the incretin action of decreasing glucagon secretion (glucagon is a major insulin antagonist) may improve diabetic control when used with insulin.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a newer class of orally administered antidiabetics that inhibit glucose absorption from the kidney. SGLT2 is located within the proximal tubule and is responsible for 90% of renal glucose reabsorption. Inhibition of renal glucose reabsorption effectively lowers blood glucose with minimal risk of inducing hypoglycemia. The SGLT2 inhibitors dapagliflozin and velagliflozin have been evaluated in healthy cats and found to be well-tolerated and result in significant urinary glucose excretion without inducing hypoglycemia. Bexagliflozin is a highly selective SGLT2 inhibitor that has been approved by the Food and Drug Administration (FDA) to improve glycemic control in otherwise healthy DM

cats not previously treated with insulin. A 15mg oral tablet is administered to cats weighing 3.0 kg or greater once daily, with or without food and regardless of blood glucose level.in cats.

Monitoring diabetic treatment and adjusting dose or schedule - Clients are happy when their diabetic pets remain energetic, eat well, maintain or improve body weight/ condition and exhibit less PU/PD. Combining assessment of clinical signs per owner observation, physical examination findings and glycemic blood values is the best way to determine treatment efficacy. Emphasis should be placed on maintaining quality of life parameters with less emphasis on achieving the “perfect” BG value. Ketoacidotic DM is less likely to develop in a reasonably controlled patient unless a concurrent medical issue arises (UTI, pancreatitis). A good goal is to maintain blood glucose between 100-250 mg/dl for 80% of the 24 hour day. Urine glucose measurements are not reflective of blood glucose values and are discouraged as a means of making insulin dose adjustment; however, urine glucose can be monitored to help determine diabetic remission status in cats. Home urine ketone monitoring may be valuable in patients at risk for ketoacidosis development.

Serial Blood glucose (BG) curves can be performed at home or in the hospital. Blood glucose is determined every 2-4 hours following an insulin dose and meal and continued for a 12-24 hour period. A veterinary specific glucometer is recommended and is more likely to be precise. The objectives of performing a BG curve are to evaluate insulin activity and insulin dosage. BG curve can provide onset of insulin action, glucose nadir (lowest BG value), time to glucose nadir, duration of insulin action and average blood glucose. This information can then be useful in determining glycemic control and making necessary adjustments in dosage. Despite the useful information that can be determined with serial blood glucose monitoring the testing may be stressful and there is often significant day-to-day variations in glucose values.
Continuous glucose monitoring (CGM) is increasingly popular, cost effective and available; it utilizes real-time measurement of interstitial glucose levels (every 1-2 minutes) via an indwelling subcutaneous flexible electroenzymatic polyurethane membrane probe/needle attached to a small sensor that adheres to the surface of the patient’s skin and a handheld telemetry recording unit (dedicated reader or smartphone). CGMs may be valuable for a variety of diabetic patients: those with a new diagnosis, those with poorly regulated diabetes, and those with complications of diabetes, such as hypoglycemia (insulin overdose or alterations of insulin requirements) and DKA. The Freestyle Libre senses glucose from 40 to 500 mg/dL. Changes in interstitial glucose lags 5 to 12 minutes behind blood glucose. Interstitial glucose may be up to 20 mg/dL lower than blood glucose at peak levels.

Glycosylated blood proteins are used to assess mean blood glucose concentration over an extended period of time. Glucose binds to several proteins in circulation, including fructosamine and hemoglobin A1c (HbA1c), creating glycated proteins. As plasma glucose concentrations increase, glycosylation increases proportionately. Fructosamine is formed by glycation of total serum proteins; albumin is the most abundant protein in plasma with a half-life of ~8 days so fructosamine concentrations

generally reflect the plasma glucose concentration over the previous 1–2 weeks. Fructosamine has been more commonly used for diabetic monitoring than HbA1c because introductory diabetic treatment is often adjusted within a 1–2 week periods. Fructosamine concentrations less than 400-450 mg/dl are generally associated with good diabetic control, serum fructosamine of 450-550 mg/dl indicates fair control, serum fructosamine greater than 550 mg/dl indicate poor glycemic control. Relative change in serum fructosamine may be more helpful than absolute values in many cases so it is critical to obtain a baseline pre-treatment fructosamine value in recently diagnosed diabetics to allow for comparison over time.
HbA1c is formed by the irreversible chemical binding of glucose molecules to the amino-terminal group of hemoglobin. Considering the long half-life of red blood cells, the concentration of HbA1c reflects the average plasma glucose concentration over the previous 2–3 months.

Considerations when encountering difficult diabetic management
When a patient remains persistently PU/PD and hyperglycemic the insulin requirement may be underestimated and a dose increase is needed. However, also consider other possible explanations such as rapid insulin metabolism, slow or impaired subcutaneous absorption of insulin and insulin administration errors (failing to properly administer insulin will mimic insulin underdosage or resistance). After teaching a client the technique of insulin administration you must follow-up to be sure that they have mastered the task. Have a nurse observe and evaluate insulin handling and administration technique. Biological activity of insulin can also be diminished by aging (outdated), overheating and inappropriate mixture which can alter insulin activity. Avoid diluting insulin preparations - use full strength solution with small insulin syringes or an insulin pen. Diluting insulin may not be as accurate as thought and may impair insulin stability. Any error resulting in “underdosage” of insulin will cause us to increase insulin dosage. This may lead to eventual insulin overdose when a new bottle is obtained or the administration is corrected.
Insulin overdosage is a common issue in our patients. Be careful to increase insulin dosage in small increments and no more frequently than once weekly in stable patients. Identify patients that are sleepy, lethargic or weak 2-6 hours post insulin administration. If transient hypoglycemia is observed during monitoring then too much insulin is being given. If a large rapid drop in glucose is observed following insulin then the dose is too high. The **Somogyi effect** results in persistent hyperglycemia and is a common occurrence with intermediate-duration (especially NPH) insulin formulations. Consider reducing the insulin dose in patients receiving relatively high insulin dosages but still showing persistent hyperglycemia especially if their dose has been rapidly escalated during initial treatment.

Make an effort to identify any concurrent medical disorders creating insulin-resistance such as acromegaly (cats), chronic pancreatitis, exocrine pancreatic insufficiency, hyperadrenocorticism, hypothyroidism, hyperprogesteronism (intact female), bacterial urinary tract infection, chronic inflammatory disorders of the skin and oral cavity and ongoing drug therapies.

FELINE HYPERTHYROIDISM
Updated Testing and Treatment Considerations

Introduction Feline hyperthyroidism (FHT) is the most common endocrine disorder in the domestic cat with a reported world-wide prevalence of up to 10% in cats > 10 years of age. The definitive cause is still undetermined. Most cats exhibit "classic" hyperthyroidism associated with clinical metabolic signs. However, routine screening and more sensitive tests now allows recognition of disease at earlier stages. Concurrent cardiac and renal co-morbidities are common. Definitive or supportive treatment options are available and present a decision to clinicians and owners as to which is appropriate for each individual patient.

Etiology Functional thyroid adenoma or adenomatous hyperplasia is responsible for approximately 95% of FHT cases. Malignant thyroid carcinoma accounts for 2-5% of cases. Most patients (>80%) have bilateral glandular involvement. There is no recognized sex or breed predilection. Siamese and Himalayan breeds have apparent decreased risk. The average age of affected cats is 13 years with individual ages ranging from 4 to 24 years of age.

Altered G-protein or tumor suppressor gene p53 expression within thyroid tissue play a role in the development of feline thyroid adenomatous tissue, however, the cause of these alterations remains undetermined. Environmental and dietary compounds have been suggested as causative factors. Phenol and halogenated hydrocarbon compounds, fire retardants (PBDEs, PFASs), deodorized cat litters, can fish and liver cat foods (higher in iodine content) have been suggested. Exposure to house dust during routine grooming may be a relevant exposure pathway for the ingestion of some PBDEs and PFASs.

History and Clinical Signs There is no single pathognomonic sign for FHT. Clinical signs are not exclusive to FHT and may be seen with other feline medical disorders. Clinical signs vary depending on the severity of disease at the time of diagnosis; signs may be subtle or absent in early FHT. The most common presenting signs include weight and muscle loss, polyphagia, polydipsia, polyuria, vomiting, diarrhea, hyperactivity, frequent vocalization and unkempt hair coat; bulky foul smelling stool is frequently noted. Ten percent (10%) of cats present with apathetic FHT with extreme lethargy, weakness, weight loss, poor appetite and cardiac abnormalities.

Physical Examination Findings Common examination findings include palpable thyroid gland(s), reduced body condition score (BCS), diffuse muscular atrophy (MCS), unkempt hair coat, tachycardia, tachypnea, systolic murmur and gallop rhythm. Ocular hypertensive changes may also be present.

Differential Diagnoses that should be considered include : Diabetes mellitus, chronic kidney disease, gastrointestinal disorders (CE, IBD, lymphoma), pancreatic disease (chronic pancreatitis, EPI), chronic hepatic disease and feline cardiomyopathy.

Laboratory Abnormalities Common laboratory findings include : mildly increased hematocrit/RBC, mild leukocytosis (neutrophilia, monocytosis); increased ALT,

increased ALP (less common); increased serum phosphorus (increased bone turnover); mild hyperglycemia (stress), decreased serum fructosamine (increased protein metabolism). BUN, creatinine and SDMA may be increased and urine specific gravity may be isothenuric/hypostenuric (effects of PU/PD and/or concurrent CKD).

Ancillary Diagnostics Blood pressure determination should be performed in FHT candidates as hypertension is a common finding. Approximately 30% of FHT patients exhibit cardiomegaly on survey thoracic radiographs; < 5% have signs of CHF (effusion, edema). Sinus tachycardia with increased R wave amplitude is the most common ECG abnormality. Echocardiography may reveal left ventricular hypertrophy and atrial enlargement; advanced chronic FHT may result in advanced systolic dysfunction with volume enlargement of all chambers associated with reduced ventricular indices.

Thyroid Testing

Five (5) clinical categories are described to aid in a systematic and categorical approach to the diagnosis of FHT :

1. Classic clinical FHT disease. Clinical hyperthyroidism and elevated serum T4.
2. Subclinical (early) FHT. Cats without overt clinical signs, but some suggestive physical exam findings and a normal serum T4.
3. Possible FHT with concurrent non-thyroidal illness. Cats with clinical hyperthyroidism signs but a normal serum T4 value.
4. Enlarged thyroid gland without clinical hyperthyroidism. Cats without clinical hyperthyroidism signs, enlarged thyroid gland(s) and a normal serum T4.
5. Clinically normal. Cats with no clinical signs of hyperthyroidism, no palpable thyroid nodule but an elevated screening T4 test.

Total T3 and T4 testing. Serum T3 determination is of no diagnostic value as T3 concentration is within reference range in a third of the cats with hyperthyroidism. FHT diagnosis is based on the findings of an elevated serum total thyroxine (T4) in association with appropriate clinical signs (category 1). The specificity of total T4 for diagnosis of FHT is 98.5%. The sensitivity of T4 is ~ 91%. Thus, T4 is rarely elevated in non-FHT cats but may be in the normal range in 8-10% of true FHT patients. This is most commonly seen in early FHT (category 2); a second T4 sample should be evaluated several weeks later as thyroid hormone fluctuations occur over days (not hours). T4 values can also be normal (usually high normal range) in FHT patients with non-thyroidal illness (category 3); the T4 will increase above normal once the underlying illness is corrected. In some cases thyroid gland enlargement can be palpated prior to T4 elevation (category 5). In other cases, serum T4 is elevated before any physical or clinical signs of FHT (category 6).

Additional diagnostic tests should be performed in cats in which FHT is suspected (categories 3-5) but initial clinical signs and T4 levels are not in agreement. In many

cases a repeat total T4 can be determined in weeks to months to confirm the FHT diagnosis especially if clinical signs are progressive.

Free T4 (fT4) evaluation. Free T4 is a very sensitive (98.5%) test for detection of FHT. However, lower specificity (~ 80%) associated with the fT4 test can lead to misdiagnosis and inappropriate treatment of euthyroid cats as cats with non thyroidal illnesses may have an elevated fT4. An elevated total T4 and elevated fT4 is confirmatory for hyperthyroidism. An elevated fT4 value along with suggestive clinical signs and a serum T4 in the upper 50% of basal resting range, while highly predictive of FHT, does not confirm a diagnosis of FHT as almost 20% of these cats may be euthyroid. In these cases evaluating total T4, fT4 and fTSH or other testing methods is recommended.

TSH evaluation. Excess autonomous serum thyroxine (T4) production associated with FHT should strongly suppress pituitary TSH production via negative pituitary-thyroid axis feedback. A canine TSH assay has been used to evaluate feline TSH but this cTSH assay cannot accurately measure very low TSH concentrations to reliably distinguish euthyroid cats with low-normal TSH concentration from hyperthyroid cats with a truly low or completely suppressed TSH concentration. A highly sensitive, feline-specific TSH assay (Truforma, Zomedica) has recently been introduced which should eliminate the problems associated with use of the cTSH assay in cats and should greatly improve the diagnostic utility of TSH testing to establish FHT diagnosis and in monitoring response to therapy.

T3 suppression test. Administering oral T3 will suppress TSH and T4 production via negative pituitary-thyroid axis feedback in normal individuals. Normal cats suppress T4 > 50% from pretreatment basal level in response to exogenous T3 administration. Test instructions : Determine basal (pre) T4 & T3 levels. Administer Liothyronine (T3) 25 ug dose PO every 8 hours for 2 days, then give a final dose on morning of day 3. Determine post T4 & T3 levels 4 hours after final dosing. Assess degrees of T4 suppression (euthyroid > 50% suppression, FHT cats < 50% suppression).

Thyroid imaging (scintigraphy). Thyroid scintigraphy provides information regarding thyroid anatomy and physiology and can play a role in the diagnosis, staging, and management of hyperthyroidism in cats. A short-acting radioactive isotope pertechnetate [$^{99m}TcO_4^-$]) is administered intravenously and concentrates in thyroid tissue. One hour later, ventral and lateral view are obtained with a gamma camera to acquire thyroid gland images. Imaging directly visualizes normal thyroid gland tissue, as well as any tumor(s) responsible for hyperthyroidism. Thyroid imaging is sensitive and can demonstrate the presence of overactive thyroid tumors even before the serum T4 concentration increases. Scintigraphy can be valuable in borderline cases when unilateral disease is present or bilateral uptake can be clearly demonstrated.

Thyroid scintigraphy can also play an integral role in staging and management considerations. The severity of hyperthyroidism cannot be adequately determined with thyroid blood tests alone. Scintigraphy identifies thyroid tumors no matter where the tumor tissue is located. The scan will detect tumor tissue that has invaded into the chest or metastasized to another part of the body. Scintigraphy accurately determines thyroid

tumor volume and a therapeutic radioiodine dose can be calculated to eliminate tumor cells while sparing normal thyroid tissue. Many hyperthyroid cats are treated with lower doses of radioiodine (<2 mCi) following scintigraphy evaluation. This is a low dose compared to the higher doses of radioiodine (3.5-5 mCi) administered in treatment facilities that do not perform thyroid scans to measure the tumor volume. Lowering the 131-I dose lowers whole body radiation exposure and lowers the prevalence of post-treatment hypothyroidism which can occur with larger radioiodine dosages.

Feline Hyperthyroid Treatment Options

Spontaneous remission of hyperthyroidism does not occur in cats. he primary goal of treatment is to normalize secretion of thyroid hormones. An additional important consideration is to remove or destroy the cat's abnormal thyroid tissue (95% benign, up to 5% malignant). Early intervention will prevent the growth and spread in case of malignant tumors. Studies demonstrate that the prevalence of malignant thyroid cancer can increase to over 25% in cats treated medically for over 4 years.

Definitive Treatments

Radioactive Iodine (I-131). Following subcutaneous administration, radioiodine (I-131) concentrates within and destroys abnormal overactive thyroid tissue but has minimal impact on normal thyroid tissue and non-thyroidal tissues. Radiotherapy is 95-98% effective in permanently resolving benign FHT and avoids surgery, anesthesia, and anti-thyroid drugs. T4 production generally reduces to the normal range 7-10 days following treatment. The patient will require hospitalization at a certified radioactive center for up to 3-7 days until radiation emission levels are minimal. Iatrogenic hypothyroidism can develop as a consequence of treatment. This has been associated more often with fixed-dose protocols with iatrogenic hypothyroidism developing in 30% to 80% of cats within 6 months of treatment. An individualized dosing, algorithm resulting in a lower median dose, has been described that results in a >96% cure rate, but also decreases the incidence of clinical hypothyroidism (~ 4%) following therapy. Iatrogenic hypothyroidism may “unmask” chronic renal disease due to reduced GFR. Recurrence of hyperthyroidism may occur in a small percentage of I-131 treated cats.

Surgery. Complete surgical excision of affected thyroid gland(s) with preservation of the parathyroid glands can be performed as a definitive FHT treatment. Patients should receive pre-operative medical or dietary therapy to reduce thyroid hormone level to reduce anesthetic risk. Pre-operative scintigraphy imaging can determine unilateral vs bilateral involvement and identify any ectopic or metastatic thyroid tissue in the neck or thoracic cavity. Staged thyroidectomy has been suggested to reduce the likelihood of post-op hypothyroidism and hypoparathyroidism. Less common complications may include laryngeal paralysis and Horner’s syndrome. Restoration of euthyroid status following bilateral thyroidectomy has been reported in 66-90% of patients. A recent study reported only 40% returned to euthyroid status after bilateral thyroidectomy, and two-thirds of those did develop hypothyroidism. Recurrent hyperthyroidism following bilateral thyroidectomy is reported in 10-60% of cats.

Ethanol Ablation. Ethanol can be injected directly into abnormal thyroid tissue if it can be visualized with ultrasound. Chemical ablation of affected tissue will result in reduced T4 production. Laryngeal paralysis and Horner's syndrome may occur if the adjacent recurrent laryngeal nerve is affected.

Supportive Treatments

Anti-Thyroid Medications

Methimazole, carbimazole and propylthiouracil (PTU) act by blocking conversion of iodothyronines to T3 and T4. Methimazole is most frequently prescribed. PTU can have significant hematologic side effects so is less frequently used. Methimazole (Felimazole) is initially dosed at 2.5 to 5 mg PO QD. Compounded transcutaneous methimazole is also effective. Following treatment initiation, total T4 should be rechecked along with CBC & renal values every 1-2 weeks for the first 30 days. Dose adjustments are made based on subsequent total T4 values. Once a normal total T4 is established the dose should be continued and the patient should be monitored for signs of hypothyroidism or hyperthyroidism. Total T4 (and fTSH) should be monitored every 3-6 months on a serial basis. The most common adverse drug effects are anorexia, vomiting and diarrhea occurring most commonly in the first month of treatment; approximately 15% incidence is reported. A potentially more serious adverse reaction is neutropenia; this can usually be reversed by stopping the medication. Cat and owner compliance my be a concern with ongoing daily oral treatment. Methimazole does not address continued growth of the abnormal thyroid tissue.

Iopanoic acid (Telepaque) is an oral iodinated contrast agent which blocks peripheral conversion of T4 to T3. A dose of 50 – 200mg PO BID is suggested. It is safe with no significant side effects. Treatment efficacy is 60-70% in cats with mild to moderate FHT. Monitoring treatment is primarily based on reduction of clinical signs and serum T3 value; the total T4 value will remain elevated.

Dietary Management of FHT

A commercial diet (Hill's Prescription y/d, iodine 0.2 ppm dry, 0.1 ppm can) is available for FHT treatment. Limiting dietary iodine below 0.32 ppm has been shown to reduce thyroxine levels in most clinical FHT cats generally within 3-4 weeks following introduction. The diet appears safe and effective in multiple studies although whether the diet restores true euthyroidism and whether long term iodine and protein restrictions are safe is debated. An FHT patient must eat this diet exclusively which can be problematic if the cat has outdoor exposure and in multi-cat households. Dietary iodine restriction, similarly to methimazole, will not address continued growth of the abnormal thyroid tissue.

Hyperthyroidism and Anesthesia

If a clinical / classic FHT patient is going to receive general anesthesia for thyroidectomy it is advisable to reduce serum thyroxine level prior to anesthesia to reduce potential complications associated with hypermetabolism, tachycardia, hypertension, etc… Clinical FHT cats can be treated with oral or transdermal methimazole (2.5 – 5 mg PO QD) for 2 weeks or Science Diet Prescription y/d for 3-4 weeks to reduce total T4 concentration to the mid to higher normal range.

Hyperthyroidism and Renal Disease

The hypermetabolic state produced by thyrotoxicosis is associated with many metabolic alterations, one of which is increased glomerular filtration rate (GFR). This effect may "mask" the diagnosis or severity of chronic kidney disease (CKD) in geriatric cats. Thyroid treatment does not result in direct kidney damage but the reestablishment of euthyroidism will reduce GFR and some increase in serum creatinine and SDMA is expected. Some treated cats, especially if treatment results in hypothyroidism, can develop significant azotemia or clinical uremia due to this "unmasking" treatment effect and survival time decreases significantly in this population. Age (older), sex (F), pre-treatment serum TSH concentration (detectable), bilateral and homogeneous 99mTc-pertechnetate scintigraphy uptake, severity score, and percent I- 131 uptake (high) are factors that may predict post-treatment iatrogenic hypothyroidism. Pretretment with methimazole does not affect the treatment outcome. Levothyroxine can be administered to any cat developing clinical signs and /or azotemia associated with post-treatment iatrogenic hypothyroid in order to establish and maintain a normal serumT4 value and stable GFR.

Hyperthyroidism and Heart Disease

In patients with concurrent FHT and cardiac disease it is imperative to correct the hyperthyroidism while providing appropriate heart disease therapy if indicated. Correction of FHT may spontaneously improve cardiac status over time if cardiac disease is a direct result of hyperthyroidism and/or hypertension. Serial monitoring of cardiac status during and following FHT treatment is imperative. NT-proBNP values increase in cats with hyperthyroidism and usually decrease within 3 months of establishment of euthyroidism; a persistent increase in NT-proBNP would suggest ongoing cardiac disease and should be investigated.

HYPOTHYROIDISM
Updated Testing and Treatment Considerations

Introduction

Hypothyroidism is the most common and frequently diagnosed endocrinopathy in dog. Studies suggest approximately 1 in 200 dogs is affected. Naturally occurring hypothyroidism is a rare medical disorder in cats. Under the influence of pituitary thyrotropin (TSH), the thyroid glands produce the thyroxine (T4) and 3,5,3'-triiodothyronine (T3) hormones. Thyroxine (T4) and T3 direct many aspects of cellular metabolism and their levels in the body are thus tightly regulated. Dysregulation of T3 and T4 levels has far reaching effects. Signs of thyroid hormone deficiency are often vague, non-specific and not pathognomonic. No single test exists with which to make a definitive diagnosis. Instead, a diagnosis of hypothyroidism is made based on a combination of clinical signs, physical examination findings, biochemical abnormalities and thyroid function tests. With a combination of tests, a diagnosis of hypothyroidism can be reached with confidence in a patient with suggestive clinical signs. However, clinicians must keep in mind that age, non-thyroidal illness, some medications, physical activity level and antithyroglobulin antibodies, may alter results of thyroid function tests. Once a diagnosis has been made this disease is controlled with oral thyroid hormone supplementation and euthyroidism is reestablished. A rare but serious complication of severe hypothyroidism is myxedema coma.

Etiopathogenesis

Congenital hypothyroidism is an inherited autosomal recessive trait causing thyroid peroxidase deficiency (rat terriers, toy fox terriers) or thyroid-stimulating hormone(TSH) or thyrotropin-releasing hormone (TRH) deficiency (giant schnauzers).

Adult-onset primary hypothyroidism, the most common form, is caused by lymphocytic thyroiditis or idiopathic thyroid atrophy. Reported mean age is 7 years (range, 0.5–15 years). Spayed and neutered dogs are at increased risk compared with intact dogs. Golden retrievers, Doberman pinschers, Boxers and spaniels are predisposed but any breed may develop hypothyroidism. Lymphocytic thyroiditis is characterized by immune infiltration of the thyroid gland by lymphocytes, plasma cells, and macrophages resulting in eventual glandular tissue destruction and replacement with fibrous connective tissue. Lymphocytic thyroiditis is heritable in beagles and borzois; heritability is suspected in other breeds. Hypothyroidism secondary to lymphocytic thyroiditis appears to develop at a younger age than idiopathic thyroid atrophy. Idiopathic thyroid atrophy is characterized by replacement of the thyroid parenchyma by adipose tissue; fibrosis and inflammation are minimal. Thyroid carcinoma is a rare cause of hypothyroidism, which does not develop until at least 75% of the thyroid glands have been destroyed.

Secondary hypothyroidism, caused by decreased thyroid-stimulating hormone (TSH) release from the pituitary, has rarely been reported. Tertiary hypothyroidism, caused by hypothalamic dysfunction, has not been proven in dogs.

Clinical Signs

Clinical signs associated with hypothyroidism are vague and involve many different systems. The most commonly reported clinical signs include dermatologic abnormalities, weight gain, lethargy, and weakness. Most changes appear to be related to the effects of decreased metabolism.

Dermatologic changes, including alopecia, seborrhea and pyoderma are common. However, changes in the epidermis and hair coat are often breed specific and are not noted in every patient. Bilateral symmetric nonpruritic truncal alopecia is reported in 88% of hypothyroid dogs. Thyroid hormones initiate and maintain anagen (active hair growth) so most hair follicles are retained in telogen (resting phase of the hair cycle) in hypothyroidism. The hair coat becomes dry, scaly, dull and brittle. Hair loss is noted in areas of increased wear and usually includes the ventral thorax and neck, ventral abdomen and tail. Loss of primary hair is most common with guard hairs being retained, resulting in a short fine hair coat. Clipped hair is slow to regrow. Hyperpigmentation may be noted in areas of alopecia. Skin biopsies reflect similar changes to other endocrine disorders however, certain findings, including dermal thickening, myxedema and vacuolation of arrector pili muscles, are most characteristic of hypothyroidism.

Pyoderma, dermatitis, seborrhea, hyperkeratosis, myxedema and otitis externa are less common skin features. Lack of thyroid hormone reduces the lymphoid immune response making the skin more susceptible to infection.

Neurologic abnormalities are reported but uncommo. Most neurologic signs are associated with polyneuropathy and include weakness, facial nerve paralysis, vestibular signs (usually peripheral) and hyporeflexia. The pathogenesis is likely multifactorial with muscular and peripheral nerve contributions including segmental demyelination and axonopathy and myxedema causing compression of cranial nerves. Megaesophagus and laryngeal paralysis have both been suggested to be associated with hypothyroidism; however, there are no data to support this association. Central nervous system signs, including seizures, ataxia, behavior changes and coma, are rarely seen.

Cardiovascular abnormalities are uncommon but reported. Conduction and direct myocardial effects may be noted. Slower heart rate, decreased systolic contractility and diastolic dysfunction have been reported. In the hypothyroid state there is a decreased B-adrenergic receptor number, accounting for decreased contractility and lower heart rates. A direct link to congestive heart failure has not been documented in dogs but hypothyroidism with concurrent primary cardiac disease may result in CHF.

Ocular changes can include corneal cholesterol deposits, keratoconjunctivitis sicca and conjunctivitis, however, these signs are reported in less than 1% of all hypothyroid dogs.

Myxedema coma is a very rare, life threatening, extreme manifestation of severe hypothyroidism and is considered an endocrine emergency. Mortality is reportedly high (up to 60%).· Myxedema coma must have a precipitating event, such as a serious

infection, that overwhelms normal homeostatic mechanisms. The greatest challenge with treating myxedema coma is recognizing the syndrome.

Several reproductive abnormalities have been suggested to be associated with hypothyroidism. There has been no conclusive data to support an association between decreased thyroid hormone levels and reproductive failure in either males or females dogs. When reproductive failure is documented, causes besides hypothyroidism must also be investigated.

Laboratory Findings

Hypercholesterolemia, hypertriglyceridemia and hyponatremia are commonly noted. These changes are the result of the decrease in normal lipid metabolism accompanying hypothyroidism. Hypothyroid dogs have increased very low density lipoproteins, low density lipoproteins and high density lipoproteins. Increased triglyceride levels may play a role in the development of gastrointestinal dysfunction and/or pancreatitis. Elevated levels of cholesterol and triglycerides have been associated with atherosclerosis in dogs, though clinical effects are rare.

Alkaline phosphatase (ALP) & alanine aminotransferase (ALT) may be slightly elevated.

Anemia is common finding. Approximately 1/3rd of hypothyroid dogs demonstrate mild normochromic, normocytic and non-regenerative anemia. Decreased erythropoietin production, reduced response of progenitor cells to erythropoietin and decreased response of early hematopoietic stem cells are reported. The hypothyroid state does not affect peripheral red blood cell life span.

Thyroid Function Tests

Quantitative technesium scans and thyroid biopsy are considered the gold standard for the diagnosis of hypothyroidism. Other tests are more routinely used to help clinicians evaluate thyroid function, thyroid hormone levels and antithyroglobulin antibody levels. These tests include total T4 (TT4), free T4 (fT4), endogenous canine TSH (cTSH), antithyroglobulin antibodies (ATA), anti-T3 antibodies and anti-T4 antibodies.

A common initial test to screen thyroid function is TT4. **Total T4** is a direct assessment of the functional ability of the thyroid tissue to produce hormone. Total T4 measures both the protein bound T4 and the fT4. A decreased TT4 is a common finding in a true hypothyroid patient with suggestive signs making this a very sensitive and predictive test. However, it is a nonspecific screening test so a low TT4 is not diagnostic of hypothyroidism as some euthyroid dogs may have low TT4 levels because of age, individual variation, nonthyroid illness, or concurrent drug administration. Euthyroid sight hounds and sled dogs often have TT4 levels below the reference range.

Free T4 (fT4) measures the metabolically active portion of TT4. This fraction of the hormone is able to enter the cell, be converted into T3 and interact with the thyroid hormone receptor. Hypothyroid animals would be expected to have a low fT4. This test, like TT4, has most value as a screening test. Concurrent illness has less effect on fT4

levels, compared to TT4. However, glucocorticoids, phenobarbital and hyper-adrenocorticism have been noted to cause a decreased fT4 values. There are different methods by which to measure serum fT4. Measurement by equilibrium dialysis has been demonstrated to be most reliable in the past, however, veterinary-specific chemiluminescent and BAW assays appear to have comparable diagnostic accuracy as the free T4 ED test.

Measurement of **endogenous canine TSH (cTSH)** is available. In the hypothyroid state, endogenous TSH level would be expected to be elevated, due to lack of negative feedback. Increased TSH in conjunction with decreased TT4 or fT4 is specific for hypothyroidism; however, 33% of hypothyroid dogs have normal TSH concentration. cTSH is a test with a high specificity and low sensitivity. Since TT4/fT4 and TSH are both elements of the feedback mechanism of the hypothalamic-pituitary-thyroid axis, they should be interpreted together. In other words to accurately understand the significance of a TSH level, the clinician should know the TT4 or fT4 level.

Immune-mediated lymphocytic thyroiditis may result in the production of **antithyroglobulin, anti-T3 or anti-T4 antibodies**. It is possible to test for ATA and a positive titer is predictive of immune mediated thyroiditis and suggestive of developing hypothyroidism. Anti-T3 and T4 antibodies may create a problem when attempting to make a diagnosis of hypothyroidism. The antibodies are similar to T3 and T4 and will cross react to falsely elevate total T3 & T4 assay levels. Therefore if anti-T4 antibodies are present, the TT4 level will be reported to be higher than it actually is. This situation is of most concern for animals whose TT4 is truly just below the normal range. With the presence of anti-T4 antibodies, these animals may actually appear to be euthyroid, thus delaying diagnosis and treatment of hypothyroidism. Free T4 measured by dialysis is not affected by the presence of antithyroglobulin, anti-T3 or anti-T4 antibodies. In some situations the ATA will be positive but the TT4 and fT4 levels will be well within normal ranges and the animal will not be exhibiting any clinical signs associated with hypothyroidism. These cases demand close monitoring and re-evaluation, as these may be animals at risk of developing hypothyroidism.

TSH and TRH stimulation testing using human recombinant hormones is expensive with limited availability.

Cervical **ultrasound** of the thyroid gland may be able to distinguish between hypothyroid and euthyroid dogs. A significant difference in thyroid gland volume and echogenicity between hypothyroid and euthyroid patients is reported. There is no significant difference between euthyroid and sick euthyroid subjects. Thus ultrasonography may be an adjunctive diagnostic tool but limitations include the need for high quality and resolution probes and a skilled and trained operator to complete the test.

Diagnostic Conclusions

Investigation of hypothyroidism should be based on an increased index of suspicion. All available tests are tools veterinarians can combine to help arrive at the diagnosis of

hypothyroidism. While owners may want to avoid additional diagnostics beyond decreased TT4 concentration, treatment without appropriate diagnostics should be avoided. Cost of treatment is expensive over time, and inappropriate diagnosis may lead to delayed diagnosis of another disease. It is also important to consider that an animal does not become hypothyroid overnight, a diagnosis of early hypothyroidism may require multiple serial measurements of TT4, fT4 and eTSH. A rising eTSH is very suggestive of ongoing thyroid destruction associated with immune mediated primary hypothyroidism.

In a patient with suggestive signs, the first step is to perform a highly sensitive test (TT4 and/or fT4) for screening and a more specific test (cTSH) to help confirm the diagnosis. When concurrent illness is present and cannot be resolved (i.e. diabetes mellitus, chronic renal failure), the TSH will be minimally affected the use of a combination of tests will arrive at a highly reliable result. Evaluation TT4 or fT4 and cTSH iwhen used in conjunction with has a specificity of 98%. There will be situations where the results of the tests are unclear. This may occur when there is early (subclinical) hypothyroidism, secondary hypothyroidism (sick euthyroid), athletic conditioning or anti-T4 antibodies are present. In these instances, a rational approach would be to retest the animal in 4-8 weeks time.

Treatment of hypothyroidism is easily achieved with levothyroxine supplementation. Clinical improvement and resolution of signs and laboratory abnormalities can also be used as a diagnostic test to confirm the diagnosis in difficult cases.

Treatment

Oral levothyroxine supplementation is initiated at 0.02 mg/kg q12h. Dose may be based on surface area for larger dogs (0.5 mg/m2). FDA-approved legend and generic products are recommended, as bioavailability varies among products. Administration with food decreases bioavailability.

TT4 and cTSH levels should be assessed 4 weeks after initiation of levothyroxine therapy or dose adjustment. a 4 hour post-pill blood sample is generally recommended. TT4 concentrations should be in the middle of the reference range to just above the reference range. The cTSH concentration should be decreasing or normalized if it was increased at time of diagnosis. Most importantly, clients should note an increase in the energy level in 1–2 weeks after instituting therapy, but consistent weight loss and dermatologic improvements are not usually obvious for at least a month, and hair regrowth can take several months.Patients that respond to therapy and have appropriate TT4 concentrations can be switched to q 24h therapy but may require a return to q 12h dose if response is not maintained.

Lack of a therapeutic response is common with an incorrect diagnosis based on only a low TT4 value. Other considerations for a poor clinical treatment response include decreased GI absorption, poor owner compliance, and concurrent unidentified skin problems (eg, flea hypersensitivity, atopy). Chronic levothyroxine overdosage may result in intermittent vomiting, diarrhea, hyperactivity, weight loss, hypertension, tachycardia, and tachypnea.

ADRENAL FUNCTION TESTS FOR DIAGNOSIS OF CUSHING'S & ADDISON'S

Introduction

Hyperadrenocorticism (Cushing's syndrome) and hypoadrenocorticism (Addison's disease) are common differential diagnoses for dogs with a variety of abnormal clinical signs and laboratory abnormalities. Serum cortisol determination, ACTH Stimulation testing, Dexamethasone Suppression testing and adrenal imaging are commonly performed diagnostic tests to evaluate adrenal gland function and anatomical structure. Performing and interpreting these diagnostic tests can be complicated, frustrating, unaffordable and inaccessible in some situations. Endogenous ACTH (eACTH) blood testing is an often overlooked test that is available to aid in the diagnosis of adrenal disorders allowing for accurate diagnoses and initiation of timely treatments.

Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine pathway and feedback loop that functions to maintain physiological glucocorticoid (GC) homeostasis. The HPA axis is governed by a closed-loop GC-dependent negative feedback system. HPA function is highly influenced by the amount and duration of GC exposure. The paraventricular nucleus of the hypothalamus contains neuroendocrine neurons that synthesize and secrete corticotropin-releasing hormone (CRH). CRH regulates the anterior lobe of the pituitary gland. In particular, CRH stimulates the secretion of adrenocorticotropic hormone (ACTH), also known as corticotropin. ACTH is transported by the blood to the adrenal gland, where it rapidly stimulates biosynthesis of glucocorticoids, including the end-product cortisol, in the zone fasciculata of the adrenal cortex. Cortisol is a major stress hormone with many physiologic effects on tissues throughout the body. Circulating glucocorticoids act via negative feedback on the hypothalamus and anterior pituitary to suppress CRH and ACTH production insuring tight regulation of the HPA neuroendocrine system. Hypoadrenocorticism (Addison's disease) and hyperadrenocorticism (Cushing's disease) result from deficient or excessive levels of these various hormones within the HPA axis.

Hyperadrenocorticism (Cushing's syndrome)

Cushing's syndrome, refers to an increase in adrenocortical hormones, regardless of cause. This includes pituitary-dependent hyperadrenocorticism (PDH), adrenal-dependent hyperadrenocorticism (ADH), and iatrogenic hyperadrenocorticism.
Pituitary-dependent hyperadrenocorticism (PDH), also referred to as ACTH-dependent HAC, arises from functional autonomous adenomatous tissue within the anterior pituitary gland, resulting in persistent and excessive ACTH production, ultimately stimulating excessive cortisol production by the adrenal glands. The adenomatous pituitary tissue does not respond to the negative cortisol feedback resulting in persistent production of ACTH and cortisol.
Adrenal-dependent hyperadrenocorticism (ADH), also referred to as ACTH-independent HAC, is associated with a functional adenoma(s) or adenocarcinoma(s) originating within the adrenal gland cortex and resulting in excessive cortisol production. Central

CRH and ACTH production is drastically reduced via negative feedback, however, excess cortisol is continually produced by the autonomous adrenal tumor.
Clinical signs of Cushing's syndrome are typical of cortisol (glucocorticoid) excess and include polydipsia, polyuria, polyphagia, "pot-belly" abdominal enlargement, panting, muscle weakness, alopecia, thin fragile skin, comedones, cutaneous hyperpigmentation, calcinosis cutis and pyoderma. Laboratory abnormalities are common including increased serum alkaline phosphatase (ALP), increased ALT, hypercholesterolemia, hyperglycemia, erythrocytosis and leukocytosis with a stress leukogram.

HyperAdrenoCorticism Diagnosis - The diagnosis of Cushing's syndrome is based on adrenal function tests that demonstrate excess circulating serum cortisol. The ACTH Stimulation Test or the Low Dose Dexamethasone Suppression Test (LDDS) are traditional adrenal function screening tests to determine the presence of cortisol excess.

The **ACTH Stimulation Test** assesses adrenocortical reserve. A basal (baseline) serum cortisol is obtained immediately prior to administration of Cosyntropin (Cortosyn®), a synthetic polypeptide containing biologically active amino acids of ACTH. The drug is often dosed intravenously at 5 mcg/kg; however, a 1 mcg/kg IV dose is also reported as effective in providing maximal adrenocortical stimulation. Peak adrenal cortisol secretion occurs by 60 minutes. A 1 hour post-Cosyntropin serum cortisol is performed and compared to the basal cortisol value to determine the degree of adrenal cortisol stimulation. Excess cortisol stimulation is suggestive of HAC. The sensitivity of the ACTH Stimulation test ranges from 80-83% for suspected PDH but decreases to ~ 60% for suspected ADH. Thus a negative (normal) ACTH Stimulation test does not exclude the diagnosis of HAC limiting its diagnostic usefulness as a screening test for spontaneous HAC. Specificity ranges between 60-93% so normal patients are less likely to test positive. Cortrosyn is expensive but can be reconstituted and frozen in aliquots and frozen in plastic syringes for 6 months. ACTH stimulation testing can be performed at any time of day. The effect of feeding on test results is unknown so fasting is recommended for this test. Exogenous glucocorticoids, progestagens, and ketoconazole suppress the HPA axis and decrease the response to ACTH; phenobarbital does not affect results. ACTH Stimulation is the test of choice for iatrogenic hyperadrenocorticism.

Low Dose Dexamethasone Suppression Test evaluates the negative effect of glucocorticoids on the HPA axis. A reduced ability to suppress cortisol production following dexamethasone is characteristic of HAC patients. Dexamethasone is given at a dose of 0.01 mg/kg IV with baseline, 4 hour and 8 hour serum cortisol determinations. The dose is calculated based on the parent dexamethasone compound (i.e., 1.3mg dexamethasone SP is equivalent to 1mg dexamethasone). HAC is confirmed by a cortisol concentration > 1.5 ug/dl at 8 hours following dexamethasone administration. The reported sensitivity of the LDDST ranges from 85-100% making it the ACVIM Consensus Panel screening test of choice hyperadrenocorticism unless iatrogenic HAC is suspected. The specificity of the LDDST ranges from 44 to 73% with false positive results common in patients with non-adrenal illness. The traditional LDDS test requires

3 serum cortisol samples and requires an 8+ hour time commitment.

Urine Cortisol : Creatinine Ratio (UCCR) testing provides an estimation of cortisol production while adjusting for fluctuations in blood concentrations over time. Urine should be collected at home to avoid stress-induced increases in blood cortisol. The UCCR sample should be collected in the morning because it usually represents several hours of urine production. This is a very sensitive test (range 75-100%) and can be useful to rule out to cortisol hypersecretion associated with HAC. Specificity is reported at 20-25% so it cannot be used to confirm HAC diagnosis. Normal daily activity and nonadrenal disease may result in endogenous stress and increased cortisol secretion. Therefore, high UCCRs in dogs without a high degree of clinical suspicion of HAC should be interpreted cautiously.

HyperAdrenoCorticism (Cushing's) discriminatory testing

Once hyperadrenocorticism is confirmed, discriminatory testing is undertaken to distinguish PDH (ACTH dependent) vs. ADH (ACTH independent) in order to plan appropriate treatment. Traditionally, this discriminatory testing is based on either the LDDS pattern, the High Dose Dexamethasone Suppression Test (HDDS) or adrenal gland imaging (ultrasound or CT). LDDS testing may exhibit a partial or escape suppression pattern suggestive for PDH in 60% of dogs. If the LDDS test is not diagnostic for PDH then historically HDDS testing or adrenal imaging is performed to discriminate between PDH or ADH. HDDS testing is not recommended based on the finding that up to 50% of dogs with PDH do not suppress on the HDDS test.

Diagnostic imaging of the pituitary and the adrenal glands can be performed via abdominal radiography, ultrasonography, CT, or MR in any dog that fails to suppress on LDDS or HDDS testing. Abdominal radiographs may reveal a mineralized mass in the area of the adrenal glands. Abdominal ultrasonography is a more sensitive way to identify adrenal tumors. CT or MRI of the abdominal cavity and/or pituitary gland may demonstrate an adrenal mass, pituitary macroadenoma or pituitary microadenoma. Disadvantages associated with diagnostic imaging are operator experience, potential need for patient referral, lack of local availability and associated cost.

Measurement of **endogenous plasma ACTH** concentrations is another way to discriminate between PDH and adrenal tumors (ADH). Dogs with adrenal tumors have significantly low to undetectable ACTH concentrations; in contrast, dogs with PDH have normal to increased ACTH concentrations. Endogenous ACTH hormone undergoes rapid degradation following sample collection. Samples for reference lab submission must be collected in whole blood EDTA tubes spun in a refrigerated centrifuge and frozen immediately or mixed with a protease inhibitor (aprotinin) to inhibit eACTH degradation. Recently an analyzer (Truforma®, Zomedica, Ann Arbor MI) has been validated to provide immediate point-of-care in-clinic eACTH determination.

Hypoadrenocorticism (Addison's disease)
Hypoadrenocorticism (HA) is a deficiency of adrenocortical hormones, seen most commonly in younger to middle-aged dogs; females are over represented. The disease may be familial in Standard Poodles, Nova Scotia Duck Tolling Retrievers, West Highland White Terriers, Great Danes, Bearded Collies, and Portuguese Water Dogs. Primary hypoadrenocorticism is caused by bilateral adrenocortical atrophy or destruction. It most commonly occurs as the result of a chronic autoimmune process but can also be caused by infiltrative granulomatous disease, metastatic cancer, hemorrhage, or infarction. Iatrogenic primary hypoadrenocorticism can result from adrenolytic agents (mitotane) or adrenal enzyme inhibitors (trilostane).
Clinical signs are generally non-specific and characterized by recurrent episodes of gastrointestinal signs, gradual progressive loss of body condition, and failure to respond appropriately to stress. Concurrent glucocorticoid and aldosterone deficiencies can result in acute circulatory collapse, acute renal injury due to progressive blood volume reduction and hypotension and significant electrolyte disturbances (hyperkalemia, hyponatremia). Clinical and laboratory abnormalities associated with primary hypoadrenocorticism will depend on the extent of adrenocortical destruction. Typical hypoadrenocorticism is associated with both glucocorticoid and aldosterone deficiencies. Isolated glucocorticoid insufficiency ("atypical" hypoadrenocorticism) can be seen in dogs with vague GI signs, weight loss, normal electrolyte concentration, hypoalbuminemia and hypocholesterolemia. Dogs with "atypical" primary hypoadrenocorticism can develop into typical cases over time as aldosterone production declines with ongoing adrenocortical destruction.
Secondary hypoadrenocorticism is the result of reduced endogenous ACTH production resulting from pituitary dysfunction. Secondary hypoadrenrocorticism will result in an "atypical" appearance as production of aldosterone remains intact. Glucocorticoid administration will result in reduced pituitary ACTH production and transient secondary hypoadrenocorticism may occur following abrupt glucocorticoid discontinuation.

HypoAdrenocorticism Diagnostic Testing - Adrenal function testing to confirm hypoadrenocorticism should be completed before replacement hormone therapy is started. The ACTH Stimulation Test assesses adrenocortical reserve and is the gold standard test for the diagnosis of hypoadrenocorticism. Affected HA dogs have low to undetectable baseline cortisol levels (<2.0 mcg/dL) and there is little to no response to ACTH administration in both primary and secondary cases. The cost and lack of readily available synthetic ACTH preparations (Cortrosyn®) in some practices limits the routine use of ACTH stimulation testing. Baseline (resting) cortisol concentrations are thus often substituted; a cortisol value >2.0 mcg/dL effectively excludes the diagnosis of hypoadrenocorticism (high specificity), whereas values <2.0 mcg/dL are not diagnostic for HA and require the use of ACTH stimulation testing to confirm the diagnosis.

Endogenous plasma ACTH determination can be valuable in establishing a diagnosis of hypoadrenocorticism and discriminating primary versus secondary causes. In cases of primary hypoadrenocorticism, the pituitary production of endogenous ACTH concentration is typically very elevated in an attempt to stimulate cortisol secretion from the damaged adrenal glands. Determination of concurrent serum cortisol and plasma

eACTH values can overlap in some healthy and hypoadrenal patients limiting their use. However cortisol-to-eACTH (CAR) Ratio values do not overlap allowing use of the hormone pairs in an endocrine feedback system. Thus, cortisol-to-eACTH ratio can reliably distinguish dogs with primary hypoadrenocorticism from healthy dogs with sensitivity of 100% and a specificity of 99%. Only one blood sample is needed, and the cost and inconvenience of an ACTH Stimulation test procedure is not required.
In HA dogs presenting with atypical hypoadrenocorticism (normal sodium and potassium levels) it is often not known whether typical HA will develop over time requiring additional mineralocorticoid supplementation along with glucocorticoid supplementation. The eACTH level can help determine this, as dogs with atypical primary HA have intact pituitary function with an elevated endogenous ACTH level but are likely to continue to destroy adrenocortical tissues over time allowing an eventual transition to typical HA. Dogs with secondary HA should very low to undetectable endogenous ACTH concentration due to pituitary disease and will maintain remain atypical only over time due to normal aldosterone production.

Urine Cortisol : Creatinine Ratio (UCCR) - A recently published 2022 retrospective study involving a small number of hypoadrenocortical dogs reports that UCCR may be helpful in diagnosing hypoadrenocorticism. The advantage of this test would be the requirement for only a single urine sample. The UCCR was significantly lower in dogs with hypoadrenocorticism as compared to healthy dogs and those with diseases mimicking hypoadrenocorticism. A UCCR cut-off value of <1.4 yielded 100% sensitivity and 97.3% specificity in hypoadrenocorticsm diagnosis in this small population study but significant limitations were reported.

PRACTICAL TREATMENT FOR CUSHING'S AND ADDISON'S PATIENTS

Introduction

Most canine patients with either pituitary-dependent or adrenal-dependent hyperadrenocorticsm (HAC) are treated with oral medication. Vetoryl® (trilostane) is the only drug approved by the FDA to treat both pituitary- and adrenal-dependent Cushing's in dogs. Anipryl® (selegiline), is FDA-approved to treat uncomplicated canine pituitary-dependent Cushing's. The human chemotherapy drug, Lysodren® (mitotane), has also been used as an "off-label" medical treatment for canine Cushing's disease for decades. Surgical removal of an adrenal tumor is generally reserved for patients with an uncomplicated tumor that hasn't invaded adjacent tissue structures and shows no evidence of metastatic spread. Surgical techniques to improve the ability to excise pituitary tumors in dogs are being continually investigated but surgery is not a widely prescribed treatment.

Dogs with hypoadrenocorticism (Addison disease) are medically treated. Treatment is generally lifelong but highly successful. Dogs with atypical Addison disease require only oral prednisone replacement. Dogs with typical Addison disease also require longterm mineralocorticoid replacement therapy with desoxycorticosterone pivalate (DOCP) or fludrocortisone acetate.

Medical Treatment of Hyperadrenocorticism

Most dogs with hyperadrenocorticism should be medically treated, however, that decision should be made on a case by case basis taking into consideration the patient's clinical signs, quality of life and the owner's desired goals. Drugs used for HAC treatment are expensive and have potential serious adverse effects. If clinical signs are truly mild or cosmetic (poor haircoat) only then treatment may be delayed or not initiated. If clinical signs are moderate to severe or associated with other comorbidities (hypertension, proteinuria, immunosuppression) then a decision to treat is more urgent.

Trilostane (Vetoryl®)

Trilostane is a 4a, 5-epoxysteroid competitive inhibitor of 3B-hydroxysteroid dehydrogenase-isomerase. The drug competitively inhibits adrenocortical progesterone metabolic pathways blocking end product synthesis of cortisol & aldosterone hormones. Trilostane was used in the treatment of Cushing's disease in humans decades ago but lost favor due to poor efficacy. Therapeutic use in dogs with PDH & ATH hyperadrenocorticism has been associated with good treatment efficacy. It was proposed that this drug, through its competitive inhibition of steroid production, would prove safer than mitotane (Lysodren®) which permanently destroys adrenal tissues. Vetoryl® (trilostane) received FDA approval in 2009 in dogs for treatment of pituitary-dependent hyperadrenocorticism and for treatment of hyperadrenocorticism due to adrenocortical tumor. The FDA label dose is 2.2-6.7 mg/kg PO QD. The FDA field study included 107 patients - 97/107 had some adverse reactions noted; 5 died, 2 developed permanent hypoadrenocorticism. Early post-release clinical experiences with trilostane noted adverse effects including anorexia, vomiting, diarrhea and weakness. Uncommon deaths due to acute adrenal necrosis and/or rupture were also reported. Post-release clinical experiences also provided evidence that trilostane has rapid drug response following oral administration but often does not suppress adrenal cortisol production beyond 12 hours following oral dosing in most patients. Serious side effects, including adrenal necrosis from pituitary ACTH hypersecretion, have been shown to result in a dose-dependent manner. These observations initially led to a suggested off-label dosing revision of 1-3 mg/kg PO BID. A subsequent study using a dosage of 3 mg/kg PO BID demonstrated adverse reactions in 25% of treated HAC patients. A later study using an average starting dosage of 1 mg/kg PO BID reported adverse reactions in only 10% of patients. The current off-label Vetoryl® (trilostane) dosing recommendation is a starting dose of 0.5 to 1.0 mg/kg PO BID with dose adjustments as needed based on clinical and laboratory monitoring. Larger breed dogs (>25kg) generally require less trilostane to control clinical signs. Trilostane should be given with food to improve intestinal absorption.

Trilostane therapy for HAC may lead to different outcomes including good clinical control and improvement in clinical signs, unsatisfactory control and ongoing HAC clinical signs or cortisol deficiency leading to hypocortisolemia. Close monitoring of patient status every 2 weeks is recommended initially. Clinical signs often improve within the first 2 weeks of therapy. Dermatologic signs can take 3-6 months before noticeable improvement is observed.

Trilosane dose adjustments are made immediately if clinical signs indicate hypocortisolemia. If the patient is stable and/or improving then dose adjustments are usually not considered for at least 4 weeks after initiating treatment as cortisol levels generally continue to decrease over the 30 day period with the patient receiving the same daily dose. Once satisfactory clinical control is achieved then patient status is checked every 3-6 months.

The best techniques to monitor and adjust trilostane dosage remains a controversial topic. It is well accepted that using clinical signs (owner perception) and serum cortisol value(s) are important monitoring tools; however the most appropriate protocol for serum cortisol evaluation remains unclear. ACTH Stimulation testing can be used to determine the effect of trilostane on cortisol production. Following a trilostane dose given with a normal meal, an ACTH Stimulation test is performed in 2 - 6 hours. The optimal timing of this test for all patients is unknown but it is important to perform all subsequent monitoring tests at the same time to reduce individual variability. The desired pre- and post-ACTH cortisol values are in the 1.5-5.5 ug/dL (40-150 nmol/L) range and indicate safe continuation of therapy. Cortisol values up to 9.0 ug/dL (250 nmol/L) are acceptable if clinical signs are well controlled. The dose should be stopped or reduced if the cortisol value is below 1.5 ug/dL (40 nmol/L) and the patient has clinical signs consistent with hypocortisolemia. If the patient is doing well and the cortisol value is below 1.5 ug/dL (40 nmol/L) the current dose can be reduced or a repeat ACTH Stimulation test could be performed later (8-9 hours) to determine if cortisol levels increase later in the administration interval. If owners report continued clinical signs and the post-ACTH cortisol value is > 5.5 ug/dL (150 nmol/L) then the trilostane should be increased gradually with close monitoring. In some cases an owner may report continued clinical signs with a cortisol value < 5.5 ug/dL – consider a TID dosing schedule trial in these patients.

Evaluation of using solitary pre-pill and/or 3 hour post-pill cortisol values have also been described. In Europe, a solitary pre-pill cortisol determination at the end of the administration interval just prior to the scheduled trilostane dose is suggested. If the serum cortisol valve is < 2 ug/dL (55 nmol/L) an ACTH Stimulation test should be performed. If the serum cortisol valve is > 2 ug/dL (55 nmol/L) and the patient is doing well clinically then the current trilostane dose can be continued. If a patient is exhibiting HAC clinical signs and the pre-pill cortisol is < 2 ug/dL (55 nmol/L) an ACTH Stimulation test should be performed; if the pre-pill cortisol is between 2 - 5 ug/dL (55 - 150 nmol/L) then the dosing frequency can be increased (QD to BID, BID to TID) or the dose can be cautiously increased; if the pre-pill cortisol is > 5 ug/dL (150 nmol/L) then the dose can be increased.

Excess adrenal suppression can occur with trilostane therapy and warrants discontinuation of the drug. Despite trilostane's action as an enzyme inhibitor, adrenal suppression can be rapidly reversible (e.g. within days) but suppression can last weeks to years in some patients. Basal cortisol or ACTH stimulation testing is recommended to document adequate return of cortisol production prior to reinitiating treatment. Compared to Lysodren®, trilostane causes less aldosterone suppression, however, serum electrolytes should be evaluated in any patient that becomes clinically ill.

Pituitary-dependent HAC has a good prognosis when appropriately treated with trilostane. Median survival times on trilostane have been reported in the 662 days (QD treatment) to 930 days (BID treatment) range. Adrenal-dependent HAC has been treated with trilostane when surgical tumor removal is not feasible or desired. Insufficient information is reported to determine treatment efficacy, however, in one report of adrenal tumor dogs treated with trilostane BID, the median survival was 14 months (range 3.3-55.0). A higher maximum trilostane dose may be required in these cases to adequately reduce cortisol production.

Mitotane (Lysodren, o,p'-DDD)

Mitotane (Lysodren®) has been used for more than 3 decades for the control of HAC in people and dogs. It is a potent adrenocorticolytic agent derived from the insecticide dichlorodiphenyltrichloroethane (DDT). This drug acts by destroying adrenocortical tissue. The drug causes progressive necrosis of the zona fasciculata and zona reticularis and, at higher doses, may also cause necrosis of the zona glomerulosa. The goal of mitotane therapy is to limit adrenal cortisol production on both pre- and post-ACTH stimulated values to the normal resting range (2–6 mcg/dL, 55-165 nmol/L).

When used and monitored appropriately, Lysodren® is efficacious in dogs and reportedly controls Cushinoid clinical signs in ~ 80% PDH patients with a more variable response in adrenal tumor patients. Treatment involves a daily induction phase to cause adequate adrenocortical cellular destruction and a maintenance phase to limit circulating cortisol values. Administering the drug with food improves its gastrointestinal absorption. The recommended mitotane induction phase is begun at a total dose of 50 mg/kg PO divided twice daily for 5 to 10 days, or until measured water consumption decreases to less than 100 mL/kg/day. Mitotane should be discontinued immediately if decreased appetite, depression, diarrhea, or vomiting is observed. Once the induction phase is completed an ACTH stimulation test should be performed to evaluate the cortisol response. If adequate cortisol suppression is not achieved then the daily induction phase can be continued for another 5-7 days and ACTH stimulation testing should be performed as soon as satisfactory reduction in clinical signs is noted.

Maintenance therapy with Lysodren® 50 mg/kg PO weekly or 25 mg/kg q 72 hours is started once the ACTH stimulation test demonstrates adequate suppression (pre- and post-cortisol measurements of ≥ 2 and ≤ 6 ug/dL, respectively). The goal of maintenance therapy is to limit adrenocortical tissue regrowth, limit cortisol production and control clinical signs. Clinical success is based on reduced Cushinoid clinical signs and maintainance of a post-ACTH cortisol value < 6 ug/dL (165 nmol/L). Follow-up

ACTH stimulation testing should be evaluated 1 month after starting maintenance therapy and then performed every 3-6 months or at any time if abnormal clinical signs are noted by the owner.

Because there is a variable treatment response in individual patients these are only guidelines. The induction dosage and time to control as well as the maintenance dose and follow-up monitoring periods should be individually adjusted as needed in each patient. The total weekly dose of mitotane required for long-term maintenance over time is quite variable (26–330 mg/kg/week); and should be titrated to effect based on clinical signs and subsequent ACTH stimulation test results.

Potential adverse effects include drug intolerance, reduced appetite, vomiting, diarrhea, lethargy, weakness, ataxia, hypoadrenocorticsim, permanent mineralocorticoid and glucocorticoid deficiency, and clinical HAC relapse (loss of response over time).

I do not routinely use oral prednisone treatment during Lysodren induction treatment. Glucocorticoids were typically administered in combination with mitotane therapy for many years, but it is no longer common to administer these drugs concurrently. However, prednisone therapy (0.2–0.5 mg/kg/day) should be initiated in patients with clinical signs of hypocortisolemia until results of the ACTH stimulation test are known. A small supply of prednisone should be made available to the owner in the event of overdose of mitotane. Dexamethasone can be used preferentially for emergency situations because it does not interfere with measurement of serum cortisol concentrations. If an individual patient experiences clinical signs (lethargy, hyporexia, vomiting, diarrhea) during treatment associated with a rapid drop in cortisol levels then a physiologic dosage of prednisone (0.25 – 0.5 mg/kg PO QD) can be administered and gradually tapered once a satisfactory clinical response is seen.

Other Medical HyperAC Treatments

At the present time there are no other practical or effective medical therapies for canine hyperadrenocorticism. Selegiline (Anipryl®) was approved for PDH patients but has exhibited limited success for this use. Ketoconazole has been used for HAC treatment as it inhibits adrenal cortisol production. The clinical effect is modest and its use now is primarily in countries where mitotane and trilostane are not available, or when these agents have failed to correct hypercortisolism or resulted in adverse reactions.

Medical Treatment of Hypoadrenocorticism (HA)

Emergency treatment of acute HA crisis is covered in detail elsewhere.
Maintenance HA treatment involves the administration of mineralocorticoid and/or glucocorticoid therapies. Dogs with primary HA generally require supplementation with both replacement hormones, however, in earlier stages of primary HA adequate aldosterone production may be present and the patient may only be deficient in glucocorticoid production (“atypical” HA). These patients usually will go on to develop typical HA with further loss of adenocortical cells over time. Secondary HA dogs are “atypical” glucocorticoid deficient only due to isolated loss of pituitary ACTH production.

All HA patients (typical or atypical) will require oral glucocorticoid replacement therapy. Prednisone or prednisolone should be provided at a starting dose of 0.5 to 1.0 mg/kg/day. This dose should be gradually tapered or increased over several weeks to an adjusted dose that controls signs of hypoadrenocorticism and avoids steroid side effects (e.g., PU/PD, polyphagia, panting). Maintenance prednisone doses are generally 0.1 to 0.22 mg/kg/day, but may be as low as 0.03 mg/kg/day in some patients. Larger dogs seem to be more sensitive to the side effects of glucocorticoids and can often receive a low daily dose. Hydrocortisone is preferred by some clinicians to reduce side effects. Dosage adjustments should be based on clinical signs only as there is no value to monitoring basal cortisol or ACTH stimulation testing. Electrolytes should be monitored in patients with atypical primary HA or undetermined status. Periodic sodium and potassium determination is recommended 2 weeks after diagnosis, then every month for 3 months, then every 3 months for 1 year.

Primary HA patients with mineralocorticoid (aldosterone) deficiency require replacement therapy to maintain normal serum electrolytes and fluid volume. Mineralocorticoid supplementation is available in 2 forms: daily oral (fludrocortisone) and monthly injection (desoxycorticosterone pivalate [DOCP]).

DOCP is a pure mineralocorticoid, thus concurrent glucocorticoid supplementation is always necessary and the GC dose can be adjusted independently. DOCP is more likely to normalize renin activity, so it may be a more effective mineralocorticoid supplement. Two brand formulations of DOCP are available: Percorten-V (Elanco) and Zycortal (Dechra). FDA label recommends an initial dose of 2.2 mg/kg every 25 days. A lower 1.5 mg/kg dose is effective in most dogs. Zycortal is labeled for SC administration; Percorten-V is labeled for IM administration only but can also be given SC off-label. After the initial DOCP dose of is provided, electrolytes should be checked at 14 days to assess dose response and at 25 days to assess the dose interval. If hyponatremia or hyperkalemia is present, plan to increase the next dose by 10% to 15%; if hypernatremia or hypokalemia is present, plan to decrease the next dose by 10% to 15%. At 25 days, if hyponatremia or hyperkalemia is present, shorten the subsequent dosing interval by 1 to 2 days; if electrolytes are within reference range, you may lengthen the dosing interval to 28-30 days. If electrolytes continue to remain within reference range the dosing interval can continue to be extended. Once the optimal dose and interval are determined, clients can be taught to give DOCP at home.

Fludrocortisone acetate (Florinef) possesses both glucocorticoid and mineralocorticoid activity. Although the dual functions may seem like a benefit, this can make it more difficult to titrate the drug to an acceptable dosage. Increasing the fludrocortisone dose to maintain sodium and potassium parameters, may result in a higher than necessary glucocorticoid effect and undesirable cortisol excess.
The starting dose for fludrocortisone is 0.01 mg/kg PO BID.

EARLY CHRONIC KIDNEY DISEASE
Recognition, Diagnostics and Treatment Considerations

Introduction
Approximately 1/3 cats and 1/10 dogs will develop CKD over their lifetime. CKD is more prevalent in older cats (> 10 years age) and mature dogs. The type of kidney disease associated with CKD differs with tubulointerstitial fibrosis predominating in cats and glomerulotubular disease predominating in dogs. Systemic and glomerular hypertension and proteinuria occur in both species.

Diagnosis of Early CKD

Diagnosis of early CKD prior to clinical signs and illness is vitally important to allow for intervention and slow progression. **Serum creatinine (sCr)** has long been the marker associated with renal function. sCr is freely filtered at the glomerulus and is not reabsorbed by renal tubules making it a surrogate for glomerular filtration rate ([GFR] estimation. Creatinine has an inverse but nonlinear relationship to GFR; as GFR declines sCr rises. However, this GFR and sCr relationship has limited sensitivity for detection of early CKD and a 75% GFR loss occurs before sCr rises above the laboratory reference interval. Conversely, in advanced CKD a significant increase in sCr is noted with minimal further small GFR decline. A further limitation of sCr is that production is dependent on individual patient muscle mass; higher sCr is present in well muscled individuals but sCr is lower in individuals with reduced muscle mass.

Symmetric dimethylarginine (SDMA) is a molecular by-product produced during routine metabolism in all mammalian cells. SDMA has small size and positive charge also allowing free glomerular filtration and no tubular reabsorption. SDMA begins to increase with 40% loss of GFR much earlier in the course of renal dysfunction. SDMA production is also not dependent on muscle mass. SDMA is used clinically to identify changes in renal function earlier compared to serum creatinine.

Fibroblastic Growth Factor (FGF23) is released by osteocytes in response to increased blood phosphorus levels. The net actions of this hormone are reduced renal tubular phosphate reabsorption and reduced intestinal phosphate absorption. Alterations in calcium, phosphate, vitamin D, parathyroid hormone, FGF23, bone metabolism and soft tissue calcification occurs early in CKD. Intact FGF23 can be measured in blood providing early insight into bone-mineral disease associated with CKD allowing appropriate early therapy considerations.

Computer-assisted **neural network algorithms (AI)** to predict CKD are available (Renaltech, Antech Diagnostics) in feline medicine. The practical importance of this testing to accurately predict future kidney disease is currently undetermined.

Urine examination for renal albumin loss **(proteinuria)** is another critical biomarker to uncover early CKD and is recommended as standard diagnostic screening evaluation as patients age. IRIS staging has established normals for urine protein:creatinine ratios (UPC) and microalbuminuria (MA) for dogs and cats. Proteinuria may be present with normal GFR early in renal disease process when all other blood-based and imaging

anomalies are lacking. Confirmation of persistent renal proteinuria serves as a warning signal that renal damage is present and treatments to reduce or resolve are necessary. Studies conducted in humans, dogs and cats demonstrate increased mortality associated with chronic proteinuria. Further testing should be undertaken to determine whether a secondary extra-renal disease process, such as chronic inflammation (teeth, skin, ears, GI, immune-mediated); infection (HWD, tick-borne, other regional); endocrine (adrenal, diabetes, thyroid) or neoplastic disease is present resulting in chronic glomerular entrapment of circulating immune complexes. If other disorders are eliminated then a primary glomerular disease is likely (immune-complex glomerulonephritis, degenerative glomerulonephopathy). Renal tissue biopsy or urine SDS-PAGE electrophoresis is recommended in patients with suspected primary glomerular disease to establish disease type, assess treatment options and determine prognosis.

Renal tissue cytology and/or biopsy may provide definitive information as to the cause of ongoing renal disease and should be considered when the information obtained is likely to alter patient management. Examples of such clinical situations might include evaluation of diffuse uniform renomegaly in dogs (lymphoma, fungal) and cats (lymphoma, FIP, fungal) and discreet nodular infiltrates and masses (tumors). Persistent proteinuria without an identifiable cause is also a reason for histologic examination. If kidney biopsy will not be performed in a dog with proteinuria, submission of urine for SDS-PAGE (sodium dodecyl sulfate polyacrylamide) electrophoresis may be helpful in suggesting an immune-complex glomerulonephritis versus other causes of glomerular and tubular protein loss.

Treatment of Early CKD

CKD treatment should be tailored to the individual taking into consideration the species, presumptive cause, current IRIS stage and co-morbidities. Serial monitoring is necessary and treatment should be modified according to CKD status over time. Avoiding risk factors that promote further renal injury is critical to reduce progressive renal damage. Risk factors associated with renal injury and declining function include : volume depletion, systemic hypertension, proteinuria, nephroureterolithiasis, ureteral obstruction, nephrotoxic drugs inappropriate diet constituents, urinary tract infection and co-morbid medical conditions (diabetes mellitus, hyperadrenocorticism, heart failure).

In general, there are few if any clinical signs in early CKD (IRIS 1 and 2) thus the therapeutic emphasis is on slowing progression.

Dietary Treatment of early CKD

Adjusting dietary phosphorus and protein content are important considerations in early CKD. Phosphorus retention in CKD is a driving force for ongoing progression. Adult maintenance dog and cat foods generally have high phosphorus content. Reducing dietary phosphorus intake will reduce early bone-mineral disease associated with CKD and slow progression and should be instituted as soon as CKD is recognized. Reduced sodium content, increased B vitamins, potassium supplementation, increased omega-3/omega-6 ratio and added fiber are additional attributes of what makes renal formulated

diet beneficial early stages. Recently studies support IRIS stage 1 CKD introduction of significant phosphorus restriction and adjustment of protein content to the lower end of the recommended daily requirement. Prolonged protein restriction in carnivorous felines has been questioned as it may result in protein malnutrition and physical debilitation. Recent studies in cats have confirmed that a modest reduction in total dietary protein and adjusted amino acid balance is beneficial in slowing CKD progression. Initiating a protein restricted renal diet in proteinuric patients is indicated at any stage to decrease urinary protein loss and reduce tubular damage. Renal diets are potassium supplemented to restore potassium that is washed out through hyperfiltration and polyuria; additional potassium supplementation may be necessary in some patients, especially cats. Hyperkalemia associated with supplemented renal diets has been documented in dogs and should be addressed if persistent; a balanced and complete home-made or personalized renal diet may have to be considered in these dogs.

Omega-3-fatty acids are renoprotective and included in prescription renal diets. Oral supplementation should be encouraged in patients not receiving a commercial CKD diet.

Maintaining optimal hydration is critical even in early kidney disease as dehydration can result in rapid renal injury. Patients should always have fresh drinking water available; consider adding a nutrient-enriched osmolyte hydration supplement (ProPlan Veterinary HydraCare) in cats.

CKD-related hypertension and proteinuria treatment

Maintaining normal systemic and glomerular blood pressure and reducing proteinuria are necessary treatments to slow CKD progression. Drugs that inhibit renin-angiotensin -aldosterone activity will reduce systemic blood pressure, reduce glomerular transcapillary pressure and decrease proteinuria. Angiotensin Converting Enzyme inhibiting drugs (ACEI), such as benazepril and enalapril, and Angiotensin Receptor Blocker drugs (ARB), such as telmisartan are available for this purpose. These drugs generally produce a modest reduction in systemic blood pressure, which alters intraglomerular hemodynamics providing renoprotection , reduces proteinuria, and reduces renal tissue fibrosis associated with renin, angiotensin and aldosterone excesss.

Proteinuria. Dogs and cats with confirmed renal proteinuria (defined as UP/C > 0.5), should be treatments to reduce urine protein loss. Dogs and cats with confirmed glomerular proteinuria (defined as UP/C > 2.0) should be biopsied to determine whether immunosuppressive therapy for immune-complex glomerulonephritis is indicated. Supportive treatments include dietary protein restriction, omega-3-FA supplementation and use of an ACEI or ARB drug. Recent studies suggest telmisartan (ARB) is superior to ACE-I treatment. Supportive therapies are maintained lifelong. Immunosuppression (mycophenolate, cyclosporine or cyclophosphamide) are considered based on the result of renal biopsy, SDS-PAGE or as a clinical trial. A good response to 4-6 weeks of continuous therapy is 50% reduction in UPC value. A modest increase in blood creatinine (< 25%) is expected as GFR may decline slightly. No change or an increase

in UPC is consistent with disease progression. If initial dietary and drug therapies are ineffective in reducing proteinuria then several options exist. Increasing the ACEI or ARB dose is most commonly employed; switching from ACEI to ARB or visa versa; or combining an ACEI with an ARB drug. A modest (up to 25% increase) in serum creatinine is expected with increasing doses of ACEI, ARB or ACEI+ARB combination therapy. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual basis with careful monitoring required to ensure any deterioration in kidney function is detected.

Hypertension. Systolic blood pressure is ideally maintained in the 120 to 140 mmHg range to minimize the risk of progressive renal injury and extra-renal target organ damage (CNS, retinal, cardiac). Average blood pressure determination should be established with multiple measurements over a 1-2 week time period (which may be difficult in dogs and cats). Hypertensive systolic blood pressure of 160 to 179 mmHg is associated with moderate risk of organ damage. Severely hypertensive systolic blood pressure > 180 mmHg is associated with high risk of organ damage. Blood pressure treatment should be initiated carefully and only once a CKD patient is stable and hydrated as a mild drop in GFR is anticipated.

The benefit of ACEI / benezapril or ARB / telmisartan drugs in normotensive patients may be considered but a proven benefit has not been established. Management of mild to moderate hypertension should include dietary sodium (Na) reduction and ACEI or ARB therapy. Management of severe hypertension (> 200 mmHg) should include a calcium channel blockade drug (CCB / amlodipine). CCBs act directly on preglomerular vascular smooth muscle to reduce blood pressure and do not directly alter glomerular hemodynamics.

If initial dietary and drug therapy is ineffective in maintaining blood pressure in the 120 to 160 mmHg range then several options exist to achieve better blood pressure regulation. A prudent increase in the ACEI or ARB dose is most commonly employed; additional considerations may include combining an ACEI with an ARB drug or combining an ACEi or ARB with a CCB drug. The risk benefit analysis of combining ACEI with ARBs or CCBs needs to be made on an individual dog basis with careful monitoring required to ensure any deterioration in kidney function is detected.

General Comments. A drawback to ACEI drugs is the fact that over time some patients will experience loss of efficacy (often referred to as aldosterone breakthrough / ABT) which is associated an increase angiotensin and aldosterone to pre-treatment levels, loss of blood pressure control and loss of renoprotective effects. The ABT phenomenon likely occurs secondary to non-ACE kinases converting AT1 to AT2 or increased metabolism and excretion of ACEI drugs. Angiotensin Receptor Blockers (ARB) are possibly more effective in chronic maintainence of blood pressure and favorable glomerular hemodynamics in veterinary patients but may still undergo ABT. ARBs provide a more effective reduction in both angiotensin and aldosterone effects by directly binding with the tissue AT-1 receptor resulting in vasodilation, reduced vasopressin release and reduced aldosterone release.

ACEI, ARB & CCB are generally well tolerated. Reducing blood pressure will reduce GFR and may lead to small and persistent increase in serum creatinine concentration (<25% increase) and/or SDMA (< 2 µg/dl); a marked increase in values suggests an adverse drug effect. Progressively increasing values indicates progressive kidney damage/disease.

ACEI = *Benazepril (dogs) 0.5 - 1.0 mg/kg PO BID; (cats) 0.5 - 1.0 mg/kg PO QD.*

ARB = Telmisartan (dogs, cats) 1.0 mg/kg PO QD, titrate to 3.0 mg/kg QD if necessary

CCB = Amlodipine (dogs) 0.1 - 0.5 mg/kg PO QD; (cats) 0.625 mg < 4 kg; 1.25 mg > 4 kg.

Vitamin D (Calcitriol) treatment in CKD

Vitamin D has many actions throughout the body. It enhances calcium absorption from the GI tract, promotes reabsorption of calcium by the renal tubules, and regulates calcium metabolism in bone. Vitamin D levels and ionized calcium levels gradually decrease in CKD, usually by IRIS 2 stage involvement, along with a compensatory increase noted in serum FGF23 and parathyroid hormone (PTH) levels. PTH hyperactivity causes uremia and other detrimental systemic organ effects. Calcitriol (1,25-dihydroxyvitamin D) is a vitamin D analog that may be useful in dogs and cats for treatment of bone-mineral derangement and renal secondary hyperparathyroidism associated with CKD. Unlike other forms of vitamin D, calcitriol does not require renal activation to be effective and restores active vitamin D activity in CKD patients.. Oral calcitriol administration provides for a rapid onset of increased vitamin D activities but has a short duration of action. This may be advantageous in CKD patients as it has a shorter impact on calcium absorption but a longer and potent effect on serum PTH production. Surveys and clinical impressions suggest use of this drug in CKD dogs results in clinically improved mentation, activity, appetite and longer survival times are documented in CRF patients. A positive effect in cats is postulated but has not been proven to date. The development of hypercalcemia and hyperphosphatemia is a concern, but hypercalcemia is unlikely unless concurrent calcium-containing phosphorus binder therapy is ongoing. Hyperphosphatemia is best avoided by normalizing serum phosphate levels before therapy is begun. A formulated daily dose of 2.5 to 3.5 ng/kg PO q 24hr has been suggested in dogs and cats. However, a pulse dosing strategy (giving 3x dose every 72 hours) has been suggested to lessen GI calcium absorption while still providing prolonged PTH suppression. Calcitriol is obtained via a formulating pharmacy to ensure proper dosing.

Periodic monitoring of serum calcium and phosphorus levels is mandatory when using vitamin D analogs. Use may have to be discontinued in advanced IRIS stages if calcium x phosphorus product (> 60) is increased. Newer vitamin D analogs are being studied that do not cause an increase in blood ionized calcium levels.

As previously discussed, early introduction of oral (dietary) phosphorus intake or early use of phosphorus binding agents may also play a critical role in vitamin D and PTH interactions.

ADVANCED CHRONIC KIDNEY DISEASE

Treatments that Improve Clinical Status & Quality of Life

Introduction
Approximately 1/3 cats and 1/10 dogs will develop chronic kidney disease (CKD) over their lifetime. Early recognition and initial therapy is important to slow progression of disease and extend a clinical disease-free period. Unfortunately, in most patients CKD does eventually progress causing potentially debilitating clinical signs and impaired quality of life. International Renal Interest Society (IRIS) guidelines describe supportive treatments for patients with advanced CKD Stage 3-4. Nutritional and hydration support, gastrointestinal support, control of blood phosphorus and mineral-bone anomalies, and red blood cell support form a basic framework for managing advanced CKD patients. With proper treatment and owner dedication many advanced CKD patients can experience good quality comfortable life for an extended time period.

Nutritional considerations in advanced CKD.
Diet therapy is a critical component of CKD treatment. In advanced CKD, dietary phosphorus restriction, protein restriction, high quality bioavailable amino acids, buffering capacity, reduced sodium content, omega-3-fatty acid and potassium supplementation and water soluble vitamins are important considerations. Caloric density is important as many patients may experience hyporexia. The addition of dietary fiber enhances intestinal trapping and excretion of nitrogenous waste products. Feeding of a commercial renal prescription diet in IRIS 2-4 CKD patients with a serum creatinine > 2.0 mg/dL is associated with less uremic crises and increased survival time.

Maintaining optimal hydration is critical in all stages of kidney disease but especially in advanced CKD as dehydration can result in rapid progression of renal failure. All patients should have fresh drinking water available at all times. Nutrient-enriched osmolyte hydration supplement (ProPlan Veterinary HydraCare) can increase water intake and cellular hydration. Any patient developing clinical signs with poor fluid intake or fluid losses, should be treated to correct dehydration with subcutaneous or intravenous isotonic polyioinic replacement fluid solutions (e.g. lactated Ringer's, Normosol-R) promptly until they resume satisfactory oral water intake.

Prevention of systemic acidosis.
CKD patients can develop chronic metabolic acidosis (blood bicarbonate or total CO2 <18 mmol/l) and are at risk for ongoing issues including generalized muscular weakness, lethargy, poor appetite, negative protein balance (increased protein catabolism, decreased protein synthesis). Renal Rx diets provide unique buffering capacity. Treatment with oral sodium bicarbonate (or citrate if hypokalemic) to effectively maintain normal blood bicarbonate / total CO2 in the range of 18-24 mmol/l is recommended iCKD-associated acidosis is noted on laboratory examinations.
Reducing hyperphosphatemia.
Renal phosphorus excretion is a key regulatory mechanism of maintaining phosphate balance. CKD impairs phosphorus homeostasis allowing positive phosphate balance (hyperphosphatemia) due to severely impaired renal phosphate excretion and other

bone-mineral derangements in advanced disease. Hyperphosphatemia promotes progressive renal damage, increases FGF-23 and PTH levels, is a strong contributor to uremic clinical signs and contributes to soft tissue and vascular calcification. A major goal in CKD treatment is maintenance of normal blood phosphorus levels for as long as possible. Extra-renal mechanisms to reduce phosphorus include strict dietary phosphate restriction and intestinal phosphate binding. Initial goals are to maintain serum phosphorus concentration > 2.6 mg/dl but < 4.6 mg/dl. In advanced CKD a more reasonable goal is serum phosphorus < 6.0 mg/dl. Monitoring serum FGF-23 levels may also become a practical blood biomarker evaluating the effect of phosphorus reducing therapies.

Enteric phosphate binders, such as aluminum hydroxide/carbonate, calcium carbonate/ acetate, lanthanum carbonate, are used to bind ingested phosphorus within the intestinal lumen and promote fecal excretion. Iron-based (ferric) binders may become more widely used as they have higher phosphorus binding coefficient.
Aluminum hydroxide remains a preferred choice for enteric phosphate binding. A starting dose of 30-60 mg/kg/day in divided doses is mixed with each meal. The dose required will vary according to the amount of phosphate being fed and the stage of CKD. Monitoring serum calcium and phosphate concentrations every 4 weeks until a stable phosphorus is achieved will allow for dosage adjustments. Clinical GI signs (constipation, anorexia) associated with higher doses may develop in some patients. The finding of RBC microcytosis and/or generalized muscle weakness suggests aluminum toxicity necessitating a switch to another form of phosphate binder should this occur.

Calcium carbonate can be an effective and inexpensive intestinal phosphorus binder. It is often combined with chitosan and bicarbonate in veterinary renal supplements. However, effective intestinal phosphate binding generally requires high elemental calcium dosing. Hypercalcemia may develop when using vitamin D therapy and calcium containing binders. Constipation may be associated with calcium-containing binders.

Lanthanum carbonate (Fosrenal) binds dietary phosphate and form highly insoluble lanthanum phosphate complexes that are then eliminated in the feces. Lanthanum has a potential advantage over calcium or aluminum containing phosphate binders in that it has minimal intestinal absorption and systemic levels, even at high dosages or with continued use. Vomiting and constipation has been reported and food avoidance can occur when lanthanum carbonate is mixed into food especially in cats. Expense is also a concern although recent generic formulation and veterinary compounding has reduced cost.

Iron-based (ferric) phosphorus binder have a the highest intestinal phosphate binding coefficient. Ferric citrate is partially absorbed which may help maintain erythroid production in CKD. Naraquin® (Nutramax) is a veterinary iron-based binder containing ferric citrate, calcium acetate, chitosan and OM-3 FAs.

Treatment of CKD-associated non-generative anemia.
Erythropoietin (EPO) is a hormone produced in the kidney that regulates bone marrow erythropoiesis via negative feedback. Various uremic toxins and renal tissue loss/ fibrosis result in decreased production of EPO in advanced CKD. Gradual development of progressive non-regenerative anemia is a common feature of advanced chronic renal disease. Chronic anemia is associated with renal hypoxia and accelerates CKD injury and dysfunction. Restoration of normal red blood cell numbers is important in preserving renal oxygen delivery and helps restore attitude, strength, and appetite. Human-recombinant erythropoietin-stimulating drug therapies are available. Treatment is considered when anemia is affecting the patient's quality of life: typically, this occurs when the PCV is < 20-25%. Human Epoeitin alfa (r-HuEPO-alpha) has been used as a substitute for endogenous EPO in dogs and cats with renal disease. Autoantibody development often results in rapid treatment failure or immune-destruction of marrow RBC precursor; use of this formulation is highly discouraged. Darbepoetin (Aranesp®) is a human recombinant DNA protein related to erythropoietin. It stimulates erythropoiesis via the same mechanism as endogenous erythropoietin by interacting with progenitor stem cells and increasing RBC production. Darbepoetin is less immunogenic in cats and dogs because of its molecular structure which "shields" sites of greatest antigenic potential. Another advantage of darbepoetin is it can be administered less often to maintain PCV following induction treatment. Darbepoetin is currently the drug of choice in cats and dogs to effectively increasing marrow red blood cell production. Significant adverse effects have not been reported in cats. However, in a small study, some dogs did develop elevated blood pressure, seizures, vomiting and diarrhea and possible antibody-related loss of effect was reported so close monitoring is required. An initial weekly SQ dose of 0.5 to 1.0 micrograms/kg in dogs and cats has been reported. The dose and frequency are then adjusted based on RBC values. Once a suitable increase in RBC is achieved the administration frequency can be reduced to q 2 weeks. If the hematocrit continues to rise then administration frequency may be reduced to q 3 weeks. A reduction in dose may also be possible in some patients with continued use. Intermittent iron dextran administration is recommended to support RBC production.

Anabolic steroids are of no proven benefit and may be detrimental in CKD patients.

Gastrointestinal Support in advanced CKD patients.
Gastroduodenal hyperacidity, mucosal erosion and ulceration is not a typical finding in dogs and cats with advanced renal disease. Chronic administration of acid suppressants to dogs and cats with CKD is unnecessary and may not be benign. Prolonged administration of acid suppressants has been associated with derangements in serum calcium and PTH concentrations, osteoporosis, and pathologic fractures in at-risk human populations. Gastric acid suppression should be restricted to dogs and cats with renal disease that have additional risk factors for ulceration or when GI bleeding (eg, melena, iron deficiency anemia) or persistent vomiting-induced esophagitis exists. Antiemetic therapy can be very helpful in CKD patients exhibiting frequent vomiting. **Metolcopramide (MCP)** provides antiemetic and weak promotability effects via inhibition of dopamine (D2) receptors in the area postrema and inhibition of serotonin

(5HT3) receptors in the CRTZ. MCP produces a weak prokinetic effect via inhibition of local serotonin 5-HT4 receptors which increases gastric and duodenal motility. Cats have few if any CRTZ D2 receptors and consequently it is a less effective antiemetic choice in cats. MCP undergoes extensive first pass hepatic metabolism following oral administration and has a short half-life; thus the best results are observed when MCP is given via continuous-rate infusion in hospitalized patients. MCP can causs CNS excitement from dopamine antagonism if elevated blood levels occur following high doses or accumulate from reduced renal excretion; a dose reduction by 25-50% if considered in CKD patients. Metoclopramide dosing : 0.2 – 0.5 mg/kg PO/SC/IM/IV bolus q 6-8 hours; 0.05 – 0.09 mg/kg/hour as a continuous IV infusion (CRI).

Maropitant (MRP) is a neurokinin-1 receptor antagonist blocking substance P interaction with the NK receptor. It has potent antiemetic effects via direct emetic center antagonism and other areas of central andperipheral neuronal input. MRP is an excellent broad-spectrum antiemetic effective in preventing vomiting associated with CKD uremia in cats and dogs. Patients may also appear more comfortable when given MRP as visceral pain pathways contain NK1 receptors. MCP does not consistently reduce signs of nausea or the incidence of gastroesophageal reflux. MRP has no effect on gastrointestinal motility. Maropitant 1 mg/kg is approved for SQ use in dogs over 4 weeks of age and IV use in dogs over 16 weeks of age; SQ and IV use is approved for cats over 16 weeks of age. MCP should be given slowly IV over 1-2 minutes as rapid administration has been reported to cause transient hypotension. Oral dosing at 2 mg/kg PO q 24 hr is approved in dogs for the duration of need (i.e., PRN indefinitely). The oral form has not been approved for use in cats but is widely used off-label at 1 mg/kg PO QD.

Ondansetron (Zofran®), Dolesetron (Anzemet®) and Granisetron (Kytril®) are serotonin antagonists developed as antiemetics for control of intense vomiting and nausea in human chemotherapy patients. These drugs are effective at blocking 5-HT3 receptors in the emetic center, CRTZ and peripheral serotonin receptors. They have effective antiemetic as well as antinausea activity in dogs and cats. Ondansetron HCl can be given PO or IV (0.1 - 1 mg/kg BID); oral bioavailability is a concern in cats so consider oral dosing in the higher range or administering subcutaneously. Dose-related ECG interval prolongation (PR, QRT prolongation and QRS widening) has been observed in humans but has not been noted in dogs and cats.

Mirtazapine is also a serotonin (5HT3, 5HT2) antagonist which reduces nausea, reduces vomiting and stimulates appetite. In a placebo-controlled crossover study in cats with CKD, mirtazapine treated cats had a significantly increased appetite and decreased vomiting. Recent studies also confirm this drug results in increased gastric motility in dogs.

Appetite Stimulation Therapy in CKD.

Cyprohepatadine and benzodiazepine derivatives (diazepam) are no longer suggested for appetite stimulants in dogs and cats due to the availability of more reliable and safer agents.

Mirtazapine provides GI benefits in both dogs and cats. It is a centrally-acting serotonin antagonist and alpha (norepinephrine) agonist which reduces nausea, reduces vomiting and stimulates appetite. In dogs it also provides GI promotility property. It has become an effective appetite stimulant treatment for cats with poor nutritional status relating to CKD or other medical disorders associated with poor appetite. An FDA-approved transdermal product (Mirataz) has ia available for cats. Mirtazapine is dosed orally at 1.88 to 2 mg total dose PO q 48hr in feline CRF patients and is associated with increased appetite, decreased vomiting and increased activity. Transdermal dosing is also 2 mg dose q48h. If a consistent benefit is not noted then decreasing the dosing interval to q 24h is suggested as long as significant adverse effects are not noted. Mirtazapine may also provide appetite stimulating effect and other GI benefits in CKD dogs. Mirtazipine dose for appetite stimulation is individualized in dogs at 1-2 mg/kg PO q 12-24h.

Capromorelin (Entyce^{R}, Endura^{R}) is an FDA approved (dogs, cats) drug that mimics the action of endogenous ghrelin hormone. Ghrelin is a naturally occurring peptide produced in the stomach, that enters circulation and stimulates the hypothalamic hunger center. It also a stimulates centrally-acting growth hormone secretion improving and maintaining skeletal muscle. Ghrelin is secreted and accumulates in bloodstream between meals, reaching highest concentration as time since the previous meal extends. The label dose is 3 mg/kg PO q 24h in dogs and 2 mg/kg PO q 24h in cats. Administration of capromorelin is safe and results in increased food intake and body weight. Elimination is primarily biliary-fecal so CKD dose adjustments are not necessary. Transient ptyalism, lip smacking and head-shaking may be observed but generally resolve within 5 minutes of oral dosing.

Fluid therapy. It is best to allow CKD patients to regulate their own fluid and caloric needs whenever possible. The use of gastrointestinal supportive drugs and fluid therapy is generally not necessary in the non-uremic CKD patient. Chronic fluid therapy when not required may lead to hypervolemia, increased sodium and chloride loading, increased blood pressure and increased solute excretion which all contribute to CKD progression. Appropriate subcutaneous or intravenous fluid therapy should be provided if uremic CKD patient is not able to sustain normal hydration their own. The frequency and amount of fluid therapy should be individualized and adjusted as needed.

Feeding tube. Advanced stage CRF patients can experience a substantial improvement in quality life with intensified efforts to prevent protein / caloric malnutrition and dehydration. Consideration should be given to feeding tube intervention (i.e., esophagostomy tube) to provide ongoing nutritional and hydration needs if a client is receptive to this long term treatment option.

URINARY TRACT INFECTION

When and How to Eliminate “Bad” Bacteria

Introduction

Bacterial urinary tract infection (UTI) is a leading cause of urinary disease in dogs, but has a significantly lower prevalence in cats. Antibiotic therapy is routinely prescribed and UTI treatment is a leading contributor to overall antibiotic use in companion animals. There is genuine concern about use, misuse and overuse of antibiotic therapy in veterinary patients especially in regard to development of bacterial co-selection, antibiotic resistance and intestinal dysbiosis development. In 2011 the International Society for Companion Animal Infection Diseases (ISCAID) published comprehensive guidelines to provide a consensus regarding the diagnosis and management of upper and lower urinary tract infections. These guidelines were updated in a 2019 revision (open-access publication The Veterinary Journal, Volume 247, May 2019, Pages 8-25) providing comprehensive recommendations for diagnosis and management of subclinical bacteriuria, sporadic bacterial cystitis, recurrent bacterial cystitis, pyelonephritis and prostatitis. Issues pertaining to urinary catheters, medical dissolution of uroliths and prophylaxis for urological procedures were also addressed.
The purpose of these guidelines is to improve antibiotic prescribing practices in UTI patients as part of a broader antibiotic stewardship program. Guidelines should be interpreted as general recommendations and not mandates, that are consistent with good clinical practice and appropriate for the majority of cases encountered in clinical practice. Guidelines should not be considered standards of care that must be followed in all circumstances. Rather, clinicians should make case-by-case decisions realizing that different or additional approaches may be indicated in some individual cases.

Subclinical Bacteruria

Subclinical bacteriuria is the presence of bacteria in urine as determined by urinalysis and/or bacterial culture in the absence of any clinical and cytological evidence of UTI. In this circumstance the bacteria identified are considered avirulent in almost all patients. Positive urine culture result does not differentiate subclinical bacteriuria vs virulent UTI. Subclinical bacteruria are present in many healthy dogs and cats but is more commonly identified in patients with urinary disorders and other medical issues including obesity, diabetes mellitus, hyperadrenocorticism and immunosuppressive drug treatment. Studies have determined that subclinical bacteriuria has no association with subsequent UTI development. Antibiotic treatment is generally not necessary in patients with no clinical signs of UTI even when low level pyuria is present on urine sediment exam. In fact a higher bacterium recurrence rate may be seen following antibiotic treatment. Antibiotic treatment of subclinical bacteruria may be considered if there is concern that there is a particularly high risk for ascending or systemic infection (e.g., immunocompromised patients) or in patients that are unable to display clinical signs of UTI (e.g., spinal injury). The presence of subclinical multidrug-resistant bacterium does not represent an absolute indication for treatment. Multidrug-resistant organisms may be replaced with susceptible organisms if treatment is withheld, and subsequent

treatment with routine antimicrobials may be more practical if bacterial decolonization is desired or if clinical disease develops. Treatment of subclinical *Corynebacterium urealyticum* should be considered because of its association with encrusting cystitis.

Diagnosis of Urinary Tract Infection

Whenever possible a patient with clinical signs relating to the lower urinary tract should have a urine sample collected via cystocentesis. Urinalysis generally reveals the presence of bacteriuria and pyuria supporting a virulent UTI; hematuria and proteinuria are also often present. The clinician must interpret the clinical presentation, physical findings, gross and cytological appearance of the urine in parallel to determine the likelihood of a clinically relevant virulent UTI. Urine culture is encouraged to confirm the presence of bacterial infection, identify the bacterial species present, assess for resistant bacteria that may not respond to initial antibiotic therapy, and to help differentiate reinfection from relapse should a UTI return following initial therapy. In cats, the diagnosis of bacterial cystitis should be confirmed by aerobic bacterial urine culture in all cases due to the low likelihood of bacterial cystitis in healthy cats with acute lower urinary tract signs.

Sporadic UTI

A sporadic (simple) UTI is an occasional bacterial infection of the urinary tract in an otherwise healthy individual (female or neutered male dog, occasionally a cat) with normal urinary tract anatomy and function. Clinical signs of a lower UTI are present with pollakiuria, dysuria, stranguria, hematuria, or a combination of these signs. Antimicrobial therapy is recommended for confirmed UTI. Initial therapy with amoxicillin (11– 15 mg/kg PO q 8hr) or trimethoprim-sulfonamide (15-30 mg/kg PO q 12hr) is recommended to provide a narrow spectrum antibiotic that is generally effective against bacteria associated with urinary infection while minimizing antibiotic resistance development. Uncomplicated sporadic UTIs are generally treated for 3-5 days. In dogs only, high-dose short-duration enrofloxacin (20 mg/kg PO QD) or marbofloxacin (10 mg/kg PO QD) can also be considered for 3 day treatment duration.

Providing the full course of an appropriate antibiotic has been administered correctly by the owner, then there is no followup measures necessary beyond monitoring clinical signs to determine treatment efficacy. Post-treatment urinalysis or urine culture is **not** recommended for sporadic cystitis when clinical signs have resolved. Lack of clinical response within 48 hours of starting antibiotic therapy should prompt further investigation to determine whether cystitis is actually present and identify any complicating factors. If culture and susceptibility testing is performed and demonstrates an isolate that is resistant to initial antibiotic therapy but there has been a positive clinical response, then maintaining the current antibiotic is acceptable and follow-up urinalysis, including culture, is indicated after treatment has been completed to verify resolution of infection. If culture and susceptibility results indicate that an isolate is not susceptible to the chosen antimicrobial and there is a lack of clinical response, then therapy with the original antibiotic should be discontinued and treatment with an alternative drug begun based on the culture and susceptibility result.

Recurrent Urinary Tract Infection

A recurrent (complicated) UTI occurs in association with an anatomic or functional urinary tract abnormality or a comorbidity that predisposes to persistent infection, recurrent infection, or treatment failure. Recurrent UTIs are defined as occurring twice or more in a 6 month period or 3 or more times during a 12-month period and are usually associated with an underlying cause, so identification and management of relevant risk factors and comorbidities is critical. Conditions such as urinary calculi, urinary neoplasia, brachial remnant, prostatitis, neurogenic bladder, diabetes mellitus, immunocompromising disorders (hyperadrenocorticism, immunosuppressive drug therapies) often are associated with recurrent UTIs. Recurring use of antibiotics can also predispose to repeated UTI development. A comorbid abnormality is not always identified because of the difficulty diagnosing some anatomical, functional, or metabolic abnormalities.

Recurrent bacterial UTIs can be defined as relapse, reinfection or persistent. *Relapse* is recurrence of a UTI with isolation of an indistinguishable bacterial organism from the one that was present previously; presumably relapse occurs due to failure to completely eliminate the pathogen with prior treatment. Relapses tend to occur earlier than reinfections (i.e., within weeks rather than months). *Reinfection* is recurrence of a UTI with isolation of a different bacterial microorganism; efforts should be undertaken to identify and address any predisposing factors that allows permissive infection. *Persistent* infection is similar to a relapse except that it is characterized by persistently positive culture result during treatment (despite in vitro susceptibility to the antimicrobial), without a period of negative bacteriuria during or after treatment. For relapsing, reinfections and persistent infections, it is important to be certain the antimicrobial is achieving adequate concentrations in the bladder to clear the infection. The antimicrobial dose, dosing interval, antimicrobial susceptibility pattern, anatomy of the lower urinary tract and client compliance should be determined to confirm initial therapy was appropriate.

Repeat empirical antibiotic prescribing to a patient that has not fully responded in the past, without exploration of underlying causes, is highly discouraged. A diagnostic plan should be established for every animal with recurrent cystitis to determine the presence of underlying factors that could be associated with recurrence or relapse. All drugs or supplements that are administered should be documented. A thorough physical examination, including prostatic and pelvic urethral examination via rectal palpation and examination of the vulva and prepuce is required. In addition to urinalysis and urine culture, complete blood cell count, serum biochemical profile, radiographic and ultrasound imaging and, if appropriate, endocrine testing should be performed. Lower urinary endoscopic exam (vaginoscopy, urethrocystoscopy), advanced imaging (contrast-enhanced CT) and urethral pressure profile exam, particularly in females, should be considered to further investigate underlying causes. Any underlying concurrent causes identified on physical examination or diagnostic testing should be managed appropriately, whenever possible. If an underlying cause cannot be found and corrected, it is possible therapy will ultimately be unsuccessful.

Recurrent bacterial UTI encompasses a broad range of conditions, including repeated but relatively uncomplicated infections that respond quickly to antimicrobials and others with marked bladder pathology that complicate treatment. Broad recommendations for treatment duration are difficult because of these variations. Individual treatment goals must be considered in patients with recurrent UTI depending on the identified cause. The primary objective is clinical cure with minimal risk of adverse effects (including antimicrobial resistance). Microbiological cure (elimination of the offending organism) is desirable but not necessarily achievable in all cases or required for clinical resolution.

In recurrent cases, consideration should be given to waiting on culture results before starting antibiotic therapy. Depending on the severity of clinical signs and owner's ability to observe the animal, analgesics (e.g. NSAIDs) treatment alone could be considered while awaiting final urine culture results. Empirical antibiotic therapy is reasonable but should be approached as is described for sporadic bacterial cystitis and a narrow antibiotic spectrum drug should be selected. The drug class used should be different from that used to treat prior UTI(s) (i.e., if amoxicillin was used initially, start treatment with trimethoprim-sulfa drug). Antibiotic treatment should be amended as indicated based on the results of culture and susceptibility testing. Preference should be given to drugs that are excreted in urine predominantly in an active form (individual drug descriptions and doses are presented in lecture; see drug table). Evidence supporting a standardized duration of therapy for complicated UTI does not exist. Longer-term therapy (> 14 days) is not automatically warranted for recurrent cystitis; re-infection may be successfully treated with short (3–5 days) duration therapy in patients when an identifiable cause is known (e.g., UTI in a diabetic or cushinoid patient); longer treatment courses (7–14 days duration) may be considered in persistent, and potentially relapsing infections, if factors that inhibit response to antimicrobials, such as deeper bladder wall infection or biofilm production, are suspected to be present. Antimicrobial therapy should be directed against all identified pathogenic organisms when possible. If more than one bacterial species is identified on culture, the relevance of the each organism should be considered, based on the bacterial counts and the suspected pathogenicity of the organisms. Certain bacterial species, such as Enterococcus, generally do not require specific treatment in mixed infections. In one cases, a s single effective antibiotic may not be available. Reasonable combination therapy potentially effective against all organisms based on susceptibility testing should be employed if necessary.
There is no supporting evidence for administration of additional drugs for the purpose of breaking down bacterial biofilm. There is no supporting evidence that direct instillation of antimicrobials, antiseptics, DMSO or glycosaminoglycans directly into the bladder via a urinary catheter is effective for treatment of recurrent UTIs; these compounds are quickly flushed out of the bladder when the animal urinates and may be locally irritating.

Microbiologic cure rates are poorly established for recurrent cystitis. Treatment success is generally based on clinical response, as the microbiological, cytological or hematological response to treatment can be variable depending on individual case factors. The benefit of a urine culture 5–7 days after initiation of antibiotic therapy to access the efficacy of the particular antibiotic is unclear especially if the patient is

clinically responding to treatment. A follow-up post treatment urine culture 5-10 days after completing antibiotic treatment may be helpful in patients where clinical cure is documented as part of the diagnostic process to help differentiate relapse, re-infection and persistent infection, and to guide potential future diagnostic testing, but not necessarily as an indication of a need for further antibiotic therapy. If a positive urine culture is obtained after treatment, more in-depth investigation of predisposing factors for relapse or reinfection should be considered. Unless there is clear evidence for the reason for failure, retreatment without any other investigation is not recommended. If no clinical signs of lower urinary tract disease are present, the presence of bacteriuria post-treatment should be approached as described under 'subclinical bacteriuria'.

Prophylactic antibiotic therapy for dogs and cats is not recommended. Patients with chronic non-curable underlying conditions should receive a short course (3–5 days duration) antibiotic therapy as necessary, ideally based on susceptibility testing, to alleviate clinical signs, with a focus on clinical rather than microbiological cure.

SPECIAL CONSIDERATIONS

Multidrug Resistent Infections

There are individual patient and public health concerns with regard to resistant pathogens. Multi-drug resistant bacterial pathogens, including various Enterobacteriaceae, Staphylococci, and Enterococci, are increasingly problematic. These pathogens are often harder to treat because of limited drug choices. Because of the high incidence of antimicrobial use in UTIs of dogs and cats, veterinarians must be aware of the role of inappropriate treatment in the emergence and dissemination of multi-drug resistant pathogens. Use of antibiotics in the treatment of canine and feline UTIs can be justified as long as their use is prudent and proper, and based on culture and susceptibility data. Virulent infection must be documented based on clinical, cytological and culture abnormalities. Antibiotic use in subclinical multi-drug resistant organisms is not recommended as organisms may respond to lessening antibiotic pressure and be replaced over time with susceptible organisms which can allow for self resolution or practical treatment at a later time.

Upper Urinary Tract Infections (Pyelonephritis)

Pyelonephritis is an infection of the renal parenchyma resulting from either ascending urinary tract infection or via systemic bacteremia. Pyelonephritis can be classified as 'uncomplicated' or 'complicated'; uncomplicated implies there is no underlying comorbidity; complicated suggested the presence of an anatomical/obstructive disorder such as urinary stone disease or ectopic ureter or a immunosuppressive systemic comorbid disease. The incidence of pyelonephritis in dogs and cats is difficult to determine as signs attributable to pyelonephritis can be vague. Pyelonephritis can result in severe and rapid kidney injury (AKI) or chronic progressive disease. Rapid diagnosis and treatment is desired, and the implications of treatment failure are higher as compared with bacterial cystitis.

Acute pyelonephritis should be suspected when accompanied by systemic signs such as fever, lethargy, and/or polyuria/polydipsia; renal pain on abdominal palpation; laboratory findings of azotemia, cylindruria, and peripheral neutrophilia with or without left shift in a patient with a positive aerobic bacterial urine culture. Patients may be oliguric or anuric or have vague clinical signs. Ultrasound imaging findings such as renal pelvic dilation, blunting of the renal papilla, changes in the medullary tissue appearance and pyonephrosis may be noted, but are non-specific. Care should be taken not to over-interpret the relevance of isolated renal pelvic dilation, since it can be present in normal animals and those with other renal diseases. Increased serum creatinine or SDMA support renal injury but are also not specific for bacterial pyelonephritis as the cause of kidney injury.

Ascending infection by fecal commensals, especially Enterobacteriaceae species, cause the majority of renal infections. Hematogenous spread to the renal parenchyma and pelvis occurs less frequently. Urine culture and susceptibility testing should always be performed; urine sampling should be performed by cystocentesis (or ultrasound-guided pyelocentesis, particularly if results of cystocentesis specimen are negative). Interpretation of susceptibility data should be based on antimicrobial breakpoints for serum rather than urine drug concentrations. Blood cultures are recommended at the same time as urine cultures in immunosuppressed or febrile animals. Evaluation for leptospirosis should be considered in culture-negative dogs by use of serological testing and PCR.

Treatment for AKI should be initiated immediately, while awaiting culture and susceptibility results. Initial treatment should involve antimicrobial drugs known to have efficacy against gram-negative Enterobacteriaceae. Oral antimicrobial therapy is recommended in animals that otherwise appear systemically well and have normal appetite. Intravenous therapy is recommended for animals that are dehydrated, hyporexic or anorexic, or lethargic. Treatment with a veterinary fluoroquinolone is an acceptable first choice. IV cefotaxime and ceftazidime are also options in hospitalized patients. The initial antibiotic selection should be reviewed when culture results are received and serum/soft tissue antimicrobial concentrations determined for probable efficacy. If combination therapy was initiated empirically and the isolate is susceptible to both drugs, one might be discontinued if supported by evidence of clinical response. If resistance is reported and clinical evidence of improvement is not evident, the antibiotic selection should be changed to another drug to which the offending organism is susceptible. Antibiotic treatment for at least 2 weeks is generally recommended. Treatment efficacy and monitoring is generally the same as for a complicated UTI with recheck exam and urine culture recommended 1-2 weeks following cessation of antibiotic therapy. Re-isolation of the same bacterial species as that identified initially should stimulate consideration of reasons for potential persistence, including antimicrobial resistance, urolithiasis, anatomic defects or immune deficiency. if clinical signs and azotemia have resolved, consideration has to be given to the clinical relevance of microbiological failure, as it may represent subclinical bacteriuria and not indicate a need for treatment.

PREVENTION OF RECURRENT URINARY TRACT INFECTIONS

Patients that are predisposed to UTI or have experienced recurrent infection could benefit from prevention strategies to reduce future infection. A variety of non-antibiotic drug treatment, supplement (nutraceutical) treatments and elective surgery can be considered in individual patients.

A thorough examination of the vulva should be completed in all female dogs. Superficial fold pyoderma or abnormal waxy exudate may be present. Particular attention should be directed to determining if a “hooded” (juvenile, inverted) vulvar confirmation or excessive vulvar folds are present. All of these issues can promote superficial bacterial colonization with access to the lower urinary tract. Weight loss, superficial cleansing of the perivulvar area and possibly corrective surgery (i.e., vulvoplasty) are all critical considerations in recurrent UTI prevention. The client should be questioned and the perivulvar hair and skin should be examined for evidence of moisture that might suggest mild involuntary urinary incontinence. Mild urethral hypotonus associated with incontinence allows bacterial translocation and an opportunity to for bacteria to gain easier access to the urinary bladder.Castration should be considered in intact male dogs to reduce the likelihood of recurrent bacterial prostatitis development and subsequent UTI.

Phenylpropanolamine (PPA) is approved for the control of urinary incontinence due to urethral sphincter hypotonus. This drug acts via sympathomimetic agonist activity which results in an increase in urethral sphincter tone and closure of the bladder neck. PPA-ER treatment trial (2-4 mg/kg PO q 24hr) should be considered in any individual that has recurrent UTI and clinical evidence of even subtle involuntary urinary incontinence. Promoting enhanced urethral tone helps restore an effective urethral defense mechanism to prevent ascending bacterial translocation. Long term therapy is generally safe so if a decreased incidence of UTI results with PPA treatment then continued indefinite use should be considered. Oral estrogen replacement therapy can also be considered in younger females that develop recurrent incontinence and UTI following ovariectomy.

Cranberry extract supplementation has been promoted for UTI prevention. Initially it was thought that this extract produced an inhospitable acidic urine environment. However, it has now been shown that the American cranberry (Vaccinium marcocarpon) contains a natural bioactive tannin (proanthocyanidin, PAC-A) which inhibits E. coli fimbriae adhesion to the uroepithelium. This action reduces bacterial numbers via bacterial wash-out and reduces potential pathogenic colonization and infection. A similar activity has been shown against Enterococcus faecalis. Veterinary cranberry extract supplements with PAC-A are available in concentrated formulation.