2024's FELINE TOP TEN MEDICAL DISORDERS

Gary P. Oswald DVM, MS, DACVIM (Internal Medicine)
Tampa Bay Veterinary Medical Consulting, Oldsmar, FL, USA
Visiting Faculty, Colorado State University, College of Veterinary Medicine

#1 Feline Infectious Peritonitis (FIP) remains one of the most important infectious diseases of cats. FIP may develop in an individual cat following infection with the feline enteric coronavirus (FECoV). FIP has historically been a challenge to diagnose owing to diverse clinical signs, laboratory changes and a lack of a conclusive serologic test. A correct definitive diagnosis is critical, however, as FIP, once considered a terminal disease is now treatable with a high cure rate.

Histologic or cytologic examination of affected tissues and effusion is quite specific for a diagnosis of FIP. Sampling of multiple tissues is preferred to improve sensitivity and can include lymph nodes, intestines, omentum, spleen, kidney and liver. Pathology will typically show vasculitis, perivascular necrosis, and pyogranulomatous inflammation around the vasculature. FECoV antigen can be detected by immunostaining (IHC, ICC) within target cells, fluid or tissue macrophages. The presence of a high amount of antigen, which is necessary for positive staining, indicates high virus replication rates within tissue macrophages, the key event in the pathogenesis of FIP. Negative IHC results do not exclude FIP because FCoV antigens can be variably distributed within lesions.
Another direct testing method to identify FECoV RNA (nucleic acid) can be performed by RT-PCR submission. PCR testing is an extremely sensitive method for detecting feline enteric coronavirus nucleic acid. RT-qPCR for FECoV nucleic acids can be performed on tissues, effusions, CSF and aqueous humour and can indicate the amount of virus in the sample. Cats with mutated FIP generally have high viral loads compared to healthy FECoV-infected cats, meaning that a positive RT-qPCR result with high viral load in a tissue or fluid outside the gastrointestinal tract is highly consistent with FIP infection.

Recent identification of novel antiviral drugs provides hope that an effective treatment has finally been discovered. Antivirals are small, easily absorbed molecules that target viral proteins (protease inhibitors) without causing significant harm to the host's cells. Several specific antiviral compounds (GC376, GS-441524, GS-5734) have shown to be efficacious and can cure

a high percentage of FIP infected cats. Remdesivir (GS-5734) binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. It is an FDA approved human antiviral used in treatment of COVID-19, a member of the β - coronavirus genus. It is now available in the USA by prescription; use in cats is very expensive. GS-441524 is the active metabolite of remdesivir. “Black market” GS-441524 has demonstrated very good efficacy in symptomatic FIP cats. In this USA, GS-441524 falls under the Guidance for Industry #256 and the FDA has recently allowed it to be compounded and legally prescribed. Stokes Pharmacy, working in collaboration with the Bova Group, is producing a compounded oral formulation of GS-441524 which became available on June 1st, 2024. GS-441524 has been shown to be a relatively safe and effective at an optimum dosage of 15 mg/kg PO q24h for a minimum of 12 weeks in effusive and non-effusive cases without ocular or neurological involvement; the dose should be increased to 20 mg/kg PO q 24hr in patients with ocular or neurological involvement. Rapid resolution of clinical signs associated with FIP with resolution of pyrexia and inappetence is often noted within 1 week along with improved QoL scores; resolution of icterus, effusions, and ophthalmic changes follow within 2 to 4 weeks. Clinicopathologic derangements such as hyperglobulinemia, hypoalbuminemia, and anemia tend to resolve later during treatment. This supports monitoring physical examination findings in the first half of treatment and hematologic and biochemical measurements in the latter half of treatment. Dosage increases and treatment extensions beyond 84 days might be required, as directed by individual response. The presence of hyperglobulinemia beyond the first 6 weeks of treatment should prompt a dosage increase. Repeat treatment might also be required in a minority of cases. Few side effects have been reported with oral formulations. Urinary stones containing GS-441524 have been reported.

#2 SGLT2 inhibitors for the treatment of feline diabetes mellitus were introduced in 2024. SGLT 1 and 2 cotransporters are present in the luminal membrane of renal tubule cells and are responsible for the active reuptake of filtered tubular glucose from the urine back into the blood stream. The action of the SGLT transporters recovers >90% of glucose present in the glomerular filtrate. Administration of an SGLT2 inhibitor blocks active glucose reabsorption resulting in urinary loss of at least 50% of filtered glucose, allowing a smaller amount of urinary glucose to be reabsorbed by the SGLT1 cotransporter.

SGLT2 inhibitors are used for diabetic therapy by substantially inhibiting the renal SGLT2 reabsorption of urinary glucose and increasing urinary glucose excretion which over time causes a net lowering of blood glucose levels. By “peeing out” excess glucose and lowering

blood glucose levels it is possible to reverse glucotoxicity and revive beta-cell insulin production effectively producing enough exogenous insulin to lower blood glucose. Increased urine volume (polyuria) associated with the increased urine glucose load may be observed initially but once blood glucose levels below the renal threshold there will be less urine glucose filtered which in turn will reduce osmotic diuresis and PU/PD.

Bexagliflozin (Bexacat®, Elanco; oral tablet) is a SGLT2 inhibitor FDA approved for once daily administration in diabetic cats to improve glycemic control.

Velagliflozin (Senvelgo®, Boehringer Ingelheim; oral solution) is another SGLT2 inhibitor FDA approved for once daily administration in diabetic cats to improve glycemic control.

Appropriate patient selection for SGLT2 inhibitor introduction is important as we learn how to best use this new drug class. An ideal candidate is an otherwise healthy, newly diagnosed diabetic, with a good appetite, and without significant comorbidities. Patients with significant renal dysfunction, pancreatitis, and concurrent endocrinopathies are generally not ideal candidates. Blood β-hydroxybutyrate (BHB) ketone level should be determined prior to use- in healthy non-diabetic cats, plasma BHB concentrations are usually <0.1 mmol/L (<10 mg/dL); values up to 1 mmol/L are routinely reported in well managed, insulin-treated diabetics; a value over 2.4 mmol/L indicates substantial ketosis suggestive of DKA and indicates the need for insulin treatment. Urine dipsticks identify acetoacetate ketone bodies; a 1+ color change (≥1.5 mmol/L acetoacetate) using urine samples was reported in just 2/11 cats with plasma BHB >2.5 mmol/L (Zeugswetter & Pagitz, 2009) but evaluation of plasma using the urine ketone dipstick was found to be more sensitive, with a 1+ result noted in all 11 cats with BHB >2.5 mmol/L.

Once initiated SGLT2 inhibitor effects require frequent initial monitoring over the first 2-3 weeks but if successful DM control is achieved the long term monitoring is relatively simple and straightforward. Initial recheck visits are recommended on day 2-3, day 7, day 14 and day 30 to assess patient well-being, body weight, polyuria/polydipsia/polyphagia, glycemic control and blood BHB ketone level. Clinical hypoglycemia is not expected when receiving SGLT2 inhibition. Once eugylcemia has been established, intermittent monitoring of a spot BG along with history and physical exam findings can be performed every 3-4 months. Monitoring of serum fructosamine is optional. Serial or continuous blood glucose curve monitoring is not necessary.

Since the dose of an SGLT2 inhibitor is independent of BGC and administration does not cause hypoglycemia, the only way to determine if a cat receiving an SGLT2 inhibitor is still diabetic or is in remission is to suspend drug administration for several days. Appropriate timing for stopping SGLT2 inhibitor administration cannot be predicted. Longer periods of time in a euglycemic or near euglycemic state should allow for normalization of peripheral glucose sensitivity and greater β-cell recovery. Thus, waiting at least 60 days before assessing for remission seems prudent. If the BGC rises and clinical signs of DM return, the SGLT2 inhibitor should be restarted immediately.

As SGLT2 inhibitors are a brand new introduction to veterinary medicine their role in overall clinical effectiveness, adverse effects and exact indications in feline DM management are still be determined - but early experience has been very positive. Initial experience with both bexagliflozin and velaglifozin suggest that >80 percent of naive diabetic cats exhibit excellent glycemic control without insulin use. A small percentage (~5%) of naive diabetic cats have developed traditional or euglycemic DKA during SGLT2i introduction; this has usually occurred in the first 2 weeks of treatment thus the reason for initial close monitoring during this time period. Euglycemic DKA is an emergent condition that is characterized by euglycemia, ketosis and metabolic acidosis. Unlike traditional DKA, the diagnosis of euglycemic DKA can be overlooked because of the absence of hyperglycemia. Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving an SGLT inhibitor should prompt immediate assessment for ketoacidosis, regardless of blood glucose level.

Increases in stool frequency and fecal water content are often reported and likely reflect cross-over inhibition of SGLT1 within the small intestine which results in incomplete glucose absorption from the bowel lumen and secondary osmotic diarrhea. In most cats, this side effect is not substantially problematic and is often self-limiting. Lower carbohydrate diet, probiotics, psyllium, canned pumpkin, or intestinal adsorbents may be considered if the issue persists.

Thus far, an increased incidence of urinary tract infections or genital infections have not been reported in cats receiving ongoing SGLT inhibitors.

Bexagliflozin and Velaglifozin treatment can be considered for use with insulin therapy in DM cats who are exhibiting a poor treatment response (off-label use).

#3 The role of fibroblast growth factor 23 in phosphate homeostasis and feline chronic kidney disease.

Alterations in calcium, phosphate, vitamin D, parathyroid hormone, FGF-23, bone metabolism and soft tissue calcification occur early in CKD. In healthy individuals with normal renal function, the bone, intestine and kidney work together to regulate calcium and phosphate, ensuring bone mass is maintained, ionized calcium concentration is tightly regulated and phosphate concentration is not allowed to increase persistently. FGF-23 is an independent predictor of body phosphate concentrations and is released by osteocytes in response to increased blood phosphate levels. The net actions of this hormone is to reduce renal tubular phosphate reabsorption and reduce intestinal phosphate absorption. Intact FGF-23 can be measured in blood providing early insight into bone-mineral disease associated with CKD allowing appropriate early therapy considerations.

In early CKD, the first indication of mineral bone disturbance is an increase in plasma FGF-23 concentration. This is an adaptive response to body phosphate retention as the decline in GFR reduces net renal excretion of phosphate. Initially FGF-23 activation allows the inhibition of proximal tubular reabsorption of phosphate allowing remaining nephrons to excrete more phosphate so that plasma phosphate concentration remains stable and within the normal reference range. In cats, plasma FGF-23 was shown to be elevated in apparently healthy cats that subsequently went on to develop azotemic CKD within 12 months of initial screening (Finch et al., 2013). Plasma FGF-23 appears to be an independent risk factor for all-cause mortality (independent of age and plasma creatinine concentration) and for future progression (>25% increase in plasma creatinine concentration within 12 months) of CKD in cats (Geddes et al., 2015). FGF-23 has direct values as a prognostic biomarker in feline CKD, however it is undetermined whether FGF-23 is causative of poor outcome or merely a biomarker that is indirectly associated.

FGF-23 is now offered as a diagnostic assay by commercial laboratories to assist in the monitoring of treatment of feline CKD. In early IRS Stage 1 and 2 CKD where a diagnosis has been made in the absence of an elevated plasma creatinine and phosphate concentrations, the need for dietary phosphate restriction cannot be evaluated simply by the measurement of serum phosphate as the majority of these patients have plasma phosphate concentrations below the upper limit of the IRIS target range for their stage (see Table 1). Plasma concentrations of intact FGF-23 can determine which of these cats will benefit from dietary phosphate restriction because an elevated FGF-23 concentration provides evidence of significant mineral and bone

IRIS CKD STAGE	TARGET SERUM PHOSPHATE CONCENTRATION RANGE
Stage 1	2.8 to 4.5 mg/dl (0.9 to 1.45 mmol/l)
Stage 2	2.8 to 4.5 mg/dl (0.9 to 1.45 mmol/l)
Stage 3	2.8 to 5 mg/dl (0.9 to 1.6 mmol/l)
Stage 4	2.8 to 6 mg/dl (0.9 to 1.9 mmol/l)

disturbance. In addition, establishing an FGF-23 baseline value makes it possible to assess response to early treatment. Azotemic normophosphataemic cats started on a phosphate restricted diet had a reduction in plasma FGF23 concentration 4 to 8 weeks later (Geddes et al., (2013). Once plasma phosphate concentration falls into the target range for the stage of CKD, measurement of plasma FGF23 concentration can be used to monitor the overall response to treatment. If FGF23 plateaus well outside the recommended concentration, then additional measures to restrict intestinal phosphate absorption should be instituted (e.g. change to a more phosphate restricted renal diet or use of intestinal phosphate binding agents). In more advanced CKD patients where plasma phosphate concentration is outside the IRIS target range for their IRIS stage, there is no need to measure plasma FGF23 concentration as plasma phosphate can then be used to monitor response to treatment.

Figure 1: Flow chart indicating the utility of serum FGF23 in guiding treatment of early stage CKD cats

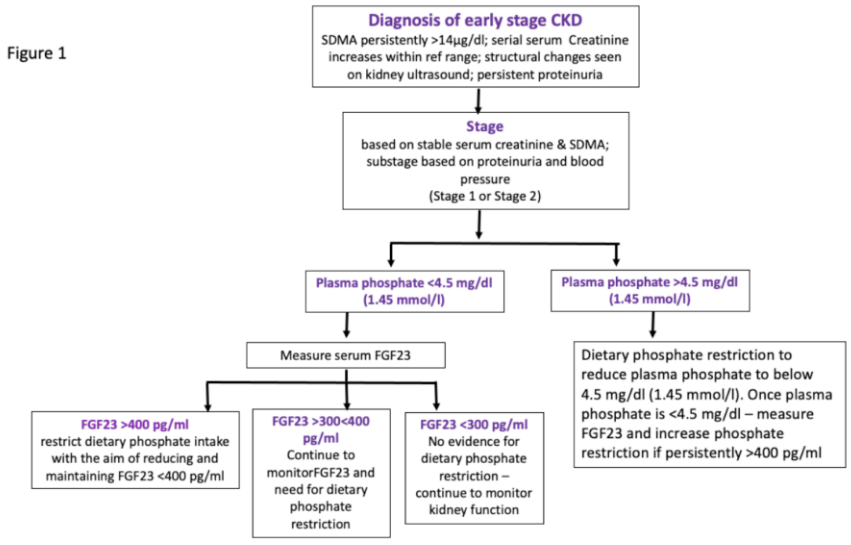
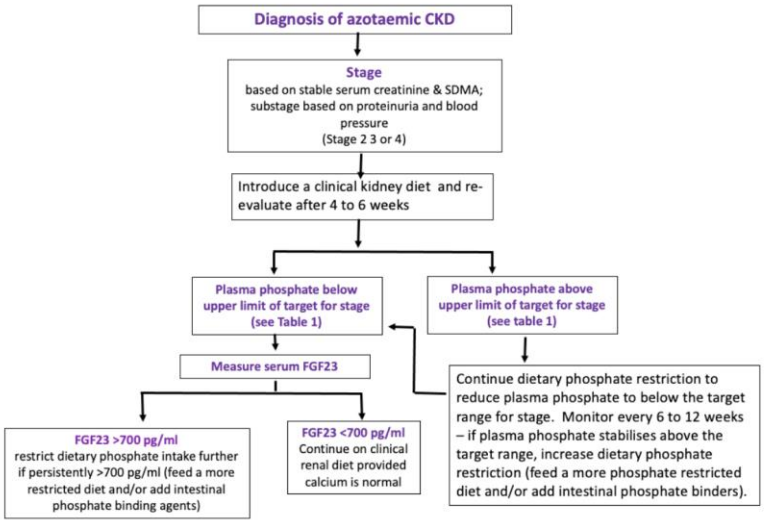


Figure 2: Flow chart indicating the utility of measuring serum FGF23 in guiding the treatment of azotaemic CKD cats



It is important to monitor plasma calcium concentration (ideally ionized calcium) in CKD cats as idiopathic hypercalcemia can occur in association with CKD. Some cats tend to develop hypercalcemia when fed a phosphate restricted diet, particularly after introduction of a markedly phosphate restricted diet. Those cats which respond to phosphate restriction with an increase in plasma calcium concentration seem to demonstrate an increase rather than a reduction in plasma FGF23 concentration, emphasizing the importance of monitoring the phosphate, calcium and FGF-23 response to dietary changes.

#4 Feline CKD and use of early prescription renal diets.

Diets specifically designed for cats with kidney disease may be beneficial as they may slow the progression of disease and enhance quality of life for an extended period of time. Phosphorus plays the major role in early CKD; restricting oral dietary phosphorus has been proven to be the most important factor in slowing CKD progression and prolonging survival. Dietary protein content in cat foods is high based on cats' carnivore metabolism. However, protein is a significant contributor to total body phosphate levels and is responsible for production of intestinal nitrogenous waste products; both of which rely on normal renal function for excretion.

However, adequate protein is necessary for cats to maintain appropriate energy metabolism, muscle mass and immune functions.

Early stage feline renal diets contain reduced (not restricted) high quality protein levels and significantly restricted phosphorus content to maintain carnivore energy metabolism while reducing renal workload and slowing the progression of CKD nephron loss. Early stage renal prescription diets are reduced in protein but still meet AAFCO minimum crude protein content and by design contain higher quantities of select bioavailable essential amino acids that are feline specific to maintain body condition, and lean muscle mass while reducing weight loss. Additionally, feline renal diets are formulated to maximize energy density so cats can meet their energy requirement while eating smaller portions. Renal diets contain higher potassium and water-soluble vitamin levels to offset the renal loss of potassium and vitamins which reduces the development of hypokalemia and vitamin deficiencies associated with CKD. Diets are also enhanced with omega-3-fatty acid fish oils (EPA and DHA) which reduces renal interstitial inflammation and decreases tubular protein loss associated with CKD progression. Dysbiosis has recently been demonstrated in CKD cats so renal diets are now supplemented with specific prebiotics and fiber to offer microbiome support and appropriate nitrogen metabolism.

Cats wth early CKD (IRIS Stage 1) fed diets with an increased caloric density, enhanced carnitine and essential amino acid concentrations and restricted phosphorus content have stable body weight, stable body condition scores, maintain GFR, and have stable to improved renal chemistry values over time compared to cats consuming a control food. CKD catkin the control groups did not consume as many calories and subsequently lost weight, had reduced GFR and had progression in renal-related blood values. Therefore, early initiation of a renal diet is encouraged to slow progression of CKD, delay onset of uremic signs and facilitate better acceptance of diet change.

Feline prescription renal diets with restricted phosphorus content and reduced but highly bioavailable amino acid-enhanced protein content are now available so that a CKD cat’s diet can be individualized based on their needs, IRIS stage and response to therapy. Dietary therapy may take 4-6 weeks to have a discernible effect on serum phosphorus and FGF-23 levels. Thus, serum phosphorus and FGF-23 concentrations should be rechecked 4-6 weeks after initiating ar feline renal diet. If the serum phosphorus level is within the IRIS stage target range and the FGF-23 level is normal, then the diet should be continued, and blood values reassessed every 4-6 months. Control of phosphorus and FGF-23 I can generally be achieved with renal diet alone in patients with CKD Stage 1 and 2 . Once a renal diet alone fails to maintain the

serum phosphorus target then the addition of an intestinal phosphorus-binding agent is necessary.

#5 New Perspective on the Use of Phosphorus and Uremia Binders in Feline CKD.

Renal phosphorus excretion is a key regulatory mechanism of maintaining phosphate balance. CKD impairs renal phosphorus excretion causing positive phosphate imbalance (hyperphosphatemia) to develop over time early in CKD. Hyperphosphatemia has many deleterious effects including promotion of 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. An IRIS Stage desired blood phosphorus levels have been established. Serum FGF-23 is also a practical blood biomarker to evaluate the effect of phosphorus reducing therapies.

Once a phosphorus-restricted diet is no longer able to maintain appropriate serum phosphorus and FGF-23 levels then traditional enteric phosphate binders, such as aluminum hydroxide/carbonate, calcium carbonate/acetate, or lanthanum carbonate, have been used to bind dietary phosphorus within the intestinal lumen and promote its fecal excretion. Newly developed iron-based (ferric) binders are becoming accepted as a first-line option in feline CKD as they have a significantly higher phosphorus binding coefficient. compared to the traditional binders such as aluminum hydroxide.

Ferric Citrate is an iron-based phosphorus binder with a high intestinal phosphate binding coefficient. Ferric citrate is partially absorbed also provides an iron source to help maintain appropriate erythroid/RBC production in CKD patients. Naraquin® (Nutramax) is a veterinary iron-based binding renal supplement that contains ferric citrate, calcium acetate, chitosan along with OM-3 FAs.

A lanthanum-based phosphorus binder (Catney-ONE) has also been recently introduced for feline use.

Nitrogenous metabolites (e.g., indoxyl sulfate, para-cresol sulfate) are produced by intestinal microbes following normal amino acid metabolism and are absorbed into the blood stream. Several of these metabolites have been identified as uremic substances and rely on appropriate

kidney function for excretion. These substances are collectively referred to as uremic toxins when they accumulate in the body associated with renal dysfunction. Uremic toxin accumulation also occurs due to increased production of certain metabolites and impaired mucosal permeability associated with CKD-induced intestinal dysbiosis. Uremia has various detrimental effects including reduced GFR, immune dysfunction, inflammatory triggering, and clinical nausea, oral ulcers,inappetence and muscle weakness.
Newer therapies have been developed to reduce the production and absorption of uremic metabolites. Maintaining an appropriate microbiome reduces the production of certain metabolites associated with uremic; probiotic supplementation (Visbiome, Azodyl) has been shown to reduce production of uremic metabolites. Intestinal luminal binding products (Porus-One) can be added to food to trap uremic precursors limiting absorption into the blood stream.

#6 New Options to Treat Feline CKD-related Anemia.

Uremic toxins and renal tissue loss/fibrosis result in decreased production of endogenous erythropoietin (EPO) in CKD patients. Chronic anemia is not only associated with clinical signs but it also perpetuates renal hypoxia and accelerates CKD injury. Restoration of normal red blood cell numbers is important in preserving renal oxygen delivery and helps restore attitude, strength, and appetite. Treatments available to address CKD-associated nonregenerative anemia include supplemental iron therapy, periodic blood transfusion, recombinant erythropoietin replacement drugs and hypoxia-inducible factor-prolyl hydrolase (HIF-PH) inhibitor therapy. The use of anabolic steroids in feline CKD-associated anemia are of no proven benefit and may be actually be detrimental to CKD patients.

Darbepoetin (Aranesp®) is a human-recombinant erythropoietin-stimulating drug that is effective in stimulating erythroid production within the bone marrow of cats and dogs. Treatment introduction is considered when non-regenerative anemia is significant and likely to affect patient's quality of life; typically, this occurs when the PCV reaches < 25%. Human Epoeitin alfa (r-HuEPO-alpha) was the original drug used as an endogenous EPO substitute in humans as well as dogs and cats with renal disease. In dogs and cats, the development of autoantibodies resulted in eventual treatment failure or immune-destruction of marrow RBC precursor; therefore use of this drug formulation (Epogen) is contraindicated in veterinary patients. Darbepoetin (Aranesp®) is a human- recombinant DNA protein related to erythropoietin that stimulates erythropoiesis by interacting with marrow 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 is administered less often while still maintaining RBC production following induction treatment. Significant adverse effects have not been reported in cats although close monitoring is still required. An initial weekly SQ dose of 1.0 micrograms/kg is suggested. The dose and frequency are then adjusted based on maintenance of adequate 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.

Molidustat belongs to the hypoxia-inducible factor-prolyl hydrolase (HIF-PH) inhibitor drug class. HIF stimulates endogenous erythropoietin production and mobilizes iron by blocking hepcidin and increasing transferrin, a protein necessary for iron transport. HIF-PH inhibitor drugs prevent the degradation of HIF, prolonging its positive effects on RBC production. Molidustat oral suspension (Varenzin™-CA1; Elanco) has received conditional FDA approval for control of non-regenerative anemia associated with CKD in cats. It is licensed to be administered by mouth once daily for up to 28 days to produce and increase in RBC production. Weekly monitoring of PCV is recommended starting 14 days after the beginning of treatment. The most common reported adverse effect in approval studies was vomiting.

#7 - Treatments to Manage Feline Hypertension and Proteinuria.

Normal systolic blood pressure is maintained in the 120 to 130 mmHg range. Systemic hypertension occurs when BP is > 140mmHg. Systolic blood pressures of 160 to 180 mmHg are associated with moderate risk of organ damage (brain, heart, kidneys, eyes). Severely hypertensive systolic blood pressure > 180 mmHg is associated with a high risk of acute severe organ damage. Thus maintaining normal systemic and glomerular blood pressure is indicated to protect target organ (brain, heart, eyes) and to slow CKD progression. Drugs that provide direct arteriole vasodilation rapidly reduce systemic blood pressure and are indicated in severe hypertension. Drugs that inhibit renin-angiotensin-aldosterone activity gradually reduce systemic blood pressure, reduce glomerular transcapillary pressure and decrease proteinuria.

Calcium channel blockers (e.g., amlodipine) act directly on preglomerular arteriole vascular smooth muscle to rapidly reduce blood pressure with minimal alteration of glomerular

hemodynamics. Amlodipine is indicated in the management of severe hypertension (> 180 mmHg) especially if target organ damage is identified or suspected. Amlodipine is initially administered at 0.625 mg total dose q 24hr for cats < 4 kg and 1.25 mg total dose q 24hr for cats > 4 kg. The dose is subsequently increased as needed if blood pressure is not adequately controlled. The most common dose adjustment is to administer the initial mg dose q 12hr.

Angiotensin Converting Enzyme inhibiting drugs (ACEI), such as benazepril and enalapril, and Angiotensin Receptor Blocker drugs (ARBs), such as telmisartan, reduce excess chronic renin-angiotensin-aldosterone activity. They generally produce a modest reduction in systemic blood pressure, but have a more profound effect on intraglomerular hemodynamics via dilation of the glomerular efferent arterioles reducing intraglomerular pressure, reducing proteinuria, and reducing renal and cardiac tissue fibrosis. ARB drugs have proven to be more effective compared to ACEI drugs in both cats and dogs, possibly due to less aldosterone breakthrough associated with chronic administration. Telmisartan is available as an FDA approved drug (Semintra®, bi-animal health) for use in cats. The feline label dose has been associated with post-release hypotension so a starting dose of 0.5 to 1.0 mg/kg PO q 24hr is suggested. The dose can be gradually increased as needed to control hypertension or renal proteinuria. A 4-6 week treatment duration is necessary to evaluate therapeutic effect. Longterm goals include maintenance of a normal systemic BP (< 140 mmHg) and a UPC < 0.5 without a significant increase in renal values. In cats with overt proteinuria, a UPC decrease of at least > 50% is indicative of therapeutic efficacy.

When initial drug therapy is not effective in providing a satisfactory decrease in systemic blood pressure or proteinuria then several options exist. A gradual titrated increase in the telmisartan (ARB) dose (up to 2-3 mg/kg PO q 24hr) is most commonly employed; combining telmisartan (ARB) with benazepril (ACEI). In cases with sustained hypertension, telmisartan and amlodipine can be combined.

When used alone or in combination, a modest increase in serum creatinine (10-20%) or SDMA (< 2 µg/dl) is an expected finding associated with reduced GFR. A marked increase in renal values suggests an acute kidney decompensation associated with drug effect indicating an immediate dose reduction is necessary. Progressively increasing renal values over time indicates progressive kidney damage/disease. The

risk benefit analysis of using amlodipne, ARBs, or ACEI drugs needs to be made on an individual basis with careful monitoring.

The benefit of an ARB / telmisartan in delaying progression in normotensive non-proteinuric CKD cats is often discussed but an absolute proven benefit has not been established and is in need of further investigation. However, telmisartan introduction in CKD cats with borderline hypertension and proteinuria should be considered.

#8 Rapamycin and 'Campten' therapies for Hypertrophic Cardiomyopathy (HCM)

Primary HCM is defined as asymmetric or symmetric thickening of the left ventricular posterior wall or interventricular septum in the absence of any hemodynamic cause. HCM is the most common cardiomyopathy in cats, with a reported prevalence as high as 15%. While some cats remain subclinical throughout life, many progress to develop left-sided congestive heart failure (CHF) or arterial thromboembolism (ATE). Currently available drug therapies have failed to delay progression of disease or show survival benefit in the subclinical setting.

Rapamycin, also known as sirolimus, an inhibitor of mTOR, has demonstrated promise as a novel therapeutic for feline HCM and is expected to be introduced to the veterinary market in 2025 (TriviumVet). mTOR is a master regulator of cell growth, metabolism, and protein synthesis, and represents a therapeutic target for HCM. mTOR is a serine/threonine protein kinase that forms 2 multiprotein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Activation of mTORC1 promotes anabolic processes that increase protein and lipid synthesis, downregulates catabolic processes to reduce autophagy (the cell's ability to remove damaged proteins and organelles), and plays a vital role in signaling adaptive cardiac remodeling in response to mechanical overload. mTORC2 plays a role in regulating glucose and lipid metabolism and promotes cardiomyocyte cell survival, cytoskeletal organization, and appropriate cell polarity.

A recent clinical trial (RAPACAT, 2023) demonstrated that mTOR inhibition with delayed-release (DR) rapamycin, administered orally once weekly, halted the progression of left ventricular wall thickness with no adverse events or clinical pathology derangements. The exact molecular effects of rapamycin in cats with HCM remain unknown. DR rapamycin was well tolerated and may reverse or prevent progressive LV hypertrophy in cats with subclinical HCM. A pivotal clinical trial (HALT HCM) is currently underway.

Cardiac myosin inhibitors are a new class of drugs that may help treat feline hypertrophic cardiomyopathy (HCM). Myosin is a key target for intervention in HCM because of its role in the dysregulation of actin–myosin cross-bridging. Novel small-molecule cardiac myosin inhibitors target actin-myosin interactions to alleviate overactive protein interactions that can lead to hypercontractility, impaired relaxation, and hypertrophy in the heart muscle. Pilot studies with Aficamten resulted in significantly decreased LV systolic function and improved LVOTO in Maine Coon HCM cats. Further studies are currently underway to evaluate the "camten" class of drugs for feline HCM.

#9 Use of NT-ProBNP and Focused Echocardiography in Feline Cardiomyopathy

NT-proBNP, a prohormone precursor of B-type natriuretic peptide (BNP), is produced by the cardiac myocytes that are exposed to stretch or pressure. BNP causes renal sodium and water loss and vasodilation counteracting the effects of RAAS. The magnitude of increase in circulating BNP is correlated to the severity of the underlying heart disease. NT-proBNP is more stable than proBNP and has a longer half-life, making it a more desirable analyte. Commercial qualitative and quantitative assays are available. Clinical uses include differentiation of cardiac vs respiratory causes of dyspnea, didentification of occult heart disease in apparently healthy cats and use for staging (low vs high risk) in cats with known cardiac disease. There is some day-to-day variation in individual cats, but in general variation is typically < 10 pmol/L. However, some cats (about 30%) can have concentrations that vary by as much as 100 or more pmol/L. The positive predictive value of the test is approximately 70%; the negative predictive value is approximately 95%. A positive SNAP result (≥ 150 pmol/L) or quantitative test (≥ 100 pmol/L) should be investigated with echocardiography.

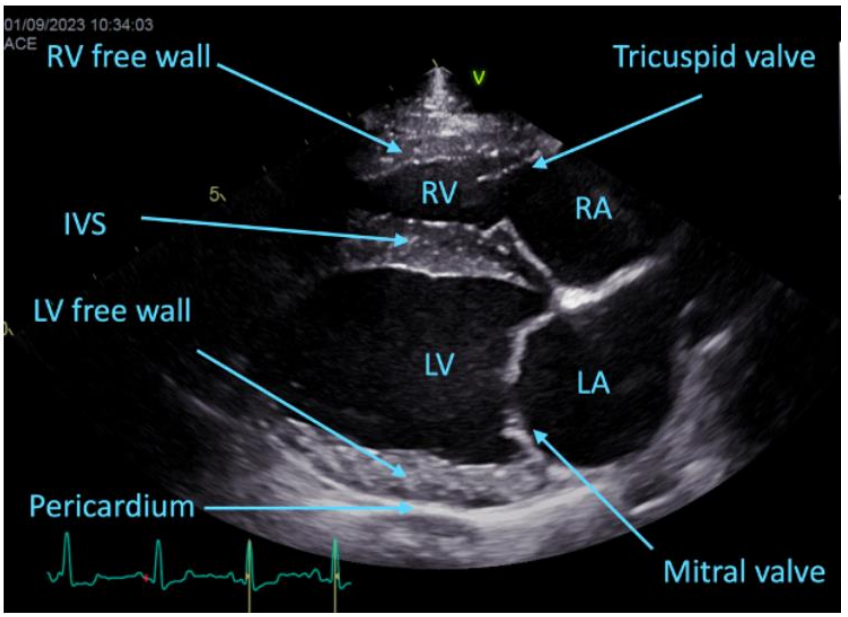
Focused Cardiac Ultrasound (FCU) is ultrasound of the heart used to answer specific questions about heart structure and function in both symptomatic and asymptomatic cats and dogs. FCU is not the same as a formal or complete echocardiogram performed by a cardiologist as only a limited number of select 2-dimensional and M-mode imaging views and measurements are acquired and used to make clinical decisions. Like other point-of-care ultrasound exams, it is designed to be quickly implemented and answer targeted questions. As such, FCU examination is generally looking for obvious, as opposed to subtle cardiac abnormalities, that recognize specific findings representing a narrow list of potential diagnoses in specific clinical settings. The primary goal of FCU in dogs and cats with acquired heart disease is to identify and evaluate basic cardiac anatomy and integrate this information with the individual's history and clinical

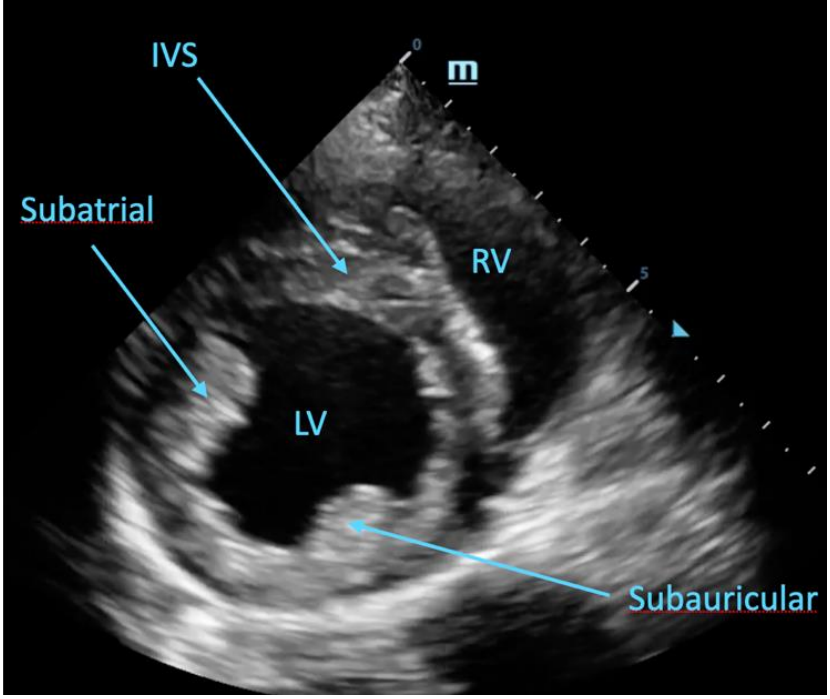
examination to determine/confirm a cardiac diagnosis, current staging and need for therapy introduction.

FCU is generally performed only from the right side. It can be performed in lateral or sternal recumbency or standing, whichever view provides a good intercostal window to view the heart. Phased-array cardiac probes are best suited to cardiac examination but microconvex (curvilinear) probes may also be used.

Once an adequate view of the heart has been optimized, the US probe is moved within to obtain key long and short axis views of the heart. The long axis view is obtained with the indicator mark on the transducer pointed towards the neck or shoulder, whereas the short axis views are obtained with the indicator mark pointed towards the elbow. To transition from long axis to short axis views, the transducer footprint stays in place while the probe is rotated 90 degrees (from the patient's shoulder towards the elbow). To move among short-axis views, the probe is angulated ("fanned") from the heart apex to base.

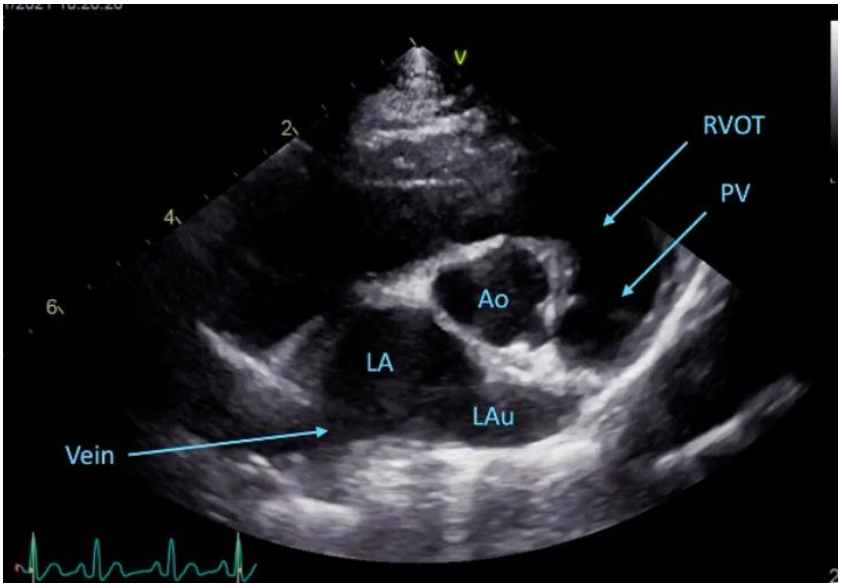
1. **Parasternal long-axis 4 chamber view (PLAX4)**
   This view is the base view: always start your examination here. It captures most of the four heart chambers, right and left, and the pericardium, in one view.





2. **Parasternal short-axis view at the level of the papillary muscles (PSAX-pap)**
   Often called the “mushroom view,” this view is useful; however, it does not provide the same overview of the heart as the PLAX4.

3. **Parasternal short-axis view at the level of the heart base (PSAX-base)**
   This is the classic “LA:Ao view.” The left atrium, left auricle, aorta and pulmonary arteries and veins can be visualized in this view.



Clinical Integration

Most of the important FCU findings in a cat

can be made with an “eyeball” or qualitative assessment. Starting with the right parasternal long axis view, assess relative cardiac chamber dimensions and wall thicknesses and LV systolic function, as well as presence or absence of fluid (pericardial or pleural). Remember: we are not cardiologists, so we are not performing a formal ECHO. We are simply trying to integrate FCU information into our clinical examination.

The following are characteristics of a **qualitatively normal feline exam**:

- In long axis, LA and RA should be roughly the same size (LA can be slightly larger).
- In long axis, LV should be 3–4 times larger than the RV. The left ventricular should be shaped like a “bullet” with parallel walls at the base and mid ventricle, and a gently pointed apex
- In short axis, the LV should be round with a curved interventricular septum
- The LA, Ao, and PA cross-sectional diameters should be approximately the same diameter in any view.

The following are characteristics of a **abnormal feline exam:**

- In cats with cardiomyopathy, the left atrium chamber is enlarged. In general, a normal LA:Ao size is about 1:1, but it can go up to 1.3. Left atrial enlargement is defined in cats > 1.4. Cats with increased risk for congestive heart failure have significant LA:Ao of > 2.0.
- Spontaneous echocontrast (“smoke”) or thrombi may be visible within a severely dilated feline LA.
- In cats with HCM, concentric LV hypertrophy will be seen, which may be symmetrical or segmental. LV wall hypertrophy is diagnosed when diastolic wall thickness > 6 mm, which may be symmetrical or segmental.
- In cats with severely decreased LV systolic function with dilated and spherical LV → supportive of dilated cardiomyopathy.

#10 Feline TSH measurement in Hyperthyroidism - Diagnosis and Monitoring

Clinical testing is recommended in individual cats when there is a suspicion for hyperthyroidism based on the presence of clinical signs, physical findings (thyroid nodule) and/or preliminary laboratory findings. Routine screening of patients with no overt signs of hyperthyroidism is debatable. False negatives definitely occur, especially in early FHT and in cats with concurrent medical comorbidities. A delay in FHT recognition and treatment can be harmful in early disease or in patients with comorbities. False positives are less common, but a misdiagnosis may lead to inappropriate and potentially harmful therapy.

Thyroxine (total T4) testing

The diagnosis of FHT is classically based on the finding of an elevated serum thyroxine (total T4) in association with appropriate clinical signs. Measurement of serum thyroxine (total T4) usually provides a clear confirmation of or rules out FHT in older cats exhibiting clinical signs consistent with the disease, especially if a palpable thyroid nodule is detected. The specificity of total T4 for diagnosis of classic FHT approaches 100% while the sensitivity is ~ 91%.

However, not all cases are “classic” so other diagnostic approaches may be necessary in individual patients to determine if an individual cat is euthyroid or hyperthyroid. Additional diagnostic tests (see below) can be considered in cats in which FHT is suspected but T4 levels are consistently normal.

Free T4 (fT4) evaluation.

When evaluating in tandem, an increase in both total T4 and fT4 is confirmatory for hyperthyroidism. However, free T4 determination should not be used by itself for FHT screening. Approximately 20% of euthyroid cats, especially if they have a non-thyroidal illness, will have an increased fT4 value (specificity 80%). Relying on fT4 testing by itself will lead to misdiagnosis and inappropriate treatment or referral of euthyroid cats.

- if total T4 and fT4 are elevated = hyperthyroidism
- if total T4 is upper half of reference range and fT4 is elevated = hyperthyroidism
- if both total T4 and fT4 are in upper half of reference range then hyperthyroidism may be developing; retest in 2-3 months
- if total T4 is upper half of reference range and fT4 is normal (or low) - not hyperthyroidism

- if total T4 is lower half of reference range, the fT4 value is not relevant as cat is not hyperthyroid

Endogenous TSH evaluation. Excess autonomous serum thyroxine (T4) production associated with FHT will suppress pituitary eTSH production via negative pituitary-thyroid axis feedback. Hyperthyroid cats should have an eTSH significantly below the normal range (non-detectable in most). Traditionally, a canine eTSH assay has been used to evaluate feline TSH; however a serious limitation occurs with this assay as it cannot accurately measure low feline TSH concentrations that are necessary to reliably distinguish euthyroid cats with low-normal TSH concentration from hyperthyroid cats with a truly low or non-detectable TSH concentration. When using the canine assay, a detectable eTSH would rule-out FHT.

Iatrogenic hypothyroidism results when treatment for hyperthyroidism causes suppression of total thyroxine (T4) below normal levels. Azotemia is a serious consequence in cats with iatrogenic hypothyroidism which can result following surgical thyroidectomy, radioactive iodine (I-131), or oral methimazole treatment. The overall prevalence of IH in cats treated for hyperthyroidism is estimated to be around 40-50%. Practically speaking, cats that are being treated for hyperthyroidism should be monitored for the development of iatrogenic hypothyroidism and this requires routine post-treatment monitoring of clinical signs and both T4 and TSH. Current pitfalls in our ability to recognize hypothyroidism in cats as weight gain, declining appetite, and decreased activity are considered normal with treatment for hyperthyroidism. Further, most cats undergo routine T4 monitoring although documentation of iatrogenic hypothyroidism requires both a low or low-normal T4 level and the complementary finding of an elevating or high-normal thyroid stimulating hormone (TSH) level. The current commercially available canine TSH (cTSH) assay lacks sensitivity for cats and as a result, we are missing the early stages of iatrogenic hypothyroidism in post-treated cats.

A highly sensitive, feline-optimized TSH assay (Truforma, Zomedica) has recently been introduced, which eliminates the problem associated with the cTSH assay in cats, and allows the diagnostic utility of feline eTSH testing and interpretation as it can accurately measure lower feline eTSH values. This allows us to distinguish between hyperthyroid cats and those euthyroid cats with low-normal TSH concentration. in addition, early iatrogenic hypothyroidism can be detected and monitored in cats following or during FHT treatment.

(Evaluation of a novel, sensitive thyroid-stimulating hormone assay as a diagnostic test for thyroid disease in cats. Am J Vet Res 2024)