COMPLEX DISEASE MANAGEMENT:
HOW I APPROACH A CAT WITH CHRONIC KIDNEY DISEASE, DIABETES, ARTHRITIS, HYPERTHYROIDISM, HYPERTENSION & DENTAL DISEASE

Margie Scherk, DVM, Dip ABVP (Feline Practice)
Vancouver, Canada

INTRODUCTION

Elderly cats often present with multiple concurrent conditions. "Age-associated" or "age-appropriate" illnesses that we expect to see in older cats include problems related to the urinary tract (chronic kidney disease (CKD), pyelonephritis, calcium oxalate ureteronephroliths, bacterial cystitis), endocrine system (hyperthyroidism, diabetes mellitus, hyperaldosteronemia), degenerative joint disease (DJD) and other musculoskeletal conditions, dental diseases and neoplasia. Constipation may become an ongoing concern. Certain infectious diseases become more likely in the older individual (e.g., FIP). A decline in functioning of the special senses occurs frequently and behaviour changes suggestive of cognitive dysfunction may be seen in some individuals.

Making management recommendations may be challenging as treatments, at first glance, may appear to be in conflict. However, all body systems communicate and interact with each other. Identifying the common issues allows development of a logical treatment plan. The four most important therapeutic considerations that must be incorporated in caring for every patient, especially those who are older, are optimizing hydration, nutrition, comfort through analgesia, and ensuring that the environmental needs are met so they can perform normal behaviours.

IDENTIFYING THERAPEUTIC CHALLENGES

In the case of a patient with Stage 2-3 CKD, hypertension, hyperthyroidism, diabetes and arthritis, the therapeutic goals for each condition are:

- *Chronic kidney disease*- optimize hydration and feed a diet that will manage serum phosphorus levels and benefit renal health in order to minimize uremic episodes, manage hypertension and proteinuria, and enhance quality of life (QoL);
- *Hypertension* - reduce the risk for target organ damage (TOD) which may affect survival;
- *Hyperthyroidism* – modulate serum T3 and T4 levels in order to reduce metabolic rate, normalize cardiac output, blood pressure and renal perfusion;
- *Diabetes mellitus* – regulate blood glucose through insulin therapy and diet to reduce glucose toxicity, achieve glycemic control, and provide nutrients to cells;
- *Degenerative joint disease* – alleviate comfort through non-steroidal antiinflammatory drugs (NSAIDs), optimize mobility, hydration, nutrition, and ensure ready access to key resources.

MEETING NEEDS COMMON TO ALL CONDITIONS

The foundation for any treatment plan is achieving patient hydration, nutrition, analgesia, and meeting behavioural and environmental needs. The pet parent also affects outcome: in a study evaluating which factors influence decision making in clients considering the use of chemotherapy in terminally ill pets, "vomiting was considered an acceptable side effect but inappetence, weight loss and depression were considered unacceptable".[1]

Successful maintenance of euvolemia will be reflected in coat and stool character as well as subjective measures of well-being including grooming, interaction and posture. Daily subcutaneous fluids (given with treats and warmed to body temperature) may be appropriate. A client handout is included in the Appendix.

Undoubtedly, meeting nutritional needs is important. Appetite may be negatively affected by renal disease from uremic toxins or uremic gastritis. Nausea associated with uremic acidosis may be alleviated with famotidine 5 mg PO q24h or another H2 antagonist. However, the proton pump inhibitor omeprazole has been shown to provide better acid suppression than famotidine in cats.[2] Additionally, twice-daily omeprazole (1 mg/kg PO BID) is more

efficacious at suppressing acid production than once daily dosing or ranitidine therapy.[3] Antiemetics (e.g., maropitant, mirtazapine, dolasetron, ondansetron), are unlikely to be required for this patient.

Appetite stimulants including cyproheptadine (1 mg/cat PO BID), mirtazapine (1-2mg/cat PO q48h)[4] may help to jump-start a cat's appetite, but it is important to calculate calories required and monitor how many are consumed. While effective in palliating vomiting, maropitant did not significantly improve appetite or support weight gain in cats with Stage II and III CKD.[5] Although capromorelin has been shown to be effective in cats, the safe and efficacious dose have yet to be determined. Cats with untreated hyperthyroidism and diabetes may have an increased appetite yet, due to increased metabolism, lose weight and muscle. Once euthyroid and normoglycemic, their appetites generally normalize.

Some loss of muscle is part of normal aging and is not caused by apparent illness. Nutrition offers the possibility to improve longevity as well as QoL. Sarcopenia, the age-related loss of lean body mass (LBM), is a gradual process: initially it is unapparent because increases in body fat persist. However, the loss of weight precedes the diagnosis of CKD and has profound effects on survival.[6] Studies have identified decreased survival associated with thin body condition.[7-9] Although not yet shown in prospective studies, preservation of body weight and lean body mass (LBM) may enhance survival and quality of life in aging cats and those with CKD.

The dietary strategy must take body weight, BCS and MCS into consideration. When MCS is poor, protein supplementation should be considered. Early nutritional intervention is recommended if a patient:

- Is hypo- or anorexic for > 3-5 days,
- Has a low BCS or MCS and is unwilling or unable to consume a sufficient number of calories to achieve and maintain an ideal BCS,
- Is dysrexic and is unwilling to eat a diet appropriate for its medical condition,

rather than waiting for malnutrition to develop.[10] Intervention includes ensuring an appropriate, low stress environment, use of appetite stimulants, low stress oral assisted (syringe) feeding and placement of medium term feeding tubes. Large bore esophagostomy tubes are quick and easy to place and use.

NEEDS SPECIFIC TO EACH GIVEN CONDITION

Chronic Kidney Disease

In most cases, the initiating cause for the CKD is not known, thus management is directed towards attenuating the rate of the deterioration of function by controlling proteinuria, hypertension and hyperphosphataemia. As 40-75% of cats with CKD present with dehydration and cachexia and weight loss, rehydration, with the goal of maintaining hydration, and improving nutritional plane are important goals.[11] Indeed, weight loss begins three years before the diagnosis of CKD is made.[6] It is generally recommended to feed cats with Stage 2 and onwards CKD, a protein-restricted, renal diet.[12] There is little data that clearly defines what the nutritional requirements for a cat with CKD are. In a review of the literature, it appears that restricting dietary phosphorus in an alkalinizing diet supplemented with potassium is beneficial to cats with CKD.[13] Many questions remain regarding the optimal composition of a renal diet, however the previous dogma that renal diets be restricted in protein regardless of underlying renal pathology or body condition has been challenged. Renal diets meet these requirements however it is critical to ensure that an individual is ingesting enough of the diet to meet their protein calorie needs.

The rate of progression or decreased survival time are affected by the aforementioned proteinuria, hypertension, hyperphosphatemia as well as anemia, azotemia, and metabolic acidosis.[11] Correcting dehydration results in improvements in azotemia, metabolic acidosis and hyperphosphatemia. Additionally, because inadequate protein may result in poor muscle condition, with increased morbidity and mortality, other means of restricting phosphorus may need to be considered. In 2018, new renal diets were introduced that have increased levels of protein while still restricting dietary phosphorus. In some cats, using intestinal phosphate binders along with a diet that the individual cat eats with enthusiasm may be desirable. Some cats will benefit through low phosphorus, protein supplementation such as cooked chicken breast or a low phosphorus whey protein (e.g., Beneprotein).

It appears that the type of dietary phosphorus (organic vs. inorganic) may affect serum phosphorus levels. Currently, research into this question is being undertaken to determine whether adjusting the source of the dietary phosphorus may play a more important role than the amount of phosphorus in affecting serum Ca:P ratios and the risk of bone mineral disorder.[14] Additionally, feeding a dry low protein, low phosphorus diet to IRIS Stages 1 and 2 cats resulted in increased total Ca and FGF-23 whereas feeding a less restricted protein and phosphorus dry with wet diet, FGF-23 levels decreased.[15]

Renal secondary hyperparathyroidism is more prevalent than hyperphosphatemia. Fibroblast growth factor-23 (FGF-23), a phosphatonin, increases in response to decreased renal phosphate clearance resulting in an inhibition of calcitriol and an increase in the fractional excretion of phosphate. At present time, to the author's knowledge, FGF-23 measurement is not available outside of research settings. It may more useful to measure and monitor serum PTH levels to ensure that phosphorus restriction or calcitriol therapy are initiated before serum phosphorus levels exceed the recommended range.

Creatinine and urea are results of muscle and protein metabolism. These are, however, only two of over 60 recognized uremic toxins. In addition, protein degradation products are not very toxic. In human studies, it has become apparent that tissue breakdown, rather than breakdown of nutritional protein, generates toxins. So, while uremic toxins can result in malnutrition, malnutrition itself results in inflammation, morbidity and mortality in human patients with CKD, therefore ensuring that an individual patient is thriving on a given diet is essential.[16] Reassessment should include evaluating not just body weight to look for trends, but also % weight changes, body condition and muscle conditions scoring.

Hypertension

Hypertension is a common disease in cats, mostly secondary to other diseases (e.g., chronic kidney disease, hyperthyroidism, hyperaldosteronism) but also occurs as a primary problem (essential hypertension). Because of the effects of untreated hypertension on highly vascular target organs (i.e., eyes, brain, kidneys, and cardiovascular system), it is very important to detect elevations in blood pressure early in order to prevent permanent damage.

As many as 65% of cats with CKD are hypertensive.[17,18] There is no linear relationship between degree of severity of CKD and the presence or severity of hypertension.[17,19] Hypertension is less common in cats with hyperthyroidism (approximately 10-23% at time of diagnosis), but approximately 25% of cats develop hypertension after initiation of therapy or even once euthyroidism has been achieved.[20,22] Diabetes mellitus is associated with hypertension in humans, but this does not appear to occur in cats. As many cats with diabetes have concurrent conditions that may be a risk factor for hypertension it is difficult to unequivocally rule out any association.[23,24]

Nephrosclerosis (renal arteriosclerosis and glomerulosclerosis) is seen in hypertensive cats with CKD.[25] It is unclear, however whether the hypertension contributes to progression of CKD (as it does in humans and in dogs). Hypertension can, however, contribute to proteinuria in CKD, and proteinuria is associated with shorter survival in cats.[26-28] Control of hypertension is important for its negative effects on cardiac function as well as progression of CKD.

The goal of treatment is to reduce the risk of TOD with an initial goal of 160 mmHg and a long term target of 140 mmHg (ACVIM 2018 Consensus Guidelines). Amlodipine will reduce blood pressure by 30-70 mmHg.[27, 30] It is the first drug of choice in treatment of hypertension as it is most effective and may be used as monotherapy.[31] Starting dose is 0.625 mg/cat PO q24h. Cats with BP of $\geq$ 200 mmHg may be started at 1.25 mg/cat PO q24h titrating cautiously up to 2.5 mg/cat PO q24h. In cats with proteinuric CKD, it may also reduce proteinuria. Telmisartan, an angiotensin receptor blocker, is licenced for treatment of CKD-associated proteinuria but has shown modest effects on hypertension at 1-3 mg/kg PO q24h.[32,33]

Hyperthyroidism

Renal disease is fairly common in untreated hyperthyroid cats. It may be masked due to increased cardiac output, renal blood flow and glomerular filtration rate (GFR). The effects of muscle wasting exacerbate the lower creatinine concentrations. Monitoring renal parameters and muscle condition during therapy is advised. Similarly, hypertension may become evident only during the course of therapy or even after the patient is euthyroid. It is

well recognized that amelioration of the hyperthyroid state by any method (i.e., medical therapy, 131I treatment or surgery) can result in decreased GFR, elevations in serum urea nitrogen and creatinine, and, in some cases, overt azotemia. The decline in GFR stabilizes by approximately four weeks. [34,35]

A practical approach to a patient with concurrent hyperthyroidism and CKD is to treat medically until the serum T4 is adequately controlled at which time the effect of permanent therapy may be predicted. If renal decline becomes apparent once euthyroidism has been achieved, exogenous thyroid hormone can be supplemented to support the kidneys. A balance must then be struck between creating iatrogenic hyperthyroidism and maintaining renal function as iatrogenic hypothyroidism appears to contribute to azotemia and decreased survival.[36-40] It is recommended to monitor serum TSH levels post radioiodine or during medical therapy to avoid iatrogenic hypothyroidism.[38,41] These cats should either receive a lower dose of medication or be supplemented with thyroxine before they develop overt disease or CKD.

From a nutritional perspective, hyperthyroidism is a hypermetabolic state that has profound effects not just on the kidneys, but also on body condition, muscle, the parathyroid and endocrine pancreas. Peterson recommends feeding: "a diet containing a large amount of dietary protein (>40% of daily calories or metabolizable energy [ME] as protein; >12 g/100 kcal), a small amount of carbohydrate (<15% of total calories or ME; <4.5 g/100 kcal), and a moderate amount of phosphate (<250 mg of phosphate per 100 kcal)". For diabetes, a catabolic condition, he recommends feeding high protein (>40% ME; >12 g/100 kcal) to help maintain muscle mass.[42]

Diabetes

In addition to feeding a higher protein diet with restricted carbohydrate (cho) content, insulin is required to reverse glucose toxicity induced by the hyperglycemic state. While evidence for benefit of feeding a high protein low carbohydrate diet is weak due to small sample size, variability in study design and the impossibility to adjust a diet for just one nutrient, at present, it suggests that feeding a diet with < 3g cho/100g metabolizable energy (ME) may be beneficial. Feeding canned food may be preferable to dry low carbohydrate food which may be preferable to feeding other dry food.[43]

Insulin choice is patient dependent as there is no one best insulin. In fact, because diabetes is such a dynamic process, the insulin dose and even type may change for optimal therapy over the lifetime of a given individual. In general, it is advisable to start with an insulin licenced for cats or veterinary patients. While not without challenges, blood glucose curves can be helpful in determining how a given patient is responding to a given insulin type.

Diabetes in cats tends to be associated with chronic inflammatory conditions. Wherever possible, the source of inflammation should be identified and treated or controlled. Due to poor glycemic control as well as low urine specific gravity, this patient may also be at risk for infectious problems, such as bacterial urinary tract infections. A culture and sensitivity profile should be determined for efficacious antimicrobial therapy. Should anaesthesia be required to diagnose or modulate the underlying problem, (e.g., gastrointestinal inflammation and gingivitis, respectively), administer half of the insulin dose on the morning of anaesthesia to a fed and hydrated cat. Monitor blood glucose during and after the procedure.

Degenerative joint disease

The cat with joint pain is often an older patient who may have concurrent problems (e.g., renal disease) including some that may affect drug metabolism. Like painful patients of any age, they may be in a physiologic state that affects drug disposition, the most common ones being dehydration, inadequate tissue oxygenation (anemia), electrolyte or acid-base imbalances and malnutrition. The most common concern regarding NSAID side effects is the possible consequence of using this class of drug in a dehydrated patient resulting in effects on gastric mucosal health or on renal function. It is equally important to make sure that it is easy for the cat to access key resources, namely food, water, litter, perching vantage spots and resting places.

Opioids are safe for pain relief in any age group and are excellent when used at the same time as other agents, especially NSAIDs. They are not, however, a first drug of choice for cats with arthritic pain as they are not very

effective for DJD. Metacam® 0.5 mg/ml oral suspension has been granted a licence in the EU for the alleviation of inflammation and pain in chronic musculoskeletal disorders in cats. The registered dose is 0.1 mg/kg on the first day followed by 0.05 mg/kg orally once daily. This is the first NSAID licensed for long-term use in cats.

Three studies have evaluated long-term safety of this agent in older cats; one concluded that this agent is safe, efficacious and palatable for musculoskeletal pain at 0.01-0.03 mg/kg PO q24h for a mean treatment duration of 5.8 months; no deleterious effect on renal function was detected in cats studied. Gastrointestinal upset in 4% of cats was the only adverse effect noted.[44] The second and third, reviewed the medical records of cats over 7 years of age treated for a minimum of 6 months with a daily maintenance dose of 0.02 mg/kg meloxicam and concluded that this dose does not hasten progression of renal disease in aged cats or aged cats with pre-existent stable IRIS stage 1-3 renal disease.[45,46]

In 2015, a paper reported on the safety of robenacoxib (1–2.4mg⁄kg) for daily, month long treatment of DJD in cats including 40 with chronic kidney disease IRIS stages 2-4. There was no evidence of increased risk in the frequency of reported adverse events, or in deterioration in renal variables in the subgroup of cats with concurrent CKD.[47] In the Australia, Canada, Japan, and the EU, robenacoxib is licensed for both acute and chronic use.[48] Another paper in 2021 showed that daily use for 4-12 weeks was well tolerated when compared to placebo treated cats with DJD with both groups showing a small increase in serum creatinine levels, even in cats with IRIS Stages 1-3.[49]

A suitable protocol for a cat with pain from musculoskeletal disease might be baseline NSAID with intermittent use of an opioid (such as burprenorphine) when "break-through" pain is evidenced by a decrease in appetite, mobility or social interaction. Gabapentin may be added for ongoing care.

Environmental modifications: Regular nail trimming helps by maintaining proper joint relationships. Ramps and steps to favourite sleeping spots are helpful. Warm, soft, padded sleeping places for stiff, painful, possibly bony joints should be considered. Raising food and water bowls may help the cat with cervical vertebral changes. Adding a litter tray to reduce the distance between boxes may reduce accidents as well as encourage regular voiding and defecation. The rim of the tray mustn't be too high, nor the opening into the box too small. It should be scooped several times a day to encourage use.

Feeding a diet that is supplemented with eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) +/- green-lipped mussel (GLM) extract and glucosamine/chondroitin sulfate may be beneficial. Disease-modifying agents such as polysulfated glycosaminoglycan, glucosamine and chondroitin sulfate may improve joint health.[50] Additional modalities (therapeutic exercise, acupuncture, cold laser therapy) while no scientific studies have been done to support efficacy, may also play a role in providing comfort for a cat with musculoskeletal discomfort.

MANAGEMENT PLAN FOR A PATIENT WITH STAGE 2-3 CKD, HYPERTENSION, HYPERTHYROIDISM, DIABETES, AND ARTHRITIS

Taking all of these factors into consideration, a reasonable plan would be to:

***Hydration*:** Daily subcutaneous fluids once rehydrated starting at 60 ml/kg ideal weight/day and ensuring plentiful fresh water stations are provide. Assess hydration based on fluid absorption and stool character.

***Nutrition*:** Feed enough of an alkalinizing diet that provides the cat with adequate protein to optimize muscle condition based on reassessment. Should phosphorus restriction be indicated, consider feeding an early renal diet or using an intestinal phosphate binder.

***Analgesia*:** Administer an NSAID daily, starting at label dose and titrating down to as low a dose that controls the discomfort. Consider multimodal additions of gabapentin and an opioid.

***Meeting behavioural and environmental needs*:** Endure easy access to all key resources.

***Medical therapies*:** amlodipine or telmisartan, methimazole, insulin, treatment for underlying inflammatory conditions.

REFERENCES

1. Williams J, Phillips C, Byrd HM. Factors Which Influence Owners When Deciding to Use Chemotherapy in Terminally Ill Pets. Animals. 2017; 7: doi: 10.3390/ani7030018
2. Parkinson S, Tolbert K, Messenger K, et al. Evaluation of the effect of orally administered acid suppressants on intragastric pH in cats. J Vet Intern Med. 2015; 29: 104-112.
3. Šutalo S, Ruetten M, Hartnack S, et al. The Effect of Orally Administered Ranitidine and Once-Daily or Twice-Daily Orally Administered Omeprazole on Intragastric pH in Cats. J Vet Intern Med. 2015; 29: 840-846.
4. Quimby JM, Lunn KF. Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: a masked placebo-controlled crossover clinical trial. Vet J. 2013;197:651-655.
5. Quimby JM, Brock WT, Moses K, et al. Chronic use of maropitant for the management of vomiting and inappetence in cats with chronic kidney disease: a blinded, placebo-controlled clinical trial. J Feline Med Surg. 2015; 17: 692-697.
6. Freeman LM, Lachaud MP, Matthews S, et al. Evaluation of weight loss over time in cats with chronic kidney disease. J Vet Intern Med. 2016;30:1661-6.
7. Scarlett JM, Donoghue S. Associations between body condition and disease in cats. J Am Vet Med Assoc. 1998;212:1725-1731.
8. Doria-Rose VP, Scarlett JM. Mortality rates and causes of death among emaciated cats. J Am Vet Med Assoc. 2000;216:347-351.
9. Freeman LM. Cachexia and sarcopenia: emerging syndromes of importance in dogs and cats. J Vet Intern Med. 2012;26:3-17.
10. Johnson LN, Freeman LM. Recognizing, describing, and managing reduced food intake in dogs and cats. J Am Vet Med Assoc. 2017: 251; 1260-1266.
11. Reynolds BS, Lefebvre HP. Feline CKD: Pathophysiology and risk factors—what do we know? J Feline Med Surg. 2013:15(1_suppl):3-14.
12. Ross SJ, Osborne CA, Kirk CA, et al. Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. J Am Vet Med Assoc 2006; 229: 949–957.
13. Scherk MA, Laflamme DP. Controversies in Veterinary Nephrology: Renal Diets Are Indicated for Cats with International Renal Interest Society Chronic Kidney Disease Stages 2 to 4. Vet Clinics Small Anim 2016; 46:1067-94.
14. Schauf S, Coltherd JC, Atwal J, et al: Clinical progression of cats with early-stage chronic kidney disease fed diets with varying protein and phosphorus contents and calcium to phosphorus ratios. J Vet Intern Med 2021;1-15 DOI: 1 0.1111/jvim.16263
15. Laflamme D, Backus R, Brown S, et al: A review of phosphorus homeostasis and the impact of different types and amounts of dietary phosphate on metabolism and renal health in cats. J Vet Intern Med 2020 34:2187-2196.
16. Vanholder R, Glorieux G, Lameire N. The Other Side of the Coin: Impact of Toxin Generation and Nutrition on the Uremic Syndrome. Seminars in Dialysis 2002: 15; 311-314.
17. Kobayashi DL, Peterson ME, Graves TK, et al. Hypertension in cats with chronic renal failure or hyperthyroidism. J Vet Intern Med 1990; 4: 58–62.
18. Syme HM, Barber PJ, Markwell PJ, et al. Prevalence of systolic hypertension in cats with chronic renal failure at initial evaluation. J Am Vet Med Assoc 2002; 220: 1799–1804.
19. Bijsmans ES, Jepson RE, Chang YM, et al. Changes in systolic blood pressure over time in healthy cats and cats with chronic kidney disease. J Vet Intern Med 2015; 29: 855–861.
20. Morrow LD, Adams VJ, Elliott J, et al. Hypertension in hyperthyroid cats: prevalence, incidence and predictors of its development [abstract]. J Vet Intern Med 2009; 23: 699.
21. Syme HM, Elliott J. The prevalence of hypertension in hyperthyroid cats at diagnosis and following treatment [abstract]. J Vet Intern Med 2003; 17: 754.
22. Williams TL, Elliott J, Syme HM. Renin-angiotensin- aldosterone system activity in hyperthyroid cats with and without concurrent hypertension. J Vet Intern Med 2013; 27: 522–529.
23. Sennello KA, Schulman RL, Prosek R, et al. Systolic blood pressure in cats with diabetes mellitus. J Am Vet Med Assoc 2003; 223: 198–201.
24. Bloom CA, Rand JS, Diabetes and the kidney in human and veterinary medicine. Vet Clin North Am Small Anim Pract 2013; 43: 351–365.

25. Chakrabarti S, Syme HM, Elliott J. Clinicopathological variables predicting progression of azotemia in cats with chronic kidney disease. J Vet Intern Med 2012; 26: 275–281.
26. Syme HM, Markwell PJ, Pfeiffer D, et al. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. J Vet Intern Med 2006; 20: 528–535.
27. Jepson RE, Elliott J, Brodbelt D, et al. Effect of control of systolic blood pressure on survival in cats with systemic hypertension. J Vet Intern Med 2007; 21: 402–409.
28. King JN, Tasker S, Gunn-Moore DA, et al. Prognostic factors in cats with chronic kidney disease. J Vet Intern Med 2007; 21: 906–916.
29. Acierno MJ, Brown S, Coleman AE, et al. ACVIM consensus statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. J Vet Intern Med. 2018; 32(6):1803-22.
30. Elliott J, Barber PJ, Syme HM, et al. Feline hypertension: clinical findings and response to antihypertensive treatment in 30 cases. J Small Anim Pract 2001; 42: 122–129.
31. Bijsmans ES, Doig M, Jepson RE, et al. Factors influencing the relationship between the dose of amlodipine required for blood pressure control and change in blood pressure in hypertensive cats. J Vet Intern Med 2016; 30: 1630–1636.
32. Jenkins TL, Coleman AE, Schmiedt CW, et al. Attenuation of the pressor response to exogenous angiotensin by angiotensin receptor blockers and benazepril hydrochloride in clinically normal cats. Am J Vet Res 2015; 76: 807– 813.
33. Sent U, Gössl R, Elliott J, et al. Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease J Vet Intern Med 2015; 29: 1479-1487.
34. Becker TJ, Graves TK, Kruger JM et al: Effects of methimazole on renal function in cats with hyperthyroidism, J Am Anim Hosp Assoc 2000; 36: 215.
35. Boag AK, Neiger R, Slater L et al: Changes in the glomerular filtration rate of 27 cats with hyperthyroidism after treatment with radioactive iodine, Vet Rec 2007; 161: 711.
36. Peterson ME. Feline focus: Diagnostic testing for feline thyroid disease: hypothyroidism. Compendium 2013; 35: E4.
37. Peterson ME. Diagnosis and management of iatrogenic hypothyroidism. In Little SE (ed): August's Consultations in Feline Internal Medicine Volume 7, St. Louis, 2014, Elsevier, 2016. 260-269.
38. Peterson ME. Advances in the Treatment of Feline Hyperthyroidism: A Strategy to Slow the Progression of CKD Proceedings ACVIM Forum 2014, 1083-1085.
39. Williams TL, Elliott J, Syme HM. Effect on renal function of restoration of euthyroidism in hyperthyroid cats with iatrogenic hypothyroidism. J Vet Intern Med 2014; 28: 1251-1255.
40. Aldridge C, Behrend EN, Martin LG, et al Evaluation of thyroid-stimulating hormone, total thyroxine, and free thyroxine concentrations in hyperthyroid cats receiving methimazole treatment. J Vet Intern Med 2015; 29: 862-868.
41. Peterson ME. Clinical Study: Information for veterinarians regarding enrolling cats into study - Monitoring the Effects of Radioiodine Treatment with a Complete Thyroid Panel (T4, T3, Free T4, TSH): http://www.animalendocrine.com/wp-content/uploads/2012/09/Vets—Complete-Thyroid-Panel-T4-T3-Free-T4-TSH-to-Diagnose-Iatrogenic-Hypothyroidism-in-Cats-.pdf Accessed June 18, 2018.
42. Peterson ME, Eirmann L. Dietary Management of Feline Endocrine Disease. Vet Clin Small Anim 2014: 44; 775-788.
43. Sparkes A, Cannon M, Church D, et al. ISFM consensus guidelines on the practical management of diabetes mellitus in cats. J Feline Med Surg. 2015 17(3):235-250.
44. Gunew MN, Menrath VH, Marshall RD. Long-term safety, efficacy and palatability of oral meloxicam at 0.01-0.03 mg/kg for treatment of osteoarthritic pain in cats. J Feline Med Surg 2008; 10: 235-241.
45. Gowan R, Lingard A, Johnston L, et al. Retrospective case control study of the effects of long-term dosing with meloxicam on renal function in aged cats with degenerative joint disease. J Feline Med Surg 2011;13: 752-761.
46. Gowan RA, Baral RM, Lingard AE, et al. A retrospective analysis of the effects of meloxicam on the longevity of aged cats with and without overt chronic kidney disease. J Feline Med Surg. 2012; 14(12):876-881.
47. King JN, King S, Budsberg SC, et al. Clinical safety of robenacoxib in feline osteoarthritis: results of a randomized, blinded, placebo-controlled clinical trial. J Feline Med Surg 2016;18 (8): 632-642.

48. Adrian D, King JN, Parrish RS, et al. Robenacoxib shows efficacy for the treatment of chronic degenerative joint disease-associated pain in cats: a randomized and blinded pilot clinical trial. *Sci Rep* **11,** 7721 (2021). https://doi.org/10.1038/s41598-021-87023-2
49. King JN, Seewald W, Forster S, et al. Clinical safety of robenacoxib in cats with chronic musculoskeletal disease. J Vet Intern Med. 2021; 1-11. Doi: 10.1111/jvim.16148
50. Lascelles BDX, Depuy V, Thomson A, et al. Evaluation of a therapeutic diet for feline degenerative joint disease. J Vet Intern Med 2010; 24:487-495.