Special Aspects of Diagnosing and Managing Chronic Kidney Disease

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The incidence of the diagnosis of CKD in cats is made 2 to 3 times as frequently compared to dogs and is especially common in geriatric cats.[1] CKD is clinically characterized by the development of variably progressive irreversible intrarenal lesions and loss of renal functions. Compensatory increases (so called adaptations) in glomerular hemodynamics and glomerular volume may actually be maladaptive in the long term as they cause increased protein trafficking across the glomerulus.

The initial diagnosis of CKD is made on some combination of findings from clinical signs, physical examination (especially large or small kidneys, irregular kidneys), renal imaging, urinalysis, and serum biochemistry. A surprising number of cats with CKD have upper urinary tract uroliths at the time of initial diagnosis.[2-4] Abdominal radiographs should be routinely obtained to determine the presence or absence of radiopaque stones. Renal and ureteral ultrasonography should be performed in all cats in which renal or ureteral stones were found on radiography in order to tell whether or not there is an obstructive component to the CKD. T4 should be measured in all cats with suspected CKD since hyperthyroidism can mask the detection of azotemia by its effects that increase GFR and RBF; hyperthyroidism may also contribute to progression of CKD through a variety of mechanisms including intraglomerular and systemic hypertension. [5] Conventional wisdom and experience suggests that client owned cats with healthy kidneys elaborate urine with a specific gravity of >1.035. This concept was recently validated in a study of cats evaluated at first opinion clinics.[6] Cats with USG < 1.035 should undergo further diagnostic investigation to determine if they have an endocrine or renal disorder with or without associated clinical signs. A surprising number of experimental [7] and clinical cats with CKD continue to be able to elaborate urine with a USG > 1.035, so the presence of "concentrated" urine and mild to moderate azotemia does NOT exclude the presence of primary kidney disease in cats as it often does in dogs. Cats that have thin body condition, prior periodontal disease or cystitis, anesthesia or documented dehydration in the preceding year, or being a neutered male (vs spayed female) were reported to be at increased risk for the diagnosis of CKD.[8]

A staging system initially based on the level of serum creatinine concentration has been developed by IRIS (International Renal Interest Society) for use in cats that are hydrated and stable. Serum creatinine is measured again on at least 2 occasions 2 weeks apart by the same lab. Sub-staging is then based on the degree of proteinuria as measured by UPC and also the magnitude of blood pressure. Staging using this system is designed to detect CKD much earlier than with traditional methods and also to potentially match treatments by stage. Normal and stage 1 CKD cats have serum creatinine concentrations < 1.6 mg/dl (< 140 µmol/L). Normal cats usually have a UPC < 0.2, with 0.2-0.4 considered borderline increased, and > 0.4 overtly proteinuric. Details of this staging system can be found online at http://www.iris-kidney.com. This staging system does not indicate the underlying cause for the CKD which requires other diagnostic workup to determine. It is important to remember that nearly all studies on the effect of diet or drugs have studied overtly azotemic cats (serum creatinine > 2.0 mg/dl). It has not been determined whether or not the salutary effects of treatment in azotemic cats confer the same benefits to CKD cats at earlier stages.

Tubulo-interstitial nephritis of unknown origin is the most common cause of azotemic CKD in the cat, as in the dog. However, cats have several renal diseases that deserve additional consideration as compared to dogs including breed related predilection for renal amyloidosis (Abyssinian, Oriental Short Hair) and polycystic kidney disease (Persian, Himalayan). Cats have greater frequency of CKD associated with renal LSA than dogs. Peri-nephric pseudocyst can be associated with CKD in cats and should be considered as a differential diagnosis for apparent renal enlargement in addition to renal LSA and hydronephrosis.

A variety of interventions (diet and drugs) can slow the progression of the renal disease, improve the quality of life for the patient, and/or extend the quantity of life. Dennis-I just moved this here as it opens your discussion re treatment.

Dietary interventions for CKD

Dietary therapy remains the cornerstone of management of CKD. Diet modifications include phosphorus restriction (most important), providing reduced quantity but high quality protein, adequate non protein calories from fat and CHOs, modifying sodium content (not the degree of restriction once recommended by some), supplementing potassium, B vitamins, alkali as needed and providing omega three fatty acids. In one 2-year study, cats with a serum creatinine > 2 mg/dl fed a renal diet had a median survival time that was 2.4 times longer than cats fed a maintenance diet (633 days vs 264 days). [9] In another study, IRIS stage 2 & 3 cats were followed for 24 months. Cats fed the maintenance diet had more uremic episodes and more renal-related deaths compared with cats fed the renal diet. [3] In a study of 175 CKD cats fed 1 of 7 different renal diets, the median survival time was 16 months (12 to 23 months) compared to a median survival time of 7 months for cats eating their maintenance diet. Interestingly, the longest survival period was found in cats eating a renal diet with the highest eicosapentaenoic acid (diet not available in North America), otherwise the renal diets were similar in composition. [10] Patients are more likely to accept a new renal diet if offered before uremia develops and a gradual transition may be needed.

The number one reason to restrict dietary protein is to provide an adequate degree of restricted intake of phosphorus, especially those associated with animal tissues in the diet. Decreased production of nitrogenous wastes can occur in those with large increases in BUN, and consequently improve the clinical well-being of the pet even though renal function remains unchanged. If proteinuria is present, dietary protein restriction may lower the magnitude of proteinuria through obscure mechanisms. Reduced dietary protein intake may also lessen inflammatory, fibrogenic and oxidative stress pathway.[11] The amount to restrict dietary protein is not known, so it is currently recommended to provide at least maintenance levels. For cats with CKD, the minimum dietary protein requirement suggested is 20% of calories, which equates to 24% protein on a dry-matter basis.[11-14]Others suggest 28–35% (DMB).[15]It is emphasized that less total dietary protein can be fed if high biologic value proteins, such as egg, are fed.[13] Lowering animal-derived protein (source of phosphates) in the diet may be essential to lower dietary phosphorus intake needed to achieve target levels of serum phosphorus.[16] Too much dietary protein restriction can and often does result in protein: calorie malnutrition. Protein malnutrition from any cause is strongly correlated with morbidity and mortality. If protein malnutrition becomes evident in a patient (hypoalbuminemia, anemia, weight loss or loss of lean muscle mass), then the amount of protein should be increased until signs are no longer evident. Cats with sarcopenia, regardless of the stage of renal disease, may require more protein than a renal diet can provide-careful monitoring and adjustment will be needed in these cats.

Pets with CKD often suffer from poor appetite that can contribute to poor body condition. This is often associated with decreased prognosis as the owner's often euthanize when quality of life is perceived as unacceptable. *Mirtazapine (Remeron)* helps not only with appetite but with uremic-associated nausea. Recent work in cats indicates mirtazapine can be administered at a low dose (1.88 mg) every 48 hours to cats with CKD, but was only studied for its effects for 3 weeks.[17,18] Remember that mirtazapine and cyproheptadine cannot not be administered concurrently. Cyproheptadine is in fact used as an antidote for serotonin effects of mirtazapine overdose. *Maropitant (Cerenia*): NK-1 receptors are in the chemoreceptor trigger zone, in the emetic center itself, as well as peripherally. Consequently, Cerenia is a great choice to treat vomiting/nausea in renal cats. Despite the label recommendation, many specialists are recommending Cerenia for longer than 5 days (personal communication with specialists and with Zoeitis scientists). Dose: 1 mg/kg PO once daily. Refrigerate to help alleviate the sting associated with injectable cerenia.[19] *Omeprazole* (*Losec*): Studies in cats have also shown Omeprazole to be more effective than H2 blockers such as famotidine and ranitidine in decreasing gastric acidity.[20] Dosage: 0.5-1 mg/kg once a day. If H2 blockers are used, dosages recommended are *Famotidine* (Pepcid®) 0.5 mg/kg IM, SQ, PO q 12 hours or *Ranitidine* (Zantac®) 1-2 mg/kg q 12 hours (cat). Studies have shown most cats with uremia do have elevated gastrin levels (and likely corresponding hyperacidity) but no GI ulcers. [20,21] Consequently, *sucralfate* is not usually indicated. The GI bleed with uremia could be from dysregulation of the vasculature and platelet dysfunction associated with uremia.[20,21] If used, a dose of 0.25 -0.5 g/cat q 12 hours is recommended. In some countries *sucralfate* is used as an intestinal phosphate binder due to its aluminum content. *Ondansetron* at the time of this writing is not highly recommended. The bioavailability is not high (maybe 30% at best in cats) and the half-life is very short (it would be best to give this drug 4 times/day).[22]

Phosphorus

Higher concentrations of serum phosphorus predicted an increase in serum creatinine > 25% above baseline over 12 months in 47% of CKD cats. [23] Serum phosphorus was the only clinicopathologic variable predictive of survival in one study of CKD cats. There was an increase in risk of death of nearly 12% for each mg/dl increase in phosphorus in the same study.[24] Higher phosphorus concentration was associated with a higher risk of death within1 month in another study.[25] Even when serum phosphorus was within the reference range, cats with CKD of one study that had phosphorus concentration > 4.7 to ≤ 6.8 mg/dl serum phosphorus had a higher risk of death compared to CKD cats in which circulating phosphorus concentration was ≤ 4.7 mg/dl. [26]

Dietary phosphorus restriction is critical at least from Stage 2 onwards; there is no data to evaluate any potential benefit of Pi restriction in Stage 1. Compared to the average grocery or pet store foods, the renal friendly veterinary diets are restricted in phosphorus by 70 to 80%. Serum phosphorus concentration may increase in CKD pets that increase their food intake following other supportive CKD treatments. Renal diets may provide sufficient dietary phosphate restriction during early stages of CKD but often the addition of dietary phosphate binders will be needed to reach targeted control of serum phosphorus. Early phosphorus restriction in CRF has been shown in dogs and cats to blunt or reverse renal secondary hyperparathyroidism.[27]

Intestinal phosphate binders

Aluminum salts are the most widely used phosphate binders in cats. Aluminum based phosphate binding agents (aluminum hydroxide, aluminum carbonate) are highly effective in lowering serum phosphate levels, forming insoluble and nonabsorbable aluminum phosphate precipitates in the intestinal lumen. THERE IS NO KNOWN SAFE DOSE OF ALUMINUM SALTS FOR HUMANS WITH CKD. Detrimental effects of aluminum based phosphate binders as described in humans seen in humans have not been systematically evaluated in small animal patients and are rarely clinically appreciated. As cats with CKD can live for years on treatment, concerns for aluminum accumulation deserve more study as to long-term safety. Calcium-based binders are not as effective as aluminum salts, having a lower affinity for phosphorous, thus effective binding of dietary phosphorous requires large doses of calcium, often enough to induce hypercalcemia in humans. The most commonly used calcium based phosphate binders are calcium carbonate and calcium acetate. Animals should be monitored for development of hypercalcemia whenever calcium-containing

phosphorus binders are used. Sevelamer hydrochloride (Renagel®, Genzyme Corporation) and the more recently FDA approved Sevelamer carbonate (Renvela®, Genzyme Corporation) are organic polymers that do not contain aluminum or calcium and are not absorbed from the gastrointestinal tract (excreted entirely in feces). Their effects on dogs and cats with clinical CRF have not been reported. Epakitin® (Vetoquinol Inc.) is marketed as a complementary feed on the veterinary market. It contains the adsorbent chitosan (8% crab and shrimp shell extract), 10% calcium carbonate, and 82% lactose and is designed to reduce GI phosphorus absorption and to lower urea nitrogen due to effects of reduced protein digestibility. The results of two studies [28,29] suggest that this supplement could be an alternative to prescription of renal veterinary diets thereby allowing some cats to continue on their regular diets while still reducing the risks for progression of CKD associated with total body phosphorus burden. We have, however, observed the development of hypercalcemia in a few CKD cats with the use of this product probably as a consequence of the calcium carbonate. Lanthanum carbonate (Fosrenol®, Shire Pharmaceuticals) is a non-aluminum and non-calcium containing intestinal phosphate binder and is indicated for use in human patients with end-stage renal failure to reduce serum phosphorous. Very little lanthanum is absorbed across GI tract and lanthanum accumulates to a far less degree following absorption compared to aluminum since lanthanum undergoes extensive hepatic excretion whereas aluminum is excreted mostly by the kidneys. Lanthanum appears to have minimal toxicity in humans. A recent abstract in a small number of CKD cats administered lanthanum carbonate in food at 95 mg/kg/day to achieve very modest serum phosphate control.[30] Several reports of the efficacy and safety of lanthanum carbonate treatment in cats have been published. [31] Lanthanum carbonate octahydrate (Lantharenol® Bayer HealthCare AG) is marketed as a feed additive for adult cats in order to decrease intestinal phosphate absorption. Renalzin® (Bayer HealthCare AG) is the proprietary name for the delivery system of Lantharenol® and comes as a pump system that delivers lanthanum carbonate along with kaolin and vitamin E at appropriate doses to food for cats. This system is widely available in the UK and Europe, but not in the USA or Canada. The proprietary formulation of human lanthanum carbonate is soon to become available as a generic product.

Pronefra® recently has been launched (Virbac, France) as a dietary supplement for cats with CKD. This product provides a combination of calcium and magnesium carbonate as the intestinal phosphate binders, chitosan for "uremic toxin" binding, vasoactive peptides (designed to maintain normal blood pressure) and an extract of Astragalus membranaceus (Chinese herb for anti-inflammatory and anti-fibrotic effects). Safety of this product was reported in 10 normal cats in which Pronefra was added to the food once daily for 12 weeks[32,33] No changes in circulating calcium or magnesium were noted at during this study. Presently there are no reported studies of safety or efficacy in clinical cats with CKD treated with this supplement.

Novartis has developed a new oral phosphate binder for cats called Lenziaren ® (SBR759). Iron oxide with starch and sucrose exist in this preparation as an insoluble complex. A dose of 0.5 to 1.0 Gm/cat/day is recommended when added to standard diets.[34] A dose of 0.25 Gm/cat/day to 1.0 Gm/cat/day is recommended when adding this phosphate binder to a renal diet. [35] Safety and efficacy of Lenziaren® in cats with CKD are not yet reported. Lenziaren is touted by the authors as a phosphate binder that does not contain aluminum, calcium, or lanthanum that could be problematic in cats with CKD. That is true for the aluminum and calcium as a factor in favor of its use, but there is no known toxicity of lanthanum yet reported.

Control of proteinuria

Cats with azotemic CKD increased their risk for death or euthanasia when the UPC was 0.2 to 0.4 compared to <0.2 and was further increased in cats with UPC of >0.4.[36] The prognosis for survival is influenced by the UPC despite what has traditionally been thought to be low-level proteinuria. The effect of treatments that lower proteinuria on survival have not been specifically studied. Since even low-level proteinuria is a risk factor for cats to not survive, it is prudent to consider treatments that lower the amount of proteinuria in those with CKD. See discussions about the potential benefits of dietary protein restriction (above) and RAAS inactivation (below) to reduce the magnitude of proteinuria.

RAAS inactivation

RAAS inactivation results in decreased generation of angiotensin-2 and aldosterone that can exert benefits to reduce progression of CKD. These beneficial effects can occur through variable combinations of reduction in systolic blood pressure, decreased intra-glomerular hypertension, decreased glomerular proteinuria, and less generation of pro-inflammatory and pro-fibrotic cytokines in patients with CKD.

Benazepril is labeled for treatment of azotemic CKD in cats in the UK, Europe, and Canada (Fortekor®), but not in the USA. The ACE-inhibitor benazepril consistently reduces proteinuria in various stages of CKD in cats even when the base line level of proteinuria is seemingly trivial. Benazepril has been shown in two clinical studies to reduce the UPC in cats with azotemic CKD.[37,38] Despite reduction in proteinuria in CKD cats with initial UPC > 1.0 that were treated with benazepril in one study, increased survival time was not found over placebo.[37] The average survival time of all benazepril treated cats in this study was 501 days vs. 391 days for placebo treated cats but this effect did achieve statistical significance. [37] In another study of 61 cats with CKD, benazepril treatment for 189 days appeared to stabilize those in IRIS stage 2 or 3 with less transition to stage 4 compared to treatment with placebo, though this effect did not achieve statistical significance (low number of cats and short duration of study.[38]

The angiotensin receptor blocker (ARB) telmisartin (Semintra® Boehringer Ingelheim) was approved by the European Commission in 2013 for use in the European Union as a drug for use in cats with CKD and is available for use in Canada but not yet

in the USA. Semintra was found to be at least as effective as benazepril in reducing proteinuria in cats with CKD and was well tolerated.[39,40] A US Patent application was filed in July 2013 by Boehringer Ingelheim. It is not clear when or if an ARB should be chosen to reduce RAAS activity instead of an ACE-Inhibitor for treatment of CKD in veterinary patients to reduce proteinuria, systemic blood pressure, or intra-renal inflammation. A veterinary review of the RAAS system, ACE-Inhibitors and ARB's provides more detail for the interested reader.[41]

Activated vitamin-D metabolites: calcitriol

Calcitriol treatments help to decrease PTH or prevent its increase in those with renal secondary hyperparathyroidism. This occurs largely through genomic effects to block PTH synthesis in addition to a mild calcemic effect, and anti-proliferative effect that prevents parathyroid gland hyperplasia. It has become increasingly apparent that calcitriol has major beneficial anti-inflammatory and anti-fibrotic intrarenal effects that are independent of effects on PTH.[27]During treatment of CRF patients with calcitriol, simultaneous monitoring of serum ionized calcium, serum phosphorus and PTH concentrations is the ideal way to document successful and safe control of renal secondary hyperparathyroidism. Calcitriol should not be administered until hyperphosphatemia has been controlled. If the Ca X P solubility product exceeds 60-70, calcitriol should be avoided because of the risk of soft-tissue mineralization.

In a recent study of dogs with azotemic CKD that were treated with calcitriol a median of 365 days survival was observed compared to 250 days in dogs treated with placebo (renal diet in both groups).[42] Similar studies were performed in cats by the same investigators who concluded that there is no advantage to calcitriol treatments in cats with CRF but the study followed cats for just one year. In order to show a difference in treatment effect, if one exists, studies in cats with CKD must be conducted for at least 2 and possibly 3 years due to the inherently slow nature of the progression of chronic renal disease in this species. The authors believe that beneficial effects of calcitriol treatment are likely to occur in cats with CKD.

A compounding pharmacy will be needed to reformulate calcitriol from the human parent drug to a concentration suitable for the dosing of cats. We recommend intermittent rather than daily dosing treatment protocols as the standard of care since less hypercalcemia occurs using this protocol. The equivalent dose given at 2.5 ng/kg daily is given instead every 3.5 days. This works out to a dose of 9 ng/kg (8.75 ng/kg rounded to 9 ng/kg). It is important to give the dose every 3.5 days, rather than on day 1 & 4. For example if a dose is given Tuesday PM the next dose should be given Saturday AM. This is the longest time in between dosing that will still suppress the parathyroid gland. This method of dosing is especially attractive for cat owners since medication will only be given twice weekly.

Systemic hypertension

Systemic hypertension is common in cats with CKD with 13-28% of cats presenting with hypertension when CKD is first diagnosed and up to 65% of cats developing hypertension at some point during the progression of their renal disease.[43-51] Cats that have systemic hypertension from a variety of causes have been shown to survive longest when their blood pressure is well controlled.

Enalapril or benazepril as monotherapy has not been very effective for treatment of hypertensive cats or dogs. The calcium channel blocker, amlodipine has been used successfully in cats at a dosage 0.625 to 1.25 mg per cat given orally once per day. Follow-up evaluations should be scheduled for one week after beginning treatment with amlodipine. Adverse effects (including hypotension) are very uncommon with the use of amlodipine in cats.[43,46,47]

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