Updates on Managing CKD and Proteinuria

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DIAGNOSING CHRONIC KIDNEY DISEASE

Azotemia in the face of inadequately concentrated urine is highly suggestive of intrinsic kidney disease, although rarely there are situations where dehydration is causing azotemia in the presence of a non-renal illness that impairs concentrating ability (e.g., Addison's disease, hypercalcemia). Azotemia does not need to be present for chronic kidney disease (CKD) to be present. Some diseases that are frequently diagnosed in the pre-azotemic phase include polycystic kidney disease and protein-losing nephropathy. Poorly concentrated urine (i.e., urine specific gravity < 1.035 in cats, < 1.030 in dogs) can be the first indicator of kidney disease, but there are a host of other diseases that interfere with urine concentrating ability. If azotemia is not present, these other diseases need to be excluded before concluding that CKD is the most likely diagnosis, unless some indicator of kidney disease is present, such as small kidneys with disrupted architecture. Specific testing of renal function by measuring glomerular filtration rate can confirm the presence of kidney disease.

While creatinine is one of the most commonly used measures of kidney function, there are some caveats to interpretation. Creatinine is relatively higher in healthy Greyhound dogs and Birman cats, and in well-muscled animals. Creatinine is relatively lower in healthy Maine Coon, Chartreux, and Persian cats, as well as young animals and animals with muscle atrophy or cachexia. Thus, a high-normal creatinine in these patients may be indicative of renal dysfunction. Different machines have different reference ranges (up to 30% different). When serially monitoring a patient, using the same machine each time allows comparison of results.

SDMA is a relatively newly introduced test that may prove helpful in diagnosing CKD, although its role has not yet been fully elucidated. SDMA is reported to be elevated at lower levels of renal dysfunction compared to creatinine. If a baseline creatinine is known, an elevation in that value (although remaining within the reference range) can indicate renal damage. If a baseline creatinine is not available, SDMA may help diagnosis CKD in borderline cases. SDMA is not affected by muscle mass, thus avoiding the pitfall associated with creatinine, which can be inappropriately low relative to kidney function if muscle wasting is present.

Other biomarkers, such as cystatin-C and neutrophil gelatinase-associated lipocalin (NGAL) are not commercially available or validated for use in dogs and cats. Glomerular filtration rate (GFR) testing can be done via a variety of methods. GFR measurement is occasionally useful to determine if a non-azotemic patient with inadequate urine concentrating ability has kidney disease. Iohexol (e.g., Omnipaque) clearance for GFR measurement can be performed in general practice. The protocol is to administer 300 mg iodine/kg IV and draw blood samples at 2, 3, and 4 hours after administration. Blood samples are sent to Michican State Uinversity Veterinary Diagnostic Laboratory Toxicology Lab.

Survey abdominal radiographs may show small or irregularly shaped kidneys, or renal asymmetry. In one study, half of cats with CKD had renal mineralization, nephroliths, or ureteroliths, although the uroliths were not obstructing urine flow in most cases. Ultrasound changes may include small kidneys, decreased distinction of the corticomedullary junction, or infarcts (flattened pole of the kidney or wedge shaped depression). Subjective estimates of size frequently overestimate the changes.

When kidney disease is first diagnosed, sometimes there is a question about whether it is acute or chronic. The disease must be present for at least 1 month (some say 3 months) to be considered chronic. Correctly identifying acute and chronic disease has diagnostic and prognostic implications, as the diseases that cause acute disease are different than those causing chronic disease. Although short-term mortality for acute kidney injury is high (50-60%), there is the potential for full recovery, whereas with CKD, the disease is not reversible.

Predicting CKD

The incidence of CKD is high in older cats, with 30-80% of cats over 15 years of age having CKD. The influence of size in dogs is unclear, with some reports finding smaller dogs more likely to have CKD and other reports not finding that association. Both dogs and cats with dental disease are more likely to have CKD.

About 1/3 of healthy older cats will develop CKD within a year, and cats with higher BUN, creatinine, PTH, or blood pressure or lower urine specific gravity are more likely to develop CKD.

Cats with proteinuria, higher BUN, creatinine, phosphate, or WBC counts or lower hematocrit have shorter survival times. Interestingly, administration of NSAIDs in cats did not accelerate progression of CKD. Urinary NGAL levels are not useful to diagnose early CKD, but higher levels do predict progression of CKD. However, this test is not yet commercially available.

TREATMENT OF CKD

Treatment of CKD consists of 3 main components: treat the underlying disease, slow progression, and treat uremic signs. In many cases, the underlying cause is not known or not treatable. Efforts to slow progression of CKD should be started at diagnosis, even in stable compensated patients.

Treatments of factors associated with progression of CKD

Renal diets have been shown to slow progression of CKD in both dogs and cats. Renal diets are phosphate and protein restricted. Phosphate restriction is likely more important than protein restriction. Proteinuria is a strong predictor of progression. Treatment of proteinuria has been shown to slow progression of CKD in dogs. Although this has not clearly been proven in cats, an appropriately designed study has not yet been performed. Hypertension in dogs (systolic blood pressure > 160 mmHg) is associated with faster progression and worse survival. Hypertension in cats, when controlled, does not shorten survival. In dogs, but not in cats, calcitriol prolonged survival by 3 months compared to placebo. Hyperphosphatemia and anemia both predict more rapid progression of disease. Studies evaluating the impact of control of these factors on survival are not available in naturally occurring disease. Benazepril has been investigated as a treatment for CKD in cats in several studies, but has not been shown to prolong survival.

Diet

Nutritional management of CKD is one of the earliest and most important features of treating CKD. Renal diets should be restricted in phosphorus, to help decrease hyperphosphatemia, renal secondary hyperparathyroidism, renal mineralization, and progression of CKD. In fact, the phosphate restriction may be more important in the success of renal diets than the protein restriction, but because protein contains phosphate, renal diets are obligated to be protein-restricted in general. While protein is a significant source of phosphate, preservatives and other additives can contribute a substantial amount of phosphorous to the diet. Feline diets with either fish or green peas seem to have very high phosphorus content.

A renal diet should have a restricted quantity of high biologic value protein, characterized by an amino acid profile similar to the needs of the body, which can be used immediately for protein synthesis without the need to be converted to other amino acids. Albumin has the highest biologic value. Animal source proteins are superior in amino acid profile than vegetable source proteins. However, the phosphate in vegetable source protein is less bioavailable, which helps control hyperphosphatemia better than animal protein.

Recently, clients have been resistant to protein-restricted diets, apparently based on information gleaned from the internet. While it seems plausible that selecting protein sources with lower phosphate content may allow for more liberal protein content, conclusive evidence is lacking.

There are several commercial options available in the USA, and the list keeps expanding as more palatable options are developed. Several home-cooked recipes are available but have not been rigorously evaluated. Substitution of ingredients alters the balance of these diets and should be avoided. Many veterinary nutrition consultation services are available to formulate a diet for an individual patient, taking into account the severity of disease and patient taste preferences.

If the pet is consuming exclusively a renal diet, the BUN:Creatinine ratio should be in the range of 10 to 15 (normal 15-20), and alterations in this ratio can indicate gastrointestinal bleeding or poor patient or client compliance with dietary recommendations.

Phosphorus

The incidence of hyperphosphatemia increases with worsening kidney failure. Almost 20% of dogs with IRIS Stage I CKD are hyperphosphatemic, increasing to 100% of dogs with Stage IV CKD. In cats with uremic symptoms, 100% were hyperphosphatemic. Hyperphosphatemia is associated with worse outcomes in cats with CKD. For each 1 mg/dl increase in phosphorus, there is a 12% increase in risk of death and 40% increase in risk of progression of CKD. Dogs with CKD with a calcium x phosphate product of >70 have a 4 times increased risk of death.[3] In another study in dogs, elevated phosphate was associated with a 4 times higher risk of death or need for parenteral fluid therapy.

Diet to Control Hyperphosphatemia: The importance of controlling of phosphorus is being recognized as a key component of treating CKD. In fact, kidney diets may be improving outcome by virtue of phosphate restriction more so than protein restriction. Over the past several years, standard care for CKD has changed from keeping the phosphorus within the reference range to a desire to maintain the phosphorus concentration closer to the middle of the reference range.

IRIS CKD Stage	Recommended Phosphate Target (mg/dL)
I, II	2.7 - 4.5
III	2.7 - 5.0
IV	2.7 - 5.0

Phosphate Binders to Control Hyperphosphatemia: Because methods to increase phosphate excretion (i.e., increasing GFR by fluid therapy) are usually of limited efficiency, phosphate binders are used to prevent absorption of phosphorous that is ingested with meals if dietary restriction is insufficient. They should be administered at meal time (either shortly before or after) for maximal efficacy. They will not cause stomach upset if given between meals, but will not be effective. Dosage of phosphate binders should be titrated based on serum phosphate concentration, and higher doses will be needed with higher phosphate intake. They can interfere with absorption of other medications. Most phosphate binders supplied in tablet form are supposed to be chewed, not swallowed intact, in order to increase surface area for binding. This makes administration to dogs and cats problematic unless the pills are crushed and mixed in food or liquid.

Traditional phosphate binders: Aluminum hydroxide is one of the most commonly prescribed phosphate binders. The typical dose is 90 mg/kg/day, divided with meals. Excessive absorption of aluminum can lead to toxicity, including anemia and neurologic symptoms, but this is uncommonly recognized in veterinary practice. The true incidence of aluminum toxicity may be much higher than perceived, but no data are available. Because of the risk of aluminum toxicity, I typically do not exceed doses of 150 mg/kg/day. Calcium carbonate (Tums) avoids the risk of aluminum toxicity, but leads to hypercalcemia in 50% of people with CKD. Epakitin is a combination of chitosan (8%) and calcium carbonate (10%) that is reported to be palatable. Two small studies (6 cats and 10 cats) found it decreased serum phosphate, but hypercalcemia has been seen in unreported clinical cases.

Other phosphate binders: Lanthanum carbonate does not cross the blood-brain-barrier, and that coupled with limited GI absorption makes it unlikely to cause the type of adverse effects seen with aluminum containing phosphate binders. Unfortunately, its expense limits current use. Ferric citrate, which has been available as an iron supplement, was recently approved as a phosphate binder for people. In the USA, tablets contain 1 gm ferric citrate (210 mg ferric iron), with a dose of 6 tablets per day per person (up to 12 tablets per day). I do not have any experience with this drug. Niacinamide (Niacin, Vitamin B3) impairs the sodium-phosphate cotransporter in the intestinal tract and may have a minor adjunctive role in controlling phosphate.

Combination Therapy: If the maximum dose of one phosphate binder does not control the serum phosphate level, adding a second drug may have additive benefit. My typical protocol involves using aluminum hydroxide as a first line drug due to low cost, and adding lanathanum as a second drug if needed (keeping the same dose of aluminum hydroxide unless there are indicators of aluminum toxicity). I would not recommend adding two calcium containing products together (i.e, Tums and Epakitin). Despite my biases and preferences, no one phosphate binder has been proven superior to another.

Drug	Dose
Aluminum Hydroxide	90 mg/kg/day
Calcium Carbonate, Calcium Acetate	90 mg/kg/day
Epakitin	1 gm/5 kg BID
Lanthanum Carbonate (Fosrenol)	12.5-25 mg/kg/day
Sevelamer Carbonate (Renvela)	100-150 mg/kg/day

Proteinuria

Proteinuria is associated with more rapid progression and shorter survival times. Assessment of proteinuria should be standard in all animals with CKD. Quantification of the amount of protein using a urine protein:creatinine ratio (UPC) is warranted with a positive screening test (i.e, dipstick or microalbuminuria), unless an obvious cause of proteinuria is present (i.e., hematuria, active urine sediment, positive culture). In healthy dogs, the UPC is less than 0.5. Values over 1 are considered abnormal. Values between 0.5 and 1 are questionable, and should be monitored for persistence or worsening. In cats with chronic kidney disease, a UPC over 0.4 is associated with shorter survival, and values over 0.2 should be considered potentially abnormal. Because of the day-to-day variability in UPC, measuring UPC in urine samples collected on separate days is ideal (typically 3-4 samples). Equal volumes of these urine samples can be pooled to decrease the expense of repeated testing. In dogs, one UPC measurement is adequate to reliably estimate UPC when < 4. When

monitoring changes in UPC over time, a change of 80% is needed to demonstrate a significant difference when the UPC is around 0.5, but only a 30% change is needed when the UPC is higher (around 12).

After confirming persistent renal proteinuria, standard tests to uncover any potentially treatable cause include complete blood count, serum chemistry panel, urinalysis, urine culture if indicated, titers for common tick borne diseases (Borrelia, Ehrlichia canis, RMSF) and heartworm testing in dogs, feline leukemia virus testing in cats. Additional testing may include thoracic radiographs to screen for neoplasia, and usually abdominal imaging (radiograph or ultrasound). Other tests would be dependent on individual case characteristics.

In people, the histopathologic type of GN is used to determine appropriate therapy and is correlated to outcome. In veterinary medicine, we have been limited by rarely performing kidney biopsy and by limiting biopsy evaluation to light microscopy. After a full evaluation, including immunofluorescence and electron microscopy, approximately 50% of kidney biopsies in dogs show immune-complex disease. About 20% show glomerulosclerosis, and 15% are amyloidosis.

Protein restriction decreases the amount of proteinuria and the protein trafficking in the renal tubules. A kidney diet, containing a restricted quantity of high quality protein should be prescribed for dogs with known or suspected PLN.

Angiotensin converting enzyme (ACE) inhibitors have been proven to decrease proteinuria and delay onset of kidney failure in dogs. Enalapril (0.5-1 mg/kg PO q 12-24 hrs) is a commonly used drug; benazepril (0.5 mg/kg PO q 12-24 hrs) is an alternative. Because ACE inhibitors can decrease renal blood flow, reevaluation of a chemistry panel for worsening azotemia 1 week after starting therapy or dose adjustment is advised. Hyperkalemia is a common complication of ACE inhibitor therapy, and potassium should be monitored routinely. These drugs can be used in normotensive patients as well as hypertensive patients, although blood pressure should be monitored. If ACE inhibition does not sufficiently control proteinuria, an angiotensin receptor blocker (ARB) can be added. Losartan has poor bioavailablity in dogs and is not recommended. Telmisartan can be started at 1 mg/kg/day in dogs or cats, and increased by 0.5 mg/kg/day up to a total of 2 mg/kg/day. Telmisartan can be combined with enalapril, but since the side effects of ACE inhibitors and ARBs are similar, careful monitoring is prudent. Telmisartan can be used as a first line antiproteinuric drug (i.e., before trying enalapril); clinical experience is limited but anecdotally positive.

Thromboembolic complications are associated with PLN because of loss of antithrombin III with glomerular disease, and platelet aggregation and fibrin deposition in the glomerulus may contribute to the pathogenesis of PLN. Aspirin at a dose of 0.5-5 mg/kg q 12-24 hours may inhibit platelet aggregation. Clopidogrel (Plavix, 1.1 mg/kg/day) is an alternative to aspirin. Either drug should be discontinued for one week prior to kidney biopsy to decrease risk of hemorrhage; they can be restarted within days after the biopsy has been obtained.

In people, response to various immunosuppressive protocols varies with specific type of GN. There is limited systematic information about the effect of immunosuppression in dogs, and use is typically based on kidney biopsy results. Corticosteroids are associated with proteinuria and are not recommended in dogs unless underlying disease is steroid-responsive (i.e., systemic lupus erythematosus). Cyclosporine was not beneficial in controlled study of dogs with GN. Other immunosuppressive drugs, such as azathioprine (2 mg/kg PO q 24-48 hours in dogs only) or cyclophosphamide (50 mg/m2 PO q 24 hours for 3 to 4 days, then off for 3 to 4 days) may be used but their benefit has not been proven. Mycophenolate mofetil (CellCept, 10 mg/kg q 12 hr PO) has favorable anecdotal results in dogs. If proteinuria resolves with immunosuppression, after 3-4 months consider lowering the dose to the minimal effective dose.

Monitoring Proteinuria

Evaluation for adverse effects of RAAS inhibition (including creatinine, potassium, and blood pressure monitoring) should occur 4-7 days after starting therapy or increasing the dose. The impact on decreasing proteinuria will be maximal after 1 months, but the majority of impact will occur within 1-2 weeks. The goal of treatment is normalization of values and resolution of signs.

Response	**UPC**	**Creatinine**	**Albumin**
Complete Response	< 0.5	< 1.4 mg/dL	> 2.5 mg/dL
Partial response	> 50% reduction	> 25% reduction	Increase to 2.0-2.5 mg/dL or > 50% increase
Therapeutic failure	< 50% reduction	< 25% reduction	< 2.0 mg/dL or < 50% increase

Hypertension

Approximately 20-65% of cats with chronic kidney disease have hypertension, and as much as 60% of dogs with protein-losing nephropathy are affected by hypertension. The presence of hypertension at diagnosis of kidney disease in dogs predicts shorter survival and an increased risk of developing a uremic crisis requiring hospitalization.

About 70% of cats with hypertension have ocular lesions. Prognosis for return to vision after an acute retinal detachment is 50%, if blood pressure can be controlled in a timely fashion (within 24 hours).

IRIS guidelines categorize blood pressure based on risk of hypertensive complications.

Substage	Systolic Blood Pressure	Risk Category
Normotension	< 150 mmHg	Minimal Risk
Borderline hypertension	150-159 mmHg	Mild Risk
Hypertension	160-179 mmHg	Moderate Risk
Severe hypertension	>180 mmHg	High Risk

Treatment of Hypertension

Antihypertensive medications fall into a variety of classes including calcium channel blockers, ACE inhibitors, B-adrenergic blockers, and vasodilators.

Amlodipine is effective as a single agent in about 60% of cats, making it a rational first line drug. Dosing is 0.125-0.25 mg/kg or 0.625 – 1.25 mg/cat PO q 24 hours. Cats with higher blood pressure (i.e., over 200 mmHg systolic) may require the higher dose for adequate control. The dose of dogs starts at 0.1-0.2 mg/kg daily and can be increased to 1 mg/kg/day. Because of its vasodilatory effect, there is concern that administration of a calcium channel blocker at doses that do not control hypertension may worsen renal function by allowing vasodilation of the afferent arteriole in the kidney, increasing glomerular hypertension. Thus, if amlodipine as a single agent does not decrease the systolic blood pressure to less than 160 mmHg, and additional agent should be added (such as an ACE inhibitor). Side effects of amlodipine include gingival hyperplasia, and rarely edema.

ACE inhibitors such as enalapril and benazepril are antiproteinuric and antihypertensive drugs, making an ACE inhibitor is a rational first line drug in hypertensive patients with proteinuria. Hyperkalemia is a potential side effect of this drug category. Creatinine and potassium should be checked a week after starting this drug or increasing the dose. Angiotensin receptor blockers, such as telmisartan, can be used in place of an ACE inhibitor, and has been approved to treat hypertension in cats in the USA. Dosing for this indication is 1.5 mg/kg q 12 hours for 14 days, then 2 mg/kg q 24 hours.

MANAGING UREMIC SIGNS

Appetite Stimulants

Over 40% of cats with CKD have a diminished appetite. Appetite stimulants are sometimes helpful in managing pets with CKD. Mirtazapine (Remeron, 1.8 mg per cat PO q 48 hours; 1.1-1.3 mg/kg PO q 24 hours in dogs) is effective at increasing appetite in many cats and some dogs. Some pets may have serotonin syndrome from overdosing, which can manifest as unusual behavior with this drug; a decrease in dose or decrease in frequency of administration may correct this problem. Transdermal mirtazapine (2 mg daily) has recently been approved as an appetite stimulant in cats, and appears to have a more sustained effect than oral administration. Ghrelin is a hormone produced by the stomach that stimulates appetite. A ghrelin agonist, capromorerelin (Entyce ®) has recently become available in the USA as an appetite stimulant for dogs. Initial observations suggest that although the formulation may be a bit unpalatable, it appears effective. If control of nausea and an appetite stimulant do not lead to consumption of an adequate amount to maintain body weight, owners should be encouraged to have a feeding tube placed.

URINARY TRACT INFECTION

Cats with CKD are predisposed to developing UTI. About 30% will develop a UTI at one point, and about half of those will have subsequent infections. One quarter of these cats will have lower urinary tract signs and the other 75% are clinically asymptomatic. However, 87% had an active urine sediment. Consensus guidelines suggest that antibiotic therapy should not be instituted for asymptomatic bacteruria, unless risk factors for ascending infection are present. Pre-existing CKD constitutes a risk factor, but the magnitude of risk is unknown, making it unclear whether incidentally discovered bacteruria should be treated in the CKD patient. The presence of lower urinary tract signs or pyuria are clear indications for culture, and I would err on the side of treating, unless the organism is Enterococcus, which is thought to be non-pathogenic.

Diagnosing upper urinary tract infection can be challenging. Finding asymmetric dilation of the renal pelves may indicate pyelonephritis but is more likely an indication of partial or complete ureteral obstruction. New or worsening pelvic dilation in conjunction with an abrupt increase in creatinine may be an indicator of pyelonephritis or obstruction. It is difficult to experimentally induce pyelonephritis in the absence of obstruction in a normal dog, but it is presumed that renal abnormalities increase the risk.

Clavamox, trimethoprim-sulfonamide, or doxycycline are good first line antibiotic choices. Fluoroquinolones have good distribution to kidneys/urine and good spectrum against the most common pathogens, but should be reserved for more complex/resistant situations.

PROGNOSIS OF CKD

Survival times are related to the IRIS stage of disease in stable CKD. The degree of azotemia in a decompensated cat that requires hospitalization may be misleading in determining prognosis, as 30% of cats presenting with a creatinine over 5 mg/dl will be categorized in a lower IRIS stage after rehydration and stabilization. Cats with Stage IIb CKD have a 40% chance of dying of CKD (vs other disease process), whereas cats with Stage IV CKD have a 93% chance of dying of CKD. The presence of anemia is associated with shorter survival times, but anemia is correlated to increased creatinine concentration. Systemic acidosis did not predict decompensation, although acidosis is more common with severe uremia. The effects of proteinuria on survival are discussed above. The survival times in dogs are somewhat shorter, with median survival times of about 1 to 2 years.

Survival Times in Cats with CKD

Stage	Median Survival Time (months)	Range (months)
IIb	38	2-100
III	23	1-75
IV	1	0-46

MONITORING

Frequency of **monitoring** depends on the clinical condition of the patient. If there are ever questions about the pet's stability or a change in the status, a recheck is always in order. I have created a set of arbitrary guidelines for monitoring. Animals that are more severely affected for the stage are monitored at the more frequent interval for the stage. Routine monitoring may detect problems before clinical signs are present, and early treatment may prevent or ameliorate clinical signs.

Frequency of Monitoring in Months

Stage	I	II	III	IV
Physical Exam	6	3-6	3-6	1-3
Chemistry Panel	6	3-6	3-6	1-3
PCV or HCT	6	3-6	3-6	1-3
Urinalysis	6	3-6	3-6	1-3
Urine Culture	6	6	3-6	3-6
Urine Protein:Creatinine	6	6	3-6	3-6
Blood Pressure	6	6	3-6	3-6