CURRENT THOUGHTS AND THERAPEUTIC IMPLICATIONS
IN FELINE CHRONIC KIDNEY DISEASES

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

The term: **"chronic kidney disease" (CKD)** is preferable to chronic renal failure (CRF) as it permits us to view the condition as a progressive one, rather than imminently terminal. We are more likely to encourage our clients to treat their companions. Cats often live for many years with decreased urine specific gravity, elevations in blood urea nitrogen (BUN) and creatinine (Cr) after initial detection depending on the stage and cause of the disease. Some causes of kidney disease are more rapidly progressive or fatal than others; others are benign. Causes of *chronic* kidney disease include, in decreasing order of occurrence, chronic (tubulo-) interstitial nephritis (CIN), pyelonephritis, renal neoplasia, FIP, amyloidosis, congenital abnormalities, polycystic kidney disease, perinephric pseudocysts, nephrolithiasis, hydronephrosis, glomerulonephritis, potassium losing nephropathy, and polyarteritis nodosa. CIN and pyelonephritis are most common.

Causes of *acute* renal failure, preferably referred to as acute kidney injury (AKI), are renal ischemia and nephrotoxicosis. The former may have pre-renal, renal or post-renal causes. Reduced renal perfusion leads to prerenal azotemia but may progress to failure if ischemia of significant severity is present for long enough. Anaesthesia, hypotension, hypovolemia are causes of AKI. Monitoring blood pressure enables us to intervene with fluids and oxygen/oxygen carrying fluids generally preventing progression from pre-renal stress to renal injury. Severe ischemic injury in the cat is caused by thromboembolism of the renal arteries due to cardiomyopathy, extensive renal infarction and subsequent intra-renal AKI. Renal toxins include ethylene glycol, Easter lilies, grapes and raisins, film processing chemicals, heavy metals, aminoglycoside antibiotics (by any route), amphotericin B, and doxorubricin (uncommon in cats).

Uremia is defined as the "constellation of clinical signs" seen with markedly decreased glomerular filtration rates (GFR). Uremia is usually not seen until BUN > 80 mg/dl (28 mmol/L) and Cr > 4.0 mg/dl (354 µmol/L) AFTER rehydration. Signs include lethargy, depression, anorexia, and vomiting and are therefore non-specific.

Hypokalemia is very common in cats with kidney disease. The kidney is the main site in the body for potassium (K) homeostasis. Approximately 80% of K is reabsorbed in the proximal tubules and the loop of Henle. Three major factors affect the movement of potassium: 1) the magnitude of the concentration gradient, which is mediated by the Na-K-ATPase pump, 2) the rate of tubular flow, and 3) the electrical transmembrane potential difference across the luminal membrane of the tubular cell. Final adjustments to the net reabsorption or excretion of K occur in the collecting ducts. These are mediated by aldosterone, Na, and K concentrations, acidosis and diuretics. Animals making a lot of urine (PU/PD) have a fast rate of tubular flow, predisposing them to hypokalemia.

As glomerular filtration rate decreases in CKD, phosphorus is retained in the blood, causing transient hyperphosphatemia. Initially, the remaining nephrons compensate by increasing the levels of phosphorus excreted. This is mediated by parathyroid hormone (PTH). Eventually, as chronic kidney disease progresses and glomerular filtration rate (GFR) decreases to less than 20% of normal, this compensatory mechanism fails and persistent hyperphosphatemia results and renal secondary hyperparathyroidism ensues.

HISTORY: Clinical signs may include anorexia or inappetance, vomiting, dehydration, weight loss, lethargy, oral ulceration, ptyalism, pallor, social apathy and constipation. PU/PD is reported less commonly than dogs, perhaps due to the secretive nature of cats. Some cats retain their urine concentrating ability in the face of kidney disease. Often cats with even moderate kidney disease are asymptomatic! In assessing the degree of illness, bear in mind that both decreased muscle mass (wasting) of cats with CKD, as well as hyperthyroidism masks the severity of concurrent kidney disease, by lowering serum Cr levels.

DIAGNOSTICS

The minimum database for a cat with CKD includes a complete blood count (CBC), serum biochemistries, urinalysis, blood pressure determination and abdominal radiographs. The last are indicated due to the prevalence of

ureteronephroliths in older cats and their potential contribution to the development or progression of CKD. Additionally, they play a role in therapy by emphasizing the need for euhydration and diuresis.

If elevated levels of protein are found in urine with a quiet sediment (i.e., no evidence of infection, inflammation or hematuria), then a urine protein to creatinine ration (UPC) should be run. If bacteria or white blood cells are found in urine, culture and sensitivity is indicated.

STAGING CHRONIC KIDNEY DISEASES (IRIS)

The International Renal Interest Society (IRIS) developed a four level system for staging the continuum of progressive kidney diseases to use as a guide in diagnosis, prognosis and treatment. (www.iris-kidney.com) Staging is based on the level of kidney function as determined by creatinine **in the rehydrated** patient.

SDMA

Symmetrical dimethylarginine (SDMA) is the newest test available for use in the diagnosis of chronic kidney disease in cats and in dogs. It is able to detect decline in glomerular filtration earlier than creatinine can making it an appealing biomarker. The question is whether early detection using SDMA makes any difference in outcome for cats because we really don't have treatments for kidney disease as an entity. The factors that we know that affect progression and survival are:

1. Proteinuria - assess UPC if and when indicated by urinalysis, then treat with telmisartan or benazepril;
2. Hypertension - screen in all cats and if elevated, treat with amlodipine
3. Anemia - monitor and ensure that diet has enough protein to build hemoglobin and, when indicated, use erythropoeitin/darbopoeitin.
4. Hyperphosphatemia - once adequately hydrated, if persistent, then use intestinal phosphate binders +/- feed renal diet but only if no muscle wasting
5. Azotemia - optimize hydration
6. Metabolic acidosis - optimize hydration +/- feed renal diet but only if no muscle wasting
7. Weight loss - detect early by monitoring over time as weight loss is associated with early detection of CKD as well as w decreased survival in any condition

Dehydration/prerenal azotemia may cause "artificial" elevations of SDMA just as it affects creatinine.

Dr. Greg Grauer's 2015 ACVIM presentation followed Jean Hall's on SDMA and he had some really important things to say. We can pick up early disease simply by screening routinely creatinine and urine specific gravity but looking for TRENDS over time, rather than exceeding reference intervals/ranges.

So, the unique places for SDMA are:

1. In thin older cats with muscle wasting, because creatinine levels will be artificially lower in muscle wasted cats but SDMA levels aren't affected by muscle.
2. In hyperthyroid cats that have not yet been made euthyroid, i.e., we don't know what will be revealed re their kidney function once they are euthyroid.
3. Cats with heart disease that may also have early kidney disease, because treating the heart disease may worsen kidney disease.

This test has a place, but in select cases. Using it across the board to as a screening tool, may result in feeding cats inappropriately and possibly unwarranted euthanasia if a client doesn't wish to treat a cat with a diagnosis of CKD.

THERAPEUTIC CONSIDERATIONS IN THE TREATMENT OF CHRONIC KIDNEY DISEASES

Hydration: Undoubtedly, rehydration is of critical and key importance to perfuse tissues with oxygen and nutrient carrying and waste scavenging mechanisms. Rehydration aids in acid-base homeostasis. With an impaired ability to concentrate urine, despite polydypsia, exogenous fluids are required. Clients commonly give subcutaneously administered fluids to cats at home. Increasing oral intake of water can be encouraged through flavouring water, offering milk, and feeding mostly canned foods.

Example of subcutaneous fluid calculation for a dehydrated cat:
Use the previous hydrated weight for calculations.

Ideal healthy hydrated weight: 4 kg
Ill, dehydrated inappetant weight: 3.2 kg.
Estimated 8% deficit (firm feces, delay in skin tent, slightly dry oral mucous membranes, normal eye position):

Deficit 8% X 4kg = 320 ml
Maintenance 60 ml (6%) X 4kg/day = 240 ml
Ongoing losses unknown at present = ? ml
Fluids needed in first 24 hours = 560 ml
These 560 ml can be given IV at 23 m/hour OR, were this to be given subcutaneously for some reason, as three boluses of 185ml over the 24 hour period.

After the patient is rehydrated, then a dose of 60 ml/kg/day (6% ideal weight) = 240ml is needed daily to maintain hydration. If canned food is being fed, approximately 80% of the weight of the canned food is water and this volume can be subtracted from the amount of fluids administered subcutaneously.

An alternative is to use the following Table (Adapted from DiBartola 4th ed Fluid, electrolyte acid-base disorders p 347). 8% => 140 ml/kg/d X 4 kg = 560 ml over first 24 hours.

Maintenance (60 ml/kg/day) + % dehydration	**Ml/kg/day**
Maintenance + 1%	70
Maintenance + 2%	80
Maintenance + 3%	90
Maintenance + 4%	100
Maintenance + 5%	110
Maintenance + 6%	120
Maintenance + 7%	130
Maintenance + 8%	140
Maintenance + 9%	150
Maintenance + 10%	160

PROTEIN: TO RESTRICT OR NOT?
In **acute kidney injury**, in a protein-losing nephropathy and in mild to moderate CKD, restriction of dietary protein, may limit the kidney's compensatory response to injury. Protein restriction may lead to protein malnutrition, which impairs immunological response, decreases hemoglobin production, promoting anemia, decreases plasma protein levels and promotes muscle wasting. Inadequate protein also decreases urinary excretion of magnesium, which may result in CaPO4 precipitation in the kidneys. It is important for cats with mild to moderate CKD to maintain adequate caloric intake in order to avoid protein-calorie malnutrition. Protein-calorie malnutrition results in weight loss, hypoalbuminemia, poor hair coat quality and muscle wasting even in cats maintaining body fat.

Dietary treatment of **moderate to severe CKD** (Cr > 5 mg/dl = 440 µmol/L, BUN > 75 mg/dl) is not controversial; restriction of both protein and phosphorous are required in order to avoid uremic complications. Benefits of protein restriction are related to NON-renal effects (toxins affecting organs other than kidneys). Using protein sources of high biological value is important. Protein restriction may be especially harmful in renal patients who are inappetant, as sustained calorie deficit causes body proteins to be catabolized to provide calories and the nitrogenous end-products of this process will further exacerbate uremic signs. Inappetance is an indication for avoiding protein-restricted diets. Uremia is associated with variable dietary intake, intestinal malabsorption, metabolic acidosis and co-morbid conditions, which independently influence nitrogen balance.

Despite numerous experimental studies [Adams 1993] [Adams 1994] [Finco 1998], a survey [Hughes] and clinical trials, [Elliott J, 2000] [Plantinga 2005] [Ross SJ 2006] questions about feeding protein to the cat with renal disease still remain. These include, but are not limited to, the following:

1. What is optimal amount of protein for a cat with CKD? How much restriction is necessary?
2. Do different types of kidney disease require different dietary therapies?
3. At what point in disease progression should protein restriction be implemented?
4. Does the type of protein fed make a difference?
5. Does every meal have to be restricted?
6. Is phosphorus restriction as, or more, beneficial than protein restriction in Stages 2 and 3?
7. Might some cats with advanced disease benefit from increased protein levels?

One of the most recent clinical trials (Ross et al), states that: "the renal diet evaluated in this study was superior to an adult maintenance diet in minimizing uremic episodes and renal related deaths in cats with spontaneous stage 2 or 3 CKD." but acknowledges that: "These findings emphasize the value of considering individual dietary components in the overall assessment of the benefits of dietary therapy. Individually or in combination, similar dietary modifications in the present study may have minimized the number of uremic crises and mortality rate."

Azotemia, metabolic acidosis and, to some degree, hyperphosphatemia are affected by hydration, thus optimizing hydration through the use of canned diets, adding water to food, encouraging drinking by use of flavoured liquids or a fountain along with the use of daily subcutaneous fluids are beneficial to the well-being of the patient. The patient should enjoy the diet offered, regardless of what illness he/she has. It is always more important that they eat, rather than what they eat. The amount of food consumed must be monitored. This requires calculating the caloric requirements for each individual - 50 kcal/kg/day is a reasonable goal. The client should be told how much food this is equivalent to so that if the cat does not eat that amount, they notify the veterinarian. It also prevents confusion regarding weight loss associated with progressing disease vs. that associated with inadequate nutrient intake. This will result in a negative nitrogen balance, protein: calorie malnutrition and deterioration of protective mechanisms impacting immunity, red cell hemoglobin content, muscle mass as well as tissue healing ability.

Due to of inherent progression, IRIS staging focuses on factors which, when managed, slow progression (hypertension, proteinuria) or reduce clinical signs (azotemia, hyperphosphatemia, metabolic acidosis).

PHOSPHORUS

As glomerular filtration rate decreases in CKD, phosphorus is retained in the blood, causing transient hyperphosphatemia. Initially, the remaining nephrons compensate by increasing the levels of phosphorus excreted. This is mediated by parathyroid hormone (PTH). Eventually, as chronic kidney disease progresses and glomerular filtration rate (GFR) decreases to less than 20% of normal, this compensatory mechanism fails and persistent hyperphosphatemia results and renal secondary hyperparathyroidism ensues.

Phosphorus should be restricted in moderately azotemic patients. This was shown to be of greater importance than protein restriction to survival in remnant kidney model dogs and has been shown to produce less severe renal lesions in remnant kidney model cats. To be effective, intestinal phosphate binders must be given within two hours of a meal as they act by binding the phosphorus within the ingested food making it unavailable for absorption. The website: www.zzcat.com/CRF/supplies/binders.htm has useful information on phosphorus binders.

Epakitin™ is an alternative to feeding renal diets as a method to reduce serum phosphorus. It is composed of chitosan and calcium carbonate. There are, two studies of this agent. Serum BUN and phosphorus levels were significantly reduced during the treatment period with minimal increase in serum calcium. Pronefra ™, containing chitosan, "vasoactive peptides" and an extract of *Astragalus membranaceus* is another option.

METABOLIC ACIDOSIS

Metabolic acidosis promotes severe catabolism of endogenous proteins, exacerbates azotemia regardless of diet, promotes wasting (through degradation of protein), inhibits protein synthesis, causes a negative nitrogen balance and enhances hypokalemia. Acidosis should be aggressively corrected using fluid therapy.

POTASSIUM
As mentioned earlier, polyuria causes increased urine K loss. In addition, common dietary acidification contributes to acidosis and shifts K out of cells into the extracellular compartment (including serum) resulting in falsely elevated/normal serum K. Eliminate acidosis, and if tCO2 is subnormal, treat with NaHCO3 8-12 mg/kg PO BID or K citrate 15-30 mg/kg or 2.5 mEq PO BID. Potassium supplementation (K gluconate 2-4 mEq PO BID) can be used once acidosis is corrected. Up to 40 mEq KCl can be added to a liter of lactated Ringers solution for SC rehydration.

CALCITRIOL
The use of calcitriol is still controversial: advocates suggest that it should be started in early kidney disease when Cr is 2-3 mg/dl in renal azotemia, and phosphorus is < 6 mg/dl at a dose of 2.5-3.5 ng/kg/day. In these patients the PTH levels are often still normal and calcitriol is used to prevent PTH increase to prevent symptoms related to PTH toxicity. In patients with a serum creatinine of > 3 mg/dl and serum phosphorous < 6 mg/dl the dose is 3.5 ng/kg/day PO. Good client compliance is critical in order to monitor ionized Ca and PTH long term.

UREMIC GASTRITIS – DOES IT EXIST?
Cats may show only signs of partial anorexia, or nausea rather than outright vomiting. Quimby has shown that the most significant gastric lesions in cats with CKD are fibrosis and mineralization, rather than gastric ulceration, edema, and vascular fibrinoid change as seen in dogs or humans with uremic gastritis. Thus, there is very little available evidence on which to base recommendations for the use of acid-reducing medications such as H_2 blockers, proton pump inhibitors or sucralfate in cats with uremia. When acid reduction is needed, omeprazole may be more effective than the H2 antagonists.

UREMIC STOMATITIS
Arises from secretion of urea in the saliva. This urea is broken down by bacteria (most likely anaerobes) to ammonia; the ammonia causes a chemical burn. This is an inconsistent finding in cats with CKD, therefore is likely multifactorial. Whether an individual develops uremic stomatitis and the severity may depend on their oral microbiota as well as salivary flow, salivary pH, and severity and/or chronicity of renal disease. Uremic stomatitis is more common in cats than in dogs or humans. This may be related to the dependence on high protein diet/increased ammonia metabolism or due to the high frequency of CKD in this species.

HYPERTENSION
Cats with CKD lose the normal auto regulatory capacity of the glomerular arterioles. This may promote progression of kidney disease through glomerular injury. Treatment of hypertension should be considered in cats whose systolic BP is consistently > 160 mm Hg. Amlodipine is the most efficacious agent (0.625 mg/cat PO q24-12h, titrating as needed) as it has a direct effect on the calcium channels of the peripheral vasculature.

PROTEINURIA
Several studies have shown that plasma Cr concentration and proteinuria are highly related to survival in cats with naturally occurring kidney disease. Preliminary studies also suggest that proteinuria may predict the development of azotemia in normal geriatric cats. It is unclear whether proteinuria is a marker or a mediator of renal injury in the cat. As with creatinine, the source of the proteinuria needs to be determined before attributing significance to the value. Additionally, persistence of proteinuria must be established because transient physiologic events (such as fever, excessive physical activity) may cause non renal proteins to spill into the urine. Other prerenal causes include any increase in serum proteins such as from chronic inflammation or infection or myeloma. Post-renal protein increases are most typically from urinary tract infection and inflammation. Once one has verified that the proteinuria is persistent and of renal origin, localizing the protein as being glomerular, interstitial or tubular remains difficult. However, the latter two are less likely to cause significant proteinuria, so we presume that UPC elevations are associated with alterations in glomerular integrity or hyperfiltration associated with a decline in the number of functional nephrons.

Glomerular hypertension promotes urinary protein loss. The mechanism of action of angiotensin-converting

enzyme inhibitors (ACE-I) is a selective dilation of glomerular efferent arterioles. Benazepril has undergone a large, multi-institutional study to assess its effects on CKD in cats. Results of this and other smaller studies show that using benazepril or placebo did not make any significant difference in survival time for all CKD cats unless proteinuria was present. However, for cats with urinary protein loss, (as determined by UPC), benazepril-treated cats had longer survival times and better appetite than placebo-treated cats. Those with an increased UPC (> 0.4) on this medication should be rechecked within 3-7 days and have their renal parameters, hydration, body weight, appetite and overall health monitored. Thereafter, re-evaluation should occur every 2-4 months in a stable patient. If there is no decrease in UPC, the medication should be discontinued as the possibility of adverse effects on renal function (via decreased GFR) should not be completely discounted.

ANEMIA

Cats with CKD develop anemia by several mechanisms. These include:

- Anemia of chronic disease (believed to be associated with iron sequestration);
- Anemia from protein malnutrition, (from inappetence, being fed a diet not meeting protein requirements to meet the ability to make hemoglobin);
- Blood loss (associated with uremic gastritis-induced gastrointestinal bleeding);
- Erythropoietin deficiency.

Erythropoietin (epo) is produced in the mesangial cells of the glomerulus in response to hypoxia. When administered parenterally, epo can cause a rapid correction of anemia by stimulating marrow progenitor cells. In 1994, the first report on using human recombinant epo (r-HuEPO) (Eprex) to treat anemia associated with CRD was published. Subsequently, a multicenter study evaluated the safety and efficacy of using r-HuEPO (Epogen). The benefits reported included increased appetite, energy, weight gain, alertness, strength, and playfulness to varying degrees but also anemia, anti-r-HuEPO antibody production, seizures, systemic hypertension, and iron deficiency, albeit inconsistently, in some of the study subjects. In 2000, a study reported the development of a recombinant adenovirus-associated vector containing the feline erythropoietin gene (rAAV/feEpo). When normal healthy cats, were given an IM injection, a dose-related increase in hematocrit over a 7-week period was seen. An attempt was made to create recombinant feline epo (rfEPO) in 2004; unexpectedly, 8/26 cats developed anemia that was refractory to additional rfEPO treatments.

Despite these setbacks, erythropoeitin (r-HuEPO) therapy should still be considered in the anemic cat with CKD. As with any agent, some patients may experience adverse effects but no patients will benefit if it isn't used. The author recommends considering using epo when PCV is < 20% and to administer 100 U/kg SC 3 times/week until PCV is low normal range (35%), then reduce the dose and frequency to 50-75 U/kg SC 2 times/week. Iron administration at the beginning of treatment is recommended and until the patient's appetite is satisfactory. (Iron dextran 50 mg IM q3-4 weeks or ferrous gluconate 50-100 mg (total dose) PO per day.)

It is important to monitor PCV every 2 weeks for the first 60-90 days to check for development of anti-epo antibodies (Ab). Should they develop, epo must be discontinued immediately. The patient may be transfusion dependent for 2-4 months until Ab levels decrease. While there is a risk of Ab developing, the majority of cats will enjoy the benefits of an improved hemogram. There are numerous r-HuEPO products available including Neorecormon (Roche), Epogen (Amgen) Eprex (Janssen- Ortho). Darbopoeitin (Aranesp™) is a second-generation epo that may be less antigenic than epo and is dosed less frequently at 0.45 mcg/kg/week.

With or without epo therapy, cats with renal disease may require a transfusion. In one review from a university teaching hospital, 20% of the cats needing blood products had chronic renal disease. With diligent and proper preparation and monitoring, it has been shown that multiple red cell transfusions are well tolerated by cats regardless of underlying disease.

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