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Therapeutic implications of recent findings in feline renal insufficiency

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The term: chronic renal insufficiency (CRI) is preferable to chronic renal failure (CRF) permitting us to view the condition as a progressive one, rather than imminently terminal and encourage our clients to treat their companions. Cats often live for many years with decreased urine specific gravity, elevations in BUN and creatinine after initial detection depending on the stage and cause of the disease. Some causes of renal insufficiency are more rapidly progressive or fatal than others; others are benign. Causes of *chronic* renal insufficiency 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 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. By monitoring blood pressure we can intervene with fluids and oxygen/oxygen carrying fluids generally preventing progression from pre-renal to renal failure. Severe ischemic injury in the cat is caused by thromboembolism of the renal arteries due to cardiomyopathy, extensive renal infarction and subsequent intra-renal acute renal failure. Renal toxins include ethylene glycol, Easter lilies, grapes and raisins, film processing chemicals, heavy metals, aminoglycoside antibiotics (by any route), amphotericin B, and doxorubicin (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 serum creatinine > 4.0 mg/dl (354 µmol/L) AFTER rehydration. Signs include lethargy, depression, anorexia, and vomiting.

Renal Physiology: Functions of the kidneys

- 1) remove toxic metabolites from the body
- 2) reabsorb/conserves salts, glucose, proteins, electrolytes and water
- 3) regulate blood pressure
- 4) regulate acid/base balance

- 5) endocrine functions: produce renin, erythropoietin, prostaglandins and convert precursor to active form of Vitamin D3/ dihydroxycholecalciferol

There is no single test measure renal function. The ability of the kidney to reabsorb water from the tubules is reflected by urine specific gravity (usg). Proteins must be conserved and not lost, thus testing for proteinuria is another way to look at renal function. Removal of toxic metabolites is the renal function we usually focus on because blood urea nitrogen (BUN) and creatinine (Cr) are on chemistry panels. The ability to concentrate urine (tubular, usg) is lost when 2/3 of nephrons are lost. Later, when approximately 3/4 of nephrons are lost, impairment of glomerular function is evident by increasing BUN and SC.

Hypokalemia is very common in cats with renal insufficiency. 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 and are mediated by aldosterone, Na, K concentration, acidosis and diuretics. Animals making a lot of urine (PU/PD) have a fast rate of tubular flow. Predisposing them to hypokalemia.

As GFR decreases in renal insufficiency, phosphorus is retained in the blood, causing transient hyperphosphatemia. Initially, remaining nephrons compensate by increasing their excretion levels; this action is mediated by parathyroid hormone (PTH). Eventually, as chronic renal insufficiency 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.

Staging chronic renal disease (IRIS)

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

Stage	I Non-azotemic renal disease	II Mild renal azotemia	III Moderate renal azotemia	IV Severe renal azotemia/ "chronic renal failure"
Creatinine: mg/dL (mmol/L)	< 1.6 mg/dl (<140 mmol/L)	1.6 – 2.8 mg/dl (140-250 mmol/L)	2.8 – 5.0 mg/dl (251-440 mmol/L)	> 5.0 mg/dl (> 440 mmol/L)
Clinical signs	None	+/- inappetance, weight loss, PU/PD	Usually inappetance, weight loss, PU/PD	Uremia, clinically ill
Progression	Stable for long periods of time	Stable for long periods of time	May progress	Fragile
Therapeutic goals	Identify and treat specific primary kidney disease (e.g., acute pyelonephritis, nephrolithiasis)	Identify and treat specific primary kidney disease (e.g., acute pyelonephritis, nephrolithiasis)	Modify progression: phosphorus restriction, omega 3 fatty acids?	Ameliorate uremic signs: protein restriction, anti-emetics, erythropoietin, fluid therapy, appetite stimulation, dialysis, etc.
Proteinuria	classify	classify	classify	classify
Blood pressure	classify	classify	classify	classify

Proteinuria (Determined by evaluating sequential urine protein creatinine ratios.)
 Nonproteinuric = UPC < 0.25
 Borderline proteinuria = UPC 0.25-0.5 Re-evaluate after two months
 Proteinuria = UPC > 0.4

Classification of blood pressure
 NH = non-hypertensive = < 150 mm Hg no complications
 BP = borderline hypertensive = 150-160 mm Hg with no complications
 Hnc = hypertension no complications = consistent systolic blood pressure values >160 mm Hg
 Hc = hypertension with extra-renal complications = signs + > 150 mm Hg

Therapeutic Considerations

History Clinical signs may include anorexia or inappetance, vomiting, dehydration, weight loss, lethargy, oral ulceration, ptyalism, anemia, 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 renal insufficiency. Often cats with even moderate renal insufficiency are asymptomatic! In assessing degree of illness, bear in mind that both decreased muscle mass (wasting) of cats with CRI, as well as hyperthyroidism masks the severity of concurrent renal insufficiency, by lowering SC levels.

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 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 tinned foods.

Protein: to restrict or not to restrict? In acute renal failure, and in mild to moderate CRI, 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, thus promoting anemia, decreases plasma protein levels and promotes muscle wasting. Inadequate protein also decreases urinary excretion of magnesium; this may result in Ca PO4 precipitation in the kidneys. It is more important for cats with mild to moderate CRI to maintain adequate caloric intake in order to avoid protein-calorie malnutrition. Monitoring for evidence of protein-calorie malnutrition should include monitoring for weight loss, hypoalbuminemia, poor hair coat quality and muscle wasting.

Dietary treatment of moderate to severe CRI (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 affect 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 supply calories and the nitrogenous end products of

this process will further accentuate uremic signs. Inappetence 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.

Phosphorus It is important to restrict phosphorus in moderately azotemic patients; this is more important 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, they must be given with food; they act by binding the phosphorus in the ingested food making it unavailable for absorption into the body. Epakitin™ is a new product designed as an alternative to feeding renal diets as a method to reduce serum phosphorus. It is composed of chitosan and calcium carbonate. There is, to date, only one study of this agent. Serum urea and phosphorus levels were significantly reduced during the treatment period with minimal increase in serum calcium. www.zzcat.com/CRF/supplies/binders.htm is a good site for phosphorus binders. Renalzin™ is a new palatable liquid option recently introduced in some European countries.

Calcitriol Calcitriol use is still controversial because some people think that its use is more urgent than others do. Advocates of calcitriol suggest that it should be started at 2.5-3.5 ng/kg/day in early renal insufficiency when SC is 2-3 mg/dl, use is compatible with CRI as cause of azotemia and phosphorus is < 6 mg/dl. In these patients the PTH levels are often normal and the calcitriol is used to prevent PTH increase to slow progression of the CRF and prevent symptoms related to PTH toxicity. In patients with a serum creatinine of > 3 mg/dl and serum phosphorus < 6 mg/dl the dose is 3.5 nanograms/kg/day PO. A baseline PTH in these is useful since the levels are commonly elevated and may require higher doses of calcitriol. Good client compliance is critical for ongoing monitoring of ionized Ca and PTH.

Erythropoietin Erythropoietin will cause rapid correction of anemia by stimulating marrow progenitor cells. Consider using epo when PCV is < 20%: dose with 100 U/kg SC 3 times/week until PCV is low normal range (35%), then reduce dose and frequency to 50-75 U/kg SC 2 times/week. It is important to monitor PCV every 2 weeks for the first 60-90 days to check for development of anti-epo antibodies (Ab). If they occur, cease epo immediately. The kitty may be transfusion dependent for 2-4 months until Ab levels decrease. Administer iron at start of regime and until appetite is good. While there is a risk of Ab developing, the majority of cats will enjoy the benefits of an improved hemogram.

Metabolic Acidosis Metabolic acidosis promotes severe catabolism of endogenous proteins, exacerbates azotemia regardless of diet, promotes wasting (degradation of protein), inhibits protein synthesis, causes a negative nitrogen balance and enhances hypokalemia. Acidosis should be aggressively corrected through fluid therapy and H2 receptor antagonist use.

Potassium Polyuria => increased urine K loss. Dietary acidification => acidosis => 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.

Uremic Gastritis Cats may show only signs of partial anorexia, or nausea rather than outright vomiting. H2 receptor antagonists are beneficial: famotidine 0.5 mg/kg PO q 24-48h PO or ranitidine 2-3 mg/kg q12 h PO may be tried if inappetence is apparent.

Hypertension Cats with CRI lose the normal auto-regulatory capacity of the glomerular arterioles. This may not only cause systemic hypertension in 50% of cats with CRI but also promote progression of renal insufficiency through glomerular injury. Treatment of hypertension should be considered in cats whose systolic BP is consistently > 180 mm Hg. Amlodipine is the most efficacious agent (0.625 mg/cat PO q24-12h, titrate up as needed) as it has a direct effect on the calcium channels of the peripheral vasculature.

ACE Inhibitors Benazepril has undergone a large, multi-institutional study to assess its effects on CRI in cats. Results of this and other smaller studies show that using benazepril or placebo didn't make any significant difference in survival time for all CRI cats. For cats with urinary protein loss (urine protein:creatinine, UPC), benazepril treated cats had longer survival times and better appetite than placebo-treated urinary protein losing cats. Cats with an increased UPC (> 0.4) who are started 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.

References available upon request