

Chronic Kidney Disease, Ureteroliths, and Proteinuria 2018

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CKD: INTRODUCTION

Chronic kidney disease (CKD) is unfortunately a very common condition that we encounter in cats and dogs, but much more common in cats. It is also a condition we sometimes over-diagnose (in other words, we sometimes fail to exclude other causes of chronic azotemia). CKD is classically defined as chronic renal azotemia or non-azotemic chronic renal damage (therefore, with isosthenuria, causing structural and/or functional changes, hence IRIS Stage 1) present for at least 3 months. However, as further detailed in these notes, we will discuss how new biomarkers are helping us diagnose CKD earlier than before. There are multiple causes for CKD, but the result is that there is irreversible damage to the kidneys and a decrease in the number of functional nephrons. Fibrosis replaces normal renal tissue.

CKD often begins before we see azotemia. Azotemia is simply a reflection of increased nitrogenous waste products in the body (and we measure this readily by BUN and creatinine, but there are many other waste compounds), and its causes can be acute or chronic, and also pre-renal, renal, or post renal in origin. It is important not to assume that all azotemia is the kidney's fault. However, acute kidney injury (AKI) can occur from pre-renal and post renal azotemia, and lead to acute renal failure as well as CKD. All three forms of azotemia can co-exist, which makes differentiating them sometimes challenging.

It is generally accepted that 30% of cats may develop renal azotemia after 9 years of age. Above age 15, it is thought that over 50% of cats will have some form of CKD. In dogs, the prevalence of CKD is accepted to be less than 1% based on a recent U.K. study. Therefore, most of the discussion below will be based on cats and CKD. In the proteinuria section, we will discuss in detail glomerulonephritis and dogs.

Before moving any further, it is important to highlight we do well and also what we could do better in veterinary medicine concerning CKD.

What we do well:

- Staging CKD using IRIS guidelines
- Improving patient quality of life
- Diagnose patients once they are symptomatic and also azotemic
- Use prescription diets
- Identify and treat proteinuria and hypertension

What we could do better:

- Earlier diagnosis, which may lead to earlier treatments and possibly prevention
- We forget a lot about post renal causes of azotemia such as ureteroliths
- Understanding the pathophysiology of CKD
- Still lots of grade 4 treatments used to treat CKD

The above-mentioned points will be the focus of the following notes.

Causes

There are numerous causes of CKD.

- Congenital/familial
 - Amyloidosis (dogs)
 - Renal dysplasia
 - Polycystic kidney disease

- Acquired: very common cause in both cats and dogs, often some form of AKI (either pre-renal, renal, or post renal causes) that has led to permanent renal damage
 - Infectious causes
 - Hypercalcemia (idiopathic often in cats)
 - Neoplasia (lymphoma)
 - Pre-renal (dehydration, hypotension during anesthesia)
 - Post renal (ureteral obstructions)
 - Intoxications, medications
 - Immune-mediated
 - Endocrine disease such as diabetes mellitus (very common cause in humans)
 - Ischemia
 - Protein-losing nephropathies (much more common in dogs than in cats as a primary disease entity, in cats often secondary to CKD)
 - Idiopathic, chronic tubulointerstitial nephritis (the most common cause in cats)

Despite the numerous causes of CKD, most of the above-listed causes are usually not identified in the majority of our cases. In dogs, glomerulonephritis (primary and secondary) is an extremely important cause of CKD, whereas in cats this is certainly not the cause. In cats, tubulointerstitial nephritis seems to be the common pathologic development found in CKD kidneys. It is suspected that there is an initiating event that leads to progressive damage and changes.

Further potential causes in cats:

- Viruses, such as morbillivirus, have been associated with renal damage. Woo et al (2012) identified that 12% of feral cats in China had an association with tubulointerstitial renal disease and this virus. The incidence of this virus and its association to CKD is unknown.
- Ross et al (2007) highlighted a likely association with FIV virus and CKD
- Environmental factors that are still unknown at this point
- Age: it is known that as cats get older, there is a higher incidence of CKD. However, age by itself is likely not the sole cause of CKD. In a 2013 study by Quimby et al, it was discovered that cats with CKD had shorter telomere lengths in renal tubules (hence leading to cellular senescence in renal epithelial cells). However, telomere length was not shortened in CKD cat liver and skin samples. Therefore, shortened telomere length is not solely caused by age.
- In cats, over-vaccination is possibly a cause of CKD. In studies by Lappin (2005, 2006), it has been demonstrated that vaccines cultured using Crandell-Rees feline kidney cell lines (CRFK), which includes FVRCP vaccines of all current available vaccines, likely contain proteins from CRFK that can lead to an immune response once injected into cats.
- Changes in anti-oxidant defenses is another possible cause, but a paper by Krofic in 2014 indicates that anti-oxidant defenses are not exhausted in older cats and cats with CKD
- Dental disease has been associated with possible CKD
- Lastly, and more interestingly, there is increasing suspicion that CKD evolves from possible multiple mini active kidney injuries (IRIS Napa meeting 2016). Unfortunately, as of now we do not have biomarkers sensitive enough to catch these mini-AKIs. Here are some highlights of this theory:
 - AKI can initiate CKD in people and dogs, why not cats?
 - Tubulointerstitial changes similar to CKD are seen in recovery of AKI following ischemia model, so can AKI cause maladaptive repair mechanisms which initiate CKD
 - Kidneys with CKD are more prone to AKI insults
 - Ischemia hurts the renal basement membrane vs. toxic insults which do not, and therefore lead to maladaptive repair mechanisms
 - Schmiedt et al, 2016 Vet Path: showed that changes typical of ischemic AKI are present in experimental and naturally occurring CKD and supports that AKI can lead to CKD in cats

Therefore, tubular hypoxia may be a common initiating event, leading to one AKI or multiple AKIs, and leading to maladaptive repair mechanisms. This in turn leads to CKD which we can finally detect with our traditional functional tests.

- Causes of tubular hypoxia: multi-factorial: age, sympathetic activity, toxins, anemia, stress, dehydration, BP changes, tubular hypermetabolism of age
 - Chakrabarti 2012 JVIM: low PCV independent predictor of CKD progression in cats with IRIS stage 2
 - Lower UTIs: ongoing study by Vaden et al into early AKI markers clusterin, NGAL, and cystatin c showed that some dogs with lower UTI had elevated AKI markers, and this shows that lower UTIs may be hurting the kidneys as mini-AKIs undetectable by our current markers (creatinine and SDMA)
 - Cardiorenal syndrome is also a cause of mini AKIs. Using serum inosine as a biomarker of AKI and following the treatment of CHF in a dog with MVD, SDMA did not detect any changes in renal function but inosine went from being elevated during CHF and normalizing after treatment of CHF

All of this may indicate that multiple mini AKIs can lead to currently undetectable renal damage, until there is enough damage and maladaptive repairs that it leads to CKD that we can detect. Even if “function” returns to normal, there is likely undetectable permanent or ongoing damage.

Lastly, we know that the activation of the renin-angiotensin-aldosterone (RAAS) system is an important pathophysiology mechanism in CKD, but there is some thought that its early activation could be the cause of CKD. However, Jepson JVIM 2014: plasma renin and aldosterone concentrations in normotensive azotemic CKD and nonazotemic age-matched controls found no significant difference in RAAS, making it unlikely that RAAS activation is a cause of CKD. The same is true for systemic BP.

Predicting CKD

Predicting the occurrence of CKD in cats and dogs can be quite difficult. It is generally accepted that older cats have a greater chance of developing CKD. Evidence of proteinuria (pre-renal or renal causes) is certainly a predictor of future CKD if left untreated and not investigated. A high-normal creatinine and isosthenuria can also be indicators. Known structural damage and being exposed to risk factors (such as hypotension) are also known predictors. Preventing CKD is even more of a mystery, with no evidence that a certain therapy or lifestyle would prevent the occurrence of CKD (except for preventing the occurrence of any disease that would affect the kidneys).

Recent studies have tried to highlight predictors of CKD, and unfortunately results tend to vary.

- Finch, Syme, Elliot 2016 JVIM
 - 148 geriatric cats, longitudinal cohort study
 - What predicted development of CKD:
 - Annual/frequent (q2y) vaccination
 - Moderate and severe dental disease
 - The concern is that dental disease causes chronic inflammation which may lead to an immune response that targets organs of the body, including the kidneys. Treatment of dental disease was not a factor in the development of CKD
 - What did not predict:
 - Age
 - Diet (senior vs. adult diet)
 - Wet vs. dry diet
- Greene, Lefebvre et al 2014 JAVMA
 - Retrospective study, what predicted CKD:
 - Thin BCS

- Recent general anesthesia
- Male cat
- Dental disease
- Cystitis (type unknown, sterile vs. non-sterile)
- What did not:
 - Diet
- Jepson, Brodbelt et al, 2009 JVIM looking at biochemical variables
 - Prospective longitudinal cohort study with 118 cats aged 9+ that started as nonazotemic and followed them over 12 months
 - 30% became azotemic
 - High-end creatinine and UPC predicted the development of CKD
 - This study is quoted quite often because of the high grade of evidence
 - Hence why it is stated that 30% of cats aged 9 and above will develop CKD, and that proteinuria and high-end of reference range creatinine predict CKD
- Piyaungsri, Pusoonthornthum, 2016 JFMS
 - 101 cats with CKD vs. normal cats >5years of age, retrospective study
 - Increased risk of CKD: tap water, outdoor lifestyle, males
 - Decreased risk: eating commercial diet, filtered water, indoor lifestyle

Lastly, a 2016 JVIM study by Freeman et al evaluated weight changes. They looked at over 500 cats across the USA over 8 years. Results indicate:

- Median weight loss of -8.9% body weight in the 12 months prior to diagnosis of CKD
- Weight loss already present 3 years prior to diagnosis
 - These cats were likely in IRIS stage 1, showing that this stage is not a benign stage despite cats not have classic CKD symptoms
- Accelerated weight loss after diagnosis, association with IRIS stage
- Cats with <4.2Kg BW had shorter survival
 - But heaviest cats also had shorter survival

Predicting the progression of CKD is also difficult; however, the IRIS staging and studies around the staging have helped us predict survival. GFR studies to examine renal function are not practical for routine usage. A 2012 JVIM study by Chakrabarti et al identified the following in cats:

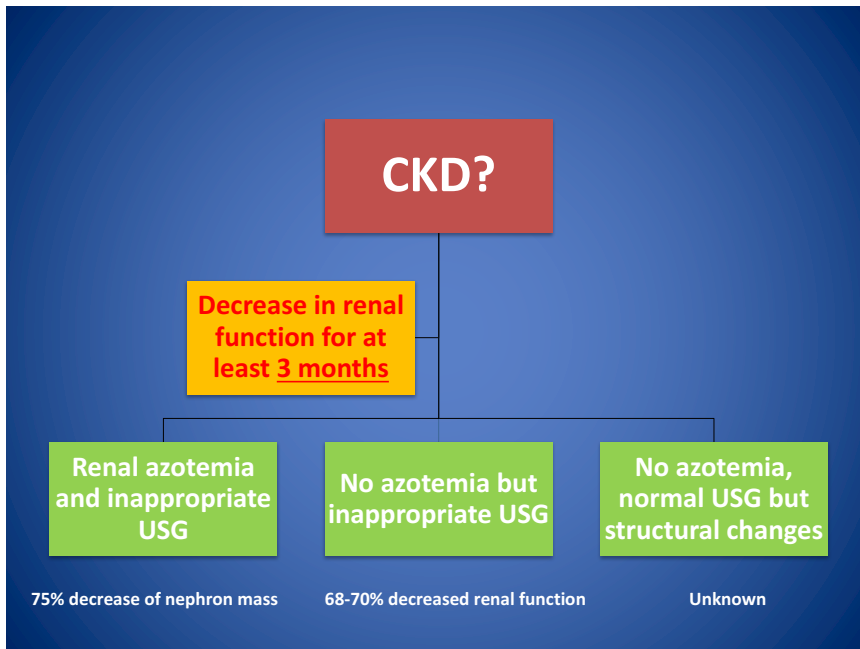
- High phosphorus and UPC predicted progression in all stages
- Lower PCV and higher UPC predicted progression in stage 2
 - UPC was 0.23 in progressive cases and 0.13 in stable cases
 - PCV was 33% in progressive cases and 36% in stable cases
- Higher phosphorus concentration predicted progression in stage 3

What is interesting about this study is that these UPC values have traditionally been considered “acceptable” (see discussion below on proteinuria) for cats with azotemia. This raises the question on if we are aggressive enough with our proteinuria treatments. Also, these PCVs are normal for cats, and it may relay back to the AKI and hypoxia theory of development of CKD (that even a small drop in PCV may lead to AKI and hence progression of CKD).

Therefore, this highlights the need to stay vigilant with our CKD patients and monitor them closely.

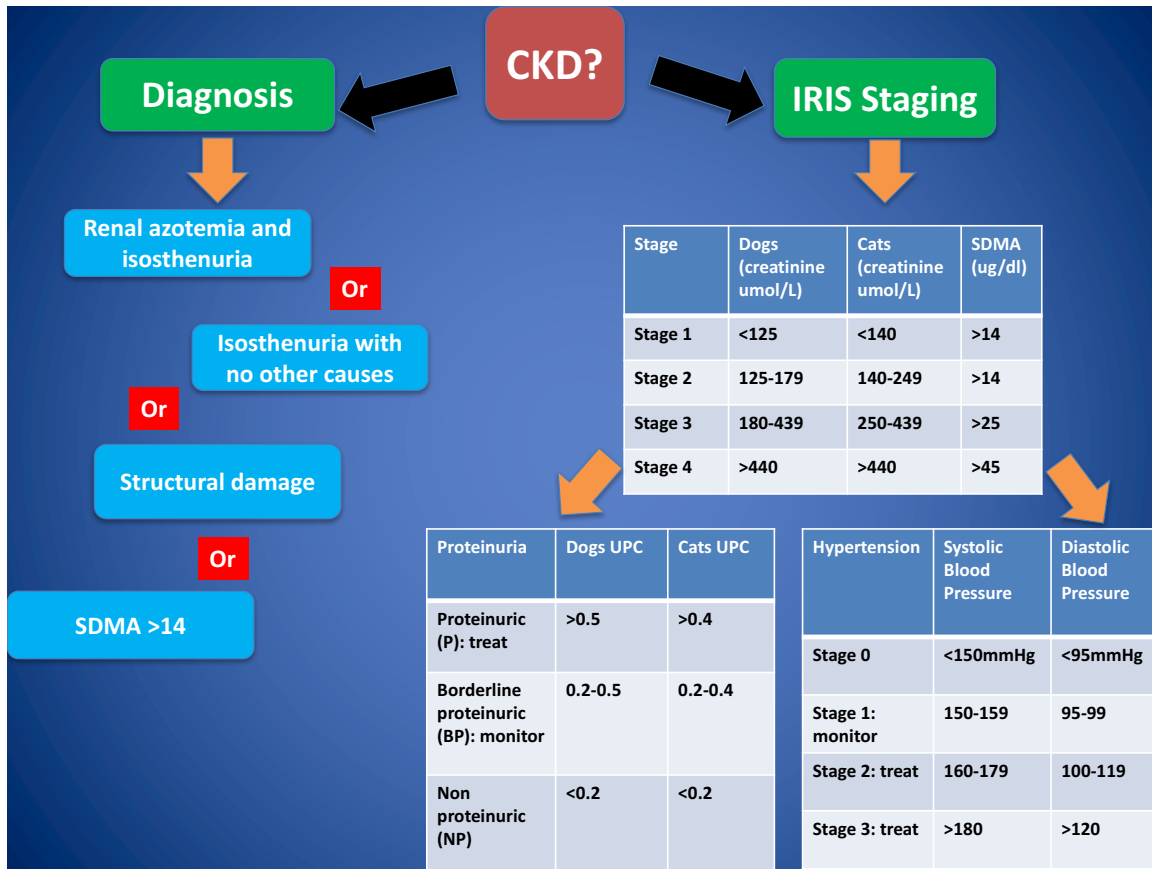
Diagnosis of CKD

Traditionally, the diagnosis of CKD has been based on the presence of renal azotemia and isosthenuria for at least **3 months**’ duration.



However, this assumes that we have eliminated post renal causes of azotemia (such as ureteroliths) AND that the azotemia has been chronic. As we can see above, our traditional biomarkers are not sensitive. It takes a 75% decrease in nephron mass for azotemia to appear, which is defined as an increase in creatinine (MUCH more stable and predictable) and/or BUN (MUCH less reliable and variable) above established reference ranges. These reference ranges can vary greatly from one reference laboratory to another. They have been established by looking at healthy cats and dogs, and not geriatric animals nor looking at breed differences (such as Greyhounds who have a much higher PCV and creatinine than others). In some instances, creatinine reference range can go up to 200umol/L. The development of isosthenuria is not much better in diagnosing CKD, as its appearance signifies a 68-70% decrease in renal function. Also, multiple conditions will affect USG (endocrine disease, afternoon urine sample, diet etc.).

Before continuing, it is important to separate out the diagnosis of CKD and the staging of CKD. IRIS staging values should NOT be used to diagnose CKD. IRIS staging assumes we have made a diagnosis of CKD, and then we can apply the staging principles for treatment and prognosis guidelines.



Therefore, diagnosis CKD is based on the above flow diagram, or by using novel biomarkers. Biomarkers may help us someday predict CKD (and AKI, ARF) and are used in human medicine. There are few studies available in veterinary medicine, and most of the biomarker assays are not bench top tests.

Biomarker	Indication	Advantages	Disadvantages	Methodology
Cystatin C	GFR, AKI	Good for CKD detection	Effect related to age and weight	Immunoassay
Retinol Binding Protein	AKI, CKD	Stable	Large variation with cats and CKD	ELISA, Western Blot
A1- microglobulin	AKI, CKD	Stable	Lower with hepatic disease	ELISA, immunoassay
B2-microglobulin	AKI, CKD	Good estimate of GFR in dogs	Non stable in acidic urine, less effective with disease progression	ELISA
Urinary clusterin	AKI	Early AKI, active AKI	Hemorrhage	Immunoassay
GGT	AKI	One urine sample	Unstable in acidic urine, hematuria, pyuria	Automated analyzer
NGAL	AKI, CKD	Urine, serum, plasma	Neoplasia, inflammation, hematuria, pyuria	ELISA

Symmetric dimethylarginine (SDMA) is a molecule that has become quite important in the early diagnosis and also staging of CKD in cats and dogs. SDMA has no physiologic role in the body. It is the methylated form of the amino acid arginine. It is produced by all cells in the body and released into circulation during protein degradation. It is excreted almost exclusively by the kidneys, hence its utility as a biomarker. Studies in veterinary medicine have shown that SDMA increases at roughly at **40% of renal dysfunction**, and in some cases will detect a 25% in renal function. A recent dog study looking at x-linked hereditary nephropathy demonstrated that SDMA increased at 20% decrease of GFR. When we compare this to isosthenuria: 67-70% function loss and azotemia: 75% function loss, we can quickly see the utility of this biomarker for the early diagnosis of CKD. This will take some getting used to because we are so used to seeing a normal creatinine and USG and concluding there is no CKD! We are now able to diagnose CKD much earlier than before, and this will hopefully lead to new treatments.

SDMA is more sensitive than creatinine at detecting CKD especially at earlier stages of CKD. It is a specific biomarker as well based on studies. In cats with CKD, SDMA shown to increase 17 months earlier; and in dogs an average of 9 months earlier (Hall et al, JVIM 2014). The SDMA molecule has a slight positive charge compared to creatinine and this makes it less affected by changes in GFR with hyperthyroidism. However, further studies are needed to identify SDMA as a more helpful biomarker of CKD with hyperthyroidism. SDMA is not impacted by muscle mass, thereby much more accurate in low BCS geriatric animals. This is very important because most of our geriatric cats have decreased muscle mass. In addition, with CKD there is progressive muscle mass loss and therefore CKD stage may be understated because of the reliance on creatinine. SDMA is stable, and intraday and interday variability negligible. There is no impact from hemolysis, icterus, lipemia.

Serum Creatinine	Serum SDMA
<ul style="list-style-type: none"> Increases at 75% function loss Specific 100% Not sensitive 17% NPV 70% Decreases with age in cats Decreases with hyperthyroidism Daily variation Affected by hydration, diet (ex. meat) Variable reference ranges 	<ul style="list-style-type: none"> Increases at 40% loss Specific 91% Sensitive 100% NPV 100% Not affected by age or muscle mass Minimal affect by hyperthyroidism No daily variation Not affected by hydration, diet One reference range

Recent data suggests that SDMA may be slightly elevated in young cats and dogs (under 2 years of age). As such, the new reference range for dogs is 16ug/dl (cat data coming).

Staging CKD:

International Renal Interest Society

Once CKD has been diagnosed, it is important to then refer to staging principles. The IRIS staging guidelines have become a mainstay of staging cats and dogs with CKD. They have permitted us to create clear and objective guidelines on how to treat our patients based on creatinine (because it is more stable and predictable than BUN), proteinuria, and hypertension. The IRIS guidelines underline the importance of regular physical exam and lab work for our

patients. For instance, proteinuria and hypertension are often silent. If left undiagnosed and untreated, not only will organ damage occur, but CKD also progresses much faster.

IRIS guidelines have been modified in 2015-2016 to reflect the addition of SDMA as both a diagnostic tool and also a staging tool. An SDMA that is persistently above 14ug/dl is consistent with CKD. This value reflects IRIS stage 1 and 2 patients if the SDMA is below 25ug/dl. These patients often have minimal to absent clinical signs. SDMA above 25ug/dl usually indicates IRIS stage 3, and this is important for cats and dogs with creatinine values in stage 2 but that have muscle mass loss. Therefore, these patients have an underestimated renal function and are likely in stage 3 with that SDMA level. This changes their prognosis and treatment recommendations. The same is true for a creatinine above 45ug/dl. If a cat or dog has a creatinine that puts them in IRIS stage 3 but an SDMA of 45ug/dl, this pet is actually in stage 4. The treatment recommendations and prognosis vary greatly between these 2 stages (prognosis 778 days for IRIS stage 3 vs. 30-60 days for IRIS stage 4).

Stage 1 has long been a mystery. It was almost impossible to diagnose as there are usually no clinical signs associated with this stage, and our diagnostics tests were not sensitive enough. However, now with SDMA we can diagnose cat in this stage. This has helped us learn a lot more about early stage CKD and discovered that in fact some cats do have symptoms such as mild weight loss. In addition, we are understanding that stage 1 is not a benign state as previously thought. Because of early diagnosis, this is allowing research to advance in early stage treatments (especially diets).

Prognosis

Predicting prognosis depends on how fast the disease progresses, and on the initiating cause (if the initiating cause has been treated, if the cause is progressive). It is also dependent on IRIS substage parameters. Many cats (less so for dogs) can have stable CKD for years. Cats with upper IRIS Stage 2 have a median survival time of 1151 days. With stage 3, it decreases to 778 days, and with stage 4, the range is 35-103 days. With dogs, the prognosis is much shorter as they do not tolerate CKD, azotemia, and uremia as well as cats do. They often have proteinuric disease that progresses faster.

Quality of life becomes an important question as CKD progresses. Uremia becomes more of a factor as CKD progresses. There are multiple consequences of uremia and circulating azotemia on all body systems. Some of these lead to clinical signs that are readily visible, whereas others are not as obvious. Some examples of uremic and azotemic clinical signs include anorexia, nausea, vomiting, diarrhea, weight loss, muscle loss, dehydration, hypertension, anemia, metabolic acidosis, hyperphosphatemia, hyperparathyroidism, hypocalcemia, hypercalcemia, hypokalemia, hyperkalemia, proteinuria, hypoalbuminemia, lethargy, GI erosions/ulcers, and advanced dental disease.

TREATMENT OF CKD

The treatment for CKD should be tailored to an individual patient's needs. It is important to avoid standard "recipes" for every case. Not every cat or dog will need the same treatments. Treatments are not benign, can lead to a decrease in quality of life (anxiety, adverse reactions) and also decreased compliance by the owner (if there are many treatments to give or if they have to struggle with the cat to administer the treatments). As CKD progresses, especially to stage 4, quality of life is primordial.

The goal of treatment should be to improve quality of life, prolong life, slow the progression of the disease, and to practice evidence-based medicine as much as possible. The goal is not to treat the "numbers" and to decrease BUN and creatinine as low as possible. It is important to remember that CKD leads to decreased GFR, and that decrease in GFR leads to azotemia (i.e. the circulating trash) that affects the body, which leads to uremia (the clinical signs associated to azotemia). Treating CKD is about correcting the effects of that reduced GFR and dehydration. In addition, our readily available measures of azotemia (BUN, creatinine) are not sensitive or

specific markers of renal function and are affected by other factors (muscle wasting, decreased protein intake, GI bleeding, liver disease).

Evidence-based medicine is often limited in veterinary medicine compared to human medicine, but studies do exist and their findings should be interpreted to guide our treatment choices as much as possible.

1. Renal Diets

The use of renal diets in cats and dogs is considered grade 1 evidence. It has been shown that cats fed a renal diet in upper-stage 2 or stage over 24 months had no uremic crisis compared to control cats eating a formulated “grocery store” diet (26% uremic crisis). Deaths from renal causes were 0% vs. 22% on the other diet. These diets generally contain reduced protein, phosphorous, sodium, and modified lipid and fatty acid content. They usually come in dry and wet food formula. Wet food diets have the advantage of bringing more water to a cat, thus limiting dehydration and pre-renal azotemia. Dogs have similar beneficial evidence. At least 3 separate studies show the benefits of a renal diet (Ross et al, Elliott et al 2000, Plantinga et 2005)

The IRIS recommendation is to feed these diets at IRIS upper Stage 2 and certainly stage 3 (dogs +/- stage 2-3). There is no known preventative effect of feeding cats these diets if they are non-CKD geriatric cats. There are multiple diets on the market and it is important to try different ones if a cat will not eat a renal diet. That being said, it is even more important that CKD cats eat regularly and not lose weight. If a cat will not eat a renal diet, then I usually recommend a good quality wet food diet that is somewhat reduced in protein and sodium. If possible, mixing 50-80% of a renal diet would most likely have an added benefit than just a commercial diet.

One common complaint is that cats will not eat the new renal diet. It is important to remember that cats with CKD are likely uremic at upper stage 2 and stage 3, and therefore have nausea. In addition, cats in general don't like change. Therefore, it may be of some value to slowly introduce the new renal diet by mixing it with the cat's old food over multiple weeks. In addition, it may be worthwhile working on nausea and appetite (mirtazapine, maropitant). There is recent debate on the use of renal diets and the fact that they may promote muscle loss in cats, which is detrimental to their survival. There are suggestions that cats with CKD should be fed higher protein diets but that phosphorus should be controlled. This is certainly an interesting debate on multiple fronts.

The Diet Controversy

The Pro and Con View of Renal Diets at Stage 2-4

The Pro View

- Renal diets proven to improve survival, decrease uremic crises
- Not just about the protein: phosphorus, sodium, omega-3, antioxidants, potassium, vitamin D, neutral effect on pH
- Protein restriction decreases uremia
- Stage 2 or 3?
- FGF-23 elevated in stage 2, linked to CKD progression
- Phosphorus unlikely controlled with binders
- Phosphorus linked to CKD progression
- High protein leads to proteinuria and glomerular lesions
- Uremia is a cause of weight loss, sarcopenia
- High protein diets untested and likely dangerous recommendation
- Promote eating, asking why cats won't eat

The Con View

- Cats are obligatory carnivores that need high protein diets, lose LBM with lower protein diets
- Remnant kidney studies showed no association between high protein intake and renal lesions, proteinuria, or decreased GFR
- No study has looked just at protein
- CKD diet effect on proteinuria unclear (Ross 2006)
- Increased mortality with lower BW CKD cats
- Phosphorus restriction alone not studied
- Sodium restriction to manage hypertension but activates RAAS
- Fatty acids?
- No studies on potassium supplementation
- What about acid-base status and correction vs. LBM?
- Geriatric cats may need more than 32-34% of calories from protein

Vet Clin Small Anim

What is still clear from the above comparison is that all parties agree that weight loss is not ideal and should be prevented. There is also the need for further studies on the matter. It also seems unlikely that phosphorus can be controlled alone with phosphorus binders with a higher protein diet, and hyperphosphatemia is detrimental.

There is a new paradigm shift when it comes to renal diets. For the longest time the recommendation was to start renal diets once a cat or dog was in IRIS stage 2 CKD. However, now that we have the ability to diagnose CKD earlier than before, we can better diagnose stage 1 and early stage 2 cats and also recognize that they would benefit from early nutritional intervention. As such, cats in stage 1 likely benefit from a geriatric-type diet or an early-stage kidney diet. A study by Hall et al demonstrated possible benefits of cats in stage 1 eating an early kidney disease diet, and a similar study done on dogs by the same author also showed a similar benefit. There are multiple reasons why these diets are likely beneficial including decreased phosphorus and increased omega-3 fatty acids.

2. Altering azotemia

Renal diets have been proven to decrease BUN in the bloodstream, and therefore reduce azotemia. The numerical reduction in azotemia is not the important point; it is the reduction in nitrogenous waste. Unfortunately, other compounds on the market that claim to reduce azotemia have not been proven to work based on objective studies.

3. Altering or preventing renal fibrosis

Studies have failed to show the efficacy of rhubarb-containing commercial products to prevent the progression of CKD in cats.

4. Appetite stimulants and anti-nausea medications

Maintaining body weight is an advantage in any disease state. CKD cats are often uremic and nauseous, and lose their appetite as CKD progresses. There is evidence that using appetite stimulants such as mirtazapine work in cats with CKD to promote eating. The recommended dose is 1.85-1.88mg PO 48h. Not only does mirtazapine work to stimulate appetite, a study by Quimby et al showed that it decreased vomiting as well. The same author has shown in another study that mirtazapine can also work as a transdermal medication.

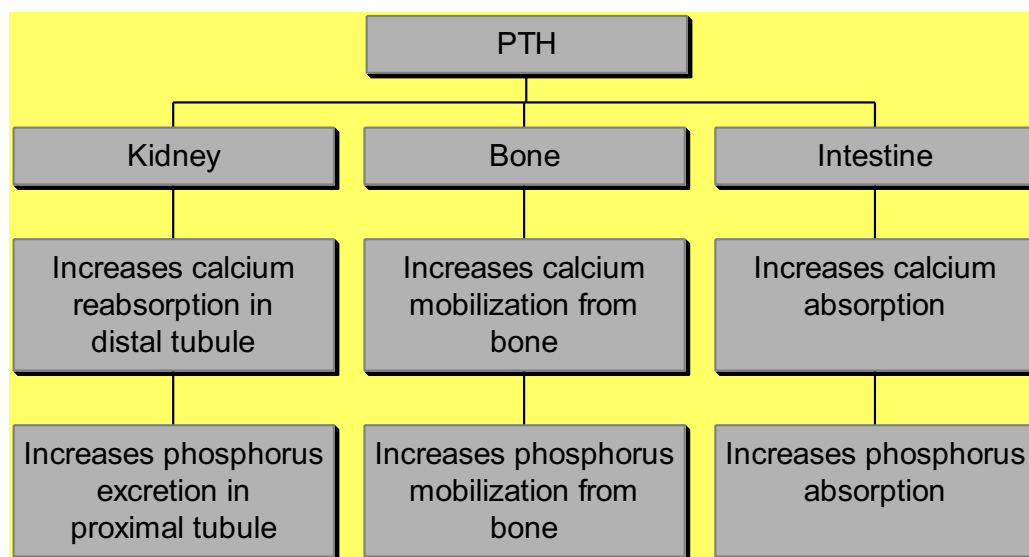
Maropitant has been shown to be safe in patients with CKD and can be given daily over a 2-week period without any adverse side effects.

5. Treating metabolic acidosis

Metabolic acidosis in CKD is a consequence of decreased renal acid secretion and buffer production. There is only grade 4 evidence about the need to specifically correct metabolic acidosis in cats with CKD. The reality is that most of us do not monitor acid-base status in these patients. Some accepted therapies for chronic clinical acidosis include potassium citrate and bicarbonate administration.

6. Secondary renal hyperparathyroidism

Parathyroid hormone, secreted by the parathyroid glands, has numerous functions in the body. It is a key hormone in the control of calcium and phosphorus in the body. Its net effect with healthy kidneys is to increase calcium and decrease phosphorus in the body.



Decreased GFR leads to hyperphosphatemia, which leads to increase PTH secretion (direct effect on parathyroid gland) and also decreased calcitriol production (by inhibiting 1-alpha hydroxylase). Increased PTH leads to increased phosphorus elimination at the level of the kidney. As CKD progresses, there is less functioning kidney to respond to PTH, which leads to even more hyperphosphatemia and also increased PTH secretion. Renal secondary hyperparathyroidism leads to calcitriol deficiency, hyperphosphatemia, hypocalcemia, and potentially conditions such as “rubber jaw” (loss of calcium in bones).

Administering calcitriol could lead to negative feedback control to the parathyroid gland, therefore slowing down PTH secretion. However, it is very important to normalize phosphorus with renal diets and phosphorus binders before using calcitriol. Unfortunately, calcitriol administration in cats has failed to show clinical relevance (no improvement in survival) in one short-term study. Many nephrologists still consider its usage in cats. There is evidence in dogs that it does prolong survival.

Fibroblast-growth factor 23 (FGF-23) is a molecule secreted by bone in response to hyperphosphatemia and promote phosphaturesis and also decreased calcitriol. It is being recognized as an even more potent and important player in phosphorus control. FGF-23 has been shown to increase in cats with CKD and correlates with staging (Geddes 2013), and FGF-23 may be an earlier marker for the prediction of CKD (Finch 2013) as it seems to increase prior to the development of azotemia in geriatric cats that develop CKD over 12 months. This all leads to greater evidence that controlling hyperphosphatemia is primordial.

7. Treating hyperphosphatemia

Treating hyperphosphatemia is important in the chronic setting. Hyperphosphatemia has multiple undesired effects. Phosphorus can complex with calcium and cause organ calcification and deposits. It is also thought to cause GI upset and anorexia. Treating hyperphosphatemia is grade 2 evidence in veterinary medicine. It may improve survival.

The best treatment is with a renal diet first. If this is not enough, then using a phosphorus binder is important. It is important to note that these only work when administered with food, as all they do is bind phosphorus in food. Current products include aluminum hydroxide, calcium carbonate, and lanthanum carbonate. All dosages should be titrated to effect to avoid side effects and to increase cat compliance.

8. Renal anemia

Anemia of renal disease has multiple causes. Gastrointestinal bleeding is possible from erosions and ulcers created by uremia; however, this has not been proven in dogs and cats (McLeland JVIM 2014). Uremia causes platelet dysfunction and may lead to increased bleeding tendencies. Red blood cells survive less long with uremia, and uremia is thought to contain inhibitors of red cell survival. Renal secondary hyperparathyroidism will lead to bone marrow fibrosis, with less red cell precursors available.

A relative iron deficiency is caused by the induction of hepcidin, an acute phase protein produced by the liver in response to chronic inflammation from CKD. Ingested iron (ferric) is absorbed from the duodenal lumen (only 5% of it) into the enterocyte (ferrous iron via a reductase enzyme) through the divalent metal transporter (DMT1) on the luminal side. In the absence of hepcidin, iron leaves the enterocyte on the basolateral side via ferroportin. Apotransferrin bound to iron (ferric iron) is called transferrin, the main method of transporting iron in the circulation. Hepcidin binds ferroportin, causing rapid internalization and degradation of ferroportin. Without ferroportin, iron efflux from the cell is prevented.

Lastly, the progressive destruction of renal cells leads to decreased erythropoietin (EPO) secretion. Without erythropoietin, the bone marrow lacks the stimulus needed for continued red cell precursor development.

The anemia is often non-regenerative and progressive. Human studies have shown that this leads to reduced oxygen delivery to organs and tissues, which leads to lethargy, progressive dyspnea, mental dullness, reduced quality of life, and increased mortality. There is a linear relationship showing improvement in quality of life with higher hemoglobin in humans. Current available studies in cats show contradictory evidence about decreased survival and renal anemia. Other consequences of renal anemia include cardiac and renal changes. It has been shown that 30-60% of cats with CKD will develop renal anemia. In addition, a 2012 study by Chakrabarti (JVIM) et al showed that a lower PCV predicted progression of CKD in cats.

Correction of renal anemia begins with reducing or treating some of the other factors involved described above. The use of erythrocyte-stimulating agents has become standard of care in human medicine in CKD patients. They are more and more used in veterinary medicine.

Human recombinant DNA erythropoietin is a drug that is almost similar to human erythropoietin and 85% similar to the canine and feline hormone. It has been used extensively in veterinary medicine.

- Protocol:
 - Starting dose: 100 U/kg three times a week until PCV at low end of target range
 - Target: PCV 25% cats, 30% dogs
 - Maintenance dose: 50-100 U/kg once to twice weekly based on PCV
 - Must supplement with iron

It has been proven effective to treat renal anemia in cats and dogs. However, some important adverse effects were noted to various degrees:

- Systemic hypertension
- Seizures
- Polycythemia
- Refractory anemia
- Injection discomfort
- Skin reactions
- Pure red cell aplasia

Pure red cell aplasia is a condition by which the body produced antibodies towards EPO molecules, both intrinsic and extrinsic. We usually see a worsening severe anemia and no reticulocytes, and a lack of response to therapy. The diagnosis is made by a bone marrow aspirate/core (very high M:E ratio). With human recombinant DNA erythropoietin in cats and dogs, the incidence is thought to be 25-40%. These animals become transfusion dependent for many months or for life.

Darbepoetin alfa, a hyperglycosylated recombinant human erythropoietin analogue, is a newer molecule that has largely replaced human recombinant DNA erythropoietin in human medicine. It has been shown to be as effective and it has to be administered at a lower frequency because of a longer half-life. It is usually given once weekly. In veterinary medicine, there is one study in cats indicated that it works as well as human recombinant DNA erythropoietin, with a similar adverse event profile. However, the incidence of pure red cell aplasia was much lower (under 10%). There may be a survival benefit as seen from the small study.

- Protocol:
 - Cats + dogs: dose of 1 mcg/kg/week SQ
 - Given weekly until reach target PCV
 - Same targets as with human recombinant DNA erythropoietin
 - Once at target PCV, decrease frequency of administration
 - Every other week, then every three weeks if at or above target PCV
 - Also dose reduction: aim for 0.45mcg/kg every 3 weeks

9. Iron supplementation

Iron supplementation on its own is not sufficient to treat renal anemia. However, the most important cause of erythrocyte-stimulating agent action failure is iron deficiency. Therefore, iron should be supplemented whenever these agents are used. Ferrous sulfate, oral liquid multivitamins, and iron tablets are all oral iron supplements. There are no studies in animals to test their efficacy. There is also thought that they may not work as well because they are poorly absorbed from the GI tract. Iron dextran is an intramuscular injection given once a month that seems to be more effective. The dose in cats is 50mg per cat once a month IM. An iron panel should be performed routinely to monitor treatment efficacy.

10. Hypertension

Hypertension is common in CKD cats and dogs, recognized in 20% of these patients. The cause is unclear but is most likely multifactorial. No matter what the cause, treating hypertension is

important as it represents a negative prognostic indicator with cats + dogs with CKD. It can lead to further renal damage, cardiac damage, ocular damage, and cause or worsen proteinuria. Hypertensive patients are three times more likely to die or to have progression of their renal disease.

Risk of End-Organ Damage	Systolic BP (mmHg)	Diastolic BP (mmHg)
Minimal risk	<150	<95
Mild risk	>150	>95
Moderate risk	>160	>100
Severe risk	>180	>120

It is therefore to include blood pressure monitoring in every veterinary exam and especially for geriatric and CKD patients. Hypertension often starts by causing silent damage. Treatments include:

- Calcium Channel Blockers (#1 for cats)
 - Reduces afterload
 - Amlodipine
 - 0.625-1.25 mg per 5 kg daily
 - Effective as single agent in 60% of cats
- ACE Inhibitors (#1 in dogs)
 - Reduce preload and afterload

11. Stem Cells

IV adipose-derived allogenic mesenchymal stem cells have been evaluated and seemed safe for use in patients with CKD but no effect on renal function was observed (Quimby et al, 2015 JFMS).

12. Urinary tract infections

Cats and dogs with CKD have an increased risk of developing UTIs. The cause is unknown but it is thought that the presence of an abnormal renal-urinary system diminishes normal defenses. CKD cats are often polyuric, which unfortunately masks the clinical signs of UTIs in many of these patients and delays the diagnosis. Therefore, it is important to consider regular urinalysis and +/- urine cultures with CKD cats and dogs. Some other findings:

- 66% of older cats with UTIs have CKD
- 30% of cats with stable CKD will develop a UTI
- 78% of UTIs susceptible to doxycycline
- 91% susceptible to Clavamox

13. Antacids

There is no objective evidence looking at the usage of antacids in feline or canine CKD. However, the use of antacids has become commonplace with anecdotal evidence of improved quality of life and appetite. As mentioned earlier, uremic gastropathy and uremic ulcers have not been proven in cats.

14. Potassium supplementation

There is also no evidence for the supplementation of potassium in CKD cats. However, this seems logical and cats that are hypokalemic despite eating well and eating a renal diet should most likely receive oral supplementation.

15. Omega-3 supplementation

Laboratory studies have shown that omega-3 fatty acids act as a natural renal anti-inflammatory and reduce proteinuria. Almost all commercial renal diets contain supplementation.

16. Uremic gastropathy

Uremic gastropathy has not been shown in cats in the only study on the subject. This puts into question how uremia affects the GI tract in cats and the thought that ulcers develop with uremia. It also puts into question the usage of antacids and their role in treating CKD cats. They are relatively benign drugs but they may not be necessary.

17. Anti-oxidants

One study has shown that anti-oxidants improve renal function in dogs with stage 2 IRIS CKD. Almost all commercial renal diets contain anti-oxidants.

18. Fluids

There are no studies evaluating the efficacy of subcutaneous (or IV) fluid administration in cats and dogs with CKD. There is an older study that observed a decrease in GFR with dehydration. It is logical that patients that are dehydrated would benefit from fluid administration. The question is what type, how much, and how frequently.

It is important to note that fluid administration corrects a volume deficit and dehydration, therefore pre-renal azotemia caused by dysfunctional kidneys that cannot concentrate urine and reuptake water. This is why we often see improved BUN and creatinine. Fluids also maximize GFR to their maximal capacity in the kidney's diseased state. Fluids do not "flush" toxins out. Once GFR is maximized and hydration restored, there is likely no added benefit to increasing the amount of fluids given. The creatinine represents the GFR and it will not improve significantly or persistently because GFR is compromised from the renal disease. Treating the numbers and not the patient may have consequences on the patient, such as fluid overload.

The most common fluid choice is the crystalloid lactated ringer's solution. The amount given depends on each cat and their needs to correct dehydration or maintain hydration.

19. Proteinuria

Proteinuria can come from the kidneys themselves, or be from a cause before the kidneys, or from after the kidneys. Proteinuria is often ignored because it is deemed unimportant or too small in magnitude. However, renal proteinuria, even in small amounts, can be detrimental in CKD patients. Some examples or proteinuria:

- **Pre-renal (pre-glomerular):** hypothermia, fever, hemoglobinuria, myoglobinuria, strenuous exercise
- **Renal (glomerular):** causes include glomerulonephritis, tubulointerstitial diseases, and chronic kidney disease
- **Post-renal (post-glomerular):** UTI, inflammation, cystoliths, metritis, prostatitis, neoplasia (transitional cell carcinoma, prostatic carcinoma), hemorrhage

The normal glomerulus maintains normal oncotic pressure and minimizes loss of serum proteins (albumin) while water, electrolytes, small solutes, and waste products pass through to the tubules for reabsorption or elimination. Proteins the size of albumin or larger do not readily pass through.

Chronic kidney disease: traditional CKD (either idiopathic/secondary to interstitial nephritis, or as a consequence of previous AKI/ARF) can lead to a renal proteinuria (hence the IRIS substaging). As CKD progresses, its ability to handle protein decreases, therefore this leads to proteinuria.

The kidneys are not meant to filter protein. With pre-renal causes, most are transient and not so concerning unless they persist. Myoglobinuria and hemoglobinuria can be quite damaging to the kidneys. The tubules can handle some protein by uptake and breaking them down in their lysosomes. However, when this becomes excessive, the lysosomes burst, causing tubular cellular damage. This leads to tubule degradation, fibrosis, and CKD. Casts can be seen in the urine from tubular damage.

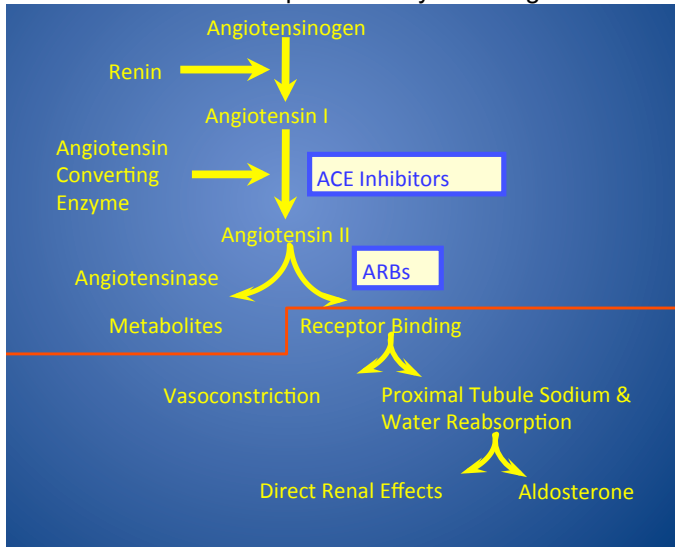
It is important to recognize that there are multiple causes of proteinuria and that it is essential to find the cause. Pre-renal and renal causes can cause renal damage and lead to CKD. This is often a silent and ongoing damage. The diagnosis is a process of elimination:

- **CBC:** Non-regenerative anemia with CKD.
- **Chemistry panel:** normal in early stages. Hypoalbuminemia. Azotemia, hyperphosphatemia. Hypercholesterolemia.
- **Urine protein (dipstick):** semi-quantitative. 1+ to 2+ protein in urine may be normal in concentrated urine, especially in cats. Lots of false negatives and false positives (alkaline urine, Hgb, myoglobin, fever, stress).
- **Urine protein-creatinine ratio:** quantitative measure of protein excreted over 24hr. A recent study shows that UPC samples can be obtained by free-catch. The UPC has been shown to be the most reliable measure of proteinuria in cats and dogs. It is specific. Microalbuminuria may be more sensitive and can detect proteinuria of earlier magnitude, but it may over represent significant proteinuria in cats and dogs. In addition, current assays vary in their efficacy. Lastly, IRIS substaging of proteinuria is based on UPC.
- **Urine culture:** to rule out common causes of proteinuria - UTI and pyelonephritis.
- **Renal biopsy:** Renal biopsies are not indicated with cats and CKD, unless an immune-mediated glomerulonephritis is suspected.
 - With a biopsy, you are looking for disease that may be reversed, such as diseases causing immune complexes into the kidneys
- **BP:** 50 – 85% of proteinuric dogs are hypertensive. It is important to measure BP as part of work-up.

The treatment of proteinuria involves identifying and treating pre-renal causes, eliminating post renal causes, and then targeting renal proteinuria.

- **Treating underlying systemic disease:** also treat sequelae of proteinuria (hypertension, hypercoagulability).
- **Treating azotemia:** following IRIS guidelines. If the patient is not azotemic, it is important to monitor for development of azotemia over time.
- **Treating proteinuria:**
 - o The treatment for renal proteinuria RARELY normalizes the UPC (especially with dogs and GN), but the goal is a decrease in magnitude to improve survival and decrease renal damage.
 - Non-azotemic cats or dogs (these are usually GN patients and usually dogs): investigate if UPC 0.5 – 2.0. Investigate and treat if UPC > 2.0.
 - Azotemic cats and dogs (these are usually CKD patients and usually cats): investigate and treat if UPC > 0.4 for cats, dogs >0.5
 - Proteinuria and hypertension are negative prognostic markers for CKD patients and thus should be treated.
 - There is evidence that CKD cats with proteinuria between 0.2-0.4 should also be treated.
 - o ACE inhibitors: enalapril, benazepril (0.5mg/kg/day to start). These medications block efferent arteriole constriction → ↓ glomerular pressure → ↓ protein loss in urine. May worsen azotemia (20-30% increase in creatinine is tolerable as cats will most likely not show clinical signs related to the increased azotemia).
 - o Angiotensin receptor blockers (ARBs): Losartan, telmisartan (licensed for usage in cats). Telmisartan (1mg/kg/day) can be used as a first line agent to treat

proteinuria in cats, and has been shown to be as effective as ACE inhibitors and is well tolerated. They can also be added to ACEI if ACEI does not decrease proteinuria by 50% or side effects of ACEi are not tolerable. A non-inferiority study (Sent et al, 2015 JVIM) demonstrated that telmisartan works as well as benazepril and may have a greater effect on renal protein loss.



- Diet: high protein diets exacerbate proteinuria and increase glomerular pressure. Renal diets are helpful in controlling proteinuria (protein restriction and better quality protein, phosphorus restriction, controlled potassium).
- **Recheck:** monitoring of UPC, renal values, and BP at 1week, 4weeks, 8weeks, and then every 2 months.
- If proteinuria reduction goals are not met, then a dose increase can be considered. ACEi dosages can be increased to 2mg/kg/day if no side effects are seen.
- **Prognosis:**
 - Proteinuria with CKD has a worse prognosis than non-proteinuric CKD (proteinuria is a negative prognostic indicator).

20. Nephroliths and ureteroliths

Cats are prone to forming calcium oxalate stones in their upper urinary tract. These can cause damage to the kidneys either directly or by obstructing the ureters. It is therefore important when we suspect ARF or CKD in cats to obtain medical imaging to rule out ureteroliths and nephroliths. There may not be effective therapy against nephroliths (and there is evidence that if these are not obstructing then they should be left alone and will likely not have an impact; Ross 2007 JAVMA), but ureteroliths can be treated. The earlier the intervention for ureteroliths, the better the outcome for renal function. The two most common procedures performed now are subcutaneous ureteral bypass (SUB) and ureteral stent placement. These procedures are generally well tolerated when patients are stable. There are no predictors of outcome for cats with ureteral obstructions after management with a stent or SUB. Prevention of calcium oxalate stones in cats is not well understood. Treating idiopathic hypercalcemia or other causes of hypercalcemia is important. Increasing food moisture or water intake may prevent stone formation, and also the use of specialized diets (Hill's C/D, U/D, W/D, G/D; Purina UR, RC S/O etc.).

If struvite stones are suspected in either the upper or lower urinary tract of cats or dogs, diet dissolution is possible. The diet that has shown the fastest dissolution is Hill's Prescription Diet S/D (Lulich et al, JVIM 2013). For dogs and struvites, if a UTI is also suspected (because struvites are often caused by UTIs in female dogs), then appropriate antibiotic therapy during the entire dissolution time is important. However, S/D should not be used as a preventative diet and also not long term.

Intervention for feline ureteroliths should be considered if there is acute azotemia, pelvic distention, abdominal discomfort, and the possibility for renal function return. However, it is very difficult to predict the return of renal function and if there is visible obstruction with pelvic distention, even if the renal parenchyma looks more thin, there is a chance for renal function return with intervention. The earlier intervention, the better.

Ureteral stents in cats were one of the first interventions besides traditional ureterotomy. A study by Kulendra et al (JFMS 2014) indicated that most cats survive to discharge after surgical placement, and cats have a median survival of 419 days. There was no significant difference in survivor vs. non-survivor initial creatinine value. However, a major recognized complication of ureteral stents in cats is the development of chronic recurrent sterile cystitis, seen in almost 35% of cats. In some cases, the cystitis is very difficult to control. In addition to this complication, and the difficulty in placing stents in cats, most specialists will opt for subcutaneous ureteral bypass devices because of their relative ease to place.

In a study by Horowitz et al (2013 JFMS), no clinical or biochemical parameter was associated with survival to discharge with either SUB or stent placement in cats, reinforcing the notion of not underestimating the appearance of the kidney prior to placement. However, cats that stabilized as IRIS stage 1-2 post procedure did have a longer survival than cats that stabilized at IRIS stage 3-4.

Long term data on SUBS is still not published, but data from the Animal Medical Center in NYC looking at 225 cases of 7 years indicates that SUBS are much easier to place, have a low perioperative mortality and complication rate, and median survival post procedure is likely over 2 years (Berent, ACVIM Forum 2016). SUBS do require regular maintenance (flushing every 3-6 months) to ensure patency.

For dogs and ureteral obstructions, the placement of ureteral stents is still the preferred approach. This can be done by surgery or endoscopically (in females).

21. Kidney transplants and chronic dialysis

Kidney transplants for cats in upper stage 3 or stage 4 IRIS CKD has been shown to have good success, with 80% perioperative survival and 60% 3-year survival. There are few hospitals in North America that provide transplant services. Kidney transplants are not recommended for dogs.

Chronic intermittent hemodialysis is not indicated in cats with CKD. Cats have a higher rate of complications compared to dogs with chronic dialysis therapy. Dogs can undergo chronic intermittent dialysis (3 treatments per week) and on average will survive 6-8 months with end-stage kidney disease. However, this is cost prohibitive for most owners.

Summary

There are multiple objective, evidence-based therapies available for cats and dogs. There are also anecdotal or grade 4 evidence therapies that also have their place in the treatment of CKD. It is important to adequately evaluate each individual pet, tailor therapy for that specific pet, and evaluate efficacy. It is important to avoid a “one size fits all” or recipe-type medical approach.

PROTEINURIA (In more detail)

What it is:

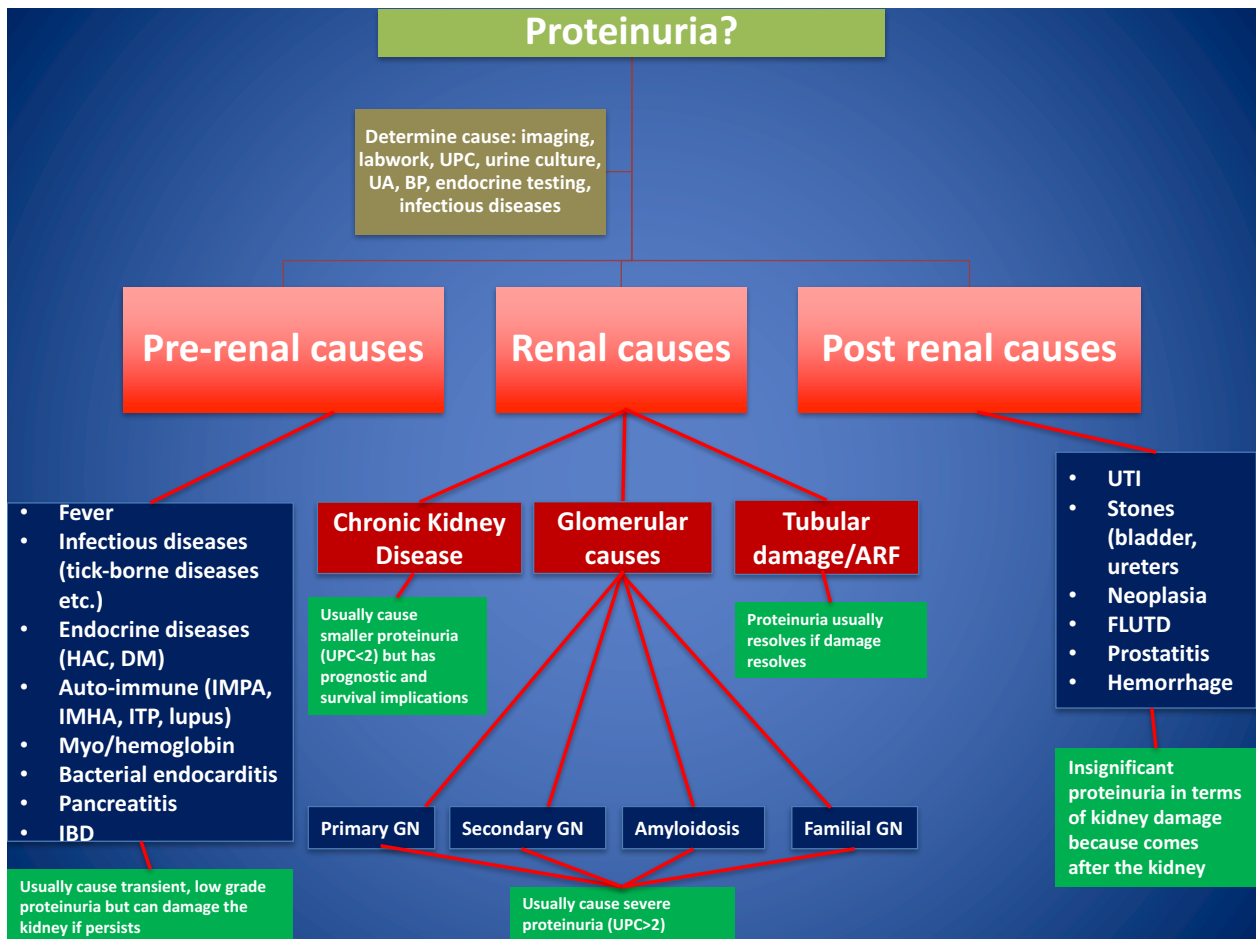
Proteinuria is when there is protein in the urine. Very small amounts of protein can be present in the urine, but proteinuria is usually not normal and should not be ignored. Every attempt should be made to find the cause.

The glomerulus functions to filter blood, and it does not usually let proteins pass through especially proteins the size of albumin or bigger. The tubules can handle some degree of protein passage, but in excess the tubules will get hurt (and often permanently). Therefore, the kidney does not like protein to pass through.

There are 3 broad categories of why proteinuria develops:

1. **Pre-renal causes:** examples include fever (inflammatory proteins brought to the kidney), an excess of smaller proteins being brought to the kidneys (myoglobin, hemoglobin), strenuous exercise, and systemic diseases (pancreatitis, endocrine disease, immune diseases, hypertension)
 - a. These causes are usually transient, but in excess or if prolonged can hurt the kidney
 - i. Myoglobin/hemoglobin can really hurt the kidneys quickly
 - b. Systemic diseases can cause small amounts of pre-renal proteinuria, and can disappear when the disease is treated. HOWEVER, sometimes the proteinuria does not go away (especially with endocrine diseases) and CAN LEAD TO SECONDARY GN AND RENAL DAMAGE.
 - c. Proteinuria magnitude in these causes is usually not great (UPC under 2), until they lead to glomerulonephritis
2. **Renal causes:** in these cases the kidney is to blame for letting more protein to pass through. There are many causes but let's look at two broad causes.
 - a. **Glomerular causes (dogs):**
 - i. **Primary (idiopathic) glomerulonephritis (GN)** is where the glomerulus (only at first) is damaged (cause unknown) and allows greater passage of proteins. The rest of the kidney is fine at first, until protein passage through the tubules causes too much damage and then you are left with severe kidney disease.
 1. Primary GN may be caused by immune complexes dropped into the kidney or not, we don't know why this happens.
 2. The patient has NO clinical signs until kidney damage from the passage of protein causes enough damage to lead to azotemia and uremia.
 3. Proteinuria magnitude is usually greater (UPC up to and greater than 2)
 - ii. **Secondary glomerulonephritis** is where the glomerulus is damaged, but this time there is a known cause. Causes include endocrine disease (such as diabetes mellitus, hyperadrenocorticism), immune disease (lupus, pemphigus, IMHA etc.), pancreatitis, infectious diseases (tick-borne diseases, Lyme disease being an especially bad one), neoplasia etc.
 1. Secondary GN may also be caused by immune complexes dropped into the kidney or not, and we don't know why this happens.
 - iii. **Familial glomerulonephritis**
 1. Familial predisposition to develop GN and severe proteinuria.
 2. Proteinuria magnitude is usually more (UPC up to and greater than 2)
 - iv. **Amyloidosis**
 1. Deposits of amyloid into the kidneys, either primary/idiopathic (such as in Beagles and Walker Hounds) or secondary (such as secondary to Shar Pei Fever)
 2. Proteinuria magnitude is usually greater (UPC up to and greater than 2)
 - b. **Chronic kidney causes (cats and dogs):**
 - i. In these cases, the entire kidney is already damaged because of chronic kidney disease (CKD). In some CKD patient, the kidney degenerates to the point that the glomerulus and the tubules do not do their jobs and protein starts to go through.

1. Therefore, in these instances we START with CKD that LEADS to renal proteinuria SOMETIMES, whereas in GN proteinuria occurs immediately and causes damage to the kidneys
2. This is important because for CKD and IRIS Staging, proteinuria is part of substaging and is a negative prognostic indicator when present
 - a. This means the CKD will PROGRESS faster when proteinuria is present
 - ii. The proteinuria magnitude is usually NOT AS SEVERE as GN cases
 1. UPC 0.5-2 usually but can be higher
- c. **Acute renal failure**
 - i. Toxins, pyelonephritis
 1. All can cause proteinuria because of an acute renal dysfunction, but rarely are they sustained unless you are left with chronic kidney disease after the acute kidney injury
3. **Post renal causes:** In these cases, the proteinuria does NOT COME from the kidneys. It is created below the kidneys (usually bladder, prostate etc.). Therefore, this type of proteinuria DOES NOT HURT the kidneys. However, it needs to be identified so you do not miss renal or pre-renal proteinuria that can hurt the kidneys. Also, post renal proteinuria needs to be treated for its cause (for example, if you have a UTI), but not for the actual proteinuria. You often have an ACTIVE SEDIMENT if you have inflammation, but not necessarily active infections.
 - a. **Urinary tract infections**
 - b. **Feline Lower Urinary Tract Disease (FLUTD)**
 - c. **Bladder, ureteral, urethral stones**
 - d. **Chronic cystitis**
 - e. **Prostate disease (prostatitis, neoplasia, cysts)**
 - f. **Urethral disease**
 - g. **Hemorrhage**



What does it mean:

Proteinuria originating before or at the kidneys can hurt the kidneys. It is why it is important not to ignore proteinuria and to find the cause.

1. Pre-renal causes:

- Most of the causes will give you a transient proteinuria, but in some instances the proteinuria can persist and hurt the kidneys.
 - Classic example: diabetes mellitus or hyperadrenocorticism that you treat the primary disease, and the proteinuria does not go away, and becomes a silent killer of the kidneys
- Pre-renal causes usually have UPCs of lower magnitude, except for hemoglobin/myoglobin that can be higher
- Patients are usually clinical for whatever disease is causing the proteinuria, but not the proteinuria itself.
- A concentrated urine with a high USG can lead to a proteinuria on a dipstick of 1-2+, but not be significant on UPC (less than 0.2-0.4)

2. Renal causes:

a. Glomerular causes (dogs):

- Primary (idiopathic) glomerulonephritis (GN):** If left untreated, the proteinuria (which is usually severe) will destroy the kidneys. Once these patients become azotemic, they do not have long to live. The damage done to the kidneys from GN proteinuria is much more severe than a dog with CKD. Without treatment, these dogs live usually 6 months to one year.

- ii. **Secondary glomerulonephritis:** same as above; the secondary disease has left the kidney with GN and severe proteinuria, and the kidney gets badly injured.
- iii. **Familial glomerulonephritis:** usually not a good prognosis
- iv. **Amyloidosis:** depending on the disease, can sometimes be treated, but if the proteinuria is severe then it may be too late.
 - 1. With Shar Pei fever, often we will treat these dogs with colchicine to try and “dissolve” or prevent amyloid deposits into the kidneys before severe proteinuria or azotemia develops, and this can save these patients.
- b. **Chronic kidney disease (CKD) causes (cats and dogs):**
 - 1. Proteinuria and hypertension are both **NEGATIVE PROGNOSTIC INDICATORS**. Which means, with IRIS Staging, you need to substage for proteinuria. If you have proteinuria or hypertension and you do not treat, the kidneys will degenerate faster and the patient will not live as long.
 - a. There is a 3 times increase in mortality for a UPC above 1, and a 1.5 increased risk for every 1 UPC increase after that, and CKD progresses much faster with a UPC above 1
- c. **Acute renal failure**
 - i. Toxins, pyelonephritis
 - 1. Depends on if the initiating cause leaves you with CKD
- 3. **Post renal causes:** It is important to rule out pre-renal and renal causes, because post renal causes are more benign in the sense they do not hurt the kidneys (unless you don't treat them, such as a UTI, and it becomes pyelonephritis).

How to approach it:

- 1. **Pre-renal causes:** You usually have signs of other diseases. A good history and physical exam really helps in determining if you should pursue testing for some of these diseases.
 - a. CBC, chemistry panel, urinalysis, culture, T4, ACTH stimulation test or LDDT as necessary, medical imaging, fructosamine, blood pressure
 - b. With endocrine disease, if you see proteinuria in your urinalysis, make sure to rule out UTIs (most endocrine diseases will predispose you to UTIs, and also hypertension, so get a BP also)
 - c. So you should obtain a urine protein-to-creatinine ratio (UPC) if you see proteinuria, and if you don't have an active sediment or if your urine culture results are negative
 - i. Once you treat your endocrine disease, make sure to follow-up and see if your proteinuria disappears
 - 1. Recheck a urinalysis, and if there is proteinuria get a UPC
 - 2. These patients are not azotemic, therefore if you get a UPC of between 0.5 to 2.0 then you should investigate. If above 2, then you should investigate and treat immediately.
- 2. **Renal causes:**
 - a. **Glomerular causes (dogs):** The UPC will usually be higher than 2.0
 - i. **Primary (idiopathic) glomerulonephritis (GN)**
 - 1. Same rule: investigate if UPC 0.5-2; treat and investigate if greater than 2.0. I usually start treatment with a UPC >1.
 - a. Treatment principles
 - i. Diet (renal)
 - ii. Omega-3 fatty acids
 - iii. Anti-thrombotic therapy
 - 1. Aspirin 1mg/kg/day or clopidogrel

- a. Loss of anti-coagulant factors because of the GN, prone to making and throwing thrombi
 - iv. ACE inhibitor
 - 1. Start at 0.5mg/kg/day
 - 2. If on recheck the UPC has not improved below 0.5, or if it has not at least dropped by 50%, then increase the dose
 - a. 0.5mg/kg BID, then 1mg/kg BID max
 - b. A 20-30% increase in azotemia or mild hyperkalemia is tolerable and should not warrant discontinuation of therapy unless the patient feels worse
 - c. Recheck BP, renal values, UPC, electrolytes 3 weeks after starting, then one month later if your UPC is acceptable (or increase dose and recheck in 3 weeks), then every 3 months
 - v. If not enough, then try an angiotensin receptor blocker
 - 1. Losartan or telmisartan 1mg/kg/day
 - vi. Consider renal biopsies to look for immune complexes
 - 1. 50% of GN dogs will have immune complex deposition in their kidneys and it may be worth referring them for kidney biopsies
 - a. They will have a better prognosis if they have immune complexes and we can immunosuppress them
 - b. Mycophenolate 10mg/kg q12h seems ideal in these situations
 - c. Biopsies are ideal if UPC >2, no causes found, not azotemic or not severely azotemic
 - vii. Get a BP and treat if elevated (most proteinuric dogs have hypertension)
 - ii. **Secondary glomerulonephritis:** see above; but try to find initiating cause; damage to the glomerulus may already be done.
- b. **Chronic kidney causes (cats and dogs):**
 - 1. Investigate and treat if UPC greater than 0.4 in cats and 0.5 in dogs
 - 2. The UPC should be lower than in GN dogs
 - 3. These dogs and cats usually have signs already of CKD, and you need to substage them to see if they have proteinuria
 - 4. Treatment:
 - a. Treat based on IRIS staging and substage
 - i. When appropriate: renal diet, hypertensive medication, etc.
 - ii. ACE inhibitor or ARB (cats)
 - 1. Start at 0.5mg/kg/day (ACEi) or 1mg/kg/cat (ARB)

2. If on recheck the UPC has not improved below 0.5, or if it has not at least dropped by 50%, then increase the dose
- iii. Recheck BP, renal values, UPC, electrolytes 3 weeks after starting, then one month later if your UPC is acceptable (or increase dose and recheck in 3 weeks), then every 3 months

c. Acute renal failure

1. Treat the cause of the acute renal failure
 - a. Treating the proteinuria is not necessary until you know if your patient will recover (and to what degree) from the ARF
3. **Post renal causes:** Treat the cause (UTI, prostatitis, FLTUD etc.), not the proteinuria

Prognosis:

1. **Pre-renal causes:** Prognosis usually good if the proteinuria disappears, not good if your proteinuria persists and leads to renal damage or GN
2. **Renal causes:**
 - a. **Glomerular causes (dogs):** The prognosis is poor once they become azotemic (days, weeks); better with treatment with ACEi/ARBs (6 months-1 year), 1-2 years if immune complexes and immunosuppression
 - b. **Chronic kidney causes (cats and dogs):** prognosis depends on your IRIS Stage and if you control your substages, but usually good if you treat the proteinuria and succeed in meeting your goals of treatment
- c. **Acute renal failure**
 1. Treat the cause of the acute renal failure
 - a. Treating the proteinuria is not necessary until you know if your patient will recover (and to what degree) from the ARF
 3. **Post renal causes:** Good with treatment of cause

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