Chronic Kidney Disease (CKD) in Dogs & Cats - Staging and Management Strategies

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Learning objectives:

1. To be able to stage CKD based on levels of serum creatinine, proteinuria, and systemic blood pressure.
2. To gain further insight into how veterinary renal diets are formulated and how they potentially can help to reduce progression in patients with CKD
3. To be able to use a "targeted" level of serum phosphorus to be obtained under optimal treatment with diet and intestinal phosphate binders.
4. To understand how control of secondary renal hyperparathyroidism is important during CKD.
5. To understand how calcitriol treatment during CKD can help maintain lower levels of circulating PTH, reduce intra-renal inflammation, and provide Vitamin D receptor stimulation/activation which is helpful for overall health.
6. To understand how the use of ACE-Inhibitors may be useful in dogs and cats with CKD

Introduction

Chronic kidney disease is diagnosed commonly in dogs and cats. The incidence of the diagnosis of CKD in cats is made 2 to 3 times as frequently compared to dogs and is especially common in geriatric cats. CKD is clinically characterized by the development of variably progressive irreversible intrarenal lesions and loss of renal functions. A variety of interventions (diet and drugs) can slow the progression of the renal disease, improve the quality of life for the patient, and/or extend the quantity of life. Compensatory increases (so called adaptations) in glomerular hemodynamics and glomerular volume may actually be maladaptive in some instances as shown in the figure below.

The incidence of azotemic CKD was compared between dogs with and without periodontal disease in a recent epidemiological study. The hazard ratio for detection of azotemic CKD increased with the increasing severity of periodontal disease. Increasing severity of periodontal disease was also associated
with serum creatinine >1.4 mg/dl and blood urea nitrogen >36 mg/dl whether or not the veterinarian diagnosed CKD (Glickman 2011).

Figure 1. Concept of increased protein-trafficking as a consequence of intraglomerular hypertension and glomerular hypertrophy that occur in remnant nephrons associated with advanced CKD. Protein in urine is both a marker and a creator or more renal disease as shown in the graphic below. (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)

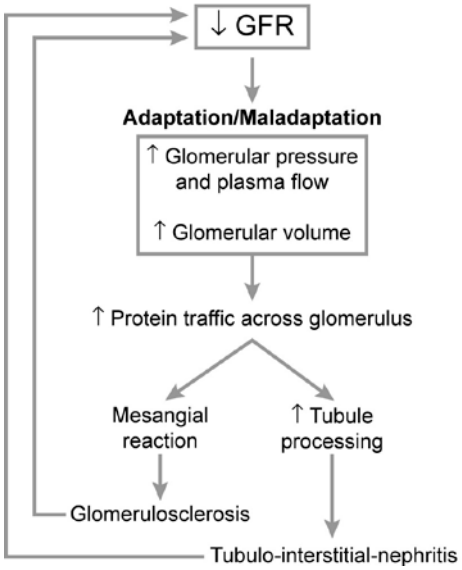


Table 1: Serum creatinine concentrations for assignment of IRIS stage of CKD in dogs and cats (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)

Stage	Serum creatinine concentration (mg/dl)	Serum creatinine concentration (µmol/L)	Comments
1	< 1.4 (dog) < 1.6 (cat)	< 125 (dog) < 140 (cat)	Nonazotemic. Often discovered fortuitously during routine examination. May have evidence of decreased urinary concentrating ability or proteinuria. Usually no obvious clinical signs. May be polyuric.
2	1.4-2.0 (dog) 1.6-2.8 (cat)	125-179 (dog) 140-249 (cat)	Mildly azotemic. Decreased urinary concentrating capacity. May have proteinuria. Clinical signs minimal. May have polyuria and polydipsia.
3	2.1-5.0 (dog) 2.9-5.0 (cat)	180-439 (dog) 250-439 (cat)	Moderate azotemia. Decreased urinary concentrating capacity. May have proteinuria. Many systemic clinical signs may be present.
4	> 5.0 (dog) > 5.0 (cat)	> 440 (dog) > 440 (cat)	Severe azotemia. Decreased urinary concentrating capacity, proteinuria. Systemic clinical signs present and may be severe.

Table 2: Proteinuria (assessed by urine protein/creatinine ratio) for assignment of IRIS sub-stage of CKD in dogs and cats (From Canine and Feline Nephrology and Urology, 2nd edition – Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)

Urine protein/creatinine ratio	Classification
< 0.2 (dogs) < 0.2 (cats)	Nonproteinuric
0.2-0.5 (dogs) 0.2-0.4 (cats)	Borderline proteinuric
> 0.5 (dogs) > 0.4 (cats)	Proteinuric

Table-3: Systemic blood pressure for assignment of IRIS sub-stage of CKD in dogs and cats (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)

Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	Risk level
< 150	< 95	Minimal
150-159	95-99	Low
160-179	100-119	Moderate
≥ 180	≥ 120	High

Table 4. Treatment Considerations for CKD (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)

Total Body Phosphate Burden Control: Dietary Modification Intestinal Phosphate Binders
H2-Receptor Blockers or Proton Pump Inhibitors
Systemic Hypertension Control: Calcium Channel Blocker (Amlodopine) ACE-Inhibitor (Enalapril/Benazepril)
Hypokalemia/Kaliopenia Control Potassium Supplementation
Metabolic Acidosis Control Alkali Supplementation
Control of UTI
Reduction of Intraglomerular Hypertension ACE-Inhibitor
Reduction of Renal Proteinuria ACE-Inhibitor Spironolactone Control of Systemic Hypertension
Renoprotection – anti adverse remodeling: ACE-Inhibitor, Spironolactone
Further control of renal secondary hyperparathyroidism Activated Vitamin D Metabolites (calcitriol) Calcimimetics (cinacalcet)
Adsorbents of Uremia Toxins Kremezin – AST-120
Recombinant Erythropoietin
Enteric Dialysis® - Azodyl
Ant-Fibrotics

Phosphorus Retention and Renal Secondary Hyperparathyroidism

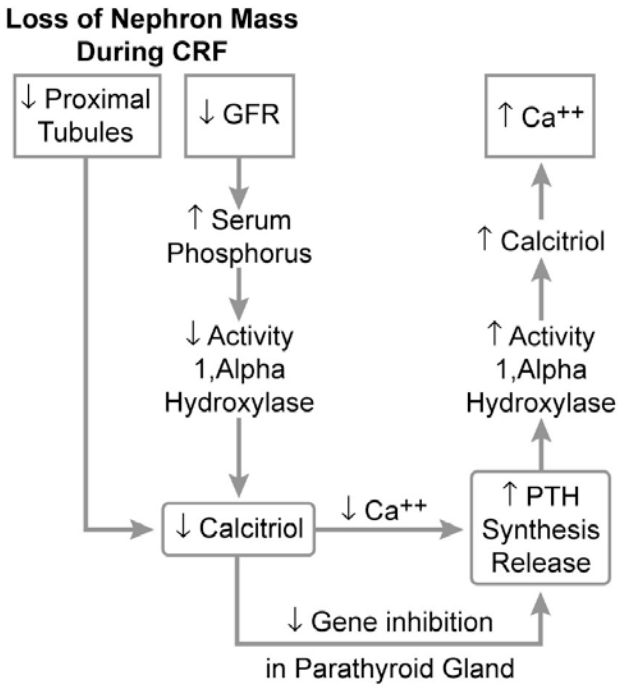
Renal secondary hyperparathyroidism (2-HPTH) occurs when parathyroid hormone (PTH) synthesis and secretion become excessive during kidney disease and is the result of increased secretion of PTH by each chief cell as well as the increased number of chief cells due to parathyroid gland hyperplasia. Ionized calcium is either normal or low. Parathyroid gland hyperplasia is the primary cause of increased PTH secretion. Underlying calcitriol deficit is the most important factor leading to uncontrolled synthesis and secretion of PTH.

Renal 2-HPTH is commonly documented in dogs and cats with chronic kidney disease (CKD). Overall frequency of renal 2-HPTH was 76% in a recent study of dogs with CKD, encountered in 36% of IRIS stage 1, 50% in stage 2, 96% in stage 3 and 100% in IRIS stage 4 (Cortadellas et al., 2010). An increasing frequency of renal 2-HPTH was similarly found in cats with CKD (Barber and Elliott, 1998), affecting 84% of cats overall (47% of cats with stable azotemia without clinical signs to 100% of cats with decompensated CKD). Hyperphosphatemia is commonly found in CKD patients with 2-HPTH but 2-HPTH can be encountered in both dogs and cats with serum phosphorus within the normal reference range. Hyperphosphatemia was noted in 18% and 2-HPTH in 36 % of dogs in IRIS stage 1 dogs (Cortadellas et al., 2010). The concept that renal 2-HPTH can precede development of hyperphosphatemia in CKD has not been well appreciated in veterinary medicine. Serum phosphorus in the upper normal reference range has recently been associated with increased PTH in CKD dogs (Cortadellas et al., 2010)

confirming an earlier report of this association (Nagode et al., 1992). Correction of hyperphosphatemia using diet alone or in combination with intestinal phosphate binders normalized PTH in many early uremic cats (Barber and Elliott, 1998) but was successful in only a portion of uremic dogs many of which required calcitriol to normalize PTH (Nagode et al., 1996). Higher concentrations of serum phosphorus predicted an increase in serum creatinine > 25% above baseline over 12 months in 47% of CKD cats (Chakrabarti 2012). Serum phosphorus was the only clinicopathologic variable predictive of survival in one study of CKD cats. There was an increase in risk of death of nearly 12% for each mg/dl increase in phosphorus in the same study (Boyd LM JVIM 2008). Higher phosphorus concentration was associated with a higher risk of death within1 month in another study (Kuwahara Y JSAP 2006). Even when serum phosphorus was within the reference range, cats with CKD of one study that had phosphorus concentration > 4.7 to ≤ 6.8 mg/dl serum phosphorus had a higher risk of death compared to CKD cats in which circulating phosphorus concentration was ≤ 4.7 mg/dl (King JVIM 2007).

Concentrations of the phosphatonin FGF-23 were higher in cats with IRIS stage 2 when serum phosphorus was > 4.5 mg/dl compared to < 4.5 mg/dl. Cats of the same study with IRIS stage 3 CKD had much higher concentrations of FGF-23 when the serum phosphorus was > 5.0 mg/dl compared to < 5.0 mg/dl (Geddes JVIM 2013). The feeding of a renal diet to cats with IRIS Stage 2, 3, or 4 CKD that were hyperphosphatemic (> 4.5, > 5.0 , 6.0 mg/dl by IRIS stage) resulted in lower serum phosphorus, PTH, and FGF-23. CKD cats classified as normophosphatemic for their IRIS stage that were fed the same renal diet decreased their circulating concentration of FGF 23 despite no change in PTH or serum phosphorus (Geddes JVIM 2013b).

Figure 2- Development of Renal Secondary Hyperparathyroidism - calcitriol trade-off hypothesis (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)



Serum phosphorous concentration depends on the dietary phosphorous intake, the degree of gastrointestinal absorption across the duodenum and jejunum, translocation into intracellular sites, and excretion of phosphorous into the urine. The kidney plays a crucial role in regulating serum phosphorous concentrations. Serum phosphate levels are maintained within a narrow

range in health. Young growing animals often have higher levels of serum phosphorous than adults. The normal serum phosphorous range of many laboratories includes that of adults and growing animals which may make it difficult to detect early rises in serum phosphorous above normal. The typical reference range for phosphorous for mature dogs and cats is 2.5-6 mg/dL (0.81 to 1.94 mmol/L). Phosphate retention and hyperphosphatemia are primarily due to impaired renal phosphate excretion. In the early stages of chronic kidney disease increased levels of parathyroid hormone (PTH) keep serum phosphorous within the reference range by increasing phosphate excretion into urine. This allows for normalization of serum phosphorous at the expense of hyperparathyroidism.

Pathophysiological Consequences of Hyperphosphatemia

Deleterious effects of phosphate accumulation are most often recognized to be a direct consequence of phosphate from calcium phosphate precipitates into the tissues (increased calcium x phosphate product). Indirect effects that increase PTH and decrease ionized calcium may also be important. It has been known since the early 1980s that dietary phosphorous restriction provided dramatic benefits to the histologic renal architecture of cats with the remnant model of chronic renal failure. Serum phosphorous and PTH concentrations were considerably increased in cats fed the normal phosphate diet compared to those fed the restricted phosphate diet(Ross AJVR 1982) . Hyperphosphatemia with renal secondary hyperparathyroidism is common in cats with IRIS stage 3 and 4 chronic kidney disease and can be documented in some with IRIS stage 2 ionized calcium and serum phosphorous (Barber JSAP 1998). Interestingly, thirteen percent of cats in this study had increased PTH despite normal concentrations of both.

Treatment of Hyperphosphatemia

Conventional wisdom and evidence dictates the importance of correcting hyperphosphatemia of CKD. Early phosphorus restriction in CRF has been shown in dogs and cats to blunt or reverse renal secondary hyperparathyroidism. In a study of cats with naturally-occurring CRF, renal secondary hyperparathyroidism was successfully managed by dietary restriction of phosphorus; one-third of the cats also required treatment with phosphorus binders. Survival time in CKD cats eating the renal diet was over twice that of those eating maintenance diets – this effect was attributed to phosphorus control and control of PTH(Barber 1999; Elliott 2000). Renal diets may provide sufficient dietary phosphate restriction during early stages of CKD but often dietary phosphate binders are needed. Diet and binders should be prescribed to effect of serum phosphorus and PTH levels. Normal serum phosphorus concentrations are desirable but do not guarantee that PTH is normal. Restoration of normophosphatemia is an initial and main goal but phosphorous restriction may be beneficial in reversing existing renal secondary hyperparathyroidism in patients that are not hyperphosphatemic at the time of initial evaluation. Secondary hyperparathyroidism can exist despite normal ionized calcium and serum phosphorous status.

Goals of Dietary Phosphorous Control

An initial goal is to attempt to return high serum phosphorus concentrations to within the normal range by the feeding of a phosphate-restricted renal diet. Intestinal phosphate binders should be added if serum phosphate remains increased after one month of consuming the renal diet or if the switch to the renal diet is not accepted by the animal. A serum phosphate concentration in the mid-normal range (< 4.5 mg/dL ; < 1.45 mmol/L) is the recommended target. It is important to serially measure serum phosphate concentrations in patients with CKD, usually monthly until the target concentration has been achieved and then every 2 to 4 months thereafter if stable. Serum phosphorus concentration may increase in CKD cats that increase their food intake following other supportive CKD treatments. It is more difficult to achieve mid-reference range target phosphate concentrations in those with more advanced levels of azotemia in CKD. Less stringent target guidelines for serum phosphorus control (≤ 6.0 mg/dl Stage 4, ≤ 5.0 mg/dl stage 3, ≤ 4.5 mg/dl stage 2) based on IRIS stage of CKD have been suggested (Geddes JVECC 2013).

A second goal is to restore PTH to normal levels or to prevent it from increasing even if serum phosphorus is in the normal range. Further phosphorus restriction with diet and phosphorus binders can be titrated to the effect of lowering PTH if possible. In some instances, PTH cannot be controlled despite dietary intervention and use of intestinal phosphate binders. Other treatments with calcitriol and calcimimetics may be indicated in these cases. In addition to serial serum phosphate measurements, serial measurement of PTH and ionized calcium from the same time may be considered a gold standard for assessment of sufficient relief of body phosphorus burden and PTH control.

Adverse effects of phosphate restriction potentially can occur. Although hypophosphatemia is one such possible consequence, it is difficult for this to develop in those with initially high concentrations of serum phosphorus and reduced GFR. Hypercalcemia can be encountered when calcium salts are used for intestinal phosphate binding. Constipation and GI effects can occur following use of some of the intestinal phosphate binders. Absorption of chemicals from the intestinal phosphate binder may occur with resulting accumulation in the tissues in some instances.

Intestinal Phosphate Binders

Phosphorus-binding agents are given orally to trap phosphorus in the gut and increase insoluble phosphate salt excretion into feces. Phosphate binders work because the cation in the binder combines with dietary phosphate, producing insoluble, non-absorbable, phosphate compounds. Intestinal phosphate binders work best when given with meals or within 2 hours of feeding to maximize their binding of dietary phosphorus. Due to varying effects of intestinal phosphate binders to limit absorption of drugs, it is advisable to give other drugs 1 hour before or 3 hours after any intestinal phosphate binder is given. The dose of any phosphate binder should be based on the meal size (phosphorus intake) and the prevailing serum phosphorus level for each CKD patient; the dose is titrated to effect. Commonly employed oral phosphorus binders include aluminum hydroxide, calcium carbonate, calcium acetate, chitosan, and lanthanum carbonate but no drug is yet licensed for phosphate binding in veterinary medicine.

Figure. Effect of orally administered phosphate binder to bind phosphate within the intestinal lumen preventing its absorption across the intestinal tract. Some binders undergo absorption across the intestine and others do not. (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)

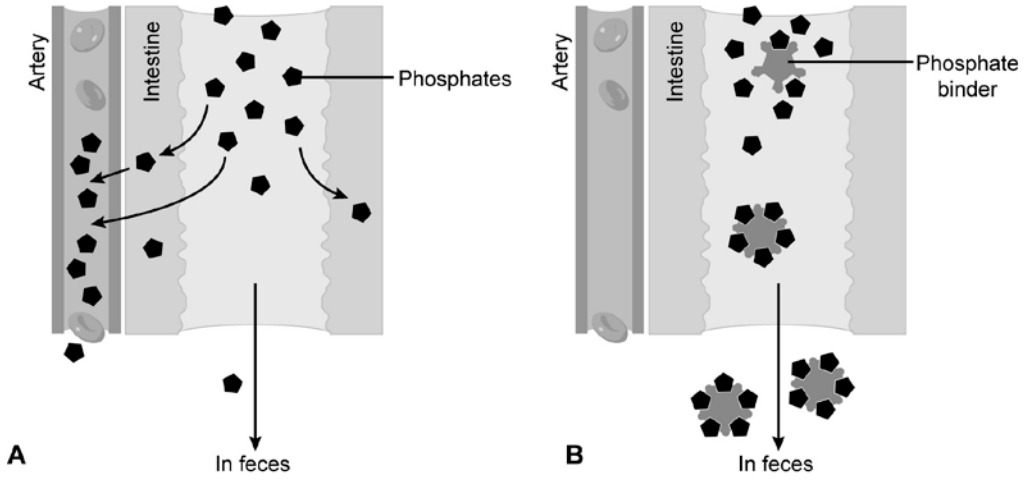
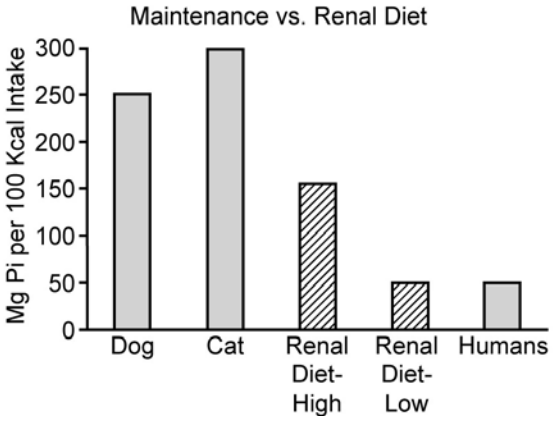


Figure. Dietary phosphorus intake between dogs and cats eating commercial or renal therapeutic foods compared to average western diet of humans. Note that dogs and cats

consume 5 and 6 times as much phosphorus as the average human which makes it difficult to achieve adequate dietary phosphorus restricion (Developed by Nutritional Support Services The Ohio State University CVM, Dr. Tony Buffington 2006) (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)



Aluminum Salts

Aluminum salts are the most widely used phosphate binders in cats. Aluminum based phosphate binding agents (aluminum hydroxide, aluminum carbonate) are highly effective in lowering serum phosphate levels, forming insoluble and nonabsorbable aluminum phosphate precipitates in the intestinal lumen. In humans with CKD, significant aluminum may be retained in the body, especially the bone, leading to osteomalacia, adynamic bone disease, microcytic anemia, and encephalopathy. **THERE IS NO KNOWN SAFE DOSE OF ALUMINUM SALTS FOR HUMANS WITH CKD**. Detrimental effects of aluminum based phosphate binders as described in humans seen in humans have not been systematically evaluated in small animal patients and are rarely clinically appreciated. As cats with CKD can live for years on treatment, concerns for aluminum accumulation deserve more study as to long-term safety.

Despite concerns for toxicity and stringent use guidelines in humans, aluminum salts remain the most commonly prescribed intestinal phosphate binders in veterinary medicine as they are very effective phosphate binders and are inexpensive. Aluminum hydroxide or aluminum carbonate is used at an initial dosage of 30 mg/kg q8h or 45 mg/kg q12h given in food. Constipation is the most common side effect encountered during treatment with aluminum phosphate binders. Lactulose treatment may help to alleviate constipation but may also contribute to dehydration due to extra fluid loss in the stool.

Calcium Salts

Calcium-based binders are not as effective as aluminum salts, having a lower affinity for phosphorous, thus effective binding of dietary phosphorous requires large doses of calcium, often enough to induce hypercalcemia in humans. The most commonly used calcium based phosphate binders are calcium carbonate and calcium acetate. Calcium carbonate can be used at a starting dosage of 30-mg/kg q8h or 45-mg/kg q12h given with food. Calcium carbonate binds phosphorous best in an acidic environment (pH approx. 5) and binding capacity is reduced in the neutral pH range. Many CKD patients receive inhibitors of gastric acid secretion potentially reducing calcium carbonates ability to bind phosphorous. Calcium acetate can bind phosphate over a wide range of pH, has about twice the phosphate binding capacity of calcium carbonate and as such can be used at lower dosage, and has been shown to cause less hypercalcemia than calcium carbonate when activated vitamin D metabolites are not also being used. Doses of 20, 30, or 40 mg/kg given with each meal approximate doses of calcium acetate recommended for humans with dialysis dependent CKD. Animals should be monitored for development of hypercalcemia whenever calcium-containing phosphorus binders are used.

Sevelamer

Sevelamer hydrochloride (Renagel®, Genzyme Corporation) and the very recently FDA approved Sevelamer carbonate (Renvela®, Genzyme Corporation) organic polymers that do not contain aluminum or calcium and are not absorbed from the gastrointestinal tract (excreted entirely in feces). These compounds are exchange resins that bind dietary phosphorous and release the counterion chloride (sevelamer hydrochloride) or carbonate (sevelamer carbonate). Many human clinical studies have demonstrated the ability of sevelamer hydrochloride to lower serum phosphorous, and parathyroid hormone levels, and control Ca x P product in dialysis patients compared with calcium containing phosphate binders. Their effects on dogs and cats with clinical CRF, however, have not been reported.

Chitosan

Epakitin® (Vetoquinol Inc.) is marketed as a complementary feed on the veterinary market. It contains the adsorbent chitosan (8% crab and shrimp shell extract), 10% calcium carbonate, and 82% lactose and is designed to reduce GI phosphorus absorption and to lower urea nitrogen due to effects of reduced protein digestibility. One short-term study of a small number of normal and CKD cats showed a reduction in protein and phosphorus digestibility along with the decreases in BUN and serum phosphorus in cats eating a normal maintenance diet supplemented with the chitosan and calcium carbonate product (Wagner 2004). Another longer-term study showed the ability of a chitosan and calcium carbonate intestinal phosphate binder to significantly decrease serum phosphorous and plasma parathyroid hormone levels when added to a maintenance diet for cats with CKD created by 11/12 nephrectomy (Brown 2008) The results of these two studies suggest that this supplement could be an alternative to prescription of renal veterinary diets thereby allowing some cats to continue on their regular diets while still reducing the risks for progression of CKD associated with total body phosphorus burden. We have, however, observed the development of hypercalcemia in a few CKD cats with the use of this product probably as a consequence of the calcium carbonate.

Lanthanum Salts

Lanthanum carbonate (Fosrenol®, Shire Pharmaceuticals) is another newly developed non-aluminum and non-calcium containing intestinal phosphate binder and is indicated for use in human patients with end-stage renal failure to reduce serum phosphorous. Very little lanthanum is absorbed across GI tract and lanthanum accumulates to a far less degree following absorption compared to aluminum since lanthanum undergoes extensive hepatic excretion whereas aluminum is excreted mostly by the kidneys. Lanthanum appears to have minimal toxicity in humans. Toxicity studies performed in dogs show that lanthanum increases in many tissues (especially GI tract, bone and liver) during treatment. Intact tablets should not be swallowed. Tablets may be crushed into food. Initial daily doses of Fosrenol® that may be extrapolated from humans for use in cats range from 12.5 mg/kg/day to 25 mg/kg/day (based upon an average human weight of 60 kgs). However doses of 35 mg/kg/day to 50 mg/kg/day are often needed since commercial cat foods contain more phosphate proportionally than what an average human consumes daily. A recent abstract in a small number of CKD cats administered lanthanum carbonate in food at 95 mg/kg/day to achieve very modest serum phosphate control (Pressler ACVIM 2013).

Several reports of the use of lanthanum carbonate in cats have recently been published. Studies of normal European Shorthair cats that were given lanthanum carbonate in maintenance food or a veterinary renal diet showed similar results when compared to findings in cats eating the same diets without supplementation. Phosphorus excretion into feces increased while phosphorus excretion into urine decreased in a dose-related manner; serum phosphorus did not differ between dose groups. Food intake did not change during treatment with lanthanum carbonate.In 2007, based upon reports of efficacy and safety in cats, the European Food Safety Authority (EFSA) approved lanthanum carbonate octahydrate (Lantharenol® Bayer HealthCare AG) as a feed additive for adult cats in order to decrease intestinal phosphate absorption. The approved dose was 1500 to 7500 mg per kg of complete feed. In a two week

study of cats with sub-total nephrectomy and mild azotemia, Lantharenol® added to wet cat food decreased dietary phosphorus availability in a dose dependent manner. Renalzin® (Bayer HealthCare AG) is the proprietary name for the delivery system of Lantharenol® was launched in 2008. Renalzin® comes as a pump system that delivers lanthanum carbonate along with kaolin and vitamin E at appropriate doses to food for cats. This system is widely available in the UK and Europe, but not in the USA. The proprietary formulation of human lanthanum carbonate is soon to become available as a generic product.

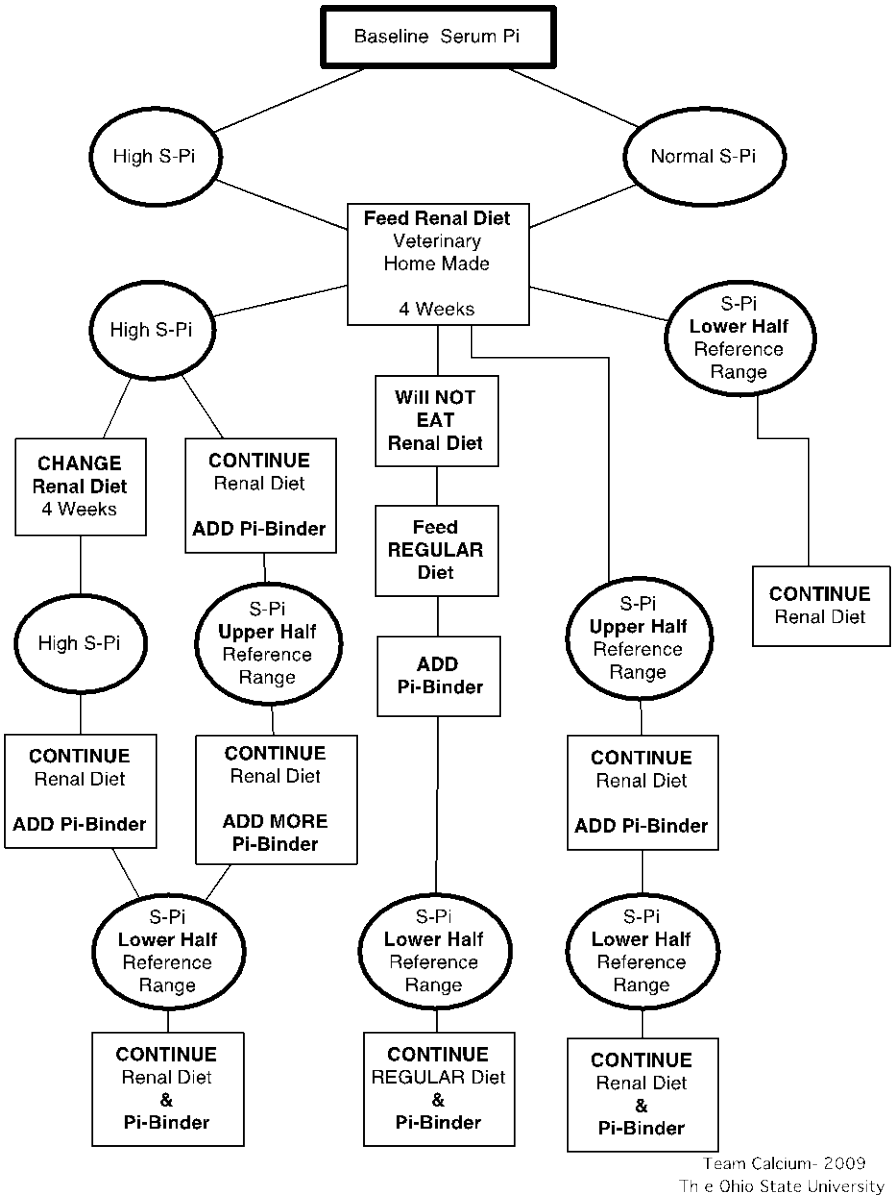
TABLE 4. Treatment with intestinal phosphate binders: dose rates

Intestinal Phosphate Binder	**Dose**
Aluminum hydroxide (Alternagel® 600 mg/5ml)	30 mg/kg PO q 8 hr; 45 mg/kg PO q 12 hr (give with meal)
Calcium carbonate (Tums® regular strength 500 mg/tablet)	30 mg/kg PO q 8 hr; 45 mg/kg PO q 12 hr (give with meal)
Calcium acetate	30 mg/kg PO q 8 hr; 45 mg/kg PO q 12 hr (give with meal)
Sevelamer hydrochloride (Renagel® 400 mg tablets)	33-54 mg/kg PO q 8 hr; 50-80 mg/kg PO q12 hr (give with meal)
Epakitin®	1 gm/10lbs twice daily with food
Lanthanum (Fosrenol® 500 mg chewable tablets)	12.5-25 mg/kg/day PO; 6.25-12.5 mg/kg PO q12 hr starting dose (give with meal, do not force tablet whole)
Lanthanum (Renalzin®) Not available in US	2 mls applied to cats food once or twice daily (200 mg/ml)

Table 5. Target Serum-Pi Concentration in CKD by IRIS Stage

IRIS Stage	Target Phosphate
Stage 1	Any Pi- Restriction ?
Stage 2	0.81 to 1.45 mmol/l 2.5 to 4.5 mg/dl
Stage 3	0.81 to 1.61 mmol/l 2.5 to 5.0 mg/dl
Stage 4	0.81 to 1.94 mmol/l 2.5 to 6.0 mg/dl

Figure. Algorithm for Feeding and Pi-Binders to Gain Control of Phosphorus



ACE-Inhibition

Angiotensin-II plays a pathophysiologic role in proteinuria and the progression of renal disease. Angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril, benazepril) may have protective effects in patients with chronic renal disease due to their ability to block adverse effects of angiotensin II. ACE-inhibition reduces glomerular capillary hydraulic pressure by decreasing postglomerular arteriolar resistance. Proteinuria is decreased secondary to decreased glomerular hydraulic forces and development of glomerulosclerosis is limited when protein trafficking across the glomerulus is decreased. Remnant nephrons in animals with CRF have glomerular hypertension that can benefit from reductions in transglomerular forces. An additional potential benefit from ACE-inhibition is improved control of systemic blood pressure. This beneficial effect must be balanced against their potential to worsen azotemia since glomerular pressure provides the driving force for GFR in the “super-nephron”.

Figure. - ACE-Inhibition Provides Glomerular Afterload Reduction. High pressures of the supernephron (left panel) are created by dilatation of the afferent arteriole. In the right panel, intraglomerular pressure has been restored to normal during treatment with ACE-inhibition. ACE-inhibitors reduce the effect of angiotensin-II to cause intrarenal vasoconstriction but the effect is greater on the efferent arteriole which lowers resistance to outflow from the glomerular

beds. (From Canine and Feline Nephrology and Urology, 2nd edition –Chew DJ, DiBartola SP, Schenck PA, Elsevier Saunders, St. Louis Missouri, 2011)

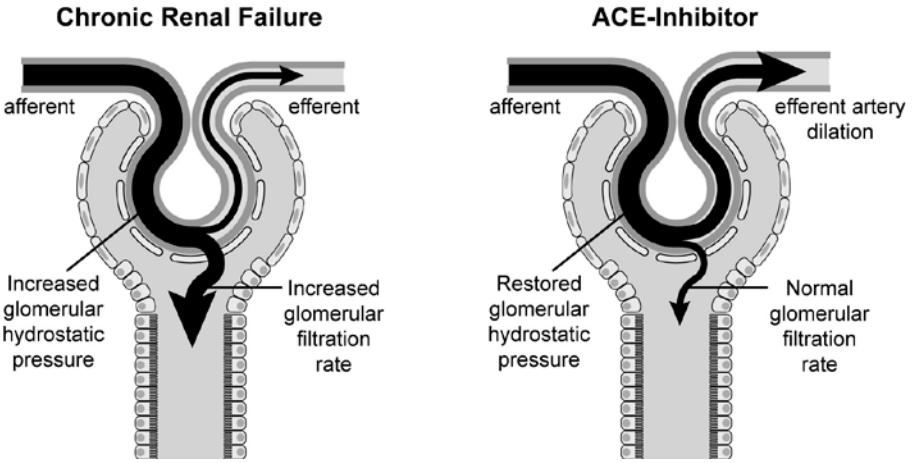
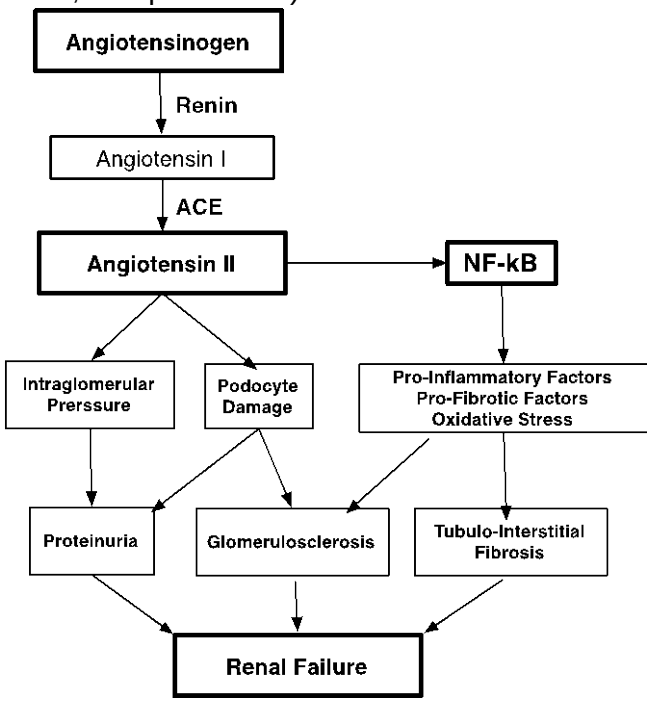


Figure. Role for Activated RAAS and Angiotensin II in Progression of CKD
(Modified from Nagode 2012, with permission)



Benazepril is licensed for treatment of CRF in cats in many regions of the world (Fortekor®), but not in the USA. Average survival of benazepril treated cats of one study was 501 days vs. 391 days for placebo treated cats but this effect did achieve statistical significance. Benazepril consistently reduces proteinuria in various stages of chronic kidney disease in cats in this and other studies even when the base line level of proteinuria is seemingly trivial. In another study of 61 cats with CKD, benazepril treatment for 180 days appeared to stabilize those in IRIS stage 2 or 3 with less transition to stage 4 compared to treatment with placebo though this effect did not achieve statistical significance (low number of cats and short duration of study) (Mizutani 2006).

In a 6 month study of dogs with modest azotemia and moderate to severe proteinuria, enalapril treatment (0.5 mg/kg PO q12-24h) reduced proteinuria (as assessed by urine protein/creatinine ratio), decreased blood pressure, and slowed progression of renal disease in dogs with biopsy-proven glomerulonephritis compared to treatment with placebo (Grauer 2000). Results from this study provided enough clinical evidence to make the use of ACE-inhibition standard of care for protein-losing nephropathy in dogs caused by glomerulonephritis. In a placebo controlled study of dogs with CKD not selected for proteinuria, benazepril treatments for 6 months resulted in higher GFR and lower magnitude of proteinuria (Tenhundfeld 2009).

General guidelines for use of ACE-inhibitors in CKD include rechecking renal function in 1 week following start of ACE-inhibition to make sure that GFR has not been reduced too much. It is common to see a small increase in serum creatinine at this time (20 to 30% increase over baseline). If creatinine has increased too much, reduce the dose of the ACE-inhibitor. Some dogs and cats are ACE-inhibitor intolerant in that their renal function will be much worse during initial treatments so that treatment must be discontinued. We also recommend to recheck the UPC 1 and 3 months after the start of ACE-inhibition. The goal is to achieve a 50% decrease in UPC in those in which it was initially increased. There does not appear to be much difference between benazepril or enalapril for clinical use in the dog or cat with CKD. Benazeprilat is cleared by both the kidney and liver compared to enalaprilat being cleared only by the kidney.

The angiotensin receptor blocker (ARB) telmisartin (Semintra® Boehringer Ingelheim) was approved by the European Commission in 2013 for use in the European Unnion as a drug for use in cats with CKD. Semintra was found to be as effective as benazepril in reducing proteinuria in cats with CKD and was well tolerated. A US Patent application was filed in July 2013 by Boehringer Ingelheim. It is not clear when or if an ARB should be chosen to reduce RAAS activity instead of an ACE-Inhibitor for treatment of CKD in veterinary patients to reduce proteinuria, systemic blood pressure, or intrarenal inflammation.

Hormone replacement: Calcitriol

Calcitriol treatments help to decrease PTH or prevent its increase in those with renal secondary hyperparathyroidism. This occurs mostly by genomic effects to block PTH synthesis in addition to a mild calcemic effect, and antiproliferative effect that prevents parathyroid gland hyperplasia. During treatment of CRF patients with calcitriol, simultaneous monitoring of serum ionized calcium, serum phosphorus and PTH concentrations is the ideal way to document successful and safe control of renal secondary hyperparathyroidism.

Calcitriol should not be administered until hyperphosphatemia has been controlled. If the Ca X P solubility product exceeds 60-70, calcitriol should be avoided because of the risk of soft-tissue mineralization. The beneficial effects of calcitriol are also lessened within the parathyroid gland when ionized calcium remains low. Phosphorus restriction relieves phosphate-mediated inhibition of the renal 1α-hydroxylase system, resulting in enhanced endogenous synthesis of calcitriol and subsequent inhibition of PTH synthesis. The effectiveness of calcitriol in control of hyperparathyroidism has been noted to increase in patients in whom serum phosphate was lowered.

Supplementation with calcitriol in CRF was initially designed as a daily therapy for life in veterinary patients as long as serum phosphorus remains within the normal range and serum calcium does not become increased. An extremely low dosage of calcitriol (2.5 to 3.5 ng/kg/day) has been used in dogs and cats with stable CRF to reverse renal secondary hyperparathyroidism. Serum PTH concentrations decrease during calcitriol administration over a period of weeks to months. Calcitriol is manufactured in capsule (250 or 500 ng) and liquid (1000 ng/mL) forms for humans. Reformulation by a compounding pharmacy is often necessary to provide accurate dosing. In a recent study, dogs with CRF treated with calcitriol survived for a

median of 365 days compared to 250 days in dogs treated with placebo. Similar studies were done in cats by the same investigators who concluded that there is no advantage to calcitriol treatments in cats with CRF but the study followed cats for just one year. In order to show a difference in treatment effect if one exists, studies in cats with CRF must be conducted for at least 2 and possibly 3 years due to the inherently slow nature of the progression of chronic renal disease in this species.

Intermittent rather than daily dosing treatment protocols are likely to become the standard of care since less hypercalcemia occurs during this protocol. The equivalent dose given at 2.5 ng/kg daily is given instead every 3.5 days. This works out to a dose of 9 ng/kg (8.75 ng/kg rounded to 9 ng/kd). It is important to give the dose every 3.5 days, rather than on day 1 & 4. For example if a dose is given Tuesday PM the next dose should be given Saturday AM. This is the longest time in between dosing that will still suppress the parathyroid gland. This method of dosing is especially attractive for cat owners since medication will only be given twice weekly.

Hormone replacement: Cholecalciferol

It is common in some human nephrology practices to treat CKD patients with BOTH activated vitamin D metabolites like calcitriol and parent vitamin D (cholecalciferol). Survival of human CKD patients correlates better with 25(OH)-vitamin D concentrations than to that of calcitriol, likely due to vitamin D receptor activation in local cells that then generate intracellular 1,25 (OH)2vitamin D. Low circulating 25(OH)D is common in humans with CKD and this has also been observed in a small number of dogs with azotemic CKD (Galler Vet J 2011). Low 25(OH)-vitamin D could be due to decreased dietary intake, decreased intestinal absorption, or to increased loss in urine. 25(OH)-vitamin D and 1,25$(OH)_2$-vitamin D are reabsorbed along the proximal tubule following glomerular filtration – this process is mediated by megalin receptors that are upregulated by calcitriol-VDR interactions (de Brito Galvao JVECC 2013).

Figure. Megalin-mediated tubular recovery of vitamin D metabolites following glomerular filtration.

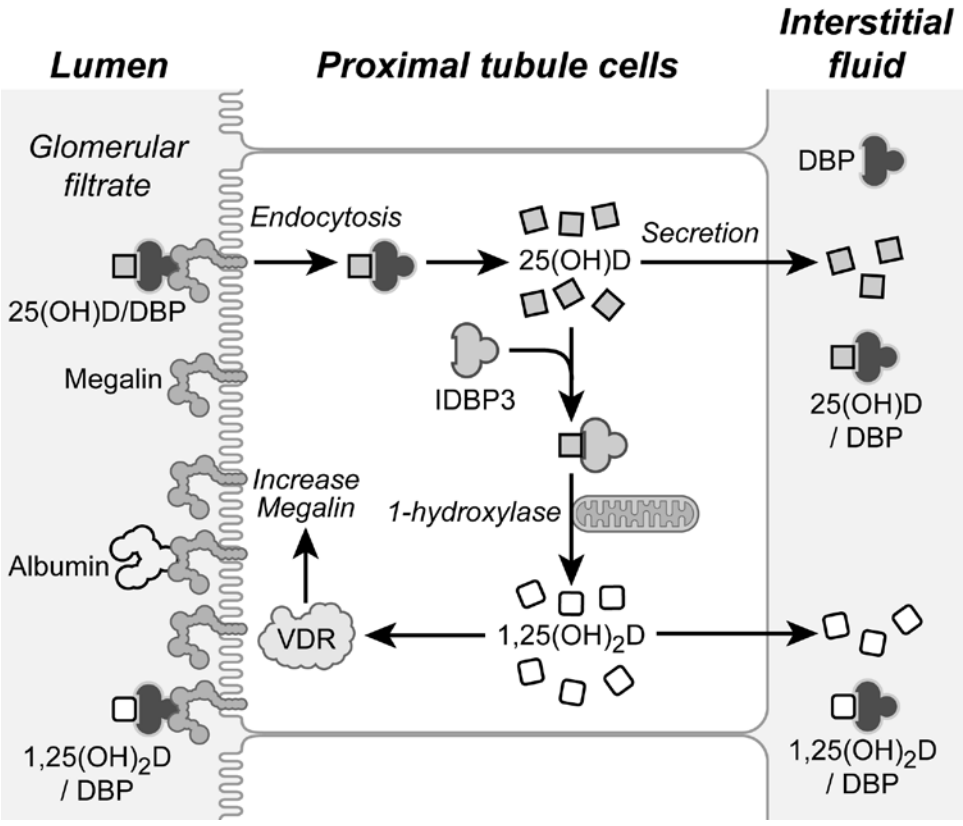


Figure. Damage to tubular cells causes both apoptosis and activation of NFkB, which in turn has numerous effects mediated through inflammatory and immunomodulatory cytokines acting on mononuclear cells of lymhocytic and macrophage lineages. NFkB also induces formation of TGF beta as a major driving cytokine of fibrogenesis, acting on myofibroblasts to produce extracellular matrix (ECM). The actions of calcitriol or other VDRA on the VDR have 4 main consequences illustrated. 1) Liganded VDR blocks transcription of the renin gene, often by over 90% thus slowing RAS activity 2) Liganded VDR complexes with NFk-B disallowing its transcription factor function including numerous cytokine regulations, TGFbeta being an important one decreasing fibrogenesis 3) Liganded VDR has direct effects to repress TGF-beta formation by genetic regulations and 4) Liganded VDR acts to decrease the epithelial-mesenchymal transition (EMT) thus decreasing formation of myofibroblasts from epithelial cells a process active in any renal injury.

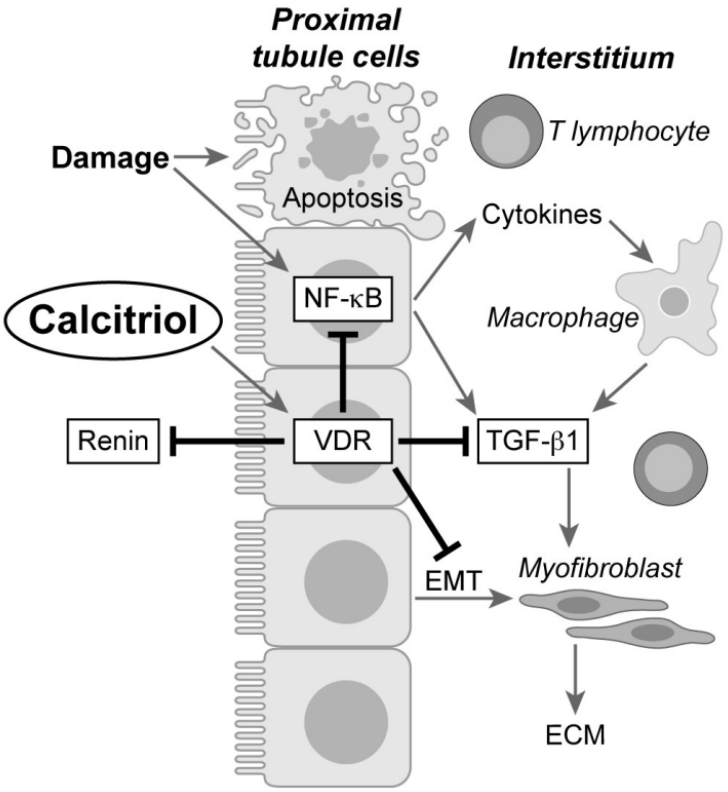


Figure 9: The NFkB and RAAS pathways are both shown to be inhibited by calcitriol. Via Ang-II as the end product of RAAS and NFkB in an uninhibited state, pro-inflammatory and profibrotic factors as well as marked generation of reactive oxygen species (ROS) are generated. Increased glomerular pressure and podocyte damage leading to proteinuria, glomerular sclerosis and tubulointerstital fibrosis combine to promote progression of renal disease. Calcltriol powerfully blocks this series of actions and via its blocking of NFkB and also by decreasing generation of angiotensinogen otherwise promoted by the NFkB.

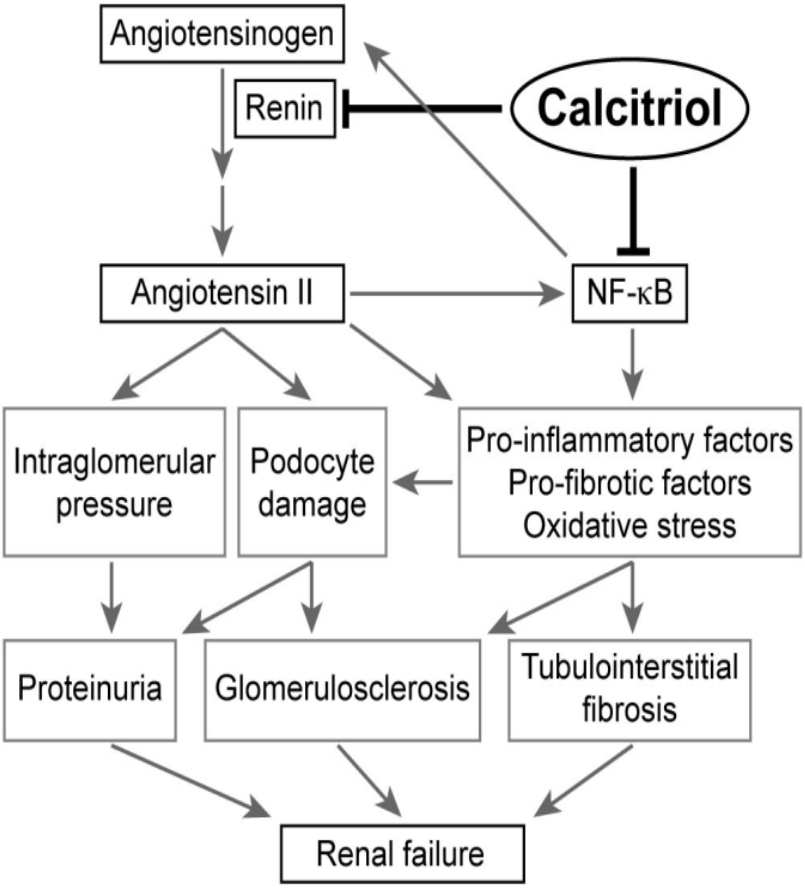
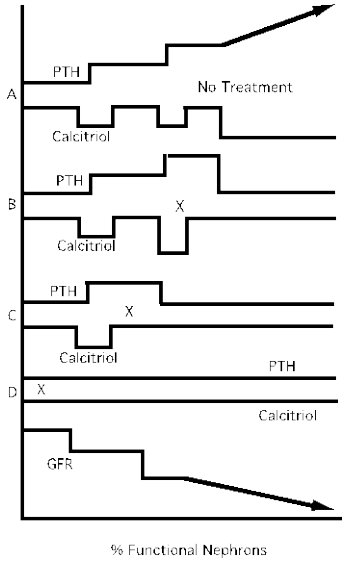


Figure 10. Different stages of CKD in which calcitriol treatment can be considered

A = No calcitriol supplementation. Calcitriol normalizes only at the expense of elevated PTH.
B = Calcitriol treatment is started at time "x" late enough in the renal disease when calcitriol is decreased and PTH is elevated with restoration of both to normal.
C = Calcitriol treatment is started at an early enough stage where calcitriol concentrations are still normal as a consequence of the increased PTH. Calcitriol supplementation remains beneficial to maintain normal calcitriol concentrations while decreasing PTH.
D = Calcitriol treatment is started very early in the course of progressive nephron loss, prior to either PTH increase or calcitriol decrease as a preventative step.



Hormone replacement: erythropoietin

Recombinant human erythropoietin (rhEPO) has been used to successfully correct nonregenerative anemia in dogs and cats with CKD. Treated animals demonstrate resolution of anemia, weight gain, improved appetite, improved haircoat, increased alertness, and increased activity. Therapy may be started in symptomatic animals with PCV values < 20% if clinical signs of anemia are present and problematic. The starting dosage is 100 U/kg administered subcutaneously 3 times per week. Iron deficiency is avoided by monitoring serum iron and total iron binding capacity and providing oral supplementation with ferrous sulfate (5 to 50 mg per cat per day). When the lower end of the target PCV range (30-40%) is reached, frequency of administration is reduced to twice a week. Depending upon the severity of anemia, it may require 3-4 weeks for the PCV to enter the target range. Although initially effective in correcting the anemia of CRF, use of rhEPO is associated with antibody formation in up to 50% of treated dogs and cats after 1 to 3 months of treatment. The resulting anemia can be more severe than that present before treatment because the induced antibodies can cross-react with the animal's native EPO. The canine EPO gene has been isolated, and recombinant canine EPO has been used to stimulate erythropoiesis in normal dogs and in those with naturally occurring CRF. It is not as effective when used in dogs that have developed red cell aplasia from previous treatment with rhEPO. Feline recombinant EPO also has been produced, but unfortunately unexplained red cell aplasia developed in some treated cats. Other adverse effects have been observed during administration of rhEPO to dogs and cats including vomiting, seizures, hypertension, uveitis, and hypersensitivity-like mucocutaneous reaction.

Due to the high rate of clinically significant side-effects with the use of epoetin, darbepoetin has been used as a replacement treatment for anemia of CKD on the premise that it would be less immunogenic due to its chemical structure. Darbepoetin was recently reported to be effective treatment for anemia in cats with CKD. Fourteen of 25 cats achieved a hematocrit of 25% or greater during treatment; nearly all of these cats were dosed at 1 ug/kg/week or higher. The most critical problem associated with epoetin, that of pure red cell aplasia, was less common with darbepoetin treatment (Calhoub 2011; Calhoub 2012). Vomiting, hypertension, seizures, and fever were noted as possible adverse effects associated with darbepoetin treatment. The overall costs for use of darbepoetin are similar to that for treatment with epoetin as darbepoetin is given less frequently.

Systemic Hypertension

Systemic hypertension occurs in 20 to 65% of cats with chronic renal failure when determined by methods that indirectly measure blood pressure. It is essential that cats be in a quiet environment before and during blood pressure measurements. Cats especially are prone to "white coat artifact" making it difficult to determine if a given cat is truly hypertensive. The correlation of unregulated arterial hypertension to the progression of CRF has not been established in cats, but there are some studies in dogs and humans that suggest a positive relationship. It is likely that high systemic blood pressure is transmitted to the glomerular vessels, which promotes further injury. Cats that have systemic hypertension from a variety of causes have been shown to survive longest when their blood pressure is well controlled. Dogs with azotemic CKD and systolic blood pressure > 170 mm Hg did not survive as long as dogs with lower blood pressure (Jacob JAVMA 2003).

Patients with systolic blood pressure readings > 170 mm Hg or those CKD patients with lower levels of blood pressure readings that also have fundic lesions consistent with hypertensive retinopathy (e.g., retinal edema, retinal hemorrhages, arterial tortuosity, retinal detachment) are candidates for anti-hypertensive therapy. Angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril, benazepril) may have protective effects in patients with CRF due to their ability to block adverse effects of angiotensin II. Beneficial effects include reduction in proteinuria, limitation of glomerular sclerosis and slowing of progression of renal failure as well as

improvement in systemic blood pressure. Enalapril as monotherpay has not been very effective for treatment of hypertensive cats or dogs. The calcium channel blocker, amlodipine has been used successfully in cats at a dosage 0.625 to 1.25 mg per cat given orally once per day. Follow-up evaluations should be scheduled for one week after beginning treatment with amlodipine. Adverse effects (including hypotension) are very uncommon with the use of amlodipine in cats (Elliott JSAP 2001; Jepson JVIM 2007; Brown JVIM 2007).

Control of Proteinuria

The detection of proteinuria provides a diagnostic index for dogs and cats with CKD. Based on the theories of glomerular hypertension that occur in "super nephrons" of the adapted kidney, protein gaining access to tubular fluid and the mesangium is also a creator of further renal injury. The magnitude of proteinuria is a function of the integrity of the glomerular barrier, GFR, tubular reabsorptive capacity, and effects from elevated systemic and intraglomerular blood pressure.

Cats with azotemic CKD increased their risk for death or euthanasia when the UPC was 0.2 to 0.4 compared to <0.2 and was further increased in cats with UPC of >0.4 (Syme JVIM 2006). The prognosis for survival is influenced by the UPC despite what has traditionally been thought to be low-level proteinuria. The effect of treatment that lower proteinuria on survival have not been specifically studied.

Since even low-level proteinuria is a risk factor for cats to not survive, it is prudent to consider treatments that lower the amount of proteinuria in those with CKD and CRF. Benazepril has been shown in two recent clinical studies to reduce the UPC in cats with CRF. Cats treated with benazepril in one study did not progress from IRIS stage 2 or 3 to the next stage as rapidly as those treated with placebo but over 6 months (Mitzutani JVIM 2006). Despite reduction in proteinuria in CKD cats with initial UPC > 1.0 that were treated with benazepril in another study, a significant increase in survival time was not found over placebo (King JVIM 2006).

Dogs with azotemic CKD and a UPC > 1.0 at initial diagnosis died more quickly than dogs with CKD and UPC < 1.0. No specific attempt was made to reduce the magnitude of the proteinuria though dogs with systemic hypertension were treated with enalapril (Jacob JAVMA 2005). Though it is possible to convert CKD dogs with UPC > 1.0 to those with < 1.0 UPC during treatment with ACE-I, survival studies following this type of targeted endpoint have not yet been reported.

"Pearls" - Chronic Kidney Disease (CKD)

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1. CKD is relentlessly progressive. Renal lesions continue to develop and renal functions are lost (GFR, urinary concentration, biosynthesis of EPO and calcitriol) during CKD. The rate of this progression can be highly variable between individuals and even in the same individual over time.

2. The endpoint of CKD is the development of extensive renal fibrosis, nephron dropout, glomerulosclerosis, and tubulointerstitial infiltration with lymphocytes and plasma cells.

3. There are many theories as to why CKD is relentless progressive even when the initial cause of the injury is removed. The most prevailing theory in modern nephrology argues that intraglomerular hypertension in remnant nephrons is "the" major cause.

4. IRIS (International Renal Interest Society) staging of CKD is important in order to detect CKD earlier and to identify risk factors for progression.

5. Staging is based on serum creatinine, proteinuria (urinary protein to creatinine ratio – normal, borderline, overtly increased), and systemic blood pressure (low, moderate, severe risk).

6. Though not well established yet, matching CKD treatments with IRIS stage is a goal.

7. The goal of all treatment for CKD is to slow the rate for the acquisition of renal lesions and to delay the rate of loss for renal functions.

8. Renal diets have been shown to increase survival in both dogs and cats with varying degrees of azotemic CKD.

9. No diet has EVER been shown to prevent the development of CKD.

10. The nutrient profile of the renal diet is altered for many nutrients. The overarching principle for renoprotection and increased life span is likely to be that of phosphate restriction in the diet.

11. Omega-3 dietary lipid supplementation at very high doses has been shown to be renoprotective in dogs with experimental CKD. Studies of Omega-3 supplementation at standard doses and in dogs with spontaneous CKD have not been reported.

12. The importance of dietary restriction of sodium is over-rated as dogs and cats do not have “salt-sensitive” hypertension. Decreased GFR can be one adverse effect of salt restriction.

13. Control of total body phosphate burden is an overarching goal in the management of CKD. Increasing phosphate retention during CKD occurs even as serum phosphorus values remain within the reference range.

14. A targeted serum phosphate of less than 4.5 mg/dl is recommended for CKD patients to ensure less phosphate burden in the bodies of these dogs and cats.

15. Diet as a single treatment is not often sufficient to achieve the recommended target for serum phosphorus. Consequently most CKD patients will benefit from treatment with intestinal phosphate binders.

16. Aluminum hydroxide or carbonate is commonly used around the world as a cheap and effective intestinal phosphate binder BUT aluminum is toxic as it is retained in the body during CKD (the kidneys are the major means to excrete aluminum that is absorbed).

17. Calcium class intestinal phosphate binders are not as good as aluminum compounds for phosphate binding and they also run the risk for the development of hypercalcemia. Calcium acetate is better than calcium carbonate for phosphate binding, and is associated with less hypercalcemia.

18. Lanthanum carbonate is a great intestinal phosphate binder. It is available as a veterinary labeled compound from Bayer under the name Renalzin ® and is mostly targeted for use in cats (expensive for larger animals).

19. All intestinal phosphate binders provide treatment of the food to prevent phosphorus in the diet from being absorbed into the circulation.

20. Progressive CKD results in either absolute or relative deficits in calcitriol synthesis. Progessive CKD can also result in lowered concentrations of circulating 25-hydroxyvitamin D (calcidiol).

21. Deficits of calcitriol and calcidiol contribute to inadequate control of the parathyroid glands as they undergo hyperplasia and secrete too much parathyroid hormone (PTH). Too much PTH is toxic to many tissues including the kidneys.

22. Inadequate vitamin D metabolites in the body also contribute to the progressive inflammatory response in the CKD kidney. This is sometimes called a “non-classic” effect of this vitamin.

23. Calcitriol supplementation to azotemic CKD dogs has been associated with increased survival. Studies in cats to date have not been conclusive as the studies only lasted for one year (2 to 4 year studies in cats are needed to show a difference).

24. The benefits of calcitriol supplementation include reduction in PTH synthesis and subsequently less PTH toxicity, but also of genomic effects within the kidney that reduces renal inflammation. Reduction of proteinuria and systemic blood pressure also occurs in some patients during supplementation.

25. Nearly all progressive CKD cases are associated in some way with increased RAAS activity. This is pivotal in enhancing renal inflammation, epithelial to mesenchymal cell transitioning, and for increasing systemic blood pressure.

26. ACE-inhibitors (enalapril, benazepril) reduce the production of Angioitensin-2 and aldosterone, both of which are pro-inflammatory and pro-proteinuria. ACE-I work in concert with calcitriol to reduce renal inflammation.

27. The anemia of CKD is mostly created by the reduced renal synthesis of erythyropoietin. Treatment with human recombinant erthryopoietin (EPO) fixes the anemia within a month in most dogs and cats BUT a substantial number of these CKD patients mount an anti-EPO antibody response that renders the treatment useless at best. It appears that the anti-EPO antibodies also cross react with native EPO meaning that the anemia can be worse after starting EPO treatments than before.

28. Darbepoetin is a less immunogenic stimulator of erythropoiesis so it can be used more safely in CKD patients. Its use has been specifically reported in cats and has replaced EPO treatments due to increased safety, similar efficacy, and costs.

29. Systemic hypertension (systolic > 165 mm Hg) that is mild is sometimes controlled with ACE-inhibitors as a single agent treatment in some dogs and cats. More serious systemic hypertension usually requires treatment with a calcium channel blocker (amlodipine) and sometimes the addition of a beta-blocker (atenolol).

30. ACE-inhibitors can provide renoprotection independent of change in systemic blood pressure – likely due to decreased intraglomerular blood pressure. Calcium channel blockers do not offer direct renoprotection, but do control systemic blood pressure much better than ACE-inhibitors.

31. “Balanced” antihypertensive protocols use BOTH ACE-inhibitors and calcium channel blockers to best control intraglomerular and systemic hypertension.

32. Nearly all of my CKD patients are on dietary phosphate restriction and intestinal phosphate binders to achieve targeted serum phosphorus of less than 4.5 mg/dl. Most of my CKD patients will also be on ACE-inhibition (whether or not they have proteinuria or systemic hypertension). A combination of ACE-I and calcium channel blocker (amlodipine) is used to achieve a systolic blood pressure of less than 150 mmHg in many CKD patients. I advocate calcitriol treatment for all azotemic CKD patients if their serum phosphorus can be maintained at less than 6.0 mg/dl. Cutting edge information suggests that some CKD dogs can benefit from parent vitamin D (chole or ergocalciferol) supplementation.

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