Chronic Kidney Disease (CKD) in Dogs & Cats: An update 2016
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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. There is evidence to support that by the time azotemic CKD is diagnosed, there is already substantial renal damage present (McLeod et al. 2015). Tubulointerstitial inflammation can be identified in cats that are considerably younger than the typical CKD demographic (Lawler et al. 2006), raising the theory that the changes identified are part of a natural aging process in the cat. Recent work has supported telomere shortening in proximal and distal tubular epithelial cells from cats with CKD, when compared with both healthy geriatric and young cats (Quimby et al. 2013). Telomeres represent the protective caps covering the end of chromosomes providing genome stability and with age, a number of factors including oxidative stress, and deletions can contribute to telomere shortening and loss, which could ultimately result in DNA damage, ultimately cell death.

The earlier the diagnosis of CKD, the better as we know inflammation and damage is underway long before azotemia is apparent. Please consider:

1. Obtaining baseline renal values early i.e. as young as 2 years of age and then watching the trend in serum creatinine over time—don’t wait for it to become abnormal before intervening
2. Monitoring weight, body condition score (BCS) and muscle condition score (MCS) on a regular basis. Freeman et al (2015) have shown a median loss of 8.9% of body weight in the 12 months before diagnosis of CKD in cats, but weight loss began as early as 3 years before diagnosis and accelerated after diagnosis of CKD. Cats below median body weight (4.2 kg) at diagnosis had a significantly shorter survival time compared to cats >4.2 kg at diagnosis (P<0.0001).
3. IRIS staging is great and should be done. For a review of IRIS staging, please visit http://www.iris-kidney.com/education/staging-system.shtml- note changes made in 2015 re treating BP earlier, treating proteinuria earlier, and correlating IRIS with SDMA results
   a) Is a methylated form of the aa arginine released into circulation during protein degradation and excreted by kidney
   b) Increases significantly earlier than creatinine (as much as 17 months in cats and 9.5 months in dogs, with about a 40% reduction in GFR) (as early as with 25% reduction in a couple of cats!)
   c) Specific for kidney function (not influenced by extra renal factors like BUN is and not impacted by lean muscle mass like creatinine can be-especially important in older cats with sarcopenia)
   d) Correlates strongly with GFR in cats and dogs
   e) New IRIS guidelines (2015) include the following information on the SDMA test.
      -A persistent increase in SDMA above 14 µg/dl suggests reduced renal function and be a reason to consider a dog or cat with creatinine values <1.4 or <1.6 mg/dl, respectively, as IRIS CKD Stage 1
In IRIS CKD Stage 2 patients with low body condition scores, SDMA ≥25 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 3 for this patient.

In IRIS CKD Stage 3 patients with low body condition scores, SDMA ≥45 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 4 for this patient.

It is very important to diagnose anything that may be contributing to the stage of CKD that is treatable. For example, periodontal disease needs to be addressed, blood pressure measured and urine cultured even if the sediment is non-inflammatory (Greene, Mayer-Roenne). In cats, radiographs should be obtained to look for upper urinary tract (kidney, ureteral) stone disease and a T4 is recommended to assess for underlying hyperthyroidism (Van Hoek). Anesthesia should be avoided if possible; if surgery is needed, IV fluids should be administered pre, during and post any anesthetic and surgical procedure. Exposure to nephrotoxic drugs needs to be avoided.

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.

**Dietary Interventions for CKD**

Dietary therapy remains the cornerstone of management of CKD. The goals of dietary modification are to meet the patient's nutrient and energy requirements, alleviate clinical signs and consequences of the uremia, minimize disturbances in fluid, electrolyte, vitamin, mineral and acid base balance, and slow progression of the disease. Diet modifications include phosphorus restriction (most important), providing reduced quantity but high quality protein, adequate non protein calories from fat and CHOs, modifying sodium content (not the degree of restriction once recommended by some), supplementing potassium, B vitamins, alkali as needed and providing omega three fatty acids.

**Renal Diets: When and Why?**

When to introduce: Currently, it is recommended that cats with IRIS Stage 2 CKD and onwards and dogs with IRIS stage 3 CKD and onwards, be fed a diet specifically formulated for CKD (Polzin 2011, Ross 2006, Plantinga). Controlled studies conducted in client-owned cats with naturally occurring IRIS Stage 2 and 3 CKD have shown that diets restricted in phosphate and protein can provide clinical and hematological benefits (Harte). In one 2 year study, cats with a serum creatinine > 2 mg/dl fed a renal diet had a median survival time that was 2.4 times longer than cats fed a maintenance diet (633 days vs 264 days) (Elliot). Patients may be more likely to accept a new renal diet if offered before uremia develops and a gradual transition may be needed.

NOTE: dogs and cats with significant proteinuria AT ANY STAGE OF CKD should also be fed a renal diet.

**Protein:**

*Is there science to support feeding a restricted protein diet to cats?* Dietary protein intake in cats been evaluated in two studies of induced renal failure conducted at separate North American veterinary colleges with conflicting results. Adams et al. showed that restriction of dietary protein to approximately 2.7 g/kg/day and energy intake to approximately 56 kcal/d resulted in fewer renal lesions in cats with induced renal failure, than consumption of approximately 6.8 g protein/kg/d and 75 kcal/d. Finco et al., did not find an effect of different protein intakes (approximately 5.3 or 9.0 g/kg/d) and showed only minor effects of energy intake on the development of renal lesions. These studies were...
short in nature; CKD is long in progression. Results from experimental subtotal nephrectomy models of CKD in cats may not provide meaningful data for cats with naturally developing disease.

So why restrict protein and how much to restrict? To decrease production of nitrogenous wastes, and consequently improve the clinical well-being of the pet even though renal function may remain essentially unchanged. Reduction of dietary protein also moderates the magnitude of polyuria and polydipsia (less solute is delivered to the kidneys in the form of nitrogenous waste products) and anemia (nitrogenous waste products are incriminated in hemolysis, shortened red blood cell survival and blood loss with uremic gastritis and impaired platelet function). In addition, if less sulfur-containing amino acids in dietary protein, the renal acid load is lessened. If proteinuria is present, dietary protein restriction is beneficial as proteinuria induces inflammatory and fibrogenic pathways and increases oxidative stress (Bartges 2012). Proteinuria (elevated UPC) is a negative prognostic indicator—anything we can do to improve the UPC is not really known so it is currently recommended to provide at least maintenance levels. For cats with CKD, the minimum dietary protein requirement suggested is 20% of calories, which equates to 24% protein on a dry-matter basis; DMB (Bartges 2012, 2014, Baldwin, Polzin). Others suggest 28–35% (DMB) (Kirk). It is emphasized that less total dietary protein can be fed if high biologic value proteins, such as egg, are fed (Polzin). One is reminded that lowering animal-derived protein (source of phosphates) in the diet is also one of the only ways to truly lower dietary phosphorus intake (Burkholder).

Is there any danger of “too much” protein restriction? Yes! Protein malnutrition from any causes is strongly correlated with morbidity and mortality. Older cats, with unique dietary needs and potential concurrent disorders (such as hyperthyroidism, diabetes, pancreatitis, exocrine pancreatic insufficiency), are prone to sarcopenia (Freeman, Sparkes). The cat, as an obligate carnivore, is unable to down-regulate hepatic enzyme activity associated with protein catabolism even when dietary protein intake is low. High quality protein sources must be used in order to prevent essential amino acid deficiency. The cat’s body weight, lean muscle mass, body condition score, serum albumin, BUN and cholesterol should all be monitored. If protein malnutrition becomes evident in a patient (hypoalbuminemia, anemia, weight loss or loss of lean muscle mass), then the amount of protein should be increased until signs are no longer evident. Cats with sarcopenia, regardless of the stage of renal disease, may require more protein than a renal diet can provide—careful monitoring and adjustment will be needed in these cats.

Phosphorus:
The kidney plays a crucial role in regulating serum phosphorous concentrations. As GFR decreases, phosphate retention occurs. Studies have shown plasma PTH may be increased prior to azotemia even in the absence of hyperphosphatemia in geriatric cats (Finch) and in CKD cats not selected for older age (Giovaninini). We also now know there are hormones other than PTH that are working to keep serum P and PTH normal for as long as possible. One such hormone, fibroblast growth factor 23 (FGF-23) has been found to be elevated in geriatric cats with normal creatinine and normal PTH levels suggesting changes are already occurring in the aging kidney and parathyroid gland prior to our detection of azotemia (Geddes 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).
Take home message: Dietary phosphorus restriction is critical at least from Stage 2 onwards and should be considered earlier.

Note: Serum phosphorus concentration may increase in CKD pets that increase their food intake following other supportive CKD treatments-monitor closely.

**Energy:** Energy (kcal) can be provided from protein, fat and carbohydrates. With protein restriction, the diet must rely on carbohydrate and fat to provide the bulk of energy requirements; otherwise protein is metabolized as an energy source which generates more nitrogenous wastes. As fat provides approximately twice the energy per gram than CHO, renal diets tend to be high fat diets. Because of this, the energy density of the diet is high allowing the cat or dog to meet its nutritional needs from a relatively smaller volume of food compared to its maintenance diet. Remember: cats are different than dogs! With increasing age, metabolic rate actually may increase in cats (other species it decreases) and cats may have reduced digestibility of fats and proteins, so ensuring adequate intake is critical (Laflamme).

**Potassium:** CKD is the most common cause of hypokalemia in cats and up to 30% of cats with CKD (especially in IRIS stage 2 and 3) are hypokalemic (Ross, Dibartola, Dow, Theisen). Inadequate dietary intake, increased urinary loss and activation of the renin-angiotensin-aldosterone system are all thought to contribute to hypokalemia. Hypokalemia contributes to muscle weakness, progressive renal injury (hypokalemic nephropathy; also kalipoenic nephropathy in the absence of hypokalemia), polyuria, polydipsia and inappetance and must be corrected. Serum potassium levels may not be representative of intracellular potassium levels and pets with low normal serum potassium may actually be systemically depleted and benefit from potassium supplementation (DiBartola 2012, Theisen). Some clinicians recommend supplementation even when serum potassium is in the low normal range, with a goal of maintaining serum potassium levels above 4 mg/dL (> 4 mmol/L). Potassium replete, non-acidifying diets should be fed to help control hypokalemia. Many cats will require additional K supplementation. Hyperkalemia is occasionally seen in end stage CKD cats that are oliguric.

Potassium supplementation: Potassium gluconate (Tumil-K: 0.5 mEq/kg PO q 12-24 hours) or potassium citrate (Polycitra-K syrup: 40-60 mg/kg/day divided into 2-3 doses) are recommended. Tumil K powder is dosed at ¼ teaspoon (2 mEq)/4.5 kg PO q 12 hours. Other sources of potassium may be used (refer to manufacturer’s dosing recommendations) but potassium chloride should be avoided due to its acidifying nature. Resolution of hypokalemic myopathy generally occurs within 5 days. Serum K concentration should be measured every 7-14 days and the dosage adjusted to achieve a maintenance level (> 4 mmol/L). Be careful with K supplements containing calcium in cats-make sure ionized calcium is normal in these cats!

**Sodium Restriction?** Sodium restriction has historically been recommended in cats to alleviate hypertension associated with failure to excrete sodium. However, a study in cats with surgically induced renal disease, failed to show any adverse effect of feeding 2 g Na/1000 Kcal (Burankarl). Burankarl et al also suggested that salt restriction (0.5 g Na/1000 Kcal) could activate neuro–humoral axes that contribute to the progression of renal disease and exacerbate renal potassium wasting. The ideal dietary sodium concentrations for cats and dogs with CKD are not yet clearly defined. Moderate sodium restriction is recommended; severe sodium restriction should be avoided because this may lead to volume depletion and pre-renal azotemia. Be careful with choice of fluids for SQ administration as most contain some sodium; although dextrose in water does not contain sodium, it should not be administered subcutaneously.
**Acid Base Balance:** As renal function deteriorates, the capacity to excrete hydrogen ions, reabsorb bicarbonate ions, and generate new bicarbonate ions is lost and metabolic acidosis results. Metabolic acidosis exacerbates azotemia, muscle wasting and renal (Elliott 2003). Renal diets are formulated to be less acidifying than most maintenance diets.

**Omega-3 polyunsaturated fatty acids (PUFA)*** are thought to be of benefit in CKD in dogs (and likely cats) for a number of reasons including reduction in inflammation (antioxidant effects), reduction in systemic arterial pressure, antithrombotic effects, and alteration of plasma lipids (Brown). Salmon or menhaden fish oil (fish body oil; not liver oil) provide an excellent source of omega 3 fatty acids. A number of renal diets are supplemented with omega 3 FA. In some cases, additional are recommended. The dose range recommended is wide at 10-200 mg/kg PO q 24 hours.

**Vitamins:** The inclusion of antioxidant Vitamins E, C and B-carotene in the diet is thought to help decrease oxidative stress in pets with CKD (Keegan). Thiamine (vitamin B1) deficiency may mimic potassium deficiency. cat: 5-30 mg/cat q 24 hours (max of 50 mg/cat/day). Some cats may require B12 especially if inappetant or concurrent thyroid or GI illness.

**Water (hydration is critical):** Encourage these cats to drink more water. How?

- Canned food –water heavy, palatable
- Multiple small meals may help. It has been suggested that, for a given energy level, the water intake significantly increases by increasing meal frequency (Kirschvink, Lhoest)
- It is important to provide easy access to fresh water at all times. Cats are nocturnal and may prefer to drink in the evening.
- Many cats appear to prefer a bowl with a wide surface area. The water bowl should be kept full at all times. Cats have very sensitive whiskers and many seem to prefer a large bowl in which the whiskers do not touch the sides of the bowl.
- A variety of water types (Brita, distilled, bottled, warm tap water, cold tap water, rain water) can be offered.
- Do not sweeten the water as cats lack sweet taste receptors (have defective Tas 1r2) (Xia)
- Flavoring the water or providing ice cubes flavored by tuna or clam juice may help encourage water consumption.
- Some cats prefer a source of running water (water fountains are available for cats although in one study of 13 cats, no difference was found in water consumption when water was offered in a fountain vs. a bowl (Grant)
- It is important to keep food and water bowls away from the litter box area. The water bowl must be clean (cats have a very keen sense of smell and are easily turned off by odors on the edge of the bowl).
- Some cats prefer a clear glass bowl; others stainless steel or ceramic. Some cats prefer not to share their bowl (especially with dogs).

**Subcutaneous fluids:** If oral hydration is not possible, fluid administration subcutaneously, intravenously or via feeding tube may be indicated. Subcutaneous fluids are generally not recommended prior to stage 3 CKD as all fluids administered in this manner contain some sodium (Adams 2013). Subcutaneous fluid therapy does not increase the renal function per se but keeping the animal well hydrated prevents additional increases of blood urea nitrogen (BUN) and creatinine from prerenal causes. It is recommended to use a balanced electrolyte solution such as lactated Ringer’s solution (LRS) or Normosol®-R and give 75-100 ml/cat daily or every 2-3 days as required. Feeding tubes
provide a more physiological route of administration of supplemental water without increased sodium intake from isotonic fluids.

**Getting cats to eat:** Pets with CKD often suffer from poor appetite which can contribute to poor body condition which in turn, is associated with decreased prognosis (owner’s often euthanize when quality of life is perceived as unacceptable). A study in dogs with CKD comparing survival and body condition score (BCS) showed that dogs with low BCS have significantly shorter survival than dogs with normal BCS and those that were overweight (Parker). In a study by Doria-Rose and Scarlett, survival curves for emaciated cats were significantly lower than those for cats of other body conditions suggesting poor nutritional intake and low body condition score are likely to impact survival in cats with CKD, similar to other species such as dogs and humans. To encourage appetite, consider the following:

- If hospitalized, remember cats are sensitive to the smell, texture and taste of food. This is not the best time to be changing diets as we may create food aversion. Have the owner bring in the “usual food” and try to have owner present to encourage intake.
- Transition with the old food in a new bowl and the new food in the old bowl. Transitioning the diet over 2-4 weeks may be necessary
- Offer small, multiple meals
- use highly odorous foods OR diets with aromatic profiles that are appealing to cats and dogs (they have a much better sense of smell than we do!)
- warming the foods prior to feeding,
- Stimulate eating by positive reinforcement with petting and stroking behavior.
- Use appetite stimulants such as mirtazapine (Remeron) helps not only with appetite but with uremic-associated nausea. Recent work in cats indicates mirtazapine can be administered at a low dose (1.88 mg) every 48 hours to cats with CKD, (3 week study with this lower dose in cats) (Quimby) Remember: mirtazapine and cyproheptadine cannot not be administered concurrently. Cyproheptadine is in fact used as an antidote for serotonin effects of mirtazapine overdose. The ghrelin receptor agonist, capromorelin, which mimics the activity of the “hunger hormone” ghrelin in stimulating appetite, is currently being studied.
- Use nasoesophageal or esophagotophy tube feeding if needed.

**Anti-Nausea Therapy and suggested therapy for “uremic gastritis”:** Mirtazapine is addressed under appetite stimulation and appears to have effects on nausea/vomiting and appetite. Other select drugs to help with nausea include:

*Maropitant (Cerenia):* NK-1 receptors are in the chemoreceptor trigger zone, in the emetic center itself, as well as peripherally. Consequently, Cerenia is a great choice to treat vomiting/nausea in renal cats! Despite the label recommendation, many specialists are recommending Cerenia for longer than 5 days (personal communication with specialists and with Zoeitis scientists). Dose: 1 mg/kg PO once daily. Refrigerate to help alleviate the sting associated with injectable cerenia (Narishetty).

*Omeprazole (Losec):* Studies in cats have also shown Omeprazole to be more effective than H₂ blockers such as famotidine and ranitidine in decreasing gastric acidity (Goldstein). Dosage: 0.5-1 mg/kg once a day. If H₂ blockers are used, dosages recommended are: Famotidine (Pepcid¹) 0.5 mg/kg IM, SQ, PO q 12 hours or Ranitidine (Zantac¹) 1-2 mg/kg q 12 hours (cat)
**Sucralfate:** Studies have shown most cats with uremia do have elevated gastrin levels (and likely corresponding hyperacidity) but no GI ulcers (Goldstein, McLeland). Consequently, sucralfate is not usually indicated. The GI bleed with uremia could be from dysregulation of the vasculature and platelet dysfunction associated with uremia (Goldstein, McLeland). If used, a dose of 0.25 -0.5 g/cat q 12 hours is recommended. In some countries sucralfate is used as an intestinal phosphate binder due to its aluminum content.

**Ondansetron:** The bioavailability is not high (maybe 30% at best in cats) and the half-life is very short (it would be best to give this drug 4 times/day) (Quimby). The subcutaneous administration does have a better bioavailability with the longest half-life of any of the other modes of administration. If the owner is capable of giving injections, then an injection prior to a meal twice a day is ok but cerenia is a better choice!

**Control of Proteinuria and the use of angiotensin converting enzyme inhibitors (ACE-I; e.g. Fortekor) or angiotensin receptor blockers (ARBs; e.g. Semintra):**

With CKD, remaining nephrons must work harder (supernephron hypothesis) in order to maintain GFR. They do so by dilating the afferent arteriole and vasoconstricting the efferent arteriole—see picture below. This vasoconstriction is the result of angiotensin 11. While initially beneficial, longer term it is detrimental in that glomerular hypertension occurs with protein leaking into the tubular interstitium and initiating further renal damage. The magnitude of proteinuria is dependent on the integrity of the glomerular barrier, GFR, tubular reabsorptive capacity, and effects from elevated systemic and intraglomerular blood pressure (Chew).

**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)

Historically, it has been recommended to treat when the UPC was >0.4 in cats and > 0.5 in dogs in the face of azotemia but the new IRIS guidelines suggest treating even in Stage 1 i.e. prior to the development of azotemia. In fact, it may be worth treating with UPCs <0.4 or 0.5 as borderline
proteinuria has been associated with a poorer prognosis. For example, 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).

ACE-I: Benazepril has been shown to reduce the UPC in cats with CRF (Mitzutani, King). 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 over 6 months (Mitzutani JVIM 2006).

The angiotensin receptor blocker (ARB) telmisartin (Semintra® Boehringer Ingelheim) is licensed for use in Canada in cats. Semintra was found to be as effective as benazepril in reducing proteinuria in cats with CKD and was well tolerated.

An additional potential benefit from ACE-inhibition and ARBs is improved control of systemic blood pressure (especially with Semintra) (Coleman).

Monitoring: recheck renal function in 1 week following start of ACE-I or ARB 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. Recheck the UPC 1 and 3 months after the start of ACE-inhibition or ARB therapy. The goal is to achieve a 50% decrease in UPC in those in which it was initially increased. Be more careful with ACE-I in advanced stages of CKD-increases in serum creatinine may necessitate dropping the dose or the drug altogether.

**Phosphorus Retention and Renal Secondary Hyperparathyroidism**

With CKD and decreased GFR, P retention occurs along with calcitriol deficiency, leading to uncontrolled synthesis and secretion of PTH by the chief cells of the parathyroid gland, a condition known as renal secondary hyperparathyroidism (2-HPHT). Parathyroid gland hyperplasia is the primary cause of increased PTH secretion.

Historically, the overall frequency of documented renal 2-HPHT was 76% in a 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-HPHT 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-HPHT but 2-HPHT can be encountered in both dogs and cats with serum phosphorus within the normal reference range!!! Hyperphosphatemia was noted in 18% and 2-HPHT in 36% of dogs in IRIS stage 1 dogs (Cortadellas et al., 2010). We now know hormones other than PTH (such as FGF-23) also play a role and such hormones are elevated prior to serum P or PTH elevations.

One is reminded that higher concentrations of serum phosphorus are negative prognostic factors (Chakrabarti, Boyd, Kuwahara, King etc).

So we need to appreciate renal 2-HPHT can precede development of hyperphosphatemia in CKD and we need to make sure we do everything to keep the serum P within the normal reference range. 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).

Even at stage 1, a P restricted diet (compared to a maintenance diet) may be indicated. If the serum P is creeping up, an intestinal phosphate binder is recommended.

**Treatment of Hyperphosphatemia**

Early phosphorus restriction in CRF has been shown in dogs and cats to blunt or reverse renal secondary hyperparathyroidism. Survival time in CKD cats eating a protein/phosph restricted 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.

**Intestinal Phosphate Binders** should be added if serum phosphate remains increased after one month of consuming the renal diet or if the animal needs to remain on a maintenance diet. Attempt to keep the serum phosphate concentration in the mid-normal range (< 4.5 mg/dL ; < 1.45 mmol/L). Measure serum phosphate concentrations 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).

P binders should be given orally and with a meal (or very close to a meal) to trap phosphorus in the gut and increase insoluble phosphate salt excretion into feces. 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. Please note that newer P binders are coming and this list will change!
**Intestinal Phosphate Binder** | **Dose for dog and cat** | **Side effects/concerns/comments**
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Aluminum Salts: Aluminum hydroxide (Basogel, Amphogel, Aternagel) | 90-100 mg/kg PO divided q 8-12 hours Increase as needed | Constipation Concern for potential aluminum accumulation/toxicity.
Calcium Salts: Calcium carbonate (Tums® regular strength 500 mg/tablet) Calcium acetate | 30 mg/kg PO q 8 hr or 45 mg/kg PO q 12 hr | Hypercalcemia Calcium carbonate binds phosphorous best in an acidic environment (pH approx. 5) and binding capacity is reduced in the neutral pH range. Calcium acetate binds 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.
Eปากitin® (Vetoquinol Inc.) contains the adsorbent chitosan (8% crab and shrimp shell extract), 10% calcium carbonate, and 82% lactose | 1 gm/4 kg twice daily with food | Hypercalcemia risk (cats) Not as effective as other P binders
Pronefra (Virbac) contains chitan and calcium carbonate and magnesium carbonate | 1 ml/4 kg (cat) twice daily with food 1 ml/5 kg (dog) twice daily with food | Hypercalcemia risk (cats)
Sevelamer hydrochloride (Renagel® 400 mg tablets) exchange resins that bind dietary phosphorous and release the counterion chloride | 33-54 mg/kg PO q 8 hr; 50-80 mg/kg PO q12 hr | No studies in dogs and cats
Lanthanum (Fosrenol® 500 mg chewable tablets) | 12.5-25 mg/kg/day PO; 6.25-12.5 mg/kg PO q12 hr starting dose Intact tablets should not be swallowed (crush into food) | Toxicity studies performed in dogs show that lanthanum increases in many tissues (especially GI tract, bone and liver) during treatment.

**Hormone replacement with Calcitriol (information from Dr. Chew’s notes):** Renal production of calcitriol, the active form of Vitamin D, is decreased in CKD and hyperphosphatemia further inhibits its synthesis. Calcitriol is an important inhibitor of parathyroid hormone and low levels contribute to renal secondary hyperparathyroidism which has multiple deleterious consequences. Calcitriol treatments help to decrease PTH or prevent its increase in those patients 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.

Calcitriol should not be administered until hyperphosphatemia has been controlled. 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.

If the Ca X P solubility product exceeds 60-70, calcitriol should be avoided because of the risk of soft-tissue mineralization.

Dose: 2.5 to 3.5 ng/kg/day (may need compounding). In one study, dogs with CRF treated with calcitriol survived for a median of 365 days compared to 250 days in dogs treated with placebo (Polzin). Monitor serum ionized calcium, serum phosphorus and PTH concentrations to document successful and safe control of renal secondary hyperparathyroidism. Assess serum calcium concentration on days 7 and 14 after initiation of calcitriol therapy and every 6 months thereafter. If hypercalcemia is detected, stop therapy and see if hypercalcemia resolves-dose adjustment necessary. Serum P and PTH levels should be reassessed 4-6 weeks following initiation of calcitriol. If still elevated, then increase the dose by 1-2 ng/kg depending on prior response (do not exceed 6.6 ng/kg/day unless you are following ionized calcium carefully). Pulse therapy protocols are also available (Nagode).

For cats (and some dogs), 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.

**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).
Anemia and use of erythropoietin and darbepoeitin

*When to start replacement therapy:* if PCV values < 20%; if clinical signs of anemia are present and problematic.

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<tr>
<td>Induction dose</td>
<td>100 IU/kg SQ three times weekly (50 IU/kg if hypertensive)</td>
<td>1 µg/kg SQ once weekly</td>
</tr>
<tr>
<td>Maintenance dose (When the lower end of the target PCV range (25-30%) is reached)</td>
<td>Frequency of administration is reduced to twice a week.</td>
<td>Reduce dose by 20–25% or extend dose interval to every 2 weeks</td>
</tr>
<tr>
<td>Side effects</td>
<td>-antibody formation in up to 50% of treated dogs and cats after 1 to 3 months of treatment-consequently, worsening of anemia -red blood cell aplasia -vomiting, seizures, hypertension, uveitis, and hypersensitivity-like mucocutaneous reaction</td>
<td>-Vomiting, hypertension, seizures, and fever (but less common than with epoetin)</td>
</tr>
</tbody>
</table>

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).

Depending upon the severity of anemia, it may require 3-4 weeks for the PCV to enter the target range.

**Patient monitoring during therapy:**

a) Monitor the PCV at every administration of Epogen or Darbepoeitin and at least once weekly in animals receiving recombinant human erythropoietin products. PCV monitoring is important to monitor response to and to adjust dosage to avoid overdosing complications, such as erythrocytosis and hyperviscosity.

b) A reticulocyte count should be submitted weekly until the patient is in the maintenance phase of therapy, and then a reticulocyte count should be done monthly.

c) Blood pressure should be assessed as hypertension is one of the most common side effects of EPA therapy. The mechanism of hypertension is not known but may include increased blood viscosity or peripheral vasoconstriction. BP increases in as little as 2 weeks of initiating therapy and tends to stabilize by month 4. Increased BP has been reported in 40-50% of dogs and cats treated with ESAs (Cowgill 1992).

d) Iron panel (serum iron and ferritin concentrations, total iron-binding capacity, and % transferrin saturation) before and one month after starting iron therapy and every three months after that to estimate iron stores and prevent overdosing.
Other things to consider to treat or help lessen the degree of anemia:

1. use pediatric blood tubes- require a smaller volume of blood for optimal blood-to-anticoagulant ratio to minimize blood loss from sampling.
2. Manage uremic gastritis-omeprazole discussion
3. transfusion of whole blood or packed red blood cell preparations is indicated when there is acute blood loss or when a patient demonstrates clinical signs of anemia that require rapid correction or in big dogs prior to EPA admin. Disadvantages of blood transfusions include the possibility of immune reactions, incompatibility, reduced lifespan of infused blood products in a uremic patient, availability, costs, and the lack of long-term effectiveness of these products.

Systemic Hypertension
Systemic hypertension is common in cats and dogs with CKD; approx 13-28% of cats present with hypertension when CKD is first diagnosed and up to 65% of cats develop hypertension at some point during the progression of their renal disease (Jepson 2007, 2011, Syme 2002, Brown 2007, Cowgill 2012, Elliott 2001, Henrik 1997, Kobayashi, Mishina). It is essential that pets 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. 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 > 160 mm Hg (new 2015 IRIS guidelines) 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) and ARBs (Semintra) work well in dogs but cats most often need the calcium channel blocker, amlodipine (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). Semintra works to control BP in dogs (Coleman).

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