Topics:

1. SDMA & Biomarkers – How Do They Help Us?
2. The stages of CKD - implications and management
3. Controversies in Nutrition for the Renal Patient
4. Fluid Therapy for Renal Patients: Challenges and Solutions
5. Current Views of Treatment of Glomerular Diseases in Dogs - I
6. Current Views of Treatment of Glomerular Diseases in Dogs – II
Key Points:

1. Key diagnostic tests for recognizing kidney disease include: BUN, Serum Creatinine, SDMA, Urinalysis and Urine Protein: Creatinine (UPC) ratio.

2. BUN, creatinine and SDMA are markers of glomerular filtration rate (GFR), the principal measure of overall kidney function. They are best interpreted together.
   a. Creatinine and SDMA are key measures of GFR.
   b. Increases in creatinine and BUN can result from prerenal, renal or postrenal causes.
   c. SDMA appears to be able to detect CKD (chronic kidney disease) earlier than BUN or creatinine. Prerenal, renal or postrenal causes may influence SDMA.
   d. Creatinine is affected by dog breed and size as well as body muscle mass (both dogs and cats), thus creatinine can be altered by factors other than GFR. SDMA does not appear to be influenced by these factors, thus facilitate interpretation of serum creatinine values.
   e. Many non-renal factors may influence BUN; thus, it is a poor measure of GFR and should be used with serum creatinine and/or SDMA when assessing kidney function.

3. Urinalysis and UPC ratio are markers of specific kidney functions other than GFR. These tests are best interpreted with measures of GFR, and may even detect kidney disease in patients with normal GFR values.

4. Dogs and Cats with Chronic Kidney Disease (CKD) are categorized using the IRIS CKD Staging System to provide treatment and prognosis guidance. This staging system includes serum creatinine values, proteinuria and blood pressure. SDMA may modify the stage assigned.

Definition of Kidney Disease.

Kidney disease is defined as either functional or structural abnormalities in either one or both kidneys. Functional renal diseases are most commonly recognized by the presence of azotemia or other laboratory abnormalities, whereas structural renal disease may be detected by physical examination, imaging studies or renal biopsy. These abnormalities are considered “markers” of kidney disease in that they should prompt further investigation to determine whether they result from kidney disease. (table 1)

Interpretation of Serum Creatinine Concentration.

Serum creatinine concentration, a surrogate for glomerular filtration rate (GFR), is the primary diagnostic test used to identify impaired kidney function. Unfortunately, it is a relatively insensitive estimate of glomerular filtration rate until a substantial reduction in overall kidney function has already occurred. It requires about a 75% reduction in GFR before serum creatinine values consistently exceed the upper limit of normal for many laboratories. The insensitivity of serum creatinine results from at least two important factors. The first is the innate relationship between GFR and serum creatinine and the second is that factors other than intrinsic renal disease can cause serum creatinine concentration to increase.

The relationship between serum creatinine and GFR is such that every time the GFR declines by half, the serum creatinine concentration doubles. For example, if a dog has a baseline creatinine of 0.5 mg/dl and its GFR declines by 50%, the serum creatinine only increases to 1.0
mg/dl, still well within the normal range. If a further reduction of 50% in GFR occurs (to 25% of the original GFR), the creatinine will rise to 2.0 mg/dl where it might begin to be recognized as elevated. A further decline of 50% in GFR (to 12.5% of normal) and the creatinine increases to 4.0 mg/dl. As can be seen by this example, the slope of the rise in serum creatinine concentration becomes much more acute after a substantial loss of GFR has already occurred, but the slope is flat over most of the range of GFR. It follows that the wider the normal range is for serum creatinine concentration, the less sensitive it is for intrinsic kidney disease. However, if the range becomes too narrow, serum creatinine will lose specificity because other factors may influence the creatinine value including body muscle mass, breed of dog, and other factors. This conundrum is intrinsic to the nature of serum creatinine and limits its utility in diagnosis of early CKD.

Blood Urea Nitrogen Concentration (BUN).

Although BUN has traditionally been viewed as an additional surrogate for estimating changes in GFR, it is influenced by several important factors that do not relate to GFR, including renal perfusion, protein ingestion, upper gastrointestinal hemorrhage, sampling interval between food intake and blood sampling, drugs (e.g. corticosteroids), urine flow rate, and liver function. In addition, urea excretion is the sum effect of glomerular filtration and renal tubular reabsorption. Thus, BUN values may diverge substantially from serum creatinine concentrations due to factors unrelated to GFR. BUN may be a better measure of the patient’s burden of uremic toxins and thus tends to correlate better than serum creatinine concentration with clinical signs and prognosis. However, interpretation of BUN values can be complex and even potentially misleading. One goal of dietary protein restriction is to lower levels of uremic toxins, and as expected reducing dietary protein intake will typically lower BUN values, seemingly a favorable change. However, low BUN levels may also occur when patients eat little or no food. The low BUN in this instance can be misinterpreted as a favorable response to therapy when it actually results from starvation. Simultaneous measurement of serum creatinine and blood urea nitrogen
(BUN) concentration has been shown to be of limited benefit compared to measuring serum creatinine alone.

**Urine Specific Gravity.**

Knowledge of the urine specific gravity obtained simultaneous with a serum creatinine concentration is pivotal in interpreting the meaning of the serum creatinine value. As stated above, urine specific gravity is essential for immediate differentiation between prerenal and primary renal azotemia. Urine samples obtained after administration of fluids and some drugs are likely to be altered, thus rendering the urine specific gravity uninterpretable. In general, serum creatinine concentration is interpreted as being primary azotemia when urine specific gravity is 1.030 or greater in dogs and 1.035 or greater in cats. However, most dogs and many cats with CKD will have urine specific gravity values between 1.006 and 1.020, and, when in advanced stages of CKD, isosthenuria (1.008-1.012) is common. Finding isosthenuria indicates the kidneys are not modifying the concentration of urine from the concentration of plasma. Urine specific gravities between 1.001-1.005 are not consistent with renal azotemia because it requires adequate kidney function in order to reduce urine concentrations below isosthenuria. Some cats with CKD may retain substantial urine concentrating ability (i.e. 1.020 to 1.035 and occasionally above 1.035).

An alternative means of differentiating primary from prerenal azotemia is to repeat the serum creatinine concentration after an appropriate intravenous fluid challenge that eliminates the prerenal condition. If azotemia resolves 24-48 hours after fluid administration, the patient is considered to be “fluid responsive” and therefore azotemia is due to prerenal causes.

**Using SDMA for diagnosis of CKD.**

Symmetric dimethylarginine (SDMA) is a novel kidney biomarker in dogs, cats and humans. SDMA, a methylated form of the amino acid arginine, is released into the circulation during ongoing intranuclear protein degradation and is excreted almost exclusively by renal filtration (≥90%). Its small size and cationic properties allow it to be ubiquitous and freely filterable by the glomerulus. During the process of protein degradation arginine is methylated resulting in formation of numerous molecules including two dimethylarginines, asymmetric dimethylarginine (ADMA) and SDMA. ADMA is an endogenous inhibitor of nitric oxide synthase and is associated with endothelial dysfunction, vasoconstriction, and elevation in blood pressure. It is cleared by metabolism within the liver and by the kidneys. In contrast, SDMA has not been found to participate in endothelial dysfunction or management of blood pressure and has been shown to have little physiologic activity. It is eliminated primarily by the kidneys with little or no liver metabolism. Renal clearance is through filtration, without tubular reabsorption.

Serum SDMA concentrations correlate well with GFR in cats and dogs. In dogs with X-linked hereditary nephropathy, serum SDMA correlated well to both creatinine and GFR estimated by iothalamate in a canine model of CKD, there was a significant correlation between GFR and SDMA which was stronger than the correlation between GFR and creatinine. In 69 client-owned cats with CKD, SDMA concentrations were increased and correlated with creatinine; SDMA also correlated well with a range of GFRs in aged cats.

SDMA has been shown to be a marker for early kidney disease in dogs, cats and humans. Dogs with X-linked hereditary nephropathy rapidly progress from normal at birth to end stage renal disease. In a cohort of male X-linked hereditary nephropathy dogs the measurements of serum SDMA, creatinine and GFR estimated by iothalamate clearance were followed over the course of their disease. SDMA increased earlier than creatinine by identifying a GFR decline as early as a 30% decline compared to serum creatinine that did not increase until there was a 50-60% loss of kidney function. Creatinine was evaluated both as a single serum cutoff value and as
trending over time and in both instances SDMA proved to be an earlier indicator of loss of kidney function. Trending of serum creatinine increases the sensitivity of serum creatinine in detecting changes in kidney function. This study confirmed that trending creatinine is better than a single point in time measurement of creatinine; however, SDMA outperformed creatinine trending and proved to be a better indicator of early kidney disease.

Retrospective longitudinal studies in dogs and cats that developed CKD provided further evidence that serum SDMA increases earlier than creatinine. Two retrospective studies that looked at both dogs and cats over several years as they developed naturally occurring CKD showed SDMA increased before creatinine by a mean of 17 months in cats (range 1.5-48 months) and 10.2 months in dogs (range 0.5-32 months). SDMA identified a reduction in GFR on average 40%, and in one case early as a 25%.

SDMA is useful for identifying and monitoring kidney disease in sarcopenic patients. A major shortcoming of creatinine is its relationship to muscle mass. Increased muscle mass promotes higher creatinine values while reduced muscle mass is associated with lower creatinine values. For example, aged cats with CKD often develop severe sarcopenia. Because of loss of muscle mass in these cats, serum creatinine concentrations will be low relative to GFR thereby underestimate the severity of renal dysfunction. In contrast, SDMA is minimally impacted by muscle mass in dogs and cats. In a study in dogs comparing the relationship between lean body mass, age, serum creatinine and SDMA showed that lean body and age were significant variables for serum creatinine concentration but not SDMA.

SDMA is best interpreted as a complement to existing kidney tests. Serum SDMA concentrations exceeding 14 ug/dl are considered abnormal in dogs and cats. An elevated SDMA and serum creatinine concentration with concurrent inappropriately concentrated urine is consistent with the diagnosis of kidney disease. An elevated SDMA with a concurrent normal serum creatinine concentration suggests early kidney disease. However, when SDMA persists elevated over months this is stronger evidence of the diagnosis of kidney disease. Further, SDMA documented to be elevated for at least 3 months duration in dogs with serum creatinine <1.4 mg/dl or cats with serum creatinine <1.6 mg/dl are consistent with a diagnosis of IRIS CKD Stage 1.

Unlike creatinine, SDMA is not influenced by lean body mass and will therefore be a better marker of kidney disease in animals with low body condition scores. The IRIS board provides guidelines for using SDMA to adjust treatment recommendations in patients with low body condition scores (see below is CKD staging system).
Table 1: Markers of Kidney Damage

Blood markers:
- Azotemia
- Hyperphosphatemia
- Hypoalbuminemia
- Hyperkalemia
- Hypokalemia
- Metabolic acidosis
- Hypocalcemia
- Hypercalcemia
- Hypoproliferative anemia
- Hypoalbuminemia
- SDMA

Urine markers:
- Impaired urine concentration
- Impaired urine dilution
- Proteinuria
- Cylinduria
- Hematuria
- Pyuria
- Inappropriate urine pH
- Inappropriate urine glucose
- Cystinuria
- Bacteriuria

Imaging markers – abnormalities in kidney:
- Increased or decreased kidney size
- Renal mineralization, nephroliths or ureteroliths
- Abnormal renal shape
- Absence of a kidney
- Abnormal renal echo texture by ultrasonography

Arterial hypertension
- Measured blood pressure
- Retinal lesions consistent with hypertension

* Markers must be confirmed to be of renal origin to be evidence of kidney damage.

Table 2: IRIS CKD Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine Values (mg/dl)</th>
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<tbody>
<tr>
<td></td>
<td>Dogs</td>
</tr>
<tr>
<td>Stage 1</td>
<td>&lt;1.4</td>
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<tr>
<td>Stage 2</td>
<td>1.4-2.0</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2.1-5.0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>&gt;5.0</td>
</tr>
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Table 3: IRIS CKD Subclassification by Proteinuria (Urine Protein:Creatinine Ratio)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Urine Protein:Creatinine Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Dogs</td>
</tr>
<tr>
<td>Proteinuric (P)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Borderline proteinuric (BP)</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Non-proteinuric (NP)</td>
<td>&lt;0.2</td>
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</table>

Table 4: IRIS CKD Subclassification by Blood Pressure Stages for Dogs and Cats

<table>
<thead>
<tr>
<th>Arterial Pressure</th>
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<tbody>
<tr>
<td>Category</td>
<td>Systolic Blood Pressure</td>
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<tr>
<td>--------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normotension (N)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Systolic mmHg</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Diastolic mmHg</td>
<td>&lt;95</td>
</tr>
</tbody>
</table>

(www.iris-kidney.org)

### The stages of CKD – implications and management

Chronic kidney disease (CKD) is defined as the presence of structural or functional abnormalities of one or both kidneys that have been present for an extended period, usually 3 months or longer. As is apparent from this definition, CKD may be characterized by a wide spectrum of disease ranging from a minor structural lesion in a single kidney to extensive loss of nephrons affecting both kidneys. Thus, the clinical presentation and diagnostic and therapeutic challenges presented by patients with CKD may vary greatly from patient to patient.

Recognizing kidney disease requires consideration of evidence from multiple sources including renal function tests, serum electrolyte concentrations and acid-base status, urinalysis and renal imaging studies. Kidney disease is usually suspected on the basis of reduced kidney function or “markers” of kidney disease. Markers of kidney disease may be recognized from hematologic or serum biochemical evaluations, urinalysis or imaging or pathology studies (Table 1). Findings suggesting kidney disease may also be found by physical examination or from the medical history (e.g. changes in kidney size or shape, changes in urine volume, etc.). Markers of kidney disease should be viewed as hints that kidney disease may be present and should be pursued diagnostically; they do not necessarily confirm the presence of kidney disease.

### Acute Versus Chronic Kidney Disease

Because they differ in diagnostic, therapeutic and prognostic implications, acute kidney injury (AKI) and CKD must be diagnostically discriminated. However, AKI and CKD may occur together in some patients (so-called acute on chronic kidney disease). In general, CKD is viewed as irreversible disease that is often progressive, while AKI may be reversible.

Chronic kidney disease is defined as kidney disease that has been present for an extended period. Kidney disease present 3-months or longer is considered to be chronic. Duration of CKD may be estimated from the medical history or inferred from physical examination findings or renal structural changes identified through imaging studies or renal pathology (Table 2).

### Staging Chronic Kidney Disease

Dogs and cats with CKD are staged according to guidelines developed by the International Renal Interest Society (IRIS) and accepted by the American and European Societies of Veterinary Nephrology and Urology. The 4 tier staging system is based on renal function, proteinuria and blood pressure (Tables 3-5). Staging CKD in this fashion facilitates application of appropriate clinical practice guidelines for diagnosis, prognosis and treatment.

The stage of CKD is based on the level of kidney function as measured by the patient’s serum creatinine concentration. Staging should be based on a minimum of two serum creatinine values obtained when the patient is fasted and well hydrated. In addition, creatinine values should ideally be determined over several weeks to assess stability of CKD.

The stage of CKD is further characterized by the magnitude of proteinuria, as measured by the urine protein-to-creatinine ratio (UPC), and arterial blood pressure. Before performing the UPC, the urine sediment should be confirmed to be inactive and urine culture sterile. Unless the UPC is markedly elevated or less than 0.2, persistence of proteinuria should be confirmed by
reexamining the UPC 2 to 3 times over at least 2 weeks. The average of these determinations should be used to classify the patient as non-proteinuric; borderline proteinuric or proteinuric.

As with proteinuria, arterial pressure should ideally be determined two to three times over several weeks to establish the blood pressure classification. The arterial pressure classification should be based on the lowest repeatable blood pressure values obtained.

Chronic Kidney Disease: Conservative Management (Achieving Adequate Nutrition & Slowing Progression of CKD)

Conservative medical management of CKD includes therapies other than treatment of active renal diseases (e.g. pyelonephritis, urinary obstruction, etc.), dialysis or transplantation. It includes therapy designed to: 1) prevent and/or treat complications of decreased kidney function, 2) manage comorbid conditions that accompany kidney disease (table 5), and 3) slow loss of kidney function. In planning conservative medical management, it is important to recognize and specifically treat active renal diseases in the patient.

Managing Chronic Disease

In contrast with acute disease, management of patients with chronic disease requires a long-term plan that includes education and engagement of the pet owner as well as a plan for monitoring the patient’s progress. A principal reason for developing an ongoing relationship with the pet owner is that they must adhere to treatment recommendations and monitoring protocols over a long period. Failure to do so will result in suboptimum therapeutic response which may lead to owner discouragement and unsatisfactory outcomes.

Factors likely to influence the success of a therapeutic plan include: 1) pet owner attitude toward and acceptance of the therapeutic plan, 2) patience and sometimes creativity in promoting owner and pet acceptance of the recommended treatments, and 3) maintaining continuing owner commitment to the treatment plan for the duration of the illness. The first step in developing a long-term management plan for dogs and cats with CKD is to develop a treatment plan that “works for the pet owner as well as the pet.” The final “key” to optimizing the long-term outcome of patients with chronic disease is a plan for active follow-up initiated by the veterinarian.

Managing Gastrointestinal Signs of Uremia

Gastrointestinal complications of CKD, including reduced appetite with reduce food intake, nausea, vomiting, uremic stomatitis and halitosis, gastrointestinal hemorrhage, diarrhea, and hemorrhagic colitis, are common in dogs and cats with CKD stages 3 and 4. Treatment for these complications of CKD is largely symptomatic. Diet therapy, and specifically protein restriction, may limit or ameliorate many of the gastrointestinal signs of uremia. Although a link between the products of protein metabolism/catabolism and clinical signs of uremia is clear, the precise “toxins” remain unknown, and improvement in clinical signs often correlates with a reduction in BUN as protein intake is reduced. Thus, the presence of gastrointestinal complications of CKD is sufficient justification to warrant reducing dietary protein intake.

Management of anorexia, nausea and vomiting typically includes: 1) limiting gastric acidity using H2 blockers, 2) suppressing nausea and vomiting using antiemetics, and 3) providing mucosal protection using sucralfate. Of these treatments, H2 blockers are most commonly employed and few adverse effects have been attributed to their use. The most commonly used H2 blockers include famotidine and ranitidine. However, their efficacy remains unproven.

Antiemetics are typically added when anorexia, nausea or vomiting persist despite the use of an H2 blocker. Antiemetics commonly used in patients with CKD include metoclopramide, 5-HT3 receptor antagonists such as ondansetron HCl or dolasetron mesylate, and the neurokinin (NK1) receptor antagonist maropitant citrate. Studies in uremic humans have shown the 5-HT3 receptor antagonist ondansetron to be twice as effective as metoclopramide in reducing uremic nausea.
and vomiting. Sucralfate should be added when gastrointestinal ulcerations and hemorrhage are suspected. Appetite may be enhanced with mirtazapine.

Maintaining Hydration
Dehydration is a common complication of CKD and is often responsible for deterioration in kidney function and episodes of acute uremia. Because compensatory polydipsia prevents dehydration, lack of access to good quality drinking water, certain environmental conditions and intercurrent illnesses limiting fluid intake or facilitating fluid losses (e.g. pyrexia, vomiting or diarrhea) promote dehydration. Cats with CKD appear to be particularly susceptible to chronic dehydration, perhaps because they fail to achieve an adequate compensatory polydipsia. Withholding water from patients with CKD is inappropriate and potentially dangerous.

Chronic dehydration may promote anorexia, lethargy, weakness, constipation, and prerenal azotemia, and predispose to AKI. Additional loss of kidney function due to AKI is an important cause for progression of CKD. Owners of pets with CKD should be taught that vomiting or diarrhea or inadequate access to water may lead to dehydration which may promote deterioration in kidney function or precipitate uremic crisis.

Fluid therapy is indicated for clinically dehydrated patients. The goal is to correct and prevent dehydration and its clinical effects. Acute correction of fluid needs may be administered intravenously or subcutaneously, depending of the severity of dehydration and specific needs of the patient. Long-term administration of subcutaneous fluid therapy may be considered for patients with signs consistent with chronic or recurrent dehydration. The principal benefits of subcutaneous fluid therapy may include improved appetite and activity and reduced constipation. Not every patient with CKD requires or will benefit from fluid therapy; the decision to recommend administration of subcutaneous fluids should be made on a case-by-case basis. Cats appear more likely to benefit than dogs.

For long-term administration, a balanced electrolyte solution (e.g. lactated Ringer’s solution) is administered subcutaneously every one to three days as needed. The volume to be administered depends upon patient size; a typical cat requires about 75 to 100 ml/dose. If the clinical response of the patient is suboptimal, the dose may cautiously be increased. However, overzealous fluid administration may fluid overload the patient. Balanced electrolyte solutions do not provide electrolyte-free water; a more physiologically appropriate approach is to provide water via a feeding tube. Further, evidence suggests excessive sodium intake may be harmful to the kidneys, and excessive salt intake may impair effectiveness of antihypertensive therapy.

Response to long-term subcutaneous fluid therapy should be monitored by serially assessing hydration status, clinical signs, and renal function. If a detectable improvement in clinical signs and or renal function does not accompany fluid therapy, the need for long-term therapy should be re-assessed.

Management of Anemia of CKD
Anemia of CKD is common in dogs and cats with CKD stages 3 and 4. It results primarily from impaired ability of the kidneys to produce a sufficient quantity of erythropoietin; however, iatrogenic and spontaneous blood loss, poor nutrition, and reduced red blood cell lifespan may also contribute. Optimum response to therapy requires recognition of all causes contributing to anemia.

Chronic, low-grade gastrointestinal hemorrhage often contributes to anemia in CKD. Key signs suggesting gastrointestinal hemorrhage include an anemia that is disproportionately severe relative to the level of azotemia, an unusually rapid decline in hematocrit, and elevation in the BUN/creatinine ratio. Iron deficiency may provide indirect evidence of occult gastrointestinal blood loss. Gastrointestinal signs or melena are inconsistently present in these patients. A therapeutic
trial with an H2-receptor antagonist and sucralfate may be used to support the diagnosis. An increase in hematocrit supports the diagnosis.

Options for treating anemia of CKD include hormone replacement therapy, anabolic steroids, and correcting factors promoting red blood cell loss or impairing red blood cell production. Erythropoietin therapy is generally the most effective therapy, but optimum therapeutic response requires addressing all of the factors contributing to the patient’s anemia.

Erythropoietin products most commonly employed in dogs and cats include the recombinant human erythropoietin Epogen® (EPO) and darbepoetin alpha (DPO). Administration of EPO has been shown to result in a dose-dependent rise in hematocrit resulting in correction of anemia and its associated clinical signs within approximately 2 to 8 weeks. While EPO is usually effective in correcting anemia of CKD initially; development of antibodies directed at EPO may render it ineffective. Further, continued administration despite development of anti-EPO antibodies may render the patient’s own endogenously produced erythropoietin largely ineffective as well, leaving the patient potentially transfusion-dependent. Because of this, EPO use has usually been reserved for patients with advanced CKD requiring correction of anemia to maintain a satisfactory quality of life. Thus erythropoietin therapy is recommended only for dogs and cats with relatively advanced CKD with clinical signs attributable to anemia and hematocrit values below about 22 vol%. Hormone replacement therapy with rHuEPO is described elsewhere.

Darbepoetin alpha (Aranesp®), a longer-acting form of erythropoietin, has supplanted EPO as the product currently recommended for use in dogs and cats. The duration of action of DPO is approximately 3 times longer than EPO. Preliminary, uncontrolled observations on the use of DPO in dogs and cats with anemia of CKD suggest that it may be substantially less likely to induce anti-erythropoietin antibodies, perhaps because of the structural modifications responsible for its longer duration of action. Unlike EPO, DPO is supplied in µg rather than units with 1 µg DPO being the equivalent of 200 units of EPO. Patients currently receiving EPO may be switched to DPO based on providing an EPO-equivalent dosage (consult the product package insert for details), but with a dosing interval is extended three-fold.

Therapy with DPO includes an induction phase and a maintenance phase. The induction phase is designed to correct anemia while the maintenance phase sustains the normal hematocrit for the remainder of the pet’s life. In the induction phase, DPO is administered at a dose of 1.5 µg/kg SC once weekly. Higher doses may accelerate the response to therapy, while lower doses may slow the response. It is critical that the hematocrit be measured weekly during this phase to prevent overdosing. When the hematocrit reaches the lower end of the normal range, the frequency of administration of DPO is reduced to every other week to transition the patient to the maintenance phase.

During the early part of the maintenance phase, the hematocrit should be measured monthly and either the dose or frequency of administration of DPO adjusted to maintain the hematocrit in the normal range. While the optimum therapeutic target hematocrit has not been established for dogs and cats with CKD, a reasonable cost-effective target would be to target the lower end of the normal range. Studies in humans have suggested that maintaining hematocrit values at the lower end of the normal range may be as effective as and possibly safer than maintaining higher hematocrit values. Once the hematocrit has been stabilized within the target range, the hematocrit should be monitored approximately every 3 months. Maintenance of a normal hematocrit requires ongoing hormone therapy and monitoring. Failure to monitor the hematocrit and adjust the dose of DPO can result in severe polycythemia and death, particularly during the induction phase.

The demand for iron associated with stimulated erythropoiesis is high, and human patients without pre-existing iron overload will exhaust iron storage during erythropoietin therapy. The same appears true of dogs and cats. Iron supplementation is therefore recommended for all patients
receiving erythropoietin therapy. At a minimum, an intramuscular injection of iron dextran (50 to 300 mg) should be provided at the time EPO or DPO are initiated.

The most important complication associated with use of hormone replacement therapy is refractory anemia and hypoplasia of the erythroid bone marrow associated with formation of neutralizing anti-erythropoietin antibodies. A test for anti-EPO antibodies is not currently available. However, failure of an increase in EPO or DPO dosage to increase hematocrit in absence of an identifiable cause for treatment failure strongly suggests development of anti-erythropoietin antibody formation. Demonstrating an increase in the bone marrow myeloid/erythroid ratio provides further support that erythropoietin resistance results from antibody formation. If anti-erythropoietin antibody formation is suspected, EPO or DPO therapy should be terminated immediately. Because anti-erythropoietin antibodies may interfere with both administered and endogenous erythropoietin, anemia may become worse than before initiation of erythropoietin therapy. However, antibody titers typically decline with cessation of therapy, and early recognition of development of anti-erythropoietin antibodies will minimize the extent and duration of bone marrow suppression. Persistent administration of EPO despite formation of antibodies may result in persistency of antibodies. After therapy is stopped and antibody titers decline, suppressed erythropoiesis may be reversible and pre-treatment levels of erythropoiesis may be attained.

Calcitriol Therapy
Patients with CKD typically have reduced levels of calcitriol. With mild CKD, the decline in calcitriol production may be ameliorated by limiting phosphorus intake. However, as CKD progresses calcitriol supplementation becomes necessary to maintain normal levels of calcitriol.

It has generally been believed that the effects of calcitriol therapy in patients with CKD are mediated by its effects on PTH and mineral metabolism. However, a variety of important renal effects unrelated to PTH and mineral metabolism have recently been recognized, including suppression of activity of the renin-angiotensin system, systemic activation of vitamin D receptors, and reducing podocyte loss associated with glomerular hypertrophy. These effects appear likely to be important in mediating the recently recognized benefits of calcitriol in limiting progression of CKD and improving survival of patients with CKD. A masked, RCCT performed on dogs with CKD stages III and IV indicated that calcitriol therapy increased survival time by slowing progression of CKD. These findings are consistent with results of recent studies in human patients with CKD which demonstrated a similar survival benefit of calcitriol therapy. However, a RCCT performed in cats failed to reveal similar benefits for calcitriol in altering the course of feline CKD. The reason for these divergent results in cats is unclear, but may relate to the relatively indolent course of CKD in many cats.

Calcitriol therapy is indicated for dogs with CKD stages III and IV (and possibly CKD stage II) to slow progressive deterioration in renal function. A recommendation for or against use of calcitriol in cats with CKD can not be supported at this time. In preparation for calcitriol therapy, serum phosphorus should be managed to achieve treatment targets described previously, and absence of hypercalcemia should be confirmed by measuring ionized calcium levels. Serum phosphorus and (ideally) ionized calcium concentrations should be monitored during calcitriol therapy. Total serum calcium values may not accurately portray ionized calcium levels in dogs with CKD.

Calcitriol should initially be provided at a dose of 2.0-2.5 ng/kg every 24 hours. Monitor ionized calcium and PTH levels to establish the proper dose. The goal is to minimize PTH without inducing hypercalcemia. Because it enhances intestinal absorption of calcium and phosphorus, calcitriol should not be given with meals; administration in the evening on an empty stomach reduces the risk of hypercalcemia. When calcitriol therapy is associated with hypercalcemia, the daily dose may be doubled and given every other day, thereby reducing calcitriol-induced intestinal
Calcitriol dosage should not exceed about 5.0 ng/kg/day. Life-long treatment will be necessary to achieve the desired effect of reduced renal mortality. Details on dosing and monitoring are available elsewhere.

FOLLOW-UP MONITORING PATIENTS WITH CKD
Because CKD tends to be progressive, patient needs may change with time. As a consequence, regular monitoring of patients is an essential component of the treatment plan. Treatment goals should be clearly recorded and compared to regular measurement of the patient’s progress. Patients in CKD stages 3 and 4 should typically be evaluated about every 3 to 4 months. Patients in CKD stages 1 and 2 often require less frequent monitoring, about every 4 to 6 months once they have been established to have stable renal function. However, patients with progressive CKD, proteinuria or arterial hypertension should be monitored more frequently. A typical monitoring visit should include at least a medical history with medication review, physical examination, body weight and nutritional assessment, hematocrit, chemistry profile, urinalysis, and blood pressure. Depending on the patient and results of the urinalysis, the urine protein: creatinine ratio and a urine culture may also be included.

Checklist for Managing Chronic Kidney Disease:
1. Confirm that the patient has kidney disease
2. Confirm that the kidney disease is chronic
3. Establish the IRIS CKD Stage of the patient
4. Develop a treatment plan for the patient’s CKD
   a. Determine the treatment options appropriate for the patient
   b. Prioritize the treatment options
   c. Prioritize treatment options based on medical priority and pet owner’s preferences
5. Review treatment plan with pet owner and confirm their willingness to engage in the selected treatments
6. Schedule follow-up appointment(s) to assess patient response to therapy
7. Arrange for regular telephone updates to evaluate response to therapy and confirm owner compliance and commitment to the treatment plan
   a. Assess owner’s understanding of the treatment plan
   b. Determine if the owner is having compliance issues
   c. Assess patient’s response to therapy and determine whether the patient needs to be seen before next scheduled appointment
Controversies in Nutrition for the Renal Patient

Dietary Therapy of CKD
No other single therapeutic modification is more likely to enhance the long-term outcome for patients with CKD stages 3 and 4 than feeding a renal diet. As a consequence, the standard of care is to recommend feeding a renal diet to dogs with CKD stages 3 and 4 and cats with CKD stages 2-4. Results of several clinical trials strongly support the beneficial effect of renal diets on preventing or delaying the onset of uremia and premature death due to complications of CKD. In addition, renal diets have been shown to maintain or improve nutrition and owners report higher quality of life scores than when maintenance diets were fed. The studies here refer to commercial renal diets; however, diets formulated by boarded veterinary nutritional diplomats specifically for use in dogs or cats with CKD also qualify as “renal diets” in this discussion.

The term renal diet has been misinterpreted to mean just restricting dietary protein intake; however, renal diets include other diet modifications that are probably as or more important and effective than protein restriction. Because of this, substituting maintenance or senior diets that are lower in protein content than the pet’s usual diet is not a satisfactory substitute for feeding diets specifically formulated for dogs and cats with CKD. Diets specifically designed for dogs and cats with CKD are modified from typical maintenance diets in several ways including reduced protein, phosphorus, and sodium content, increased B-vitamin and soluble fiber content, increased caloric density, a neutral effect on acid-base balance, supplementation of omega-3-polyunsaturated fatty acids and the addition of antioxidants. Feline renal diets are supplemented with potassium.

While some dogs and a few cats readily accept the change to a renal diet, in many pets, a more gradual approach should be used. A 7 to 10 day gradual switch from the old diet to the renal diet is appropriate for dogs, and a transition period of several weeks may be needed for some cats. The transition may be made by gradually mixing increasing amounts of the renal diet into the old food. Alternately, both the old and the renal diet may be made available while gradually reducing the amount of the old diet that is available. It is important to be certain that metabolic, gastrointestinal and dental complications are well controlled before introducing the renal diet. Introducing a renal diet to a patient that is uremic or experiencing any medical issue that may promote a dietary aversion is likely to doom introduction of a new diet to failure.

The nutritional response to diet therapy should be regularly evaluated by monitoring body weight, body condition score, food intake (calorie intake), serum albumin concentration, packed cell volume and quality of life should be monitored. The primary goal is to assure adequate food intake, stable body weight, and a body condition score at or near 5/9. If the patient is not meeting nutritional goals, the patient should be evaluated for uremic complications, dehydration, and progression of CKD, metabolic acidosis, anemia, electrolyte abnormalities, UTI, and non-urinary tract diseases. In addition, feeding practices should be examined.

When patients fail to spontaneously consume adequate quantities of food, placing a feeding tube should be seriously considered. Feeding via gastrostomy or esophagostomy tubes is a simple and effective way to provide an adequate intake of calories and water. In addition, feeding tubes simplify drug administration.

As defined above, “renal diets” will sustain the patient in a good nutritional condition when adequate calories are consumed. When caloric needs do not meet requirements, nutritional deficiencies may develop. There is also controversy concerning the need to provide higher amounts of protein to geriatric cats. This recommendation may be correct, but has not received adequate clinical confirmation of this recommendation. Feeding high protein diets and/or diets not restricted in phosphorus content are inappropriate and not recommended for dogs and cats with CKD.
Managing Hyperphosphatemia

Retention of excess phosphorus in the body can promote renal secondary hyperparathyroidism, mineralization of tissues and progression of CKD. Increased serum phosphorus concentrations (Pₛ) have been linked to increased mortality in humans, cats and dogs with CKD, and consuming diets high in phosphorus has been shown to increase mortality in dogs with induced CKD. Therefore, minimizing phosphorus retention and hyperphosphatemia is an important therapeutic goal in dogs and cats with CKD.

Because the kidneys are the primary route of phosphorus excretion, declining kidney function results in phosphorus retention and its consequences. However, reducing phosphorus intake in proportion to the decline in kidney function largely prevents retention of phosphorus and its adverse consequences.

In patients with CKD stages 1 and 2, Pₛ typically remains within the normal range due to a compensatory reduction in phosphorous reabsorption in surviving nephrons, thereby enhancing phosphaturia. This compensatory adaptation is a consequence of the phosphaturic effects of fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH). Increases in FGF-23 and PTH levels occur subsequent to phosphorus retention, even though Pₛ initially remain within the normal range. The “trade-offs” or consequences of ameliorating development of hyperphosphatemia include renal secondary hyperparathyroidism and impaired production of calcitriol. In dogs and cats with CKD stages 3 and 4, the usual compensatory mechanisms typically fail to prevent hyperphosphatemia.

At some point in the development of CKD, presumably during CKD stage 2, phosphorus retention and hyperphosphatemia begin to promote progression of CKD. In humans with early CKD, plasma FGF-23 concentrations, an early measure of phosphorus retention, has been shown to predict progression of CKD. The association between phosphorus retention and progression of CKD provides the basis for the recommendations for managing Pₛ in dogs and cats with CKD.

Therapeutic management of Pₛ is indicated for dogs and cats with CKD stages 2-4. The goal of therapy is to maintain Pₛ within specific target ranges which vary according to the stage of CKD (table 6). Target ranges were established based on expert opinion and have not been evaluated in clinical trials. The Pₛ target ranges are below the upper limits of many established laboratory normal ranges because the stated goal is to limit phosphorus retention which precedes overt hyperphosphatemia.

The first step in minimizing Pₛ is to feed a diet reduced in phosphorus content (typically a “renal” diet). Manufactured renal diets are substantially reduced in phosphorus content and are often successful in achieving serum phosphorus targets into CKD stage 3. Approximately 4 to 6 weeks after initiating dietary therapy, measure Pₛ to determine whether the treatment target has been met. Samples obtained for determinations of serum phosphorus concentration should be collected after a 12-hour fast to avoid postprandial hyperphosphatemia. If after 4 to 8 weeks the target Pₛ has not been achieved, addition of an intestinal phosphate binding agent should be considered.

Intestinal phosphate binding agents induce formation of nonabsorbable salts of phosphorus within the lumen of the gastrointestinal tract, thus rendering phosphorus contained in the diet poorly absorbable. Because dietary phosphorus is the target of such therapy, it is essential that phosphate binding agents be given at or about meal time. If the patient is fed more than one daily, the total daily dose of phosphate binder should be divided and a portion administered with every meal. Administering the binders away from meal time markedly reduces their effectiveness.
The most commonly used intestinal phosphate binding agents in dogs and cats contain aluminum as hydroxide, oxide or carbonate salts. Various salts of calcium (acetate, carbonate, citrate) and lanthanum (carbonate) have also been used. Because of concern about aluminum toxicity in humans, aluminum-containing binding agents are becoming more difficult to obtain. Although aluminum-containing binding agents usually appear to be well tolerated and safe in dogs and cats, aluminum toxicity characterized by neurological and microcytosis has been reported in dogs with advanced CKD treated with high doses of aluminum-containing phosphate binding agents.

The risk of inducing aluminum toxicity may be minimized by adding calcium- or lanthanum-containing intestinal phosphate binders to minimize the amount of aluminum that may be required for effective phosphorus binding. Experience with these drugs in dogs and cats are limited, but hypercalcemia may be a problem with the calcium-based products, particularly when administered with calcitriol or between meals. The newest product, lanthanum carbonate and other salts of lanthanum appear to be quite effective and are associated with minimal side-effects.

Phosphorus binders should be dosed “to effect,” meaning the dose is adjusted to assure that the serum phosphorus target is achieved. Therapy usually begins at the lower end of the recommended dose range and adjusted upward as needed every 4 to six weeks until the therapeutic target is reached.

Recommended starting dose for aluminum-containing intestinal phosphorus binding agents (e.g. aluminum hydroxide, aluminum carbonate, and aluminum oxide) is 30 to 100 mg/kg/day. Because calcium-based phosphorus binding agents may promote clinically hypercalcemia, serum calcium concentrations should be monitored when using these drugs. The recommended dosage for calcium acetate is 60 to 90 mg/kg/day and 90 to 150 mg/kg/day for calcium carbonate. The initial dose for lanthanum carbonate is 30 mg/kg/day.

Current Controversy in Feeding Renal Diets to Cats with CKD

Feline “renal diets” are specifically formulated for the purpose of clinical management of cats with chronic kidney disease (CKD). These diets include commercial products and diets specifically designed for cats with CKD formulated by boarded veterinary nutritionists. “Renal diets” have been considered the “gold standard” therapy for managing cats with CKD for many decades. Based on evidence from clinical studies, the IRIS Board suggests renal diets be considered for cats with IRIS CKD Stage 2 and recommend feeding renal diets to cats with IRIS CKD Stages 3 and 4.

Veterinarians typically use therapeutic diets in much the same way as they use pharmaceuticals to manage medical conditions. When they prescribe feeding a “renal diet” for cats with CKD, they expect the diet to achieve four specific goals: 1) to ameliorate or prevent clinical consequences of CKD including signs of uremia; 2) to slow progression of CKD and prolong survival; 3) to minimize derangements of electrolyte, calcium and phosphorus, and acid-base balance; and 4) to maintain adequate nutrition. To achieve these multifaceted goals, modifications beyond just reduced protein content are incorporated when formulating renal diets, including: reduced content of phosphate and sodium; increased content of omega-3-polyunsaturated fatty acids, antioxidants, fiber, vitamin D and potassium; and a neutralizing effect on systemic pH. Clinical trials have supported clinical benefits of “renal diets” formulated similar to these dietary modifications.

Recently, use of “renal diets” in treating cats with CKD has become controversial, weighing the potential benefits of these diets mitigating the clinical consequences of CKD versus the purported potential risk of protein malnutrition consequent to the high protein requirements of cats. As a result, some veterinarians have recommended feeding diets containing high levels of
dietary protein instead of “renal diets”. This divergence in therapeutic opinion has evolved from recent studies suggesting that senior cats may require more protein than younger cats and the observation that at least in some cats with CKD, body weight, body condition score and/or muscle mass may decline over time. Further, substantial loss of lean mass has been shown to be associated with increased mortality in cats with CKD. The specific point of disagreement between these two schools of thought is focused on how much protein should be fed to cats with CKD. More specifically, those advocating feeding higher protein diets to cats with CKD have generally recommended feeding commercial or non-renal therapeutic diets containing more protein instead of feeding the currently available “renal diets” specifically designed for cats with CKD. These high protein diets do not include the other dietary modifications found in “renal diets”.

What is the Rational for Limiting Dietary Protein in Renal Diets?
It has been known for over a century that reducing protein intake reduces clinical signs of uremia. Most uremic signs are caused, at least in part, by accumulation of protein metabolites which are excreted by the kidneys. While reducing protein intake to ameliorate clinical signs of uremia has been standard practice for decades, the decision as to when protein restriction should be initiated remains controversial. Some veterinarians argue that initiating protein restriction should be delayed until the cat begins to display clinical signs of uremia, typically during later IRIS CKD Stage 3 or IRIS CKD Stage 4. Others argue that dietary protein restriction should begin early in IRIS CKD Stages 2 or 3 because it may slow progression of CKD, delay onset of uremic signs and facilitate better acceptance of diet change. In addition, delaying diet therapy until the owner recognizes that the cat is manifesting clinical signs of uremia risks development of a uremic crisis before diet treatment can be started. One possible concern regarding “renal diets” in some cats with IRIS CKD Stage 2 is that initiating protein restriction with a calorically dense food may contribute to body fat gain with lean mass loss if protein requirements are not met with the “renal diet”.

Evidence Supporting Effectiveness of Renal Diets in Cats with CKD
Three studies address the effectiveness of feline “renal diets” compared to typical feline maintenance diets in mitigating uremic crises and extending survival. The consistent findings in these three studies using different diets and methodologies and performed in different countries by independent groups of researchers strongly support the conclusion that “renal diets” favor better clinical outcomes (longer survival and fewer uremic crises).

The first study compared a manufactured protein- and phosphorus-restricted “renal diet” to continuing to feed the cats’ regular (non-renal) diets. (Elliott et al, 2000) This study was neither randomized nor masked; cats that chose not to eat the “renal diet” continued on their usual diet. Cats that consumed the “renal diet” survived significantly longer (n=29; median survival time = 633 days) than cats that continued to consume their regular diet (n=21; median survival time = 264 days).

The second study was a randomized and masked clinical trial with 22 cats fed a “renal diet” and 23 cats fed a feline adult maintenance diet (Ross et al, 2006). The principal dietary modifications in the “renal diet” included reduced protein, phosphorus and sodium, and supplementation with polyunsaturated fatty acids. While there were no uremic crises or renal deaths over the two-year study among the 22 cats fed the “renal diet”, 6 cats fed the maintenance diet developed clinical and biochemical evidence of uremia and 5 cats fed the maintenance diet died of consequences of kidney disease.

The third study was a retrospective study performed in 31 first-opinion veterinary practices in The Netherlands and compared survival times for cats fed one or more of 7 commercial feline
“renal diets” to those not fed a “renal diet”. (Plantinga, 2005) Median survival time for cats fed a “renal diet” was 16 months compared to 7 months for cats fed their usual (non-renal) diet.

Phosphorus and Renal Diets

“Renal diets” are formulated to be low in phosphorus content in part because excessive dietary intake of phosphorus has been linked to progression of CKD in cats and other species. Although dietary phosphorus content is not directly linked to protein content in pet foods, protein is a significant source of phosphorus in foods. Thus, limiting dietary protein is a strategy for limiting dietary phosphorus intake. The goal of limiting dietary phosphorus intake may influence the maximum amount of protein that can be fed. While the amount of dietary phosphorus can be mitigated somewhat by administration of intestinal phosphorus binders, the ability of intestinal phosphorus binders to limit phosphorus uptake from diets containing high levels of phosphorus is finite. This limitation combined with the fact that many cats resist administration of medications increases owner frustration and reduces quality of life for cats having to receive unpalatable medications with every meal. This lowers adherence and makes the strategy of supplementing high protein foods with phosphorus binders of questionable efficacy. Administering phosphorus binders at dosages above the recommended dose range can also lead to adverse drug effects, toxic effects due to absorption of cations associated with the binders (e.g. aluminum, calcium, lanthanum, etc.). Hypercalcaemia is sometimes seen in cats with CKD. The risk factors for its occurrence, including its association with restricted phosphate intake (accomplished by formulated diets or phosphate binding agents) remains to be determined. Anecdotally, increasing phosphate intake leads to normalization of serum calcium concentration in some cases of hypercalcaemia diagnosed after institution of diets or binders. Further research is warranted to facilitate identification of the minority of cats with CKD at risk of hypercalcaemia and to understand how treatment can be better tailored to meet their specific physiological needs.

Is the Protein Content of Renal Diets Optimal for Cats with CKD?

The effect of CKD on protein requirements in cats has not been determined. Studies on the effectiveness of “renal diets” in cats with CKD were performed using “renal diets” as commercially produced. Evidence that these “renal diets” cause loss of lean body and protein malnutrition is lacking. Many cats with CKD lose weight and become underweight. However, this often occurs before the diagnosis of CKD and initiation of a “renal diet”, thus suggesting that CKD itself promotes weight loss. Clinical trials on “renal diets” in cats with CKD have shown that cats with CKD fed “renal diets” may have stable body weight and body condition scores; however, these studies did not measure lean body mass, a better indicator of protein malnutrition. Studies on the effects of different levels of dietary protein intakes will be needed to establish whether or not “renal diets” should be formulated with higher protein content.

Conclusion and Recommendation

Clinical trials of feeding “renal diets” to cats with spontaneous CKD have shown them to be effective in improving survival, reducing uremic crises, and improve blood urea nitrogen and phosphorus concentrations. It has also been shown that when food intake is adequate, “renal diets” can maintain body weight and body condition scores for up to two years. While some have questioned whether “renal diets” provide adequate protein and have advocated feeding higher protein diets to cats with CKD, no convincing clinical trial evidence has been provided to support this proposal. Best current evidence supports the recommendation to feed cats with CKD “renal diets”. The current IRIS clinical guidelines support feeding renal diets to cats with IRIS CKD Stages 2, 3 and 4. The guidelines also recommend monitoring response to treatment, recognizing that there are individual cats at each stage which will need adjustments to their dietary therapy (increasing phosphorus restriction if serum phosphorus fails to meet the target level through the addition of phosphate binders, or reducing phosphorus restriction in
cases where serum calcium increases and hypercalcemia is a concern). The concept is that dietary therapy, like any other kind of therapy needs to be tailored to the individual cat.

Recommended Reading:

Recommended Serum Phosphorus Concentrations Target Ranges Adjusted for CKD Stages

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Target Serum Phosphorus Range</th>
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<tbody>
<tr>
<td>Stage 2</td>
<td>3.5 to 4.5 mg/dl</td>
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<tr>
<td>Stage 3</td>
<td>3.5 to 5.0 mg/dl</td>
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<tr>
<td>Stage 4</td>
<td>3.5 to 6.0 mg/dl</td>
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Intestinal Phosphate Binding Agents

<table>
<thead>
<tr>
<th>Intestinal Phosphate Binder</th>
<th>Dosage Recommendations</th>
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<tbody>
<tr>
<td>Aluminum hydroxide (Alternagel: 600 mg/5 ml)†</td>
<td>30 to 90 mg/k/day* PO</td>
</tr>
<tr>
<td>Lanthanum carbonate (Fosrenol:500 mg/chewable tablet)</td>
<td>12.5 to 25 mg/kg/day* PO</td>
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<tr>
<td>Lanthanum carbonate octahydrate (Renalzin; 200 mg/ml)</td>
<td>2 ml PO in food 1-2x daily</td>
</tr>
<tr>
<td>Calcium Carbonate (Tums: 500 mg/tablet)</td>
<td>30 mg/kg* PO</td>
</tr>
<tr>
<td>Chitosan and calcium carbonate (Epakitin; powder)</td>
<td>4.4 g/10 kg* PO</td>
</tr>
<tr>
<td>Sevelamer hydrochloride (Renagel; 400 mg tablet)</td>
<td>33-54 mg/kg* PO</td>
</tr>
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</table>

†Aluminum hydroxide USP is also available as a powder.

*D每日 dosage should be divided among daily meals – (usually 2-3 feedings/day). Product should be either mixed into the food or administered immediately before or after each meal.
Fluid Therapy for Renal Patients: Challenges and Solutions

Indications for Fluid Therapy
Principal indications for fluid therapy in kidney patients are correction of reduced effective circulating volume and management of acute uremic crises or abrupt decline in kidney function. Kidney function is highly influenced by kidney perfusion, so any condition reducing kidney perfusion may further impair kidney function. It is important to correct such deficits early in the process to limit additional irreversible loss of functioning nephrons. In addition, many of the clinical signs of uremia are caused or exacerbated by dehydration. Symptomatic relief can be provided by appropriate fluid therapy.

General guidelines
Volume depletion is a consistent finding in patients with uremic crisis. Some patients appear to be normally hydrated but have historical findings consistent with fluid losses. It is practical to assume these patients are subclinically dehydrated; carefully administer fluids to them at the rate of 2 to 5 percent of body weight on the premise that mild over hydration is less likely to be harmful than unrecognized volume depletion. Even mild volume depletion may promote hypoxic kidney injury in patients predisposed to acute kidney disease.

A substantial portion of volume depletion should be corrected either by bolus administration or over the first 2 to 6 hours unless the patient has known cardiac dysfunction, demonstrates intolerance to fluid administration, or becomes over hydrated (e.g. dyspnea, elevated neck veins, rales, S3 gallop rhythm, pulmonary edema). Administration of fluid at this rate will help to rapidly restore adequate kidney perfusion. In addition, in patients with physiologic oliguria, urine volume will increase. Careful monitoring of the patient's response to fluid therapy is essential! Monitoring of central venous pressure may be appropriate for patients with cardiac dysfunction or intolerance to fluid therapy. If fluid overload occurs, the rate of fluid administration should be reduced or at least temporarily discontinued. If the patient is rehydrated and yet remains oliguric, DO NOT continue to administer fluids. Fluid overhydration will not only cause the patient’s condition to deteriorate, it may also promote oliguria due to development of renal edema. The kidneys are covered by a capsule that does not expand with swelling of the kidneys. Renal overhydration (edema) will result in increased pressure in Bowman’s space and the renal tubules and interstitium resulting in a reduction in glomerular filtration and urine production.

The therapeutic goal should be restoration/stabilization of tissue perfusion as opposed to administering a calculated fluid volume. A favorable clinical response and improved physical evidence of adequate perfusion and blood pressure usually indicate successful restoration of tissue perfusion. The goal of subsequent fluid therapy is to maintain fluid balance and prevent hypovolemia or overhydration.

Patients may be predisposed to dehydration during maintenance and recovery phases of acute kidney disease because involuntary urine losses are often great. In order to prevent dehydration, the volume of parenteral fluids administered and oral fluids consumed should equal the sum of: 1) urine volume, 2) contemporary fluid losses (e.g. fluid lost via vomiting, diarrhea), and 3) insensible fluid losses (20 to 25 ml/kg/day). Because estimation of contemporary and insensible fluid losses may be inaccurate, serial determinations of body weight should be used to guide fluid therapy. However, if the patient is not receiving adequate calories, some weight loss may occur.
Maintenance therapy typically involves approximately 1/3 saline (or balanced electrolyte solution) to replace urinary losses and 2/3 dextrose 5% in water to replace respiratory and other insensible losses. Fluids similar to this combination are commercially available as maintenance fluids. It is quite common for veterinarians to continue to administer replacement fluids as maintenance fluids, often with no adverse effects. However, this approach may be unsatisfactory for patients with kidney disease leading to electrolyte disturbances. Increased urinary losses in polyuric patients should be replaced by saline or a balanced electrolyte solution.

Once hydration has been corrected, the principal goal of therapy is to maintain hydration by providing maintenance fluids and replacing ongoing losses in order to prevent exacerbating azotemia and kidney hypoperfusion. When the patient has improved sufficiently so that fluid therapy can be withdrawn, fluid therapy should be gradually withdrawn over several days. Initially, intravenous administration may be reduced, then the patient may be switched to oral or subcutaneous fluid therapy.

Significance of fluid balance in kidney disease
The kidneys are the primary organs responsible for maintaining body fluid balance, conserving or excreting water and electrolytes as necessary to maintain an internal milieu appropriate for sustaining life. It is commonly accepted that fluid therapy in patients with normally functioning kidneys is relatively simple because the kidneys accommodate for errors in prescribing fluid therapy (i.e. “The dumbest kidneys are smarter than the smartest clinician.”). The great risks of fluid therapy in patients with kidney disease are: 1) failure to adequately rehydrate a dehydrated patient, thus sustaining prerenal azotemia and promoting ischemic kidney injury, and 2) over-hydrating a patient with limited urine production.

Fluid balance in patients with polyuric kidney disease is maintained by compensatory polydipsia. If water consumption is insufficient to compensate for polyuria, dehydration is the result. This may occur as a consequence of lack of intake or lack of access to fresh, clean, unadulterated water. Cats and some dogs with CRF fail to consume sufficient water to prevent chronic or recurrent dehydration. In addition, acute gastrointestinal fluid losses resulting from kidney or non-renal causes may lead to extracellular fluid volume depletion.

Dehydration and volume depletion promote kidney hypoperfusion and prerenal azotemia that may exacerbate the clinical and laboratory abnormalities of chronic kidney insufficiency/failure. In addition to prerenal azotemia, dehydration may be associated with electrolyte disturbances such as hyperphosphatemia, hyperkalemia, and metabolic acidosis. Clinical signs characteristic of dehydration include decreased appetite, lethargy, and constipation. In some patients, prerenal azotemia may precipitate uremic crisis. Further, if dehydration and decreased kidney blood flow are allowed to persist, additional ischemic kidney damage may occur.

Management of Fluid Balance in Nephrotic Patients
Impact of Proteinuria and Hypertension in Dogs and Cats
It has been well established that the magnitude of proteinuria influences survival in cats with CKD. Hypertension does not appear to be a primary determinant of survival in cats with CKD, although this may be masked by the effect of antihypertensive therapy. Any effect hypertension may have seems to be mediated by its influence on proteinuria. However, unlike in humans and dogs, amlodipine therapy of hypertension in cats is associated with a reduction in proteinuria which does influence survival stratified by IRIS staging.

Less information has been reported on prognosis and risk factors for dogs with CKD. Proteinuria has been identified as a risk factor for development of clinical signs of uremia and for death in dogs with CKD. In this study, proteinuria had a progressively adverse effect on outcome in that the risk of death associated with CKD increased by 60% for each unit of urine protein-to-creatinine ratio above 1.0. Arterial hypertension has also been identified as a risk factor mortality in dogs with CKD: however, as in cats, the adverse effect of hypertension in dogs may be mediated, at least in part, by the influence on proteinuria. The baseline systolic blood pressure has been shown to significantly influence the risk of uremic crises and death in dogs with CKD. Increased risk of developing a uremic crisis and of death was observed in the patients with the highest blood pressure values. In addition, a greater decline in renal function over time was observed in these dogs. While this does not prove a cause-and-effect relationship between hypertension and progressive renal disease, it does suggest that initial blood pressure values should be considered in formulating a prognosis for dogs with CKD.

Proteinuria
Proteinuria - Detection
Proteinuria reagent strips are quite sensitive for detecting proteins in urine, particularly albumin. They are used to screen for pathologic proteinuria of any origin; however, small amounts of protein in urine are considered normal. Proteinuria is an important sign of kidney disease in dogs and cats; however, urinary tract hemorrhage and inflammation may also be associated with proteinuria. Results of the urine sediment are useful in differentiating these conditions. In patients with pyuria, it is necessary to first eliminate pyuria (e.g. antibiotics for UTI) and then re-evaluate the patient for proteinuria. It usually requires at least visible hematuria to cause even a small increase in proteinuria.

Urine reagent strips provide a semiquantitative estimate of the magnitude of proteinuria. It is difficult to extrapolate the clinical implications of a positive proteinuria dipstick from just the dipstick reaction and urine specific gravity. To confirm the clinical importance of a positive protein dipstick obtained on a patient without pyuria, hematuria or bacteria, it is necessary to measure the urine protein:creatinine ratio (UPC; see below). The UPC should probably be performed on dogs with 1+ or greater proteinuria (especially when the urine specific gravity is 1.012 or lower). (Zatelli A et al, 2010) Proteinuria of any magnitude should prompt consideration of performing the UPC in cats.

Proteinuria – Possible Causes
Finding isolated proteinuria (i.e. proteinuria which occurs in absence of other signs of inflammation such as hematuria and/or pyuria) gives rise to two important questions: (1) does proteinuria reflect underlying renal disease, and, if so, (2) will the disease eventually cause morbidity or death? Isolated proteinuria does not always indicate renal disease as strenuous exercise, extremes of heat or cold, stress, fever, seizures, or venous congestion have been reported as causes of isolated proteinuria. These causes are termed functional proteinuria. They are characteristically mild and transient, and therefore are considered non-pathologic.
Proteinuria may also result from increased plasma concentrations of certain proteins (e.g. hemoglobin, myoglobin, or immunoglobulin light-chain monomers and dimers) which are small enough to pass through the glomerular barrier into urine. Because they overwhelm tubular reabsorptive mechanisms, they are called overload proteinuria. Proteinuria resulting from immunoglobulin fragments should be suspected when protein is detected by turbidometric techniques for urine protein (e.g. SSA), but not by dipstick methods.

Because transient proteinuria is often of non-renal origin, persistent proteinuria should be confirmed by repeating the urinalysis after several days. If the second urinalysis confirms proteinuria, further diagnostic inquiry is indicated because persistent proteinuria in absence of active urine sediment is almost invariably a sign of renal structural disease even when other aspects of renal function are normal. The amount of protein excreted by such patients is of considerable diagnostic significance. Heavy proteinuria associated with hypoalbuminemia is called the nephrotic syndrome and indicates generalized glomerular disease. Urinary excretion of lesser quantities of protein may indicate either glomerular or non-glomerular renal diseases (proteinuria in non-glomerular diseases may result from glomerular hyperperfusion/hypertension or renal tubular dysfunction in which tubular reabsorption of filtered proteins is impaired).

Depending on the magnitude of proteinuria (based on the UPC), pathological proteinuria may result from renal tubular or interstitial disorders (mild proteinuria; UPC values less than about 2.5) or glomerular diseases (potentially any magnitude of proteinuria, but especially when UPC exceeds about 2.5). Moderate to marked increases in proteinuria are consistent with protein-losing nephropathies which may be associated with the nephrotic syndrome.

**Rule-Outs For Glomerular Proteinuria**

Many, but not all glomerular diseases are immune mediated. These may result from infectious diseases, granulomatous diseases and neoplastic diseases may lead to secondary glomerular disease. Primary glomerular diseases related to defects in structural components of the glomerulus have been identified. Renal amyloidosis may also cause proteinuria (of any magnitude).

**Treatment for Proteinuria**

**Standard Therapy**

“Standard Therapy” of glomerular disease is indicated for dogs (and cats) with glomerular proteinuria, regardless of the inciting cause for glomerular disease, morphology of glomerular lesions, or whether renal lesions are primary or secondary. It consists of suppression of the renin-angiotensin-aldosterone system (RAAS), dietary therapy, and antithrombotic therapy. In addition, when indicated, it also may include treatment of systemic hypertension (including any associated target organ damage) and fluid management including hydration and management of edema.

The magnitude of proteinuria, as measured by serial UPC values, should be used to guide therapeutic recommendations. Dogs with spontaneous glomerular disease have been shown to exhibit more adverse outcomes when UPC values exceed 1.0. In dogs with induced kidney disease, lesions associated with secondary glomerular disease improve when therapy reduced UPC values below 0.5. Based on these observations, “Standard Therapy” should be considered whenever renal proteinuria persistently exceeds a UPC value of 0.5. Reduction of the UPC to below 0.5 or alternately a 50% reduction in the nadir UPC from the baseline values should be considered as evidence of therapeutic success. Although evidence that reducing proteinuria improves clinical outcomes in dogs (and cats) with spontaneous glomerular disease is limited, drug-induced reduction in albuminuria in humans has been reported to favorably alter renal outcomes in a wide range of studies.
Inhibition of the Renin-Angiotensin-Aldosterone System (RAAS). Inhibition of the RAAS has been shown to reduce the magnitude of proteinuria using a variety of drug strategies. The magnitude of proteinuria reduction achieved appears to be greater than could be explained solely by the antihypertensive benefit of these drugs. Rather, the antiproteinuric benefit of inhibiting the RAAS is thought to derive from modifying renal hemodynamics. Principal drug-classes used to target the RAAS include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and aldosterone-receptor blockers. Although not commonly used in dogs, renin inhibitors have also been used successfully to suppress the RAAS in human patients.

While there is evidence that inhibition of the RAAS reduces proteinuria and may be renoprotective, ACEi and ARBs can also be associated with adverse effects. Suppression of the RAAS may reduce renal function and promote hypotension and hyperkalemia. Reduced renal function and hypotension are the result, at least in part, of vasodilatory consequences of reducing angiotensin II concentrations systemically and locally within the kidneys, while hyperkalemia results from reduced aldosterone concentrations. As a consequence, serum creatinine and potassium concentrations as well as blood pressure should be monitored regularly. Small increases in creatinine and potassium concentrations and decreases in blood pressure are expected and not of concern. However, large changes beyond the normal ranges should prompt careful reconsideration of drug and dose choices and investigation of other factors that may predispose to these adverse events.

Angiotensin-Converting Enzyme Inhibitors: Administration of ACEis is considered “Standard Therapy” for dogs with glomerular disease because they reduce proteinuria and may preserve renal function and structure by decreasing efferent glomerular arteriolar resistance, thus promoting a decline (or normalization) in glomerular hydraulic pressure. Other proposed mechanisms by which suppression of RAAS may reduce the magnitude of proteinuria include preservation of glomerular heparin sulfate, decreased size of glomerular capillary endothelial pores, improved lipoprotein metabolism, slowed glomerular mesangial growth and proliferation, and inhibition of bradykinin degradation.

The ACEi drugs used for management of glomerular disease in dogs include enalapril, benazepril, ramipril, and imidapril. While renal actions of these drugs are similar, their pharmacokinetics vary. Benazepril and its active metabolite, benazeprilat, are excreted largely via the biliary route with a lesser portion excreted in urine, whereas enalapril and its active metabolite, enalaprilat, are excreted largely by the kidneys. Changes in the patient’s renal function may have divergent effects on blood concentrations of these two drugs. However, the pharmacokinetics of both drugs are complex and unpredictable, and there currently are no published studies justifying a preferred recommendation for any one ACEi over others in the class.

It is recommended that ACEi therapy begin at the lowest recommended (or starting) dose given once daily. Serum creatinine should be measured immediately before and shortly after beginning ACEi treatment to assess the impact of therapy on renal function. We recommend creatinine be measured 3 to 5 days after beginning ACEi therapy in dogs with serum creatinine values > 2.0 mg/dl and about 7 to 14 days in dogs with serum creatinine values \( \leq 2.0 \) mg/dl.

ACEi can induce a small reduction in glomerular filtration rate which is recognized as an increase in serum creatinine concentration secondary to its effects to reduce glomerular hydraulic pressure. A small increase in creatinine concentration indicates effective reduction of glomerular hydraulic pressure, and in most dogs this increase is small and not clinically important. However, the degree to which worsening of renal function can be tolerated varies according to the IRIS CKD Stage. Dogs with IRIS CKD Stages 1 and 2 can usually tolerate an
increase in serum creatinine concentration of up to 30% above baseline. However, the occasional dog will respond with a greater increase in serum creatinine concentration (i.e. an increase greater than 30% above the measured baseline value) that may be accompanied by clinical consequences. Most commonly this occurs in dogs with volume contraction due to dehydration. In contrast to dogs with IRIS CKD Stages 1 and 2, stable renal function should be the goal in dogs with IRIS CKD Stages 3 and 4. In these patients, reduction in renal function should prompt therapeutic intervention, with fluid therapy and possibly dosage reduction. Dogs with IRIS CKD Stage 4 are particularly susceptible to developing a uremic crisis should renal function decline after initiating ACEi therapy. As a consequence, ACEi should be initiated conservatively and monitored closely in dogs with more advanced renal dysfunction, and supportive therapeutic intervention should be provided as needed.

The goal of ACEi therapy is to reduce UPC to below 0.5 or, if values below 0.5 cannot be achieved, to reduce the pretreatment UPC by at least 50% to its lowest nadir. Since the starting dose of ACEi rarely reduces UPC values to the stated goal, the dose should be increased progressively either until the treatment goal is achieved or to a maximum dose of 2.0 mg/kg/day. Although the renoprotective benefits of ACEi appear to be independent of baseline renal function in humans and therefore appropriate at all levels of renal dysfunction, caution is warranted in dogs with serum creatinine values greater than 5 mg/dl. At a minimum, increased monitoring of renal function is indicated in these patients, and an abrupt decline in renal function should prompt reconsideration of the dose and/or use of ACEi. Serum potassium and blood pressure also should be monitored as dosage increases are instituted to optimize control of proteinuria.

Angiotensin-Receptor Blockers (ARBs): The ARBs suppress the RAAS by blocking the angiotensin II type 1 receptor. Losartan and Telmisartan have been used in dogs with glomerular proteinuria, and telmisartan is approved in Europe for treatment of proteinuria in cats with chronic kidney disease. While these drugs have been used extensively in humans with glomerular disease and found to reduce proteinuria similar to ACEi, experience with ARBs in dogs is limited. Until recently, losartan has been used most commonly in dogs. There is evidence confirming it exerts predictable pharmacodynamics effects in dogs despite the apparent inability of dogs to produce one of the major active metabolites of losartan. Preliminary evidence also suggests telmisartan may be effective in reducing proteinuria and blood pressure in dogs. Telmisartan has a longer half-life, and has a higher affinity for the angiotensin II type 1 receptor than losartan and may prove to be superior in dogs. Telmisartan has shown more efficacy than losartan and enalapril in attenuating the blood pressure response to angiotensin I administration.

Combined Therapy with ACEi and ARB (Dual Drug Therapy): When treatment with a single class of drug fails to achieve the recommended UPC treatment goal or adverse effects are seen with a single agent, combining ACEi and ARB is a reasonable next strategy. An ACEi may incompletely block formation of angiotensin II, particularly within the kidneys, and blockage of the angiotensin II receptor with an ARB can promote a compensatory increase in renin activity and incomplete block of the RAAS. Thus, blocking both angiotensin converting enzyme and the angiotensin II type 1 receptor is likely to be more effective than monotherapy with either drug class at suppressing angiotensin II activity and reducing proteinuria. An additional potential benefit of combining these drugs is that it may be possible to reduce the doses of both drugs, thus reducing the risk of adverse side effects of either drug.

The safety and effectiveness of dual drug therapy in dogs with glomerular disease has not been documented. The results of studies on the safety and effectiveness of dual drug therapy in humans have been inconsistent. A meta-analysis / metaregression of trials in human patients with primary glomerulonephritis showed that the antiproteinuric response to ACEI plus ARB
therapy versus either monotherapy is consistently greater and strictly related to baseline proteinuria with only moderate increase in serum potassium levels. A more recent systematic review and meta-analysis of all randomized controlled trials reported between January 1990 and August of 2012 comparing dual blockers of the RAAS with monotherapy showed that while dual drug therapy had seemingly beneficial effects on surrogate endpoints (e.g. proteinuria), it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalemia, hypotension and renal failure compared to monotherapy. The authors of this comprehensive meta-analysis indicated the risk-benefit ratio argues against using dual drug therapy in humans. While these results are specifically intended for humans with glomerular disease, it appears prudent to be particularly cautious and vigilant when using dual drug therapy for dogs with glomerular disease.

Aldosterone-Receptor Blockers. In humans receiving ACEis and/or ARBs, it is common for serum aldosterone levels to increase progressively (i.e. aldosterone escape). Prolonged hyperaldosteronism may have adverse effects on the heart and systemic blood vessels as well as the kidneys where it manifests as proteinuria. Aldosterone receptor blockers have been shown to reduce proteinuria and stabilize renal function in humans treated with ACEi and ARB drugs. The reduction in proteinuria would be expected to be most prominent when aldosterone concentrations are high. Spironolactone and eplerenone are aldosterone-receptor blockers that can be used when ACEi and/or ARB therapy is associated with persistent proteinuria and hyperaldosteronism. However, evidence that any aldosterone-receptor blocking drug is effective in lowering the magnitude of proteinuria in dogs is lacking.

IRIS Canine GN Study Group Consensus Recommendation for Managing Proteinuria with RAAS Inhibition. “An ACEi should be the initial treatment for most dogs with proteinuria. The initial choice of drug and starting dose may vary, but can be gradually increased to achieve a therapeutic target. The ideal therapeutic target is a reduction in the UPC to <0.5 without inappropriate worsening or renal function. However, as this ideal target is not achieved in most dogs, a reduction in UPC of 50% or greater is the recommended alternate target.”

Dietary Therapy in Dogs with Glomerular Disease. Diet therapy is generally accepted to be important in management of chronic kidney disease (CKD) because it has been shown to favorably influence renal function and mitigate the magnitude of proteinuria, renal lesions, and the rate of progression of kidney disease in dogs. (Polzin, 1984; Polzin 1988, Jacob, 2002; Brown, 2013) Studies on this subject are based primarily in dogs with spontaneous or induced CKD and secondary glomerular disease. Dietary therapy has been shown to reduce proteinuria, but it has yet to be established whether diet therapy alters the course of primary glomerular disease in dogs. Dietary components that may have a salutary impact on proteinuria and glomerular disease include polyunsaturated fatty acids (PUFA), protein, and salt. (Brown, 2013) Because diets formulated for dogs with CKD include all of these modifications, putatively they are appropriate for dogs with glomerular disease.

Arterial Hypertension

RATIONALE FOR TREATMENT. CKD is the most commonly recognized cause for hypertension in dogs and cat and has has been linked to renal, ocular, neurological and cardiac complications. Hypertensive retinopathy occurs in 60% of hypertensive cats and is the most common overt clinical manifestation of hypertension in cats. Clinical signs seen with hypertension in cats include lethargy, blindness, retinal hemorrhage and detachment, cerebral hemorrhage, seizures, stupor, and ventricular hypertrophy. In a one study, retinopathy and hypertensive encephalopathy were reported in 3 of 14 dogs with blood pressure values exceeding 180 mmHg. Pre-existing CKD reportedly increases the vulnerability of the kidneys to hypertensive injury. Elevated blood pressure has been reported to be an independent risk factor for
progression of CKD in dogs; although proteinuria was not included in the statistical model used to confirm this association. However, in cats with CKD hypertension appears to promote progressive renal injury by enhancing the magnitude of proteinuria. Importantly, hypertension is associated with increased proteinuria in dogs and cats, and, since proteinuria appears to promote progressive renal injury in both species, lowering blood pressure to limit proteinuria is an appropriate goal.

Clinical evidence from humans, dogs and cats indicates that pharmacological reduction in blood pressure is likely to reduce the risk of hypertensive organ injury. Subcutaneous administration of the antihypertensive drug hydralazine has been reported to reduce the prevalence of seizures developing as a consequence of hypertension following renal transplantation. Further, in an induced model of hypertensive renal kidney disease, only 2 of 10 cats receiving the antihypertensive agent amlodipine developed evidence of hypertensive retinal lesions compared to 7 of 10 cats receiving placebo.

INDICATIONS FOR TREATMENT. The indication for antihypertensive therapy is to treat and/or prevent development of end-organ injury including the kidneys, eyes, brain and heart. However, the blood pressure above which progressive renal injury may be induced is unknown. The IRIS recommendations for treatment of hypertension are based on an estimate of the risk of end-organ injury developing in specific blood pressure ranges in a dog or cat with CKD. Therefore, in dogs and cats with hypertension (systolic pressures 160 mmHg to 179 mmHg) the blood pressure should be confirmed on the basis of at least three distinct determinations of blood pressure, ideally over 1 to 2 months. Treatment should generally be withheld until the patient’s blood pressure establishes that hypertension is persistent. In dogs and cats with severe hypertension (systolic pressures 180 mmHg or greater) the blood pressure should generally be reconfirmed on the basis of at least three distinct determinations of blood pressure, ideally over 1 to 2 weeks. However, when there is evidence for hypertension-related organ injury or the systolic blood pressure is greater than 200 mmHg, the decision to initiate anti-hypertensive therapy should be considered an emergency and treatment begun immediately. Reasonable efforts should be made to minimize the risk that measured elevations in blood pressure represent a transient “white coat” effect, rather than a sustained elevation in blood pressure. It is deemed unlikely that systolic pressures greater than 200 mmHg reflect “white coat” effect. Note that some dog breeds, notably sight hounds, may have normal blood pressure ranges up to 40 mmHg higher than those provided in these guidelines, and decisions on diagnosis and treatment should be adjusted accordingly.

TREATING HYPERTENSION. Patients with IRIS CKD stage 1-4 and confirmed hypertension or severe hypertension should be treated because evidence suggests that dogs and cats with CKD may be at increased risk for sustaining additional renal injury or developing complications associated with elevated blood pressure. The ideal goal of therapy is to reduce systolic blood pressure to persistently below 160 mmHg and diastolic blood pressure to persistently below 100 mmHg. Except in patients with acute, severe ocular or neurological lesions, rapid reduction in blood pressure is generally not necessary. Hypertensive dogs may require several dosage and drug adjustments and it may take weeks to months to achieve satisfactory blood pressure control. In contrast, cats often achieve satisfactory blood pressure control quickly. Reducing blood pressure is a long-term process where gradual and sustained reduction should be the goal. Sudden or severe decreases in blood pressure should be avoided because they may promote hypotension.

Treatment should be carried out in a step-wise fashion. Treatment should escalate until the therapeutic endpoint is achieved (i.e. systolic pressure < 1.60 mmHg). While it is unclear whether sodium restriction is effective in lowering blood pressure in dogs or cats with hypertension, a gradual change to a lower sodium diet is recommended at the same time that
pharmacologic intervention is begun. Generally avoid initiating antihypertensive therapy until hydration is cautiously restored to avoid abrupt decreases in blood pressure and/or renal perfusion.

Angiotensin converting enzyme inhibitors (ACEI) such as enalapril and benazepril, and the calcium channel blocker amlodipine are typically the mainstays of antihypertensive therapy in dogs and cats. Telmisartan appears to have significant effects on managing hypertension in addition to proteinuria. These drugs may have unique renoprotective benefits and are therefore appropriate initial options for managing hypertensive renal patients.

In dogs, treatment should begin with an angiotensin converting enzyme (ACEi) administered at the standard dose rate; dosage may be doubled if needed. If the target has not been achieved, the calcium channel blocker (amlodipine) may be added. The dosage may be increased as needed. If ACEi and amlodipine at its highest dosage, either and angiotensin receptor blocker (ARB) and/or hydralazine may be added. There is evidence in humans treated for proteinuria that the combination of ACEi and ARB may be associated with an excessive risk of adverse events such as hyperkalemia, hypotension and renal failure compared to monotherapy. Consider terminating the ACEi before adding or during addition of the ARB and monitor for hyperkalemia, hypotension and/or progressive azotemia.

In cats, treatment should begin with the calcium channel blocker amlodipine. If the initial dosage fails to normalize blood pressure, the dosage may be gradually increased to a maximum of 1.25 mg/kg/d. If additional antihypertensive drug support is needed, consider adding ACEi to the calcium channel blocker.

Treatment for arterial hypertension is usually life-long. Once treatment has achieved the stated target blood pressure, ongoing monitoring is essential to assure adequate control of blood pressure. Dogs and cats on antihypertensive therapy be should have their blood pressure at least every 3 months. Retinal examinations for retinal lesions of hypertension should be performed regularly with the blood pressure measurements. Using the step-wise medical scheme described above, adjustments in blood pressure treatment may be made as need to keep blood pressure below 160/100 mmHg.

Increases in serum creatinine concentration, low blood pressure and clinical signs of hypotension should prompt reassessment of the antihypertensive drugs and dosage. Small increases in serum creatinine that are not progressive may safely occur with antihypertensive therapy. However, large or progressive increases of creatinine concentration may reflect drug or dosage problems. If systolic blood pressure persistently declines below 120 mmHg or signs of hypotension such as weakness or tachycardia develop, antihypertensive drugs and dosages should be adjusted to increase the blood pressure and ameliorate clinical signs of hypotension.

Immunotherapy
Renal biopsies are useful to guide decisions on whether to consider immunotherapy in glomerular disease. When pathologic studies support or confirm a role for immune deposits, immunotherapy can usually be deemed a reasonable therapeutic option. Absent a biopsy, the probability that immune mechanisms are present is about 50:50.

Immunotherapy, notably including corticosteroid therapy, has been a mainstay of therapy of many forms of glomerular disease in humans. Anecdotal reports of such therapy in dogs with glomerular disease have become increasingly common. Since corticosteroids are known to increase proteinuria in dogs, often substantially, they are either not used or used sparingly (moderate doses for short periods) in treatment of glomerulopathies in dogs.

For patients with glomerular diseases that are rapidly progressing associated with severe secondary consequences such as nephrotic syndrome should be considered candidates for
immunosuppressive therapy. Such patients have severe, persistent, or progressive glomerular disease and supporting evidence of immune pathogenesis. Specific recommendations are based largely on uncontrolled experience of therapeutic effectiveness, and it should be remembered that treatment recommendations remain anecdotal and consensus-based. As such, they should be applied cautiously on a case-by-case and trial basis.

Specific drug selections should be based on disease severity & progressivity. Conditions requiring rapid onset of therapy include nephrotic syndrome, marked proteinuria, consequent hypoalbuminemia, rapidly progressive azotemia or clinical signs associated with either above (e.g. edema or uremia). Patients with proteinuria and/or azotemia with a more protracted, less severe disease course generally can be treated with drugs that do not necessarily have as rapid onset of activity.

Mycophenolate (10-20 mg/kg PO q 12h alone or with a short course of corticosteroids) or cyclophosphamide (continuous therapy at 50 mg/m^2 PO 4 days/week or pulse therapy at 250 mg/m^2 IV q 3 weeks, alone or in combination with a short course of corticosteroids) are first-choice drug selections for patients with peracute and rapidly progressive disease requiring drugs with a rapid therapeutic response profile. Glucocorticoids are recommended either as pulse therapy using an immunesuppressive dose, or a single “pulse” dose with a total duration of therapy no longer than 7 days.

For dogs with a more protracted course of glomerular disease, drug choices may include: 1) chlorambucil at 0.2 mg/kg PO q 24-48h, with or without azathioprine at 2 mg/kg PO q 24h for 2 weeks then alternate days with chlorambucil, 2) mycophenolate at 10-20 mg/kg PO q 12h, 3) cyclophosphamide 50 mg/m^2 PO 4 days/week with prednisolone at 0.5-1.0 mg/kg PO q 12h tapered, or cyclosporine.

Patients treated with any of these protocols should be assessed initially at 1-2 weeks, thereafter every 2 weeks up to 6 weeks, monthly for the next 3 months, and quarterly until resolution. Follow-up evaluations should include a medical history, physical examination and appropriate laboratory testing (minimum CBC, chemistry profile, urinalysis, urine culture as indicated and UPC ratio). A favorable response would be defined as one or more of the following: 1) clinical improvement, 2) a significant reduction in UPC ratio, 3) improvement in renal function, or 4) improved serum albumin concentrations.

Treatment should be discontinued if clinically intolerable or life-threatening adverse effects attributable to therapy (“first do no harm”) develop. Absent adverse effects, treatment should be continued at least for 6 weeks of “rapidly acting therapy” or 8-12 weeks of “slow-acting drug therapy.” Should therapy be associated with complete or partial response to initial therapy, continue therapy for up to 3-4 months, and then terminate therapy unless there is a specific indication to continue therapy (e.g. deterioration upon withdrawal of therapy). Should the response to initial therapy be unsatisfactory, consider an alternate drug or dosing protocol. If there is no response after 3-4 months, consider discontinuing immunotherapy.
IRIS CKD Subclassification by Proteinuria (Urine Protein:Creatinine Ratio)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Urine Protein:Creatinine Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dogs</td>
</tr>
<tr>
<td>Proteinuric (P)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Borderline proteinuric (BP)</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Non-proteinuric (NP)</td>
<td>&lt;0.2</td>
</tr>
</tbody>
</table>

IRIS CKD Subclassification by Blood Pressure Stages for Dogs and Cats

Arterial Pressure

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension (N)</td>
<td>&lt;150 mmHg</td>
<td>&lt;95 mmHg</td>
</tr>
<tr>
<td>Borderline Hypertension (BH)</td>
<td>150 to 159 mmHg</td>
<td>95-99 mmHg</td>
</tr>
<tr>
<td>Hypertension (H)</td>
<td>160 to 179 mmHg</td>
<td>100-119</td>
</tr>
<tr>
<td>Severe hypertension (SH)</td>
<td>≥180 mmHg</td>
<td>≥120 mmHg</td>
</tr>
</tbody>
</table>

(www.iris-kidney.org)

Tiers Recommended for Grouping Dogs with Glomerular Diseases

Tier I – Persistent renal proteinuria without hypoalbuminemia or azotemia

Tier I-A – Persistent subclinical renal proteinuria that is not accompanied by any discernable renal-related signs or sequella

Tier I-B – Persistent renal proteinuria with hypertension as the only discernable renal-related sign or sequellae, with or without evidence of target organ damage

Tier II – Renal proteinuria associated with hypoalbuminemia, but not azotemia

Tier II-A – Persistent renal proteinuria with hypoalbuminemia, with or without any of its associated complications or sequellae (mainly edema and thromboembolic events), but without hypertension or azotemia

Tier II-B – Persistent renal proteinuria with hypoalbuminemia, with or without any of its associated complications or sequellae (mainly edema and thromboembolic events), plus hypertension (with or without evidence of target organ damage), but without azotemia.

Tier III – Renal proteinuria associated with renal azotemia

Tier III-A – Renal proteinuria with renal azotemia but not hypertension or hypoalbuminemia

Tier III-B – Renal proteinuria with renal azotemia and hypertension (with or without evidence of target organ damage), but not hypoalbuminemia

Tier III-C – Renal proteinuria with renal azotemia and hypoalbuminemia, with or without any of its associated complications or sequellae (mainly edema and thromboembolic events), which often (but not always) are accompanied by hypertension (with or without evidence of target organ damage).

Drugs Used to Management Proteinuria and Hypertension in Dogs and Cats

1 Apply tier classification criteria after initial patient stabilization including correction of dehydration, if present.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Initial Dose</th>
<th>Escalating Dose Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>ACEi*</td>
<td>0.5 mg/kg PO q 24h</td>
<td>Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg/d</td>
</tr>
<tr>
<td>Enalapril</td>
<td>ACEi</td>
<td>0.5 mg/kg PO q 24h</td>
<td>Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg/d</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>ARB</td>
<td>1.0 mg/kg PO q 24h</td>
<td>Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg/d</td>
</tr>
<tr>
<td>Losartan</td>
<td>ARB</td>
<td>0.125 mg/kg/d PO</td>
<td>0.25 mg/kg/d in azotemic dogs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 mg/kg/d PO</td>
<td>1 mg/kg/d in nonazotemic dogs</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>CCB</td>
<td>Cats:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 5 kg - 0.625 mg PO / cats ≥ 5 kg 1.25 mg PO starting dose; Double dosage if blood pressure remains elevated (dose is per cat)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dogs:</td>
<td>Can increase dosage incrementally up to 0.75 mg/kg PO until blood pressure reduced to target pressure (systolic BP &lt; 160 mmHg)</td>
</tr>
</tbody>
</table>

* ACEi = angiotensin converting enzyme inhibitor  
† ARB = angiotensin receptor blocker  
** CCB = calcium channel blocker