Diagnostic Staging and Management of Dogs and Cats with Chronic Kidney Disease

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Abstract:
Chronic kidney disease (CKD) is defined as primary renal disease that has persisted for months to years. The International Renal Interest Society (IRIS) has recently introduced a staging system for the classification of chronic kidney disease in dogs and cats to facilitate the application of clinical practice guidelines for each stage of CKD. This lecture outlines the staging system and proposed therapeutic recommendations for each stage of CKD in dogs and cats.

Diagnosing Chronic Kidney Disease
Chronic kidney disease is a common clinical diagnosis in middle-aged to geriatric cats and dogs that may significantly affect the quality of life of both the patients and their owners. Although “old age” is not a disease, it is a time when many diseases are more likely to occur, often concurrently. Early disease detection of disease conditions allows earlier intervention and more successful outcomes once treatment has been initiated. Routine monitoring is also helpful to monitor therapy, follow trends and identify any emerging conditions.

Many pets in the early stages of kidney disease may be asymptomatic, or they may show subtle, non-localized clinical signs often mistaken for age-related changes by owners. Detecting CKD in the early stages is important so that appropriate therapeutic measures may be instituted to minimize the progression of disease and delay the onset of uremia.

The diagnosis of CKD requires a very thorough medical history from the owner in addition to a physical exam and laboratory findings. Owners may report increased thirst, increased urination or accidents in the house. Gradual weight loss, selective appetite, deteriorating haircoat, may all be signs of CKD as well. Physical exam findings of poor body condition, poor haircoat, small kidneys, also indicate chronicity. Many laboratory findings are not that helpful in distinguishing acute from chronic kidney disease, but there are some subtle differences that do occur. For example, a non-regenerative (hypoproliferative) anemia may be found with chronic kidney disease.

The laboratory diagnosis of CKD is typically based on demonstrating azotemia (elevated BUN and creatinine) concurrently with inadequately concentrated urine. In most cases, urine specific gravity values less than 1.030 in dogs and less than 1.035 in cats in an azotemic patient strongly suggests the diagnosis of primary renal failure. It is important to note that animals with kidney disease do not typically have urine specific gravities less than 1.006. Values below this specific gravity indicate urine-diluting capacity, which requires functional kidneys.
Due to the influence of many factors, a “normal range” for urine specific gravity does not really exist. Urine concentrating ability is best described as appropriate or inappropriate. Appropriate urine concentration means that the kidneys are responding appropriately to the current situation. For example, a urine specific gravity of 1.065 would be appropriate in a cat that was dehydrated. If this same cat had a urine specific gravity of 1.020, it would be inappropriate and could indicate kidneys disease.

The most commonly used test for assessing kidney function is the serum creatinine concentration (SCr). Serum urea nitrogen concentration (SUN) is also used for this purpose, but many factors other than renal function influence SUN values. Although the SCr is determined primarily by kidney function, it may also be affected by the patients muscle mass. Very thin animals may have an artificially low serum creatinine while heavily muscled animals may have a relative increase in creatinine. Differences in “normal” creatinine ranges among different dog breeds have also been established.

### Staging Chronic Kidney Disease

The International Renal Interest Society (IRIS) has introduced a staging system for the classification and stratification of chronic kidney disease in dogs and cats. The purpose of the staging system is to facilitate the application of clinical practice guidelines for evaluation and management of each stage of chronic kidney disease. Patients are assigned a specific stage of renal disease based on kidney function as determined by serum creatinine concentration.

(Table 1) It is important to understand that evidence of kidney disease beyond just an elevated serum creatinine level should be obtained in order to verify a diagnosis of chronic kidney disease. Ideally, two or more serum creatinine values obtained when the patient is fasted and well hydrated should be determined over several weeks to stage CKD. Serum creatinine should never be interpreted without consideration of other clinical and laboratory findings from the patient (e.g. urine specific gravity). Although the specific cut-off values used to categorize patients with CKD into these stages are inherently arbitrary, staging is useful for establishing prognosis and managing patients with CKD.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>&lt;1.4 (&lt;125)</td>
<td>&lt;1.6 (&lt;140)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>1.4-2.0 (125-179)</td>
<td>1.6-2.8 (140-249)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2.1-5.0 (180-439)</td>
<td>2.9-5.0 (250-439)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>&gt;5.0 (&gt;440)</td>
<td>&gt;5.0 (&gt;440)</td>
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The patient is then further classified according to the presence or absence of proteinuria and their systolic blood pressure. (Tables 2 and 3). Proteinuria and hypertension have been shown to influence progression of CKD and are also amenable to therapeutic
intervention. Quantification of proteinuria should be done by measuring the urine protein: creatinine ratio of a urine sample without evidence of infection, inflammation or hemorrhage. Proteinuria should also be shown to be persistent by checking the urine protein: creatinine ratio 2-3 times over at least 1 or 2 months. Patients with borderline proteinuria should be re-evaluated after 2 months to reassess classification. It is also important to note that, in some patients, the classification if proteinuria may change due to the natural course of the disease or in response to therapy. The classification scheme for proteinuria adopted by IRIS is based on the ACVIM consensus statement on proteinuria in dogs and cats (Lees, 2005).

Table 2: Quantifying and Classifying Proteinuria

<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>Non-proteinuric (NP)</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Borderline Proteinuric (BP)</td>
<td>0.2 – 0.5</td>
</tr>
<tr>
<td>Proteinuric (P)</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

Hypertension has become a well-recognized complication of CKD in both cats and dogs. It is very important that pets with CKD have their blood pressures measured frequently as many animals do not show clinical signs associated with hypertension. Left untreated, hypertension may lead to end organ damage (kidneys, brain, eyes, and heart). For example, a common presenting signs of hypertension in cats is acute blindness due to retinal detachment. Immediate and aggressive control of the blood pressure may allow the retinas to reattach and the pet may regain some vision.

Blood pressure measurements should ideally be done by the same individual in a quiet room, after the animal has been allowed to acclimate to the surroundings. Blood pressure equipment is also very important as the accuracy and precision of many machines is questionable. The current recommendation is that blood pressure be determined using an oscillometric technique in both cats and dogs. Several readings should be obtained and the cuff size and location should be consistent. Studies have demonstrated that hypertension is a risk factor for shortened survival times in dogs with CRF and the same is likely true of cats.

The difficulty and variability encountered when measuring blood pressure in dogs and cats has contributed to the lack of consensus as to what blood pressure values constitute true hypertension. The following hypertension classification system is based on the 2003 ACVIM hypertension consensus group findings and is the same system advocated by IRIS.
Table 3: Risk Associated with systolic blood pressure in cats and dogs with CKD

<table>
<thead>
<tr>
<th>Blood Pressure Sub-stage</th>
<th>Systolic Blood Pressure</th>
<th>If breed specific reference range is available</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 minimal risk</td>
<td>&lt; 150</td>
<td>&lt;10mmHg above reference range</td>
</tr>
<tr>
<td>1 low risk</td>
<td>150-159</td>
<td>10-20 mmHg above reference range</td>
</tr>
<tr>
<td>2 moderate risk</td>
<td>160 – 179</td>
<td>20-40mmHg above reference range</td>
</tr>
<tr>
<td>3 high risk</td>
<td>≥ 180</td>
<td>≥ 40mmHg above reference range</td>
</tr>
<tr>
<td>No complications (NC)</td>
<td>No evidence of end organ damage/complications</td>
<td></td>
</tr>
<tr>
<td>Complications (C)</td>
<td>Evidence of end organ damage/complications</td>
<td></td>
</tr>
<tr>
<td>Risk not determined (RND)</td>
<td>Blood pressure not measured</td>
<td></td>
</tr>
</tbody>
</table>

Management of CKD: A Staged Approach

The general goals of medical management of patients with chronic primary kidney disease are to: (1) ameliorate clinical signs of uremia, (2) minimize disturbances associated with excesses or deficits of electrolytes, vitamins, and minerals, (3) support adequate nutrition by supplying daily protein, calorie, and mineral requirements, and (4) minimize progression of kidney disease. Although all treatment regimens must be tailored to the individual patient, some general recommendations can be made for patients at each stage of chronic kidney disease. Each patient should have a thorough evaluation to identify any clinical abnormalities that may potentially be improved with therapy. Some clinical abnormalities are more likely to be seen at certain stages of disease, however there may be many exception so careful evaluation is important. It is equally important that patients are closely monitored after any therapeutic intervention to ensure that the therapeutic goals have been met.

Stage 1 CKD

Once a diagnosis of stage 1 CKD has been made, it is important that all potentially nephrotoxic drugs are discontinued and the patients remaining renal function is protected. The patient should be evaluated to ensure that they do not have treatable conditions such as pyelonephritis. In addition, the presence of urolithiasis should be ruled out using radiographs and/or abdominal ultrasound. This is particularly important in cats as nephrolithiasis and ureteral obstruction is an emerging cause of CKD in this species. Additionally, it is important that patients with any stage of CKD remain well hydrated at all times to preserve remaining renal function.

Hypertension

As discussed above, hypertension may lead to progressive CKD and may develop at any stage of CKD. Once confirmed, hypertension should be aggressively managed, although sudden or excessive decreases in blood pressure should be avoided. Our goal is to reduce the systolic blood pressure to <160mmHg to minimize the risk of systemic
Amlodipine (a calcium channel blocker) is currently the drug of choice for managing hypertension in cats. It has been shown to be effective in at least one clinical trial in lowering blood pressure. In contrast to amlodipine, ACE inhibitors and Beta-blocking drugs have not appeared to be as effective in lowering blood pressures in cats. Hypertension in dogs may be managed successfully with calcium channel blockers, ACE inhibitors or a combination of the two. If adequate blood pressure control is not attained with the use of a single agent, combination therapy is recommended.

**Proteinuria**
As with hypertension, proteinuria may occur at any stage of kidney disease. It is important that proteinuric animals be thoroughly evaluated to identify and concurrent disease process that could be potentially treated. If an underlying cause for the proteinuria can not be identified, a kidney biopsy may be indicated, especially in markedly proteinuric animals.

Dogs and cats with stage 1 CKD should be treated for proteinuria if their UPC > 2.0. If the proteinuria is borderline, careful monitoring is recommended. The use of ACE inhibitors to control proteinuria is recommended for dogs and cats. It is important that the patient be well hydrated before therapy with an ACE inhibitor is initiated to avoid a precipitous drop in glomerular filtration rate. It is strongly recommended that therapy be instituted at the lower end of the dosage range and gradually increased while monitoring the effect. Renal values and systemic blood pressure should be reassessed 5 days after beginning therapy to ensure that there has not been a negative impact on renal function. If adequate control of the proteinuria is not attained with an ACE inhibitor, the concurrent use of an angiotensin receptor blocker may be useful.

Additional therapies that should be considered in proteinuric animals with any stage of CKD include the use of low-dose acetylsalicylic acid (0.5mg/kg/d in dogs and every 3 days in cats) if the serum albumin concentration is <2.0g/dl. The use of a renal diet is also recommended for proteinuric animals.

**Hydration**
It is very important that patients with kidney disease always remain well hydrated. Patients with any stage of kidney disease are particularly at risk for dehydration when they are not feeling well or have had limited access to water (ex. if their water bowl becomes empty during the day) or they are not eating or drinking. Their kidneys no longer have the ability to conserve water when intake is low, so they continue to lose water through their urine.

Owners should be instructed on the basics of assessing hydration. The clinical signs of dehydration discussed below are very subjective but serve as a guide for detecting dehydration. Hydration status can be assessed in the following ways:

1. Owners should be instructed to gently pick up the skin on the back of the neck or shoulders and release it. The skin should slide right back down onto the body and not stay tented up. As animals get older, their skin becomes less elastic, which increases the time it takes to snap back during this test. Because of this, it is important to be familiar with how long it takes for each animals skin to return to normal position when they are well hydrated.
2. Eye position: As patients become dehydrated, their eyes can appear sunken into their heads. Owners should pay attention to the normal relationship between the inside corners of the pet’s eyelids in relation to the eyeball. If the distance...
increases, they may be dehydrated. This change usually does not occur until the patient is significantly dehydrated, and behavioral changes will likely be noted before this stage.

3. Check the mouth. The patient's gums should be wet and slippery to the touch. If they become sticky or dry, they may be dehydrated.

Patients that develop recurrent episodes of signs consistent with dehydration are candidates for intermediate-to long-term fluid support. For example, many cats with kidney disease present frequently to the veterinarians office for constipation. This may indicate chronic low grade dehydration. If simple management techniques (water fountains, flavoured water, multiple water bowls, etc.) do not provide adequate hydration, an enteral feeding tube or subcutaneous fluid therapy should be considered. Normal saline or lactated Ringer's solutions are the fluids most commonly used for home subcutaneous fluid therapy. They are well tolerated by most cats and dogs and appear to be reasonable choices for most patients. However, chronic administration of lactated Ringer's solution or normal saline may contribute to the progression of kidney disease because of the associated salt load. Unfortunately there is no way to administer free water to a patient via SQ fluids. By necessity, SQ fluids must be an electrolyte balanced solution. We recommend that patients requiring long term fluid support receive an enteral feeding tube. Esophagostomy tubes are well tolerated long term by both dogs and cats, and allow for the administration of free water in addition to providing a means to supplement nutrition and administer medications.

Stage 2 CKD
The therapeutic recommendations for patients with stage 2 CKD include all of the recommendations described for stage 1 along with the following. The intervention point for the treatment of proteinuria should be reduced to 0.5 in dogs and 0.4 in cats.

Serum Phosphorous
Dogs with stage 2 CKD may have elevations in their serum phosphate levels. Dietary phosphate restriction should be employed to maintain the serum phosphorous below 4.5mg/dl (<1.54mmol/l), but not less than 2.7mg/dl (>0.9mmol/l). Many cats with stage 2 CKD will have a normal serum phosphorous level, but may have an elevated PTH. Limiting dietary intake of phosphate and, if necessary, administering intestinal phosphate binding agents such as aluminum hydroxide should minimize phosphate absorption from the intestinal tract and resulting hyperphosphatemia. The ultimate goal of therapy is to prevent or minimize renal secondary hyperparathyroidism and its various adverse consequences. Dietary phosphate restriction is an important and effective first step toward normalizing phosphate balance because it may normalize serum phosphate concentrations in mild to moderate CRF, and it reduces the quantity of phosphate that must be bound by intestinal phosphate binding agents should their use becomes necessary. Serum phosphate concentrations should be determined after the patient has been consuming the phosphate-restricted diet for about 2 to 4 weeks.

Because the primary goal is limiting absorption of phosphate contained in the diet, administration of phosphate binding agents should be timed to coincide with feeding. These agents are best administered with or mixed into the food, or just prior to each meal. Aluminum-containing intestinal phosphate binding agents are quite effective for binding phosphate. The potential for toxicity of aluminum salts in dogs and cats has been confirmed with prolonged high dosages, and in cases where there has been minimal renal function (ie. dialysis dependent patients).
If adequate phosphorous control is not achieved with aluminum hydroxide therapy, concurrent administration of an additional phosphorous binder, which works by a different mechanism, is indicated. Our preference is to use Lanthanum carbonate (Fosrenol®). Sevelamer hydrochloride has also been used, but anecdotally does not appear to be as effective as Lanthanum. Experience with these drugs in dogs and cats is limited.

**Metabolic Acidosis**

Animals with kidney disease are often not able to clear acids effectively in urine. They also tend to lose an excessive amount of bicarbonate. The net result is a state of metabolic acidosis. (Blood bicarbonate < 18mmol/l) Several clinical signs have been associated with metabolic acidosis including increased protein catabolism, anorexia, nausea, vomiting, lethargy, muscle wasting, and malnutrition. Therapy for metabolic acidosis should be considered when the blood bicarbonate concentration consistently remains below 18mEq/l on consecutive determinations.

Treatment options for metabolic acidosis include alkalinization using diet, sodium bicarbonate, or potassium citrate. Most diets formulated specifically for animals with renal failure are designed to be neutral to slightly alkalinizing. Often, early acidosis may be controlled with diet alone. However, if the acidosis persists or worsens, oral alkalinization with sodium bicarbonate or potassium citrate should be considered. Response to therapy should be assessed after 10-14 days with a blood bicarbonate concentration. Ideally the sample should be collected just prior to administration of the drug. The dosage of medication should be adjusted to maintain the blood bicarbonate concentration within the normal range.

**Stage 2: additional recommendations for cats**

Additional recommendations for cats with stage 2 CKD include the strict use of a renal diet once the serum creatinine is >2.0mg/dl (>179μmol/l), and the correction of hypokalemia, if present.

**Dietary modifications in CKD**

Diet therapy has been the cornerstone in the management of canine and feline chronic kidney disease (CKD) for decades. There is grade 1 evidence to support the recommendation to feed a renal diet to dogs and cats with serum creatinine in excess of 2.0mg/dl (176μmol/l); CKD stages 3 and 4 in dogs and mid stage 2 through 4 in cats. In the past, the emphasis has been on reducing the protein content of the diets. Although protein content continues to play an important role in diet formulation, other diet modifications are also very important in managing patients with kidney disease. Compared to adult maintenance diets, diets formulated specifically for dogs and cats with chronic kidney disease typically have reduced protein, phosphorus, and sodium content; increased potassium, B-vitamin content and caloric density; a neutral effect on acid-base balance; and an increased omega-3/omega-6 polyunsaturated fatty acid (PUFA) ratio.

Although the ideal quantity of protein to feed dogs and cats with CKD remains unresolved, a general consensus of opinion supports the fact that reducing protein intake improves clinical signs in animals with kidney disease; especially stages 3 and 4.
Many of the uremic toxins are actually by-products of protein metabolism. When not excessive, limiting protein intake does not appear to have any adverse effects, and it may be easier to initiate treatment with renal diets before the onset of clinical signs of uremia. In addition, protein restriction may delay onset of clinical signs of uremia as renal disease progresses.

Many owners (and veterinarians!) are reluctant to use a renal diet as they feel that reduced palatability will adversely affect the patients food intake and nutritional status. There are some “do’s and don’ts” that are helpful to remember when recommending a diet change. While some patients easily transition from one diet to another, others (especially cats) are very selective and may require more coaxing to induce diet change. In general, it is probably best to recommend that diet changes be made very slowly rather than abruptly. Most patients can be transitioned onto a new diet in 2-3 weeks by gradually mixing the new diet into the old diet. In my experience, cats are more likely to accept a new diet if transitioned over 3 weeks. Clinical signs of uremia should be controlled prior to the introduction of a new diet. Attempting to introduce a new diet when an animal is nauseated is likely to result in food aversion.

In general, it is best to start by using the same form of diet the patient is used to eating (i.e. dry food versus canned food). Often the addition of flavour enhancers (low sodium chicken broth, tuna juice, etc, encourage food consumption. It is best to avoid additives that contain excessive protein, phosphorus, or salt.

It is important to consider metabolic causes for anorexia before assuming that poor appetite is diet-related. A variety of metabolic causes may be associated with poor appetite in dogs with renal insufficiency including: 1) anemia, 2) uremic gastritis, 3) dehydration, 4) metabolic acidosis, 5) hypokalemia, and 6) renal secondary hyperparathyroidism. Most of these conditions can be managed with appropriate therapy.

Providing frequent small meals may be helpful in increasing calorie intake in patients that are partially anorexic. Medications should not be mixed with the food as they may alter taste resulting in food aversion. If the patient is showing a progressive decline in body condition, an enteral feeding tube (esophagostomy or gastrostomy) should be recommended for longer-term nutritional support.

**Hypokalemia**

Hypokalemia is quite common in cats with stage 2-4 CKD, but less common in dogs. Clinical signs of hypokalemia may include muscle weakness and further impairment of kidney function. Renal diets are generally supplemented with potassium, however, some patients still require oral or parenteral administration of potassium salts. Potassium gluconate and potassium citrate are the preferred salts for oral administration; potassium chloride is used parenterally. It is important to avoid administering potassium chloride by mouth as it is likely to induce vomiting. Potassium should not be administered in subcutaneous fluids as it is quite painful in concentrations greater than 4mEq/L (the concentration found in LRS).

**Stage 3 CKD**

Management of patients with stage 3 CKD include all recommendations for stages 1 and 2 in addition to those listed below.
Dogs with stage 3 CKD should be fed a renal diet. There is grade 1 evidence to support the use of a renal diet in dogs with serum creatinine concentrations > 2.0mg/dl (179µmol/l).

In both dogs and cats the target serum phosphorous concentrations is raised to 5.0mg/dl (1.6mmol/l)

**Calcitriol therapy**

There is evidence to suggest that the judicious use of calcitriol in dogs with stage 3-4 CKD may prolong survival where serum phosphorous is controlled and ionized calcium and PTH are very closely monitored. There is no evidence to suggest beneficial effect of low dose calcitriol in cats to date.

The kidneys are responsible for converting 25-hydroxycholecalciferol to its most active metabolite, 1,25-dihydroxycholecalciferol, or calcitriol. Calcitriol is the major renal hormone responsible for calcium metabolism. Among its important functions is modulation of parathyroid hormone activity at the transcriptional level. Because CKD may impair production of calcitriol, calcitriol deficiency may be one factor promoting renal secondary hyperparathyroidism. Calcitriol supplementation has been advocated as a means of normalizing hyperparathyroidism. PTH has been proposed to act as a “uremic toxin.” Thus, supplementing calcitriol may ameliorate a variety of supposed toxic effects of PTH in CKD. Dogs and cats appear to require lower dosages of calcitriol than those recommended for humans (on a per weight basis). Dosage recommendations have varied widely. In dogs, the average dosage required to control PTH levels is suggested to be 2.5ng/kg.

Although potentially beneficial in CKD patients, vitamin D therapy must be undertaken with great caution because hypercalcemia is a frequent and potentially serious complication. Calcitriol therapy does not directly impair renal function, but sustained vitamin D-induced hypercalcemia can result in reversible or irreversible reduction in GFR. Hypercalcemia reportedly occurs in 30% to 57% of humans treated with 1,25-dihydroxycholecalciferol. Chew and colleagues reported that hypercalcemia was an uncommon side-effect in dogs with CRF when calcitriol was administered at low dosages. However, hypercalcemia was reported to occur when calcitriol therapy was combined with calcium-containing phosphate binding agents. Because hyperphosphatemia enhances the tendency for vitamin D therapy to promote renal mineralization and injury, serum phosphate concentration must be normalized before initiating vitamin D therapy. In general, patients should not receive vitamin D therapy unless serum calcium and phosphate concentrations will be carefully monitored throughout treatment.

Serum total and ionized calcium concentrations must be monitored during therapy with calcitriol to prevent hypercalcemia. Hypercalcemia may develop at any point during therapy with calcitriol. Calcitriol's rapid onset (about 1 day) and short duration of action (half-life less than 1 day) permits rapid control of unwanted hypercalcemia, but early detection of hypercalcemia is indicated to limit the extent of renal injury. Particular care should be taken in cats due to their propensity for forming calcium containing nephroliths. Although calcitriol has not definitively been associated with an increased risk of calcium oxalate stone formation, any factor that could potentially increase the risk for stones formation should be critically evaluated prior to implementation. The recommended endpoint of calcitriol therapy is normalization of PTH activity. This implies that PTH levels and ionized calcium concentration should be evaluated prior to instituting therapy and periodically during therapy to minimize the potential side effects of the drug.
Anemia
It is very common for patients with chronic kidney disease to develop anemia in stage 3-4 CKD. As functional kidney mass declines, the kidneys are no longer able to produce enough of the hormone called erythropoietin. Erythropoietin (EPO) is a hormone that is normally produced by the kidneys when they sense that the body requires more red blood cells. Once produced by the kidneys, EPO travels to the bone marrow where it stimulates the production of new red blood cells. As functional kidney mass decreases, the levels of EPO produced also decrease, and red blood cell production falls. To correct the anemia, we must supply the missing hormone. EPO is commercially available as Epogen® or Procrit®. However, because these products are designed to replicate the human version of the protein we may run into problems in dogs and cats. The human version of the protein may be recognized as foreign and the pet’s immune system may try to clear the EPO from their system. If this immune response develops, the EPO will become ineffective.

There is a new synthetic version of EPO (darbropoitin; Aranesp®) available that seems to be very promising in dogs and cats. Aranesp has several features that are likely to make an immune reaction less likely and therefore we prefer this drug over traditional EPO. Compared with rhEPO, darbropoitin has a longer half-life and greater potency, enabling clinical efficacy with less frequent administration. Although not yet proven by clinical trial, anecdotal reports suggest that darbropoitin has similar efficacy and safety to erythropoietin, with the significant benefit of decreased incidence of antibody production. We have used darbropoitin exclusively for the past several years and have found it to be a reliable and safe treatment for the anemia of CKD.

It is important to note that anabolic steroids are of no proven benefit and may be detrimental.

Gastrointestinal Signs
During stage 3 CKD, some patients will begin to show evidence of gastrointestinal signs. Kidney disease can directly and indirectly cause vomiting due to the accumulation of uremic toxins within the blood. Vomiting secondary to uremia is mediated both centrally due to the direct effects of uremia toxins on the chemoreceptor trigger zone in the brain, and peripherally due to gastrointestinal irritation. Treatment options include a variety of antacids and anti-emetics. Antacids, such as H2 receptor antagonists and proton pump inhibitors, may help alleviate side effects of gastritis and enteritis. Anti-emetic choices include dopaminergic antagonists such as metoclopramide, alpha-2 adrenergic antagonists such as prochlorperazine, 5HT3 receptor antagonists such as ondansetron, and the newly developed NK1 receptor antagonist maropitant.

If decreased appetite is persistent despite correction or management of these secondary causes, appetite stimulants including cyproheptadine or mirtazapine may be used short term. However, for long term nutritional support, an enteral feeding tube should strongly be considered. Anecdotal reports suggest that tube feeding can reverse the progressive weight loss associated with chronic kidney disease and improve overall quality of life. Options include either esophagostomy tubes or percutaneous gastrostomy tubes. Tube placement requires anesthesia, but can be readily performed in a short time period, and feeding tubes can remain in place as long as necessary for supportive care.

Dose-adjusting Medications
Many medications require renal elimination from the body and should thus be used with
caution in patients with stage 3-4 CKD. It may be necessary to adjust the dosage or frequency of administration to prevent excessive serum levels of some medications. Some medications may need to be avoided all together.

**Stage 4 CKD**
Management of patients with stage 4 CKD include all recommendations for stages 1 through 3 in addition to those listed below.
In both dogs and cats the target serum phosphorous concentrations is raised to 6.0mg/dl (1.9mmol/l)

Aggressive management of nutrition and hydration is indicated for patients with stage 4 CKD. Assisted feeding with enteral feeding tubes should be considered for all patients who are unable to maintain their hydration without the use of parenteral fluids and for all patients that are unable to maintain their lean body mass.

If the patient’s quality of life can not be maintained with aggressive medical management as described above, hemodialysis (dogs and cats) or renal transplantation (cats) should be considered.

**Patient Monitoring**
Response to treatment should be monitored at appropriate intervals so that treatment can be individualized to the specific, and often changing, needs of the patient. The database obtained before initiation of conservative medical management should be used as a baseline for comparison of the patient's progress. This evaluation should be repeated at appropriate intervals which vary according to specific needs of the patient. Immediately following initiation of therapy, patients should be monitored every 2 to 4 weeks to assess the response to therapy. The frequency of evaluation may vary depending on severity of renal dysfunction, complications present in the patient, and response to treatment. Certain forms of therapy, such as administration of darbepoietin, may also necessitate more frequent patient monitoring. Frequent evaluations allow for the early detection and management of many complications associated with CKD. Frequent monitoring also encourages owner compliance, thereby improving the quality of care between office visits as well.