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 AND DIAGNOSING KIDNEY DISEASE

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 suggestive of kidney disease may also be found by physical examination or from the medical history (eg, changes in kidney size or shape, changes in urine volume). 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 an irreversible disease that is often progressive, whereas AKI may be reversible.
CKD is defined as kidney disease that has been present for an extended period. Kidney disease that has been present 3 months or longer may be considered to be chronic.1 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 CKD**

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...

---

<table>
<thead>
<tr>
<th>Blood Markers</th>
<th>Urine Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated blood urea nitrogen concentration</td>
<td>Impaired urine concentrating ability</td>
</tr>
<tr>
<td>Elevated serum creatinine concentration</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Cylindruria</td>
</tr>
<tr>
<td>Hyperkalemia or hypokalemia</td>
<td>Renal hematuria</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Inappropriate urine pH level</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Inappropriate glucosuria</td>
</tr>
<tr>
<td>Imaging markers-abnormalities in kidney:</td>
<td>Cystinuria</td>
</tr>
<tr>
<td>Size</td>
<td>Density</td>
</tr>
<tr>
<td>Shape</td>
<td>Number</td>
</tr>
<tr>
<td>Location</td>
<td>Mineralization</td>
</tr>
</tbody>
</table>

* Markers must be confirmed to be of renal origin to be evidence of kidney damage. For example, hypoalbuminemia due to urinary protein loss is evidence of kidney disease, whereas hypoalbuminemia due to hepatic failure is not.


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<table>
<thead>
<tr>
<th>Characteristics of CKD</th>
<th>Characteristics of AKI</th>
<th>Reliability for Differentiationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss &gt;3 mo</td>
<td>Normal BCS</td>
<td>++</td>
</tr>
<tr>
<td>Reduced appetite &gt;3 mo</td>
<td>Recent reduction of appetite</td>
<td>++</td>
</tr>
<tr>
<td>Poor hair coat</td>
<td>Healthy hair coat</td>
<td>+</td>
</tr>
<tr>
<td>PU/PD &gt;3 mo</td>
<td>Recent change in urine volume</td>
<td>++</td>
</tr>
<tr>
<td><em>Uremic breath</em> &gt;3 mo</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Small kidney size</td>
<td>Normal/large kidneys</td>
<td>+++</td>
</tr>
<tr>
<td>Renal osteodystrophy</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Clinical signs mild despite marked azotemia</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Hypoproliferative anemia</td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

*Abbreviations: BCS, body condition score; PU/PD, polyuria-polydipsia.

a Reliability: + = weak; ++ = moderate; +++ = strong.
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 2 serum creatinine values obtained when the patient has been fasted and is well hydrated. Also, 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 determining 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 nonproteinuric; borderline proteinuric, or proteinuric (see Table 4).

As with proteinuria, arterial pressure (AP) should ideally be determined 2 to 3 times over several weeks to establish the blood pressure classification. The AP classification should be based on the lowest repeatable blood pressure values obtained.

**Conservative Management of CKD**

Conservative medical management of CKD includes therapies other than treatment of active renal diseases (eg, pyelonephritis, urinary obstruction), dialysis, or transplantation. The therapies are designed to (1) prevent and/or treat complications of decreased kidney function, (2) manage comorbid conditions that accompany kidney disease (see Table 5), and (3) slow down loss of kidney function. In planning conservative medical management, it is important to recognize and specifically treat active renal diseases in the 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 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 to 4. Results of several clinical trials strongly support the beneficial effect of renal diets in preventing or delaying the onset of uremia and premature death due to complications of CKD. Also, renal diets have been shown to maintain or improve nutrition, and owners report higher quality-of-life scores than with maintenance diets.1,3

<table>
<thead>
<tr>
<th>Table 3</th>
<th>IRIS stages of CKD in dogs and cats</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td><strong>Serum Creatinine Values (mg/dL/μmol/L)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dogs</strong></td>
</tr>
<tr>
<td>Stage 1</td>
<td>&lt;1.4/&lt;125</td>
</tr>
<tr>
<td>Stage 2</td>
<td>1.4–2.0/125–179</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2.1–5.0/180–439</td>
</tr>
<tr>
<td>Stage 4</td>
<td>&gt;5.0/&gt;440</td>
</tr>
</tbody>
</table>

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 important and effective as protein restriction or more so. Consequently, 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, neutral effect on acid-base balance, supplementation of omega-3 polyunsaturated fatty acids, and addition of antioxidants. Feline renal diets are supplemented with potassium.

Although 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 renal diet may be made available while gradually reducing the amount of the old diet. 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 with uremia or experiencing any medical issue that may promote a dietary aversion is likely to be doomed 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. The primary goal is to assure adequate food intake, stable body weight, and body condition score at or near 5 out of 9. Patients not meeting nutritional goals should be evaluated for uremic complications, dehydration,

### Table 4
Classification of proteinuria by urine

<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>Nonproteinuric (NP)</td>
<td>&lt;0.2</td>
</tr>
</tbody>
</table>

*a Based on the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on Proteinuria (Lees, 2005).

### Table 5
IRIS* Arterial pressure (AP) stages for dogs and cats

<table>
<thead>
<tr>
<th>AP Stage</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>&lt;150 mm Hg</td>
<td>&lt;95 mm Hg</td>
</tr>
<tr>
<td>Stage I</td>
<td>150 to 159 mm Hg</td>
<td>95–99 mm Hg</td>
</tr>
<tr>
<td>Stage II</td>
<td>160 to 179 mm Hg</td>
<td>100–119 mm Hg</td>
</tr>
<tr>
<td>Stage III</td>
<td>≥180 mm Hg</td>
<td>≥120 mm Hg</td>
</tr>
</tbody>
</table>

and progression of CKD, metabolic acidosis, anemia, electrolyte abnormalities, urinary tract infection, and non-urinary tract diseases. Also, 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. Also, feeding tubes simplify drug administration.

**MANAGING GASTROINTESTINAL SIGNS OF UREMIA**

Gastrointestinal complications of CKD, including reduced appetite with reduced 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 blood urea nitrogen (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 the most commonly used 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 hydrochloride or dolasetron mesylate and maropitant citrate, the neurokinin (NK1) receptor antagonist. 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.7,8 Sucralfate should be added when gastrointestinal ulcerations and hemorrhage are suspected.

**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 (Pₘₐₓ) 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.9–13 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, Pₘₐₓ typically remain within the normal range because of a compensatory reduction in phosphorus 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 after phosphorus retention, even though $P_s$ 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, have been shown to predict progression of CKD. The association between phosphorus retention and progression of CKD provides the basis of the recommendations for managing $P_s$ in dogs and cats with CKD.

Therapeutic management of $P_s$ is indicated for dogs and cats with CKD stages 2 to 4. The goal of therapy is to maintain $P_s$ 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 $P_s$ target ranges are less than 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 $P_s$ is 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 in CKD stage 3. Approximately 4 to 6 weeks after initiating dietary therapy, $P_s$ should be measured to determine whether the treatment target has been met. Samples obtained for determinations of $P_s$ should be collected after a 12-hour fast to avoid postprandial hyperphosphatemia. If after 4 to 8 weeks, the target $P_s$ has not been achieved, adding 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 around mealtime. If the patient is fed more than once daily, the total daily dose of phosphate binder should be divided and a portion administered with every meal. Administering the binders away from mealtime 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 seem to be well tolerated and safe in dogs and cats, aluminum toxicity characterized by neurologic signs and microcytosis has been reported in dogs with

<table>
<thead>
<tr>
<th>Ranges Adjusted for CKD Stages$^a$</th>
<th>Target Serum Phosphorus Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>3.5–4.5 mg/dL</td>
</tr>
<tr>
<td>Stage 3</td>
<td>3.5–5.0 mg/dL</td>
</tr>
<tr>
<td>Stage 4</td>
<td>3.5–6.0 mg/dL</td>
</tr>
</tbody>
</table>

$^a$ Ref. 13
advanced CKD treated with high doses of aluminum-containing phosphate-binding agents.\textsuperscript{15}

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 is 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 seem 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 is adjusted upward as needed every 4 to 6 weeks until the therapeutic target is reached.

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

Metabolic Acidosis

The decision to treat metabolic acidosis should be based on laboratory assessment of the patient’s acid-base status, preferably based on blood gas analysis. It has been reported that metabolic acidosis occurs in less than 10% of cats with stages 2 and 3 CKD but in nearly 50% of cats with overt signs of uremia.\textsuperscript{16} Metabolic acidosis has been incriminated in promoting progression of CKD and impairing protein nutrition.\textsuperscript{17–20} Recently, bicarbonate therapy in humans with CKD has been reported to slow progression of CKD and improve nutritional status.\textsuperscript{21}

Alkalinization therapy is indicated for dogs and cats with CKD stages 1 to 4 when blood pH level and bicarbonate concentration drop below the normal range. Changing to a renal diet may improve acidosis by providing a pH-neutral diet. When diet alone is insufficient, administration of an alkalinizing salt, usually sodium bicarbonate or potassium citrate, is indicated. Potassium citrate offers the advantage of using a single drug to treat hypokalemia and acidosis. Starting dosages of 40 to 60 mg/kg every 8 to 12 hours are recommended. Dosage of sodium bicarbonate is 8 to 12 mg/kg body weight given orally every 8 to 12 hours. It is available as 5- and 10-grain tablets. Response to alkalinization therapy should be assessed by performing blood gas analysis 10 to 14 days after initiating therapy and dosage adjusted until normalized. Urine pH level is an unreliable means of assessing the need for or response to treatment.

Hypokalemia and Hyperkalemia

Hypokalemia and potassium depletion are fairly common in cats with CKD stages 2 and 3, but they are recognized less commonly in CKD stage 4, because the marked reduction in glomerular filtration rate is more likely to promote potassium retention and hyperkalemia. The prevalence of hypokalemia in cats with CKD stages 2 and 3 is reportedly in the range of 20% to 30%.\textsuperscript{16,20,22} The cause of hypokalemia in cats with CKD has not been fully elucidated, but inadequate potassium intake, increased urinary loss, and enhanced activation of the renin-angiotensin-aldosterone system due to dietary salt restriction may play a role.\textsuperscript{23} Also, amlodipine may promote hypokalemia in cats with CKD.\textsuperscript{24}
Hypokalemia may be associated with hypokalemic myopathy, progressive renal injury, polyuria, and polydipsia. Increasing the potassium content of renal diets has reduced the incidence of overt clinical signs of hypokalemia, but hypokalemia remains a common laboratory finding in cats with CKD.

Cats with hypokalemia should receive potassium supplementation. Oral replacement is the safest and preferred route for administering potassium; parenteral therapy is generally reserved for patients requiring emergency reversal of hypokalemia or when they cannot or will not accept oral therapy. Up to 30 mEq/L of potassium chloride may be added to fluids to be administered subcutaneously.

Potassium gluconate or citrate are good choices for oral supplementation; however, potassium chloride is not recommended because it is acidifying and unpalatable. Depending on the size of the cat and severity of hypokalemia, the dosage for potassium gluconate (Tumil-K) ranges from 2 to 6 mEq per cat per day. Potassium citrate solution (Polycitra-K Syrup) is an excellent alternative that has the advantage of providing simultaneous alkalinization therapy. Potassium citrate is initially given at a dosage of 40 to 60 mg/kg/d divided into 2 or 3 doses. If hypokalemic myopathy is present, it usually resolves within 1 to 5 days after initiating parenteral or oral potassium supplements. Thereafter, potassium dosage should be adjusted based on the clinical response of the patient and serum potassium determinations. Serum potassium concentration should be monitored every 7 to 14 days and the dosage adjusted accordingly to establish the final maintenance dosage. It is unclear whether all cats require or benefit from long-term potassium supplementation; however, preliminary evidence suggests that such therapy may be required, at least by some older cats with CKD.

Diets low in potassium and high in acid content have been implicated in impairing renal function and promoting development of lymphoplasmacytic tubulointerstitial lesions in cats. Consequently, prophylactic supplementation of low oral daily dosages of potassium (2 mEq/d) has been recommended for cats with CKD. This recommendation seems to be based on the as yet unproven hypothesis that in some cats with CKD, hypokalemia and potassium depletion might promote a self-perpetuating cycle of declining renal function, metabolic acidosis, and continuing potassium losses. It is proposed that supplementation may stabilize renal function before potassium depletion exacerbates the disease. However, the value of prophylactic potassium supplementation in normokalemic cats has yet to be established.

**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 (eg, pyrexia, vomiting, or diarrhea) promote dehydration. Cats with CKD seem 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 may predispose to AKI. Additional loss of kidney function due to AKI is an important cause of CKD progression. 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 done through intravenous or subcutaneous administration depending on the severity of dehydration and the 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 benefits from fluid therapy; the decision to recommend administration of subcutaneous fluids should be made on a case-by-case basis. Cats seem more likely to benefit than dogs.

For long-term administration, a balanced electrolyte solution (eg, lactated Ringer’s solution) is administered subcutaneously every 1 to 3 days as needed. The volume to be administered depends on patient size; a typical cat requires about 75 to 100 mL per dose. If the clinical response of the patient is suboptimal, the dose may be increased cautiously. However, overzealous fluid administration may subject the patient to fluid overload. Balanced electrolyte solutions do not provide electrolyte-free water; a more physiologically appropriate approach is to provide water via a feeding tube. Furthermore, evidence suggests that excessive sodium intake may be harmful to the kidneys, and excessive salt intake may impair effectiveness of antihypertensive therapy.31

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 reassessed.

**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. Optimal 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 an 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 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 optimal therapeutic response requires all factors contributing to the patient’s anemia to be addressed.

Erythropoietin products most commonly used 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 increase in hematocrit, resulting in correction of anemia and its associated clinical signs within approximately 2 to 8 weeks.32 Although EPO is usually effective in correcting anemia of CKD, initially; development of antibodies directed at EPO may render it ineffective. Furthermore, 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. Hence, 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 fairly advanced CKD, clinical signs attributable to anemia, and hematocrit values less than about 22 vol%. Hormone replacement therapy with recombinant human erythropoietin (rHuEPO) is described elsewhere.\(^1\)

DPO (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 antierthropoietin antibodies, perhaps because of the structural modifications responsible for its longer duration of action. Unlike EPO, DPO is supplied in micrograms rather than units, with 1 \(\mu\)g of DPO being the equivalent of 200 units of EPO. Patients currently receiving EPO may be switched to an EPO-equivalent dosage of DPO (the product package insert should be consulted for details), but with a dosing interval that is extended threefold.

Therapy with DPO includes an induction and a maintenance phase. The induction phase is designed to correct anemia and the maintenance phase sustains the normal hematocrit for the remainder of the pet’s life. In the induction phase, DPO is administered at a dosage of 1.5 \(\mu\)g/kg subcutaneous once weekly. Higher doses may accelerate the response to therapy, whereas 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 the frequency of administration of DPO adjusted to maintain the hematocrit in the normal range. Although the optimal therapeutic target hematocrit has not been established for dogs and cats with CKD, a reasonable cost-effective target would be 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.\(^{33}\) Once the hematocrit has been stabilized within the target range, it 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 preexisting iron overload exhaust iron storage during erythropoietin therapy. The same seems 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 (50–300 mg) should be provided at the time that EPO or DPO are initiated.

The most important complications associated with hormone replacement therapy are refractory anemia and hypoplasia of the erythroid bone marrow associated with formation of neutralizing antierthropoietin antibodies.\(^{32}\) A test for antierthropoietin antibodies is not currently available. However, in the absence of an identifiable cause for treatment failure, the failure of an increase in EPO or DPO dosage to increase hematocrit strongly suggests development of antierthropoietin antibody formation. Demonstrating an increase in the bone marrow myeloid/erythroid ratio provides further support that erythropoietin resistance results from antibody formation. If antierthropoietin antibody formation is suspected, EPO or DPO therapy should be terminated immediately. Because antierthropoietin antibodies may interfere with administered
and endogenous erythropoietin, anemia may become worse than before initiation of
erthropoietin therapy. However, antibody titers typically decline with cessation of
therapy, and early recognition of the development of antierythropoietin antibodies mini-
mizes the extent and duration of bone marrow suppression. Persistent administration
of EPO despite formation of antibodies may result in persistence of antibodies. After
therapy is stopped and antibody titers decline, suppressed erythropoiesis may be
reversible and pretreatment 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 main-
tain normal levels.\(^{34}\)

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.\(^{35}\) However, various
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.\(^{36-38}\) These effects seem likely to be important in medi-
at ing the recently recognized benefits of calcitriol for limiting progression of CKD
and improving survival of patients with CKD. A masked, randomized controlled clinical
trial (RCCT) performed on dogs with CKD stages 3 and 4 indicated that calcitriol
therapy increased survival time by slowing progression of CKD (Polzin, unpublished
data, 2006). These findings are consistent with the results of recent studies in human
patients with CKD that demonstrated a similar survival benefit of calcitriol therapy.\(^{39,40}\)
However, an RCCT performed in cats failed to reveal similar benefits for calcitriol
in altering the course of feline CKD (Polzin, unpublished data, 2006). The reason for
these divergent results in cats are unclear but may relate to the fairly indolent course
of CKD in many cats.

Calcitriol therapy is indicated for dogs with CKD stages 3 and 4 (and possibly CKD
stage 2) to slow progressive deterioration in renal function. A recommendation for or
against use of calcitriol in cats with CKD cannot be supported at this time. In prepara-
tion for calcitriol therapy, serum phosphorus should be managed to achieve the treat-
ment 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.\(^{41}\)

Calcitriol should initially be provided at a dosage of 2.0 to 2.5 ng/kg every 24 hours.\(^{1}\)
Ionized calcium and PTH levels should be monitored to establish the proper dose. The
goal is to minimize PTH without inducing hypercalcemia. Because it enhances intes-
tinal 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
absorption.\(^{42}\) Calcitriol dosage should not exceed about 5.0 ng/kg/d. Lifelong treat-
ment is necessary to achieve the desired effect of reduced renal mortality. Details
on dosing and monitoring are available elsewhere.\(^{1}\)

**Managing Proteinuria**

Proteinuria is associated with CKD progression in dogs and cats.\(^{43,44}\) Reducing
proteinuria slows CKD progression in humans; however, evidence supporting this
benefit in dogs and cats is scant. Nonetheless, therapy designed to reduce proteinuria is recommended for dogs and cats in CKD stages 2, 3 and 4 when urine protein/creatinine ratios exceed 0.5 and 0.4, respectively and for dogs and cats with CKD stage 1 and protein/creatinine ratios greater than 2.0.

The standard management of proteinuria in dogs and cats with CKD is to initiate therapy with a renal diet and administer an angiotensin-converting enzyme inhibitor (ACEI) with the therapeutic goal of at least halving the urine protein/creatinine ratio or, ideally, bringing it into the normal range. Initial dosage for the ACEIs enalapril and benazepril in dogs and cats with CKD is 0.25 to 0.5 mg/kg given orally every 12 to 24 hours. Benazepril has been preferred to enalapril, because it is cleared largely by hepatic rather than renal excretion. Occasionally ACEI therapy is associated with a marked decline in kidney function; therefore, serum creatinine levels should be measured before and 1 to 2 weeks after initiating therapy. Large or progressive increases in serum creatinine levels should prompt reassessment of therapy. Dosage of ACEIs should be cautiously increased to maximize the impact on proteinuria. A beneficial effect of enalapril on progression of CKD in dogs has been reported using a dosage of 2.0 mg/kg/d. Serum potassium levels should be monitored, because hyperkalemia is a recognized side effect of ACEI therapy that may limit the dosage increases.

Managing Arterial Hypertension

Arterial hypertension is a common complication of CKD in dogs and cats and has been linked to renal, ocular, neurologic, and cardiac complications. Because no generally agreed value to define arterial hypertension in dogs and cats exists, APs are classified into 4 stages (see Table 5).

The diagnosis of arterial hypertension must be based on measuring blood pressure. Unless there is evidence of retinal lesions or neurologic signs or the systolic blood pressure is greater than 200 mm Hg, the decision to initiate antihypertensive therapy should generally not be considered an emergency. Blood pressure should be confirmed by at least 3 independent measurements, ideally collected over several days to several weeks.

Patients with CKD stages 2 to 4 having arterial blood pressures persistently exceeding 160 over 100 (AP stage II) are candidates for treatment. Treatment should be considered for CKD stage 1 with arterial blood pressures persistently exceeding 180 over 100 (AP stage III).

The optimal endpoint for antihypertensive therapy has not been established for dogs and cats with CKD. Without such information, treatment for arterial hypertension should be initiated cautiously, with the goal of reducing blood pressure to at least below 160 over 100 mm Hg. Except in patients with ocular or neurologic lesions, rapid reduction in blood pressure is not necessary. Particularly in dogs, it may take weeks to months to achieve satisfactory blood pressure control.

ACEIs (eg, enalapril and benazepril) and calcium channel blockers (eg, amlodipine) are the preferred antihypertensive drugs for dogs and cats with CKD, because they have potential renoprotective benefits. Although ACEIs generally produce fairly small reductions in blood pressure, their beneficial role in altering intraglomerular hemodynamics, proteinuria, and profibrotic effects of the intrarenal renin-angiotensin system have been demonstrated. ACEIs may have renoprotective effects, even in the absence of achieving adequate blood pressure control. Dosing of ACEIs for antihypertensive effects is the same as for proteinuria (see earlier discussion).

Clinical experience has shown amlodipine to be an effective antihypertensive agent in dogs and cats with CKD. Also, it has few side effects and relatively rapid onset. In
cats, amlodipine may reduce proteinuria. It is prescribed at a dose of 0.625 mg for cats lighter than 5 kg and 1.25 mg for cats heavier than 5 kg. Dosage may be doubled if needed. In dogs, amlodipine dosage ranges from 0.1 to 0.5 mg/kg given every 24 hours and it should be combined with an ACEI.

**PROGNOSIS OF CKD**

In dogs with CKD stages 3 and 4, the disease tends to be progressive. Most dogs with CKD of this severity die or are euthanized because of their disease. Dogs typically survive for months to a year or two depending on the severity of their kidney disease. Furthermore, proteinuria and arterial hypertension are associated with poorer prognoses, although this may be modifiable to some degree with therapy.43,50

Cats with CKD vary in their clinical course. Some cats have progressive disease similar to dogs, but typically CKD progresses more slowly in cats. Also, some cats with CKD seem to have stable kidney function for many months to years, often dying of causes unrelated to CKD.5 As with dogs, proteinuria heralds a poorer prognosis. Also, the stage of CKD has been shown to be related to outcome.

**FOLLOW-UP MONITORING OF PATIENTS WITH CKD**

Because CKD tends to be progressive, patient needs may change with time. Consequently, regular monitoring of patients is an essential component of the treatment plan. Treatment goals should be clearly recorded and compared with regular measurement of the patient’s progress. Patients in CKD stages 3 and 4 should typically be evaluated every 3 to 4 months approximately. Patients in CKD stages I and II often require less frequent monitoring, every 4 to 6 months approximately, once stable renal function has been established. However, patients with progressive CKD, proteinuria, or arterial hypertension should be monitored more frequently. A typical monitoring visit should include a medical history at least, 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.

**REFERENCES**


