



Evidence-based step-wise approach to managing chronic kidney disease in dogs and cats

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Abstract

Objective – To provide a framework for successfully managing chronic kidney disease (CKD) over an extended period of time with the goal of optimizing clinical outcomes by fostering a veterinarian-client relationship that facilitates successful application of evidence-based treatment.

Etiology – Ultimately, CKD results from loss of functional nephrons; however, the specific disease process responsible for this loss usually cannot be determined due to development of chronic changes (eg, fibrosis) and compensatory adaptations that have occurred in the kidneys of patients with CKD. Earlier diagnosis may foster a better understanding of the etiologies of CKD.

Diagnosis – Diagnosis of CKD is based on establishing loss of kidney function(s) due to primary kidney disease that have been present for an extended time (typically 3 months or longer).

Therapy – The goals of therapy are to: (1) slow progressive loss of kidney function, (2) ameliorate clinical and biochemical consequences of CKD, and (3) maintain adequate nutrition. These goals are achieved by: (1) managing adaptive processes that promote progression of CKD, (2) controlling intake of water, nutrients, minerals and electrolytes, and (3) correcting hormonal deficiencies.

Prognosis – The short-term prognosis for dogs with CKD varies from good to poor, while the long-term prognosis for dogs with CKD is generally guarded to poor depending on the International Renal Interest Society (IRIS) CKD stage of the patient. Both short-term and long-term prognosis for cats with CKD may vary from good to poor depending on the IRIS CKD stage. However, prognosis is more variable and unpredictable in cats.

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Introduction

In contrast to acute disease, management of patients with chronic disease requires ongoing engagement with the pet owner over months to years after initial diagnosis. As a consequence, successful management of chronic diseases will be enhanced by developing a long-term plan that includes: (1) introductory education of the owner concerning their pet's disease and its management, (2) a specific plan for monitoring the patient's progress and response to treatment, and (3) ongoing facilitation of the pet owner's engagement in the treatment plan. It is

Abbreviations

ACEI	angiotensin converting enzyme inhibitor
AKI	acute kidney injury
CCB	calcium channel blockers
CKD	chronic kidney disease
GFR	glomerular filtration rate
IRIS	International Renal Interest Society
UPC	urine protein:creatinine ratio
USG	urine specific gravity

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essential to develop an ongoing relationship with the pet owner because they will be expected to adhere to treatment recommendations and monitoring protocols over a long period. Failure to do so will result in a sub-optimum therapeutic response, which may lead to owner discouragement and unsatisfactory outcomes including premature euthanasia. A well-developed plan for facilitating

Table 1: Checklist for managing chronic kidney disease

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1. Confirm that the patient has kidney disease
 - a. Renal function tests
 - b. Urinalysis, urine protein:creatinine ratio, and/or urine culture
 - c. Imaging studies
 2. Confirm that the kidney disease is chronic
 - a. Medical history
 - b. Physical examination
 - c. Renal imaging studies
 3. Establish the IRIS CKD Stage of the patient
 - a. Two fasting serum creatinine values in a well hydrated patient
 - b. Urine protein:creatinine ratio (2–3 values)
 - c. Arterial blood pressure (2–3 values)
 4. Develop a treatment plan for the patient's CKD
 - a. Determine the treatment options appropriate for the patient
 - b. Prioritize and select which treatment options to recommend based on medical priority and pet owner's preferences (which may include cost, demands on the pet owner, and 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
 - i. Activity
 - ii. Behavior
 - iii. Appetite
 - iv. Owner's perception of the pet's well being
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initial success in implementing the treatment plan early in the course of the disease has the potential to greatly enhance long-term outcome through enhanced compliance (Table 1). After performing many clinical trials, it has become apparent to us that patient outcome is improved through an ongoing active relationship between the pet owner and the veterinarian.

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.” If a treatment plan is too involved, time consuming or expensive or if it impairs the bond between the pet and the owner, it is unlikely to be successful over time. Key factors influencing whether the treatment plan will be acceptable to the owner include: (1) educating the owner concerning what is being done and why, (2) including the owner as a partner in developing a treatment plan that the pet owner can afford and is capable of and willing to administer. Over

time, owner compliance typically declines unless active interactions between the owner and the veterinarian are pursued. In addition to discharge notes and discussions with the pet owner, providing printed or internet-based educational materials on specific treatments can enhance owner understanding of the recommended treatments. Information on how to administer treatments and introduce dietary changes should also be provided.

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. A plan for following the patient's progress should be developed before the pet is discharged. In addition to scheduling a follow-up clinic visit, a veterinary technician familiar with the treatment plan, the pet and the owner should contact the pet owner weekly by phone until the owner is comfortable that the treatment plan is going well and all questions have been satisfactorily answered. An important reason for these calls is to encourage and coach the pet owner to follow the treatment plan. In addition, these calls will provide the opportunity to assess the patient's response to therapy, determine whether there are problems with treatment compliance, and decide whether any warning signs have developed suggesting that a recheck examination or phone discussion with the veterinarian is needed. Important topics to focus on during phone contacts when following a dog or cat with chronic kidney disease (CKD) are activity, behavior and appetite as well as the owner's opinion of the pet's current overall well being. Once the treatment plan and the patient are doing well, less frequent phone contact should nonetheless continue because ongoing owner encouragement and coaching is likely to improve the long-term outcome of the patient. In addition, ongoing contact is likely to improve early recognition of developing complications leading to earlier clinic presentations of patient.

Disease Confirmation and Staging

Diagnosis of kidney disease is usually based on detection of azotemia and exclusion of prerenal and postrenal causes for azotemia. Prerenal azotemia is usually confirmed either by documenting presence of adequate urine concentrating ability (urine specific gravity [USG] values exceeding 1.030 in dogs or 1.035 in cats) concurrent with azotemia or failure of azotemia to resolve with correction of prerenal causes (eg, rehydration of a dehydrated patient). Postrenal azotemia is ruled out on the basis of the medical history (the patient is able to consciously void the full contents of the urinary bladder) and imaging of the urinary tract (absence of abnormal dilation of any portions of urinary collecting system upstream from an obstruction).

Kidney disease may also be confirmed by evidence of structural disease (eg, polycystic kidney disease detected by ultrasonography) or by recognizing specific abnormalities of kidney function (eg, persistent proteinuria originating from the glomerulus or renal tubules, glucosuria that occurs in a patient with euglycemia). These more specific forms of kidney disease may or may not lead to generalized kidney disease and systemic consequences.

Confirming that the disease is chronic

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, while AKI may have the potential to be reversible.

CKD is defined as kidney disease that has been present for an extended period, typically for 3-months or longer.¹ A diagnosis of chronic disease may be supported on the basis of: (1) duration of kidney disease as confirmed by previous laboratory findings or estimated from the medical history (eg, 3+ months of polyuria/polydipsia), (2) physical examination findings consistent with chronic disease (eg, loss of weight and lean body mass; small kidney size), or (3) evidence of chronic structural abnormalities identified through imaging studies or kidney pathology (eg, small kidneys, renal infarcts, renal fibrosis).

Establishing the IRIS CKD stage of CKD

Current clinical practice guidelines for diagnosis, prognosis and treatment of CKD in dogs and cats are largely based on the stage of their disease.¹ Staging of CKD follows guidelines developed by the International Renal Interest Society (IRIS; www.iris-kidney.com) The 4 tier IRIS CKD staging system is based on serum creatinine concentration, the magnitude of proteinuria as measured by the urine protein:creatinine ratio (UPC) and blood pressure (Tables 2–4). Staging CKD in this fashion facilitates application of appropriate treatments recommendations.

The stage of CKD itself is based on at least 2 measurements of the patient’s serum creatinine concentration obtained while the patient is well hydrated and fasted for at least 12 hours. Ideally, serum creatinine values should be determined over several weeks to confirm at least short-term stability of kidney function.

The IRIS CKD stage is then further characterized on the basis of the magnitude of proteinuria and arterial blood pressure. As with serum creatinine, multiple determinations of UPC and blood pressure are necessary to accurately reflect the patient’s disease stage. However,

Table 2: International Renal Interest Society Stages of chronic kidney disease in dogs and cats

Stage	Serum creatinine values (mg/dL)	
	Dogs (mg/dL; mmol/L)	Cats (mg/dL; mmol/L)
IRIS CKD Stage 1	<1.4; <125	<1.6; <140
IRIS CKD Stage 2	1.4–2.0; 125–179	1.6–2.8; 140–249
IRIS CKD Stage 3	2.1–5.0; 180–439	2.9–5.0; 250–439
IRIS CKD Stage 4	≥5.0; ≥440	≥5.0; ≥440

Table 3: Classification of proteinuria by urine protein:creatinine ratio*

Classification	Urine protein:creatinine ratio	
	Dogs	Cats
Proteinuric (P)	>0.5	>0.4
Borderline proteinuric (BP)	0.2–0.5	0.2–0.4
Nonproteinuric (NP)	≤0.2	≤0.2

*Based on ACVIM Consensus Statement on Proteinuria.¹⁶

Table 4: International Renal Interest Society* arterial pressure (AP) stages for dogs and cats

IRIS AP stage	Arterial pressure (AP)	
	Systolic blood pressure	Diastolic blood pressure
Stage 0	<150 mm Hg	<95 mm Hg
Stage I	150–159 mm Hg	95–99 mm Hg
Stage II	160–179 mm Hg	100–119
Stage III	≥180 mm Hg	≥120 mm Hg

*Based on ACVIM Consensus Statement on Hypertension.²

before performing the UPC, the urine sediment should be confirmed to be inactive (devoid of cells) and the urine culture sterile because urinary tract infection can be associated with a nonglomerular increase in proteinuria. Persistence of proteinuria should be confirmed by reexamining the UPC at least 2–3 times over 2 weeks or more. The average of these determinations should be used to classify the patient as nonproteinuric; borderline proteinuric or proteinuric (Table 3).

As with proteinuria, arterial pressure should ideally be determined 2–3 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. Unfortunately, current blood pressure measurement devices used for dogs and cats have not been validated according to American College of Internal Medicine (ACVIM) Hypertension Consensus Panel and Veterinary Blood Pressure Society recommendations.² Until such equipment is available, it is reasonable for practitioners to use blood

pressure devices currently available if they produce reproducible results in the veterinarian's hands. Upon arrival at the hospital, patients should be promptly placed in an examination room with the owner and allowed 5–10 minutes to acclimate to the room in order to minimize artifactual increase in blood pressure due to "white coat effect." A veterinary technician well-trained in performing blood pressure measurements in dogs and cats should quietly enter the room and obtain at least 5 blood pressure values with minimal patient restraint. It is important to obtain these values before performing any other activities with the patient (eg, physical exam, blood sampling).

Developing the Treatment Plan for CKD

Determine treatment options appropriate for the patient

Treatment options for dogs and cats with CKD should include both specific therapies directed at treatable primary kidney diseases (eg, pyelonephritis) and selected components of conservative medical management. Treatments unique to the patient are established on the basis of results of a thorough diagnostic evaluation of the patient including the medical history, physical exam findings, blood pressure determinations, complete blood count, biochemistry profile (including at least BUN and serum creatinine, phosphorus, calcium, albumin, sodium, potassium, chloride, and bicarbonate concentrations), urinalysis, urine culture, UPC, and appropriate imaging of the urinary tract. When possible, urine should be collected by cystocentesis, especially when performing urine cultures or UPC. Depending on the results of these studies, further studies may be indicated (eg, kidney biopsy in patients with glomerular proteinuria, blood gas analysis in patients with abnormal serum bicarbonate concentrations). Abnormal findings from the diagnostic evaluation identify potential areas for therapeutic intervention. The IRIS treatment guidelines provide a basis for selecting treatment components appropriate for specific stages of CKD.¹

Prioritize and select which treatment options to recommend based on medical priority and pet owner's preferences

The guiding principles to be used in developing the treatment plan are that recommended treatments be: (1) appropriate for this patient, (2) appropriate for the owners abilities and resources, (3) likely benefit to patient, and (4) evidence-based. Potential treatment recommendations should be prioritized considering the importance of their potential impact on the patient as well as the level of evidence supporting effectiveness of

the treatment. In addition, the cost, availability, invasiveness, and compatibility with the pet owner's time and abilities should be considered. Willingness of an owner to provide a treatment may be driven by personal or social beliefs or norms that may or may not be amenable to change. Asking owners to provide a treatment that exceeds their willingness or ability to provide the treatment is likely doomed to failure.

Continuing Management of Chronic Kidney Disease

Review the plan with the owner

The proposed treatment plan should be presented to the owner in a manner that allows the clinician to ascertain the owner's level of understanding and concerns regarding the treatment instructions. It is important to be certain that the owner understands what each recommendation entails and why the recommendation is being made. Any anticipated difficulties or pit-falls of the therapy should be reviewed. Owner questions should be encouraged during this discussion. The owners should be encouraged to raise any concerns they may have about the plan and they should be asked specifically about any concerns they may have about being able to provide the treatment plan over an extended period, likely the rest of the patient's life for many treatments.

Be sure that you and the owner have agreed upon all aspects of the plan. It is important for the pet owner and veterinarian to have the same goals and definition of therapeutic success. It is important for the owner to understand what can and cannot be corrected by treatment and that CKD is a life-long problem that we are managing, but not curing. The goals of enhancing long-term survival as well as maximizing quality of life should be emphasized. It is often helpful to ask the owner if they understand the chronic nature of CKD and how they feel about this. For some owners, the long-term implications may influence what treatments they are willing to provide and how dedicated they are to treatment.

Schedule follow-up visits

The timing and frequency with which follow-up visits should be scheduled depends on the stability and severity of the patient's condition. Patients more severely affected or unstable should be seen more often, while stable, less severely affected patients may be seen less often. Ideally, patients in IRIS CKD Stage 4, patients currently exhibiting signs of decreased appetite or gastrointestinal signs attributable to CKD, or patients recovering from an acute uremic crisis should probably be seen within 2–5 days of hospital discharge. Patients in IRIS CKD Stages 1–3 that appear to be stable and devoid of clinical

signs attributed to CKD should be re-examined within the first 7–14 days after beginning therapy to assess for problems with the treatment plan. It is prudent to schedule at least this visit at the time the pet is discharged because ascertaining the pet's response to therapy and adjusting treatment as needed is very important after initiating long-term treatment recommendations. Failure to perform this follow-up visit shortly after beginning therapy may lead to treatment failure. Once treatment-related problems or complications have already developed, it may become more difficult to achieve patient compliance and optimum response to therapy. As long as concerns about the patient's response to therapy or the ability of the owner to carry out the treatment plans remain, frequent visits may continue to be necessary.

The plan for subsequent follow-up visits depends on how the pet and owner are responding to the treatment plan as well as the stability and severity of their current clinical signs. Stable, less severe patients may be rechecked regularly at 3–4 month intervals, while less stable patients or more "needy" owners may require monthly visits that taper down to less frequent visits as their condition improves. Follow-up phone calls from the veterinary technician are designed to identify, with consultation with the veterinarian, when additional in-clinic appointments are necessary.

Plan follow-up calls between veterinary technicians and pet owner

In addition to regularly scheduled clinic visits, regular telephone interactions between the owner and a technician familiar with the pet's medical problems and treatment plan can markedly enhance owner compliance and, therefore, response to treatment. Among the key information to be gathered from the owner are the pet's activity, behavior, appetite and eating habits, and the owner's perception of the pet's quality of life. The goals are to: (1) assure owner compliance, (2) detect errors or problems with treatments, and (3) detect changes in the pet's condition. These contacts are designed to detect problems at home before the owner becomes discouraged by treatment problems and to alert the managing veterinarian that the patient may need to be seen sooner than had been planned.

Conservative Management of CKD

Conservative medical management of CKD includes therapies other than treatment of active kidney diseases (eg, pyelonephritis, urinary obstruction), dialysis or transplantation. It includes therapy designed to: (1) prevent or treat complications of decreased kidney function, (2) maintain adequate nutrition, and (3)

slow loss of kidney function. When possible, therapy directed at the primary kidney disease responsible for CKD should also be provided.

Dietary Therapy of CKD

Based on clinical trial findings, feeding a kidney diet (diets formulated by a veterinary nutritionist or manufactured specifically for managing dogs or cats with CKD) is the therapeutic intervention most likely to enhance long-term survival and quality of life for patients with IRIS CKD Stages 3 and 4.^{3–6} As a consequence, feeding a kidney diet to dogs with IRIS CKD Stages 3 and 4 and cats with IRIS CKD Stages 2–4 should be considered the current standard of care (strong evidence supporting this recommendation).^{3–8} Results of several clinical trials strongly support the beneficial effect of kidney diets in preventing or delaying the onset of uremia and premature death due to complications of CKD. In addition, kidney diets have been shown to maintain or improve nutrition and owners report higher quality of life scores than when maintenance diets were fed.

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 kidney diets are supplemented with potassium. Unfortunately, the term "kidney diet" has been misinterpreted to mean just restricting dietary protein intake. Substituting maintenance or senior diets that are lower in protein content is not a satisfactory substitute for feeding diets specifically formulated for dogs and cats with CKD.

While some dogs and a few cats readily accept the change to a kidney diet, in many pets, a more gradual approach should be used. A 7–10-day gradual switch from the old diet to the kidney 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 kidney diet into the old food. Alternately, both the old and the kidney 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 kidney diet. Introducing a kidney 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. 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, urinary tract infection, and nonurinary tract diseases. In addition, feeding practices should be examined.

Making the change to a kidney diet can be challenging for both owner and pet. A key point to remember is that the change in diet should be introduced gradually to facilitate acceptance and to minimize gastrointestinal complications associated with abrupt changes in diet composition. Gradual introduction may be achieved either by gradually increasing the amount of the new diet mixed into the old diet, or by providing bowls of both new and old diet next to each other and then gradually reducing the amount of old food available. While some dogs and cats may very readily switch to the new diet, we typically transition dogs to the new diet over 1–2 weeks, whereas cats may require 2–4 weeks and sometimes considerably longer. Some pets may require some of the old food to make the new food acceptable. This is acceptable, but the percentage of calories obtained from the old diet should not exceed about 10–15% of total calories. Supplementing the diet with small quantities of gravies or other foods or heating the food to enhance palatability may be helpful in supporting the transition to the kidney diet. Force feeding the diet is never recommended, particularly when the pet has gastrointestinal signs (eg, anorexia, nausea, vomiting), because it can promote dietary aversion making future use of the kidney diets difficult or impossible.

Although there is little published data to support a recommendation for pharmacological intervention to enhance appetite in dogs and cats with CKD, antiemetic drugs (eg, maropitant, ondansetron), H₂-receptor blockers or hydrogen pump antagonists (eg, famotidine, ranitidine, omeprazole), and appetite stimulants (eg, mirtazapine, cyproheptadine) may be used in an attempt to enhance food intake. The owner's observation that the pet is eating some food is an insufficient measure of food intake. The goal of therapy is to maintain a stable body weight as close to a body condition score of 5/9 as possible. When patients fail to spontaneously consume sufficient quantities of food to achieve this goal despite reasonable attempts to enhance food intake, 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.

Managing Gastrointestinal Signs of Uremia

Reduced appetite with reduced food intake, nausea, vomiting, uremic stomatitis and halitosis, gastrointestinal hemorrhage, diarrhea, and hemorrhagic colitis, are common gastrointestinal complications of dogs and cats with IRIS 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; however, antiemetic and antacid therapy may also be necessary in some patients.

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, since their efficacy remains unproven, there is only weak evidence to support the recommendation to use these drugs.^{7,8}

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 5-HT₃ receptor antagonists such as ondansetron HCl or dolasetron mesylate, and the neurokinin (NK1) receptor antagonist, maropitant citrate. Although there are no published studies on the effectiveness of antiemetics in managing uremic nausea and vomiting in dogs or cats with CKD, studies in uremic people have shown the 5-HT₃ receptor antagonist ondansetron to be twice as effective as metoclopramide in reducing uremic nausea and vomiting.⁹ Sucralfate should be added when gastrointestinal ulcerations and hemorrhage are suspected. Unfortunately, evidence supporting the use of antiemetics in dogs and cats with CKD is weak.

Maintaining Hydration

Cats with CKD appear to be particularly susceptible to chronic dehydration, a common complication of CKD often resulting in deterioration in kidney function and episodes of acute uremia. Lack of access to good quality drinking water, certain environmental conditions and intercurrent illnesses may promote dehydration by limiting fluid intake or facilitating fluid losses (eg, pyrexia, vomiting or diarrhea). Although owners often complain about polyuria in dogs and cats with CKD, 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. Owners of pets with CKD should know that vomiting or diarrhea or inadequate access to water may lead to dehydration which may promote deterioration in kidney function or precipitate a uremic crisis.

Dehydrated patients should be rehydrated either by oral or parenteral administration of fluids with the goal of correcting and preventing further episodes of dehydration and its clinical effects. Long-term administration of subcutaneous fluid therapy may be considered for patients with signs consistent with chronic or recurrent dehydration (weak evidence supporting this recommendation).^{7,8} 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 chronic administration of fluids; the decision to recommend administration of subcutaneous fluids should be made on a case-by-case basis. Only patients that show clinically apparent benefits to chronic fluid therapy should receive chronic supplementation with subcutaneous fluids.

For long-term administration, a balanced electrolyte solution (eg, lactated Ringer's solution) is administered subcutaneously every 1–3 days as needed. The volume to be administered depends upon patient size; a typical cat requires about 75–150 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 kidney function. If a detectable improvement in clinical signs and or kidney function does not accompany fluid therapy, the need for long-term therapy should be re-assessed.

Managing Hyperphosphatemia

Because the kidneys are the primary route of phosphorus excretion, declining kidney function results in phosphorus retention. Retention of excess phosphorus in the body can promote renal secondary hyperparathyroidism, mineralization of tissues and progression of CKD. Increased serum phosphorus concentrations have been linked to increased mortality in people, cats and dogs with CKD, and consuming diets high in phosphorus has been shown to increase mortality in dogs with induced CKD.¹ Therefore, minimizing phosphorus retention and hyperphosphatemia is an important ther-

Table 5: Recommended serum phosphorus concentrations target ranges adjusted for International Renal Interest Society chronic kidney disease stages

CKD stage	Target serum phosphorus range	
	mg/dL	mmol/L
IRIS CKD Stage 2	3.5–4.5	1.13–1.45
IRIS CKD Stage 3	3.5–5.0	1.13–1.6
IRIS CKD Stage 4	3.5–6.0	1.13–1.9

apeutic goal in dogs and cats with CKD (moderately strong evidence supports this recommendation).^{7,8}

Therapeutic management of serum phosphorus concentration is indicated for dogs and cats with IRIS CKD Stages 2–4. The goal of therapy is to maintain serum phosphorus concentration within specific target ranges, which vary according to the stage of CKD (Table 5). These target ranges were established based on expert opinion and have not been evaluated in clinical trials (weak evidence supporting this recommendation).^{7,8} Note that the recommended serum phosphorus concentration target ranges are below the upper limits of many established laboratory normal ranges. This is because the stated goal is to limit phosphorus retention, which precedes overt hyperphosphatemia.

The first step in minimizing serum phosphorus concentration is feeding a diet reduced in phosphorus content (typically a “kidney” diet). Kidney diets are substantially reduced in phosphorus content and are often successful in achieving serum phosphorus targets in IRIS CKD Stages 2 and 3.

Approximately 4–6 weeks after initiating dietary therapy, serum phosphorus concentration should be measured to determine whether the treatment target has been achieved. Samples obtained for determinations of serum phosphorus concentration should be collected after a 12-hour fast to avoid postprandial hyperphosphatemia. Failure to achieve the target serum phosphorus concentration after 4–8 weeks indicates that addition of an intestinal phosphate binding agent should be considered.

Intestinal phosphate binding agents render 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 once daily, the total daily dose of phosphate binder should be divided and a portion administered with every meal. 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. Although aluminum-containing binding

agents are usually well tolerated and safe in dogs and cats, aluminum toxicity characterized by neurological signs and microcytosis has been reported in dogs with advanced CKD treated with high doses of aluminum-containing phosphate binding agents.¹⁰ 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. An important reason for using a reduced phosphorus diets with intestinal phosphorus binders is to minimize the dose of phosphorus binders needed to achieve treatment targets for phosphorus.

Regardless of the phosphate binder used, they 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 4–6 weeks until the therapeutic target is reached. The recommended starting dose for aluminum-containing intestinal phosphorus binding agents (eg, aluminum hydroxide, aluminum carbonate, and aluminum oxide) is 30–100 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 60–90 mg/kg/day and 90–150 mg/kg/day for calcium carbonate. The initial dose for lanthanum carbonate is 30 mg/kg/day.

Metabolic Acidosis

The decision to treat metabolic acidosis should be based on laboratory assessment of the patient's acid-base status, preferably on the basis of 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.¹¹ Metabolic acidosis has been incriminated in promoting progression of CKD and impairing protein nutrition. Recently, bicarbonate therapy in people with CKD has been reported to slow progression of CKD and improve nutritional status.¹²

Alkalinization therapy is indicated for dogs and cats with IRIS CKD Stages 1–4 when blood pH and bicarbonate concentration drop below the normal range. Changing to a kidney 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 both hypokalemia and acidosis. Starting doses of 40–60 mg/kg every 8–12 hours are recommended. Dosage of sodium bicarbonate is 8–12 mg/kg body weight given orally every 8–12 hours. It is available as 5 and 10 grain

tablets (1 grain = 65 mg). Assess the response to alkalinization therapy by performing blood gas analysis 10–14 days after initiating therapy and adjust the dosage until normalized. There is only weak evidence supporting these recommendations based on clinical opinion and studies in rodents and people.^{7,8}

Hypokalemia

Hypokalemia and potassium depletion are relatively common in cats with IRIS CKD Stages 2 and 3 with a prevalence reportedly in the range of 20–30%.⁵ In contrast, hypokalemia is less common among cats with IRIS CKD Stage 4 seemingly because the marked reduction in glomerular filtration rate (GFR) is more likely to promote potassium retention and hyperkalemia. While the cause of hypokalemia in cats with CKD has not been fully elucidated, inadequate potassium intake, increased urinary loss, and enhanced activation of the renin-angiotensin-aldosterone system due to dietary salt restriction may play a role. In addition, amlodipine may promote hypokalemia in some cats with CKD. Urinary tract signs of hypokalemia include progressive renal injury and polyuria and polydipsia. Systemic clinical signs of hypokalemia vary according to extent of reduction in blood potassium concentration. Mild hypokalemia is often asymptomatic, while moderate hypokalemia (2.5–3.0 mmol/L [2.5–3.0 mEq/L]) may be associated with generalized muscle weakness and lethargy. Severe hypokalemia (<2.5 mmol/L [<2.5 mEq/L]) may be associated with overt hypokalemic myopathy.

It is generally recommended that cats with persistent hypokalemia below 3.5–4.0 mmol/L (3.5–4.0 mEq/L) receive potassium supplementation (weak evidence support) this recommendation).^{7,8} Oral replacement is the safest and preferred route for administering potassium. Potassium gluconate or potassium citrate are preferred for oral supplementation; potassium chloride is not recommended because it is acidifying and unpalatable. Depending on the size of the cat and severity of hypokalemia, the dose for potassium gluconate ranges from 2 to 6 mmol/L (2–6 mEq/L) per cat per day. Potassium citrate solution is a suitable alternative with the advantage of providing simultaneous alkalinization therapy. Potassium citrate is initially given at a dose of 40–60 mg/kg/day divided into 2–3 doses. If hypokalemic myopathy is present, it usually resolves within 1–5 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. Monitor serum potassium concentration every 7–14 days and adjust the dose accordingly to establish the final maintenance dosage. It is unclear whether all cats require or

benefit from long-term potassium supplementation. The value of “prophylactic” potassium supplementation in normokalemic cats has not been established.

Management of Anemia of CKD

Anemia of CKD 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. Important clinical signs of anemia in dogs and cats with CKD include lethargy and impaired appetite.

Treatment options for anemia of CKD (due to erythropoietin deficiency) 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^a (EPO) and darbepoetin alpha (DPO). Although EPO reliably promotes a dose-dependent rise in hematocrit in dogs and cats with anemia of CKD, development of antibodies directed at EPO often renders it ineffective. As a consequence, it is not generally recommended for dogs and cats with anemia of CKD.

Darbepoetin alpha (Aranesp)^b, a longer-acting form of erythropoietin (approximately 3 times longer than EPO), has supplanted EPO as the product currently recommended for use in dogs and 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. 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 PCV for the remainder of the pet’s life. The recommended induction dose of DPO is 1.0 µg/kg given once weekly until the target PCV is attained.¹³ Typically an increase in PCV occurs within 2–3 weeks. Because of the strong erythropoietic effect of DPO, parenteral iron supplementation is recommended when DPO therapy is first initiated. Iron dextran may be administered intramuscularly at a dose of 50 mg/cat or 50–300 mg/dog. Although a single injection is often all that is required, it may be repeated as needed (usually no more often than monthly). Because injected iron dextran may rarely result in anaphylactic reactions, patients should be observed after administration of this drug. Once the target range PCV (25–35 vol%) has been reached, the frequency of administration is reduced to

once every 2–3 weeks. Thereafter, the dose is adjusted to maintain the PCV within the target range. The PCV should be measured weekly during the induction phase (to avoid overdosage), every other week during transition to the maintenance phase, and monthly once a stable PCV in the target range has been achieved in the maintenance phase. There is only weak evidence supporting these recommendations based on uncontrolled clinical observations using this drug.^{7,8} In addition, the cost of the drug and monitoring may be expensive for some owners.

It is unclear how often vitamin B12 supplementation may be needed in dogs treated with DPO; however, measuring blood levels and treating to effect may be useful, especially if the response to DPO is less than robust.

Calcitriol Therapy

Calcitriol concentrations have been shown to be reduced with CKD in several species. 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 concentrations of calcitriol. While calcitriol seemingly is predominantly involved in calcium and phosphorus metabolism, it appears to be of value in slowing progression of CKD. A masked, randomized controlled clinical trial (RCCT) performed on dogs with IRIS CKD Stages 3 and 4 indicated that calcitriol therapy increased survival time by slowing progression of CKD.^c These findings are consistent with results of recent studies in human patients with CKD, which demonstrated a similar survival benefit of calcitriol therapy.^{14,15} However, an RCCT performed in cats failed to reveal similar benefits for calcitriol in altering the course of feline CKD.^d While the reason for these apparent divergent results in cats is unclear, the study did not prove that calcitriol is ineffective in cats. Based on these clinical trial results, there is strong evidence to support a recommendation for calcitriol therapy in dogs with IRIS CKD Stages 3 and 4 (and possibly IRIS CKD Stage 2) to slow progressive deterioration in kidney function.^{7,8} In contrast, there is weak evidence for or against a recommendation for calcitriol therapy in cats with CKD.

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 concentration in dogs with CKD.

Calcitriol should initially be provided at an oral 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 absorption. Calcitriol dosage should not exceed about 5.0 ng/kg/day. Life-long treatment will be necessary to achieve the desired effect of reduced kidney mortality. Details on dosing and monitoring are available elsewhere.¹

Managing Proteinuria

Increased concentrations of proteinuria has been associated with progression of CKD in dogs and cats. Therapeutically reducing proteinuria slows progression of CKD in people; however, evidence supporting this benefit in dogs is limited and scant in cats. Nonetheless, therapy designed to reduce proteinuria has been recommended for dogs and cats in IRIS CKD Stages 2–4 with UPC greater than 0.5 and 0.4, respectively, and dogs and cats with IRIS CKD Stage 1 when UPC exceed 2.0.¹⁶ There is moderate evidence supporting these recommendations in dogs but only weak evidence supporting these recommendations in cats.^{7,8} Nonetheless, these recommendations have become the standard of care and have become so widely recommended and used, they are unlikely to be further tested against a placebo group.

Standard management for proteinuria in dogs and cats with CKD is to initiate therapy with a kidney diet and administer an angiotensin converting enzyme inhibitor (ACEI) with the therapeutic goal of reducing the UPC at least in half or, ideally, into the normal range. The recommended initial dosage for the ACEI enalapril and benazepril in dogs and cats with CKD is 0.25–0.5 mg/kg given orally every 12–24 hours. Benazepril has been advocated preferentially over enalapril because it is cleared largely by hepatic rather than renal excretion. Occasionally ACE inhibitor therapy is associated with a marked decline in kidney function; therefore, serum creatinine should be measured before and 1–2 weeks after initiating therapy. Small, stable declines in serum creatinine are not of concern, but large or progressive increases in serum creatinine should prompt reassessment of therapy. Dosage of ACE inhibitors 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/day.¹⁷ Serum potassium should be monitored because hyperkalemia is a recognized side-effect of ACE inhibitor therapy that may limit the dosage increases.

Managing Arterial Hypertension

There is no generally agreed upon value that defines arterial hypertension in dogs and cats. Instead, arterial pressures are classified into 4 stages based on the likelihood of causing blood pressure-associated organ injury (Table 4). In dogs and cats, elevations in blood pressure have been linked to renal, ocular, neurological and cardiac complications.

Diagnosis of arterial hypertension must be based on measuring blood pressure. In general, blood pressure should be confirmed by least 3 independent measurements of blood pressure, ideally collected over several days to several weeks. Unless there is evidence of retinal lesions or neurological signs or the systolic blood pressure is greater than 200 mm Hg, the decision to initiate anti-hypertensive therapy should generally not be considered an emergency. Patients with IRIS CKD Stage 2 through 4 having arterial blood pressures persistently exceeding 160/100 (AP stage II) are candidates for treatment. Treatment should be considered for IRIS CKD Stage 1 with arterial blood pressures persistently exceeding 180/120 (AP stage III).²

The optimum therapeutic endpoint for antihypertensive therapy has not been established for dogs and cats with CKD. In the absence of such information, treatment for arterial hypertension should be initiated cautiously with the goal of reducing blood pressure to at least below 160/100 mm Hg. Except in patients with ocular or neurological 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 (CCB; eg, amlodipine) are the preferred antihypertensive drugs for dogs and cats with CKD. Although ACEI generally produce relatively small reductions in blood pressure, their beneficial role in altering intraglomerular hemodynamics, proteinuria, and the profibrotic effects of the intrarenal renin-angiotensin system, ACEI may have renoprotective effects even when adequate arterial blood pressure control is not achieved. Dosing of ACEI for antihypertensive effects is the same as for proteinuria; however, dosages may be increased in an attempt to further lower blood pressure.

Clinical experience has shown amlodipine to be an effective antihypertensive agent in dogs and cats with CKD. In addition, it has few side-effects and relative rapid onset. In cats, amlodipine may reduce proteinuria. It is prescribed at a dose of 0.625 mg for cats less than 4 kg, and 1.25 mg for cats greater than 4 kg. Dosage may be doubled if needed. In dogs, amlodipine dosage ranges from 0.1 to 0.5 mg/kg given every 24 hours, usually combined with an ACE inhibitor. There is only weak evidence supporting these recommendations in dogs due

to the absence of adequate clinical trials. However, moderate evidence supporting the recommendation to use amlodipine in cats with elevated blood pressure.^{7,8,18}

Prognosis of CKD

In dogs with IRIS CKD Stages 3 and 4, the disease tends to be progressive. Most dogs with CKD of this severity will die or be euthanized due to their disease. Dogs typically survive for months to a year or 2, depending on the severity of their kidney disease; however, survival times may be markedly enhanced with appropriate therapy. Further, proteinuria and arterial hypertension are associated with poorer prognoses, although this may be modifiable to some degree with therapy.

Cats with CKD vary in their clinical course. Some cats have progressive disease similar to dogs, but typically CKD progresses more slowly in cats compared to dogs. In addition, some cats with CKD appear to have stable kidney function for many months to years, often dying of causes unrelated to CKD. As with dogs, proteinuria heralds a poorer prognosis. In addition, stage of CKD has been shown to be related to outcome.¹³

Footnotes

- ^a Amgen, Thousand Oaks, CA.
- ^b Amgen, Thousand Oaks, CA.
- ^c Polzin D, Ross S, Osborne C, Lulich J, and Swanson L. Clinical benefit of calcitriol in canine chronic kidney disease. ACVIM Forum, June 2005.
- ^d Polzin DJ: Unpublished data.

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