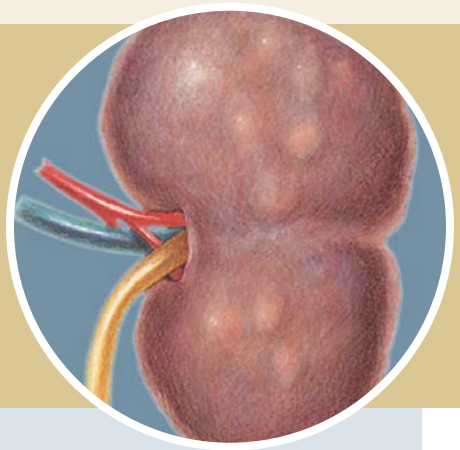
David J. Polzin, DVM, PhD, DACVIM • College of Veterinary Medicine
University of Minnesota • St. Paul, Minnesota



Treating Feline Chronic Kidney Disease: An Evidence-Based Approach

Routine clinical practice is never "blind," so clinicians and pet owners both know when active treatment is being received.

In planning therapy for cats with chronic kidney disease (CKD), veterinarians should ideally base their recommendations on results of randomized, controlled clinical trials. Unfortunately, the safety and efficacy of many therapies recommended for cats with CKD have never been examined systematically in cats with spontaneous disease. Often, treatments are recommended on the basis of less convincing evidence, such as clinical experience, expert opinion, pathophysiologic rationale, or studies performed in other species or in cats with artificial disease. Evidence from the recalled experiences of clinicians, however, tends to overestimate the efficacy of these interventions. Routine clinical practice is never "blind," so clinicians and pet owners both know when active treatment is being received. The desire of pet owners and clinicians for success, together with the placebo effect, can cause both parties to overestimate efficacy.

Key Points

- Clinicians should consider the quality of data supporting a recommendation to use (or not use) a given form of therapy.
- The safety and efficacy of many therapies recommended for feline CKD have never been examined systematically in cats with spontaneous disease.
- Clinically useful studies demonstrate that nutritional management will positively influence outcomes that are important to pets and their owners.

In examining evidence that supports or refutes a therapeutic claim, veterinarians should consider whether the evidence is clinically relevant. Treatments are indicated when they provide important clinical benefits, but studies often focus on outcomes that may or may not have any clinical relevance to pets and their owners. For example, a study linking calcitriol therapy to corrected hyperparathyroidism does not necessarily provide sufficient reason for recommending such ther-

Case Study

A 14-year-old neutered male domestic shorthair cat is examined for weight loss. The owners also report a recent increase in water consumption and frequency of urination (the litter pan must be cleaned more often than in the past). The cat weighs 7 lb (BCS = 2/5). The left kidney is small and irregular; the right kidney cannot be palpated. There is no evidence of thyroid nodules. Results of hemography reveal mild nonregenerative anemia (packed cell volume is 34%). Azotemia is detected; blood urea nitrogen is 45 mg/dl (reference range, 10–30 mg/dl) and serum creatinine level is 2.5 mg/dl (reference range, 0.4–1.8 mg/dl). Results of other laboratory studies, including serum thyroxine (T_4) level, are within reference ranges. The tentative diagnosis is naturally developing stage 2 chronic kidney disease.

apy. Laboratory measurements, such as serum parathyroid hormone levels, are often used as "substitute end points" in studies because they are easily obtained. Such results only provide a pathophysiologic rationale for applying the treatment to patients. More clinically useful studies demonstrate that the treatment will positively influence outcomes that are important to pets and their owners, such as increased activity or appetite, decreased vomiting, decreased incidence of uremic crises, or prolonged good-quality lifespan.

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Because of the very nature of cats, overtreatment can be just as deleterious as undertreatment in sustaining an acceptable quality of life. When considering their options, clinicians should consider the quality of data supporting a recommendation to use (or not use) a given form of therapy. Of course, not all recommendations can or will be based on randomized, controlled studies. Nonetheless, it is important to recognize the inherent limitations of recommendations based on less secure forms of evidence.

Therapeutic Options for the Cat with CKD

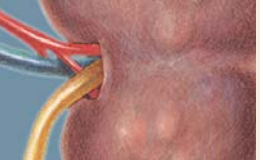
Dietary Management

Although dietary management is probably the most commonly prescribed treatment for cats with CKD, clinicians are often challenged by the notoriously finicky feline appetite. They must weigh the decision to recommend a therapeutic renal food or to allow the cat to continue its current food rather than risking reduced food intake. Two recent clinical trials support dietary management for feline CKD. In the first study, which was neither blinded nor randomized, a striking enhancement of survival time was associated with feeding a renal food compared with a regular food. The control group in this study was composed of cats that refused to eat the renal food. Although cats electing not to consume the renal food may have an intrinsically worse prognosis unrelated to their diet (the principal criticism of this study), the size of the difference in outcome suggests that the clinical benefit of feeding the renal food was likely real: median survival time was increased nearly 2.5 times when the renal food was fed.

We performed a randomized, controlled trial to assess the effect of dietary management in reducing mortality in cats with stages 2 and 3 CKD (serum creatinine values ranging from 2.0 to 3.5 mg/dl) that

Scoring the Quality of Research Recommendations

Grade I:	Highest quality; evidence obtained from at least one properly randomized, controlled clinical trial
Grade II:	Well-designed and controlled laboratory studies in the target species with naturally occurring disease
Grade III:	Average quality; data obtained from one of the following: ◗ At least one well-designed clinical trial without randomization ◗ Cohort or case-controlled analytic studies ◗ Study using acceptable laboratory models or simulations in the target species (preferably from more than one center) ◗ Multiple time series ◗ Uncontrolled experiments that produced dramatic results
Grade IV:	Weakest quality; data obtained from one of the following: ◗ Opinions of respected authorities on the basis of clinical experience ◗ Descriptive studies ◗ Studies in other species ◗ Pathophysiological justification ◗ Reports of expert committees



IRIS Staging System for Feline CKD

The International Renal Interest Society (IRIS) (www.iris-kidney.com) identifies the stage of CKD on the basis of two or more serial determinations of serum creatinine concentration (obtained while the patient is well hydrated) and further delineation of the stage according to the patient's magnitude of proteinuria and blood pressure. Each category is qualified by stating if there is clinical evidence of end-organ damage.

Primary Categorization: Serial Serum Creatinine Determinations

Stage	*Serum Creatinine, mg/dl*	*Interpretation*
1	< 1.6	Nonazotemic: Some other renal abnormality is present (eg, inadequate concentrating ability or presence of irregularity on palpation)
2	1.6–2.8	Mildly azotemic: Clinical signs usually mild (eg, polyuria or polydipsia) or absent
3	2.9–5.0	Moderately azotemic: Many extrarenal clinical signs may be present
4	> 5.0	Severely azotemic: Difficult to manage without invasive life-support methods

Secondary Categorization: Urine Protein-to-Creatinine Ratio

Urine Protein-to-Creatinine Ratio	*Interpretation*
< 0.2	Nonproteinuric
0.2–0.4	Borderline proteinuric
> 0.4	Proteinuric

Secondary Categorization: Blood Pressure

Systolic Blood Pressure, mm Hg	*Diastolic Blood Pressure, mm Hg*	*Risk Level*
< 150	< 95	Minimal
150–159	95–99	Low
160–179	100–119	Moderate
≥ 180	≥ 120	High

were fed a control food or Hill's® Prescription Diet® Feline k/d®. This study confirmed the significant benefit of nutritional management in reducing renal mortality. Significant adverse effects of feeding the therapeutic renal food were not detected in these studies. Seemingly, the greatest problem with advocating therapeutic renal foods for cats with CKD has been acceptance of the foods by cats. Food acceptance can usually be achieved by correcting the metabolic complications of CKD and by introducing the food gradually.

Phosphate-Binding Agents

Phosphorus is retained in CKD, eventually resulting in hyperphosphatemia. Hyperphosphatemia has been reported to be a reliable clinical index of hyperparathyroidism in cats with CKD. Detected in approximately 60% of cats with CKD, hyperphosphatemia becomes more prevalent as renal function declines. In one study, the prevalence of renal secondary hyperparathyroidism in cats with CKD was reported to be 84%. In this study, all cats with end-stage CKD, 87% of cats with some clinical signs of CKD, and 47% of clinically normal cats with only biochemical evidence of CKD were found to have hyperparathyroidism. This condition was even detected in nine cats with CKD that had normal serum calcium and phosphorus concentrations.

In many cats, dietary management alone appears to normalize hyperparathyroidism. Phosphate-binding agents may be useful in further reducing phosphate retention and hyperparathyroidism, but the efficacy of such therapy has yet to be established in cats. Clinical reports and clinical impressions suggest that phosphate-binding agents are useful in reducing serum phosphate concentrations, but some cats may poorly tolerate these agents. Researchers have reached the consensus that phosphate retention and hyperparathyroidism promote progression in CKD. No conclusive data confirm this association in cats, however, and mechanisms responsible for this effect remain unresolved. IV

Calcitriol Therapy

The kidneys are responsible for converting 25-hydroxycholecalciferol to its most active metabolite, 1,25-dihydroxycholecalciferol, or calcitriol. Calcitriol is the major renal hormone responsible for calcium metabolism. Among its important functions is modulation of parathyroid hormone activity at the transcriptional level. Because CKD may impair production of calcitriol, calcitriol deficiency may be one factor promoting renal secondary hyperparathyroidism. Calcitriol supplementation has been advocated as a means of normalizing hyperparathyroidism. We performed a randomized, controlled clinical trial examining the effect of low-dose calcitriol therapy on progression of CKD and clinical signs. Calcitriol was ineffective in altering renal mortality or improving appetite, activity, or quality of life. These findings fail to support a recommendation for calcitriol therapy for cats with CKD.

Antihypertensive Therapy

Hypertension is a well-recognized complication of CKD in cats, possibly affecting as many as 20% of cats with the disease. The

most profound clinical effect of hypertension in cats seems to be hypertensive retinopathy with retinal detachment, hemorrhage, and blindness, but cats with such severe ocular manifestations reflect only a small percentage of those with CKD and hypertension. More subtle ocular lesions of hypertension are much more common.

Although cats with hypertension and hypertensive retinopathy are likely to benefit from intervention with antihypertensive drug therapy, its renoprotective benefit in cats is largely extrapolated from observations in humans and experimental studies in animals. The potential benefits of intervention might include prolonging survival in cats with CKD and reducing the incidence of hypertensive retinopathy and hypertensive encephalopathy.

The calcium-channel blocker amlodipine currently appears to be the drug of choice for managing hypertension in cats. At least one clinical trial has shown the drug to be effective for lowering blood pressure. Another experimental study demonstrated that amlodipine was effective in preventing ocular manifestations of hypertension. The observations are consistent with uncontrolled clinical observations in cats with spontaneous renal disease. II

Case Study Revisited

The attending veterinarian wanted to answer the following question: For cats with early chronic kidney disease, does dietary management delay the onset of uremic crises, reduce the risk of future uremic crises, or delay death? A literature search revealed two recent clinical trials that support dietary management of CKD. One of them was a study with good evidence that feeding food with reduced protein and phosphorus levels produced tangible benefits. This cat was transitioned to Hill's® Prescription Diet® Feline k/d® and did well for three years until he was lost to follow-up. He had no uremic crises and minimal proteinuria during this time frame.

Key Points

- Introduction of dietary management has been shown to significantly reduce renal mortality.
- Observational studies have shown that phosphate-binding agents help reduce serum phosphate levels, but some cats may not tolerate these agents.
- A randomized, controlled trial of calcitriol therapy demonstrated no benefit for altering renal mortality or improving appetite, activity, or quality of life in cats with CKD.
- The calcium-channel blocker amlodipine has been shown to be more effective than ACE inhibitors for managing hypertension in cats.
- The benefits of potassium supplementation have only been demonstrated in cats with overt signs of hypokalemic myopathy.
- Human recombinant erythropoietin has been shown to correct anemia of CKD in cats but autoantibody reactions have limited its usefulness.
- Acidosis presents an unnecessary metabolic risk that can be easily corrected by administration of potassium citrate or sodium bicarbonate.

Angiotensin-Converting Enzyme Inhibitor Therapy

Angiotensin-converting enzyme (ACE) inhibitors appear to be of value in limiting progression of CKD in various forms of human renal diseases, but proteinuric patients may be the only ones to see a significant clinical benefit. The ACE inhibitor benazepril has been licensed in several countries for use in managing cats with CKD. Two studies examined the physiological effects of benazepril in cats with induced renal disease. Systemic arterial and glomerular capillary pressures were shown to be reduced and glomerular filtration rates were increased by such therapy. However, the magnitude of reduction in systemic blood pressure was small and a beneficial effect of reducing proteinuria was not evident. These initial studies failed to detect any evidence that administering benazepril resulted in long-term structural or functional renal protection.

Preliminary data have been reported from a randomized, controlled clinical trial that investigated the effectiveness of benazepril in cats with spontaneous CKD. In this study, benazepril reduced proteinuria, increased appetite, and improved survival time and quality of life, particularly in older Persian cats with marked proteinuria. In a separate study, treatment with enalapril and benazepril did not change plasma renin activity, aldosterone concentration, or indirect systolic arterial blood pressure in cats with hypertension associated with CKD. However, another study showed that benazepril is well tolerated when administered with amlodipine in hypertensive cats and may assist in managing cats with poorly controlled blood pressure. I III

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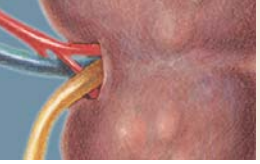
Potassium Supplementation

On the basis of Grade III evidence, it is generally accepted that



potassium supplementation is warranted for cats with chronic kidney failure and hypokalemia, even in absence of overt clinical signs. Grade IV evidence suggests that all cats with kidney failure should be given potassium supplements to limit total body potassium depletion and to prevent hypokalemia, hypertension, and progressive renal injury. Because today's feline therapeutic renal foods generally contain high levels of potassium, additional randomized, controlled clinical trials are necessary to determine if further supplementation is necessary or beneficial. Hypokalemia is often a symptom of acidosis, therefore the underlying condition should be treated early in addition to correcting the secondary potassium deficits. IV

Erythropoietin Therapy

Administration of human recombinant erythropoietin has been shown to be effective in correcting anemia of CKD in cats. Clinical trials that used patients as their own controls revealed substantial improvement in appetite and quality of life with the initiation of erythropoietin therapy. Unfortunately, the development of antibodies directed against the drug has limited the usefulness of this therapy in a substantial number of cats. Consequently, clinicians should carefully select cases that are most likely to benefit from erythropoietin. III

Alkalization Therapy

Alkalization therapy is indicated for cats with moderate to severe metabolic acidosis associated with CKD on pathophysiologic grounds and extrapolation from findings in other species. The rationale for alkalization therapy has been that acidosis: 1) can impair protein nutrition, 2) may promote progression of renal disease, and 3) can induce clinical signs similar to uremia. However, unpublished data from our laboratory indicate that mild acidosis (such as that which results from feeding a typical commercial acidifying diet) does not appear to promote progressive renal injury or impair nutrition. Nonetheless, acidosis *does* appear to impose an unnecessary metabolic risk that can easily be corrected in cats by administration of potassium citrate or sodium bicarbonate. IV

Conclusion

The concepts of evidence-based medicine can be readily applied to management of feline CKD. Quality-of-evidence guidelines previously published in the human and veterinary literature serve as an excellent example of a rigorous application of an evidence-based appraisal system. By using this system, clinicians can assume that grade I and II evidence will be the most reliable predictors of results they can expect in clinical practice. High-quality evidence exists for use of specific therapeutic renal foods and ACE inhibitors in animals with significant proteinuria; consequently, these therapeutic interventions should be recommended routinely for management of CKD in cats. Moderate quality evidence exists for the use of antihypertensive agents in animals with hypertension associated with chronic kidney disease, ACE inhibitors for renal disease other than glomerulopathies, and hormone replacement therapy for animals with anemia. At present, the lowest quality of evidence exists for use of subcutaneous fluid therapy, calcitriol, alkalinizing agents and intestinal phosphate binders, assisted feeding, and renal hemodialysis. Randomized, controlled clinical trials are needed to validate the benefits and risks of many treatments recommended for feline CKD and to better identify those animals who would benefit most from these forms of management.

This article as well as further information on the topic are available on the Web at www.HillsVet.com/ConferenceProceedings.