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Treating Canine Chronic Kidney Disease: An Evidence-Based Approach

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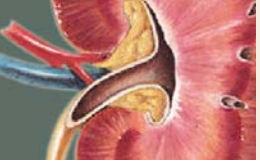
The veterinarian who is planning therapy for a dog with chronic kidney disease (CKD) should ideally look for recommendations that are based on results of randomized, controlled clinical trials. Such research is often hard to find, unfortunately, because many therapies have never been examined in an appropriate and systematic fashion in dogs with spontaneous disease. Instead, treatments may be recommended on the basis of clinical experience, expert opinion, pathophysiologic rationale, or studies performed in other species or in dogs with artificial disease. Evidence culled from such sources tends to encourage overestimation of therapeutic efficacy, so clinicians must recognize the inherent limitations of recommendations that are based on less secure forms of evidence.

Scoring the Evidence

One means for accommodating these limitations is to assign a score to define the strength and quality of the recommendation. Grade I evidence, the highest quality evidence, is obtained from at least one properly randomized, controlled clinical trial. Grade II evidence is data collected from controlled clinical studies in the target species in a laboratory setting. Grade III evidence may be data obtained from 1) at least one well-designed clinical trial without randomization; 2) case-controlled analytic studies; 3) studies utilizing acceptable laboratory models or simulations in the target species, preferably from more than one center; 4) multiple time series; or 5) uncontrolled experiments that produced dramatic results. Grade IV evidence, the weakest form of evidence, is derived from 1) opinions of respected authorities formulated on the basis of clinical experience, 2) descriptive studies, 3) studies in other species, 4) pathophysiological justification, or 5) reports of expert committees. This scoring system recognizes that the quality of the evidence supporting a recommendation is an important consideration when making therapeutic decisions.



Case Study

A 10-year-old neutered male Shih Tzu is presented for a routine health evaluation. Body weight is 16.5 lb (BCS = 3/5.) The owners report a recent increase in water consumption and frequency of urination. Results of physical examination are unremarkable, except for mild periodontal disease. Laboratory tests are performed, including a hemogram, urinalysis, and serum biochemical analysis. Azotemia is detected, with an increase in serum creatinine concentration (2.5 mg/dl [reference range, 0.4 to 1.8 mg/dl]) and urine specific gravity of 1.018. Results of other laboratory tests are normal. Subsequent microbial culture of a urine sample reveals no growth. The tentative diagnosis is naturally developing stage 2 chronic kidney disease. The attending veterinarian must consider whether dietary management will reduce the risk for future uremic crises and prolong the animal's life.

Quality-of-Life Outcomes

Most important, treatments are indicated when they provide valuable clinical benefits. Although studies often focus on outcomes that may not have any clinical relevance, veterinarians should look for evidence demonstrating that the treatment will improve appetite, increase activity levels, or reduce the incidence of uremic crises. Research end points that relate to quality of life (one of the most important considerations for dog owners) are particularly useful to note.

Key Points

- Clinicians should look for recommendations that are based on results of randomized, controlled clinical trials.
- Evidence from sources other than randomized trials may overestimate therapeutic efficacy.
- Research evidence is graded on a 4-point scale, with grade I being the highest quality (obtained from randomized trials) and grade IV being the weakest (obtained from sources like observational studies or research in other species).
- Studies are particularly useful when they demonstrate that the treatment will influence outcomes like appetite, activity levels, and overall quality of life—factors that are important to pets and their owners.

Therapeutic Options for the Dog with CKD

Dietary Management

Dietary management is probably the most commonly prescribed therapy for dogs with CKD, but dogs with selective appetites present a big dilemma to clinicians: Is it in the dog's best interest to switch to a therapeutic renal food if the unwanted food change will result in drastically reduced caloric intake? We recently completed a randomized, controlled clinical trial designed to determine if clinically important benefits were consistently gained when a typical canine maintenance food was changed to a therapeutic renal food in dogs with spontaneously occurring CKD. Other than being randomly assigned to either the renal food or the maintenance food, the dogs were managed in an identical manner with respect to other treatment interventions.

We found that feeding a manufactured renal food results in a better quality of life and a substantially longer life in dogs with stage 3 disease. Compared with dogs fed the maintenance food, dogs that consumed the renal food (Hill's® Prescription Diet® Canine k/d®) experienced fewer uremic crises and lower renal-related mortality. Feeding the renal food reduced the relative risk of a dog having a uremic crisis by over 70%. In fact, dogs fed the renal food remained free of uremic signs almost 2.5 times longer than dogs fed the maintenance food. In addition, dogs fed the renal food had a median survival time that was more than 3 times longer than dogs fed the maintenance food. Renal-related death was the primary cause for the higher rate of premature mortality among dogs fed the maintenance food. The longer survival times observed in the renal food group appeared to be attributed to much slower declines in renal function. [1]

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Dietary Phosphorus Restriction and Phosphate-Binding Agents

Phosphate retention and hyperparathyroidism are major causes of kidney disease progression in many species. Research in humans receiving hemodialysis therapy for CKD revealed that the adjusted relative risk of mortality was stable in patients with serum phosphorus concentrations below 6.5 mg/dl, but mortality increased significantly with higher serum phosphorus levels. The overall mortality risk associated with hyperphosphatemia was 1.06 per serum phosphorus elevation of 1 mg/dl. On the basis of these types of findings, researchers sought to determine whether dietary phosphorus restriction might also be beneficial for dogs.

In a model of induced CKD in dogs, combined dietary phosphorus and protein restriction were shown to slow progression of kidney disease and to improve survival. Mechanisms respon-

IRIS Staging System for Canine 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	< 1.4	Nonazotemic: Some other renal abnormality is present (eg, inadequate concentrating ability or presence of irregularity on palpation)
2	1.4–2.0	Mildly azotemic: Clinical signs usually mild (eg, polyuria or polydipsia) or absent
3	2.1–5.0	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
0.2–0.5	Borderline proteinuric
> 0.5	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

Key Points

- A study showed that dogs with CKD that consumed a manufactured renal food experienced fewer uremic crises and lower renal-related mortality.
- Combined dietary phosphorus and protein restriction have been shown to slow the progression of CKD in dogs.
- A randomized, controlled trial demonstrated that calcitriol therapy reduced renal mortality but did not appear to influence appetite, activity, or quality of life in dogs with CKD.
- No well-controlled clinical trials of ACE inhibitors in dogs with CKD have been reported, but enalapril may produce a modest reduction in blood pressure.
- Enalapril has also been shown to reduce proteinuria; therefore it may slow the progression of CKD in dogs.
- The use of human recombinant erythropoietin in dogs has been shown to correct anemia associated with CKD, but the agent should be prescribed cautiously because of the risk for adverse reactions.

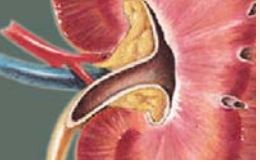
sible for the effect of hyperphosphatemia on mortality remain unresolved. Clinical or experimental studies establishing the value of adding phosphate-binding agents to dietary phosphate restriction in dogs have not been reported. II

Calcitriol Therapy

The kidneys are responsible for converting 25-hydroxycholecalciferol to calcitriol, its most active metabolite. The renal hormone primarily responsible for calcium metabolism, calcitriol modulates 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. Parathyroid hormone may act as a uremic toxin; therefore, calcitriol supplementation may also ameliorate a variety of supposed toxic effects of the hormone in CKD. We performed a randomized, controlled clinical trial examining the effect of low-dose calcitriol therapy on progression of CKD and clinical signs. Calcitriol was effective for reducing renal mortality but did not appear to influence appetite, activity, or quality of life. I

Antihypertensive Therapy

Hypertension is a well-recognized complication of CKD, often leading to hypertensive retinopathy with retinal detachment, hemorrhage, and blindness. Hypertension-related disorders of the central nervous system have also been observed, including seizures, loss of balance, abrupt changes in personality, and confusion. Studies in our laboratory have suggested that hypertension is also a risk factor for shortened survival times in dogs with kidney disease. The justification for treating hypertension in dogs is largely extrapolated from observations in humans and experimental animals. The likely benefits of



Case Study Revisited

The veterinarian found a randomized, controlled study (grade I, the highest quality) that demonstrated that dogs with mild to moderate naturally developing chronic renal failure that were fed a therapeutic food had fewer uremic crises, slower renal decline, decreased mortality rate, and improved quality of life than those dogs fed an adult maintenance food. The study also reported that feeding the therapeutically formulated diet to dogs with a lesser degree of azotemia (serum creatinine concentration, 2.0 to 3.1 mg/dl) delayed the onset of uremic crises for approximately five months.

The patient is extremely similar to dogs enrolled in the published clinical study, and the therapeutic food used in the study is readily available and economically feasible. Lower-quality evidence (grades III and IV) also exists for use of dietary modification of single nutrients in dogs with experimentally induced renal failure. On the basis of this evidence and other tenets of conservative medical management, use of Hill's® Prescription Diet® Canine n/d® should be strongly recommended for this patient, provided that owner and patient preferences are satisfied.

intervention might include retarding the progression of kidney disease and reduced incidences of hypertensive retinopathy and hypertensive encephalopathy. Well-controlled clinical trials investigating the effectiveness of antihypertensive agents in hypertensive dogs with CKD have not been reported; however, one study did demonstrate that enalapril, up to 0.5 mg/kg daily, can produce a modest reduction in blood pressure. IV

Angiotensin-Converting Enzyme Inhibitor Therapy

Research in humans has shown that angiotensin-converting enzyme (ACE) inhibitors limit the progression of kidney disease in proteinuric patients. A prospective clinical trial performed in dogs with spontaneous idiopathic glomerulonephritis recently confirmed that enalapril reduced proteinuria and may have helped to stablize the progression of kidney disease. Although ACE inhibitors are commonly prescribed for humans with CKD, more research is needed to determine whether ACE inhibitors should be regularly recommended for dogs that do not have proteinuria. I III

Erythropoietin Therapy

Administration of human recombinant erythropoietin has been shown to be effective in dogs for correcting anemia secondary to CKD. Uncontrolled clinical trials have also indicated a substantial improvement in appetite and quality of life associated with this treatment. Unfortunately, development of antibodies directed against the drug has limited the usefulness of this therapy in a substantial number of dogs. Consequently, clinicians should carefully select those patients that are most likely to benefit from erythropoietin for treatment. Dogs with CKD-related anemia may also benefit from earlier intervention, but this interesting concept has not received adequate examination. III The efficacy and safety of recombinant canine erythropoietin therapy was recently evaluated in dogs with anemia of chronic kidney disease and those with chronic kidney disease and red cell aplasia induced by human recombinant erythropoietin therapy. Although this drug showed promising results, the product is not commercially available.

Conclusion

The concepts of evidence-based medicine can be readily applied to management of canine 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 might expect in clinical practice. High-quality evidence exists for use of specific therapeutic renal foods, calcitriol, and ACE inhibitors in animals with significant proteinuria; consequently, these therapeutic interventions should be recommended routinely for management of CKD in dogs. Moderate-quality evidence exists for the use of antihypertensive agents in animals with hypertension associated with CKD, ACE inhibitors for renal disease other than glomerulopathies, hormone replacement therapy in animals with anemia, and hemodialysis. At present, the lowest quality of evidence exists for use of subcutaneous fluid therapy, alkalinizing agents, and intestinal phosphate binders. Randomized, controlled clinical trials are needed to validate the benefits and risks of many treatments recommended and used in patients with 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.