

An evidence-based review of therapies for canine chronic kidney disease

Successful treatment and prevention of kidney disease in dogs requires a multi-dimensional approach to identify and eliminate causes or exacerbating factors, provide professional evaluation on a regular basis and implement a comprehensive treatment programme when necessary. Over the years, many therapeutic and preventive interventions have been developed or advocated for chronic kidney disease in dogs, but evidence of efficacy or effectiveness is often lacking or highly variable. Accordingly, the main objective of this systematic review was to identify and critically appraise the evidence supporting various aspects of managing canine chronic kidney disease.

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INTRODUCTION

Conservative medical management of chronic kidney disease (CKD) consists of supportive and symptomatic therapy designed to correct abnormalities in fluid, electrolyte, acid-base, endocrine and nutritional balance. Therapy is designed to minimise the clinical and pathophysiological consequences of reduced kidney function. In general, this type of management should not be expected to halt, reverse or eliminate renal lesions responsible for CKD. Therefore, management strategies are most beneficial when combined with specific therapy directed at correcting the primary cause of the CKD such as hypercalcaemic nephropathy, bacterial urinary tract infections and obstructive uropathy. Diagnostic efforts should be directed at detecting treatable primary kidney diseases, complications of CKD and comorbid conditions before formulating plans for management.

Conservative medical management is intended for dogs with compensated disease, not for patients unable to eat or accept oral medications because of severe uraemia. Clinical signs of uraemia must be corrected before instituting conservative medical management. The goals of medical management are to (1) ameliorate clinical signs of uraemia; (2) minimise disturbances associated with excesses or losses of water,

electrolytes, vitamins and minerals; (3) support adequate nutrition by supplying daily protein, calorie, mineral and other nutrient requirements and (4) modify progression of renal failure (Polzin and others 2005a, Polzin 2007). These goals are best achieved when recommendations are individualised to the patient's needs on the basis of clinical and laboratory findings. Because CKD is progressive and dynamic, serial assessments of the patient and modification of therapy in response to changes are essential parts of the management strategy (Brown 1999).

EVIDENCE-BASED VETERINARY NEPHROLOGY CONCEPTS

Evidence-based medicine (EBM) represents a major, although largely untested, intellectual advance when making clinical decisions and determining patient care (Geyman 2000, Cockcroft and Holmes 2003). The concept of EBM has emerged recently in several veterinary disciplines (Polzin 1996, Keene 2000, Polzin and others 2000, Marr 2003, Moriello 2003). It has been defined as the integration of the best research evidence with clinical expertise and patient preferences (Sackett and others 2000). Best research evidence means clinically relevant research, especially from patient-centred clinical studies. Clinical expertise refers to the use of clinical skills to identify each patient's unique health state, establish a diagnosis and determine the risks and benefits of potential interventions. For veterinary medicine, the concept of patient preferences must include the unique expectations of each owner. In addition, if a therapeutic intervention is not readily available, then it is unlikely to benefit the patient. The basic tenet of EBM is that integration of these elements (clinically relevant research, clinical expertise, patient/owner preferences and availability of resources) will result in the formation of a diagnostic and therapeutic alliance that optimises clinical outcomes and quality of life (Sackett and others 2000).

In the past, information based on pathophysiological rationale and data from models of kidney disease were often

Table 1. Quality of evidence grading guidelines

Grade	Description
I	Evidence obtained from one or more properly designed, randomised, controlled clinical studies performed in clinical patients of the target species.
II	Evidence obtained from properly designed, randomised, controlled studies performed using animals of the target species with spontaneous disease in a laboratory or research animal colony setting.
III	Evidence obtained from appropriately controlled studies without randomisation, appropriately designed cohort or case-control studies, studies using acceptable models of disease or simulations in the target species; dramatic results from uncontrolled studies or case series.
IV	Evidence obtained from studies conducted in other species, reports of expert committees, descriptive studies, case reports, pathophysiological justification and opinions of respected experts developed on the basis of their clinical experience.

Adapted from Roudebush and others (2004).

used to justify clinical recommendations in dogs with CKD. The proliferation of randomised controlled clinical trials (RCCTs) has led to an increase in the quantity and quality of clinically valid evidence. When possible, veterinarians should use information derived from systematically conducted, rigorously controlled clinical studies to make diagnostic and treatment decisions. Of course, not all recommendations can be based on such studies, so it is important to recognise the inherent limitations of less secure forms of evidence. One method of accommodating concerns regarding these limitations is to assign a score defining the strength and quality of the recommendation. The classification scheme proposed for veterinary clinical nutrition may be useful for establishing rules of evidence for recommendations regarding veterinary nephrology (Roudebush and others 2004). These guidelines categorise the quality of evidence into grades I to IV based on applicability to clinical case management (Table 1). Grades I and II are evidence with the highest quality for application in the clinical environment, whereas grade IV would be evidence with the lowest quality. The quality and strength of evidence can be used to make a recommendation about use of a specific therapeutic modality. Although EBM does not always lead to a definitive answer, it does provide a framework for making decisions and understanding the risk-benefit relationship of various therapeutic or preventive plans.

APPLYING EVIDENCE-BASED CONCEPTS TO THERAPEUTIC DECISIONS FOR CKD

The grade I to IV system was used to systematically evaluate published evidence for

use of the following interventions in dogs with CKD. However, recommendation of any of the specific therapeutic strategies should be assessed not only on the basis of its evidence grade but also on the basis of the clinical expertise of the individual veterinarian, pet owner's preferences and availability of resources. In addition, the impact of providing unnecessary or unproven treatments on the pet-owner relationship should be considered. Treatments which the pet or owner find undesirable may be disruptive to the pet-owner relationship. Since providing high-quality health care to pets is based on the pet-family bond, it is important to avoid inadvertently disrupting this relationship when recommending therapy. Where appropriate, recommendations are also discussed in concordance with the scoring system (stages 1 to 4) established for CKD by the International Renal Interest Society (IRIS 2009). It is beyond the scope of this review to discuss the details of the CKD scoring system and readers are referred to the IRIS website or recent veterinary textbooks for details.

NUTRITIONAL MANAGEMENT OF CKD

Therapeutic renal foods

Therapeutic foods have been used for over 60 years in veterinary patients with CKD. Compared with typical commercial maintenance-type dog foods, therapeutic renal foods usually have reduced protein, phosphorus and sodium levels, and increased dietary buffering capacity, soluble fibre, B-complex vitamins, antioxidants and omega-3 fatty acids levels (Allen and others 2000). Veterinarians are often challenged by the dilemma of when to recommend a therapeutic renal food because of con-

cerns over risking reduced food intake by attempting a potentially unwanted dietary change. This dilemma emphasises the importance of knowing the quality of evidence supporting the recommendation to switch to therapeutic renal foods.

The effectiveness of one therapeutic renal food has been examined in dogs with stages 3 and 4 CKD by an RCCT (Jacob and others 2002). This double-masked study examined whether clinically important benefits accrued when dogs with CKD consumed a renal food compared with a standard canine maintenance food. Dogs were randomly assigned to receive either the renal food or the maintenance food and were managed in an identical manner with respect to other treatment interventions. Feeding the renal food was associated with a 72% reduction in the relative risk for uraemic crisis over the 2 years of the study. In fact, dogs fed the renal food remained free of uraemic signs almost 2.5 times longer than dogs fed the maintenance food (615 days for the renal diet group *versus* 252 days for the maintenance diet). In addition, dogs fed the renal food had a median survival time over three times longer than dogs fed the maintenance food (594 days for the renal diet group *versus* 188 days for the maintenance diet). An important reason for the longer survival times observed among dogs fed the renal food appeared to be that renal function declined more slowly in dogs fed the renal food. Dogs with CKD fed the renal food also had better owner-reported health-related quality-of-life scores than dogs consuming the maintenance food (Jacob and others 2004). These findings are consistent with previously reported uncontrolled clinical studies which also noted an overall benefit of feeding therapeutic foods to dogs with spontaneous CKD (Barsanti and Finco 1985).

In summary, there is strong evidence from an RCCT to support a recommendation to feed therapeutic renal foods to dogs with serum creatinine concentration 2 mg/dl or more (evidence grade I). The benefits of this recommendation, including increased survival, reduced risk of uraemia and improved quality of life, are of great clinical consequence to owners and pets.

Dietary phosphorus restriction and intestinal phosphate binders

Phosphorus is normally excreted by the kidneys through a combination of glomerular filtration and renal tubular reabsorption (DiBartola and Willard 2006). As glomerular filtration rate (GFR) declines in CKD, phosphorus is retained, ultimately resulting in hyperphosphataemia. Hyperphosphataemia appears to play a primary role in promoting renal secondary hyperparathyroidism, at least in part, by suppressing renal tubular conversion of 25-hydroxycholecalciferol to calcitriol. The role of dietary phosphorus intake and hyperphosphataemia in dogs with spontaneous CKD was described nearly 30 years ago (Bovee 1980, Morris 1980). Today, there appears to be a consensus of opinion that phosphate retention and hyperparathyroidism contribute to spontaneous, self-perpetuating progression of CKD in dogs as well as other species. In models of induced kidney disease in cats and cats with spontaneous CKD, there is good evidence for use of dietary phosphorus restriction (Roudebush and others 2009). In human haemodialysis patients, the adjusted relative risk of mortality was stable in patients with serum phosphate concentrations below 6.5 mg/dl but increased significantly above this level (Block and others 1998). Patients with serum phosphate in the 6.6 to 7.8 mg/dl range had 13% higher mortality than patients in the reference range (4.6 to 5.5 mg/dl); patients in the 7.9 to 16.9 mg/dl range had a relative mortality risk 34% higher. Similar data for mortality risk associated with hyperphosphataemia in dogs with spontaneous CKD are lacking although after-treatment targets for serum phosphate concentrations have been recommended (International Renal Interest Society 2009).

In 24 dogs with induced CKD, dietary phosphate restriction, when combined

with protein restriction, has been shown to slow progression of CKD and improve survival (Brown and others 1991). In this study, dogs with CKD were fed either a high-phosphorus (1.44% dry matter) or a low-phosphorus (0.44% dry matter) food for 24 months; both foods avoided excess amounts of protein (17% dry matter). Survival after 24 months was 33% in the high-phosphorus group and 75% in the low-phosphorus group. Kidney function also deteriorated at a more rapid rate in the high-phosphorus group. Two other studies in models of induced CKD in dogs support the clinical practice of avoiding excess dietary phosphorus for improving survival of dogs with spontaneous CKD (Finco and others 1992a,b). The mechanisms underlying the adverse effects of excessive dietary phosphorus are incompletely understood but may relate to enhanced renal mineralisation and renal fibrosis.

In dogs with more severe renal dysfunction, dietary phosphorus restriction alone may not prevent hyperphosphataemia (Jacob and others 2003). Intestinal phosphate-binding agents may be useful to further reduce phosphate retention and hyperparathyroidism in these dogs. High dietary phosphorus, however, may greatly limit the effectiveness of phosphate-binding agents and substantially increase the dose required to achieve the desired therapeutic effect (Yudd and Llach 2000). In a study of dogs with moderate CKD, administration of aluminium carbonate failed to consistently correct hyperphosphataemia when dogs consumed foods containing more than 1.0% phosphorus on a dry matter basis (Finco and others 1985). Although clinical experience suggests that intestinal phosphate-binding agents are useful in reducing serum phosphorus concentrations, controlled clinical studies establishing the value of adding intestinal phosphate-binding agents to dietary phosphate restriction in dogs with spontaneous CKD have not been reported. Unfortunately, aluminium-containing intestinal phosphate binders are not well tolerated by some patients. In addition, they must be given several times per day with meals, which may adversely affect the pet's acceptance of the food and decrease the pet owner acceptance of this therapy.

In summary, evidence supporting a recommendation for reducing dietary phosphorus intake to slow progression of CKD in dogs is based on laboratory studies in dogs with induced CKD (evidence grade III). An RCCT has validated the utility of a therapeutic food that incorporated dietary phosphorus restriction as part of the dietary formulation (see section on 'Therapeutic renal foods'); however, it was not possible to ascertain the role of individual dietary components in the effectiveness of this food. Evidence supporting a recommendation for further limiting dietary phosphorus intake by adding intestinal phosphate-binding agents to therapeutic foods is based on pathophysiological justification and uncontrolled clinical reports (evidence grade IV).

Omega-3 polyunsaturated fatty acids

A variety of positive effects have been attributed to dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs) including their tendency to reduce hypercholesterolaemia, suppress inflammation and coagulation, lower blood pressure, favourably influence renal haemodynamics or limit intrarenal calcification (Polzin and others 2005a). Dietary supplementation with long-chain omega-3 PUFA has been shown to be beneficial in dogs with induced CKD. Compared with dogs fed foods high in omega-6 PUFA, dogs consuming a food supplemented with long-chain omega-3 PUFA had lower mortality, better renal function, fewer renal lesions, less proteinuria and lower serum cholesterol concentrations (Brown and others 1998). In dogs fed the omega-3 PUFA-supplemented food, renal function actually increased and remained above baseline for over 20 months of the study. Lesions of glomerulosclerosis, tubulointerstitial fibrosis and interstitial inflammatory cell infiltrates were also diminished in dogs fed the omega-3 PUFA food.

In summary, evidence supporting a recommendation for supplementing long-chain omega-3 PUFA to slow progression of CKD in dogs is based on laboratory studies in dogs with induced stages 3 and 4 CKD (evidence grade III). The optimum quantity of omega-3 PUFA supplementation and ratio of omega-3 to omega-6

PUFA appropriate for therapeutic renal foods or supplementation have not been conclusively established. Additional supplementation may not be needed for dogs already consuming a therapeutic renal food enhanced with omega-3 PUFA.

Antioxidants

Oxidative damage, via generation of reactive oxygen species, may be a cause of renal injury that contributes to the progression of CKD (Brown 2008). Effects of dietary supplementation of a dry therapeutic renal food with antioxidants (vitamins E and C, and carotenoids) were evaluated in a masked study of 10 dogs with spontaneous stages 2 to 3 CKD living with their owners (Yu and others 2006). Dogs were fed a renal food for 6 weeks and then the same food was supplemented with antioxidants and fed for an additional 4 weeks. Compared with baseline, antioxidant supplementation significantly reduced oxidative stress and serum creatinine concentration compared with dogs receiving the renal food without antioxidants (Yu and others 2006). In another study of dogs with induced CKD, dietary supplementation with omega-3 PUFA and antioxidants (vitamin E, carotenoids and lutein) both independently were renoprotective and their effects were additive when used together (Brown 2008). In this model, addition of antioxidants reduced proteinuria, glomerulosclerosis and interstitial fibrosis independent of the ratio of dietary omega-3 PUFAs to omega-6 PUFAs (Brown 2008).

In summary, evidence supporting a recommendation for supplementing antioxidants to provide renoprotective effects in dogs is based on a small clinical study of dogs with naturally occurring CKD and a study of dogs with induced CKD (evidence grade III). The optimum quantity of antioxidants has not been conclusively established. Additional supplementation may not be needed for dogs already consuming a therapeutic renal food enhanced with antioxidants.

Assisted feeding

Malnutrition is among the most important complications of CKD as it contributes to mortality in most dogs that die of or are euthanased for uraemia. It mani-

festes as weight loss, declining values for serum albumin or total plasma protein concentrations, anaemia and decreased muscle mass. Malnutrition in patients with CKD usually results from inadequate food intake. Commercially available foods designed for pets with CKD contain sufficient protein, calories and other nutrients to sustain adequate nutrient intake when consumed in appropriate quantities. Dogs with stage 4 CKD often fail to eat sufficient food voluntarily, regardless of the palatability or nutrient content (Cowgill and Francey 2004, Polzin 2007).

When malnutrition is suspected, clinical recommendations often include a stepwise approach to facilitate adequate food intake (Polzin and others 2005a, Polzin 2007). The first step is to ensure that metabolic and other causes of decreased appetite have been corrected including dehydration, gastrointestinal haemorrhage, metabolic acidosis, hypokalaemia, anaemia, urinary tract infection and drug-associated anorexia. When these causes have been excluded or corrected, therapy for uraemic gastroenteritis should be initiated. This recommendation assumes that nausea and gastrointestinal distress may be the cause of anorexia even in patients that are not vomiting. Therapy for gastrointestinal complications of uraemia usually includes administration of an H₂ antagonist, often combined with an antiemetic and a gastric mucosal protectant such as sucralfate (Schulman and Krawiec 2000).

If therapy for uraemic gastroenteritis fails to restore normal appetite, assisted feeding should be considered. Long-term use of percutaneous gastrostomy tubes has been successful for delivering food, extra water and medications to patients with CKD (Elliott and others 2000). Anecdotal reports suggest that tube feeding can reverse the progressive weight loss associated with CKD and patients can have extended periods of improved quality of life (Cowgill 2004, Polzin and others 2005a).

In summary, evidence supporting a recommendation for assisted feeding for dogs with CKD that fail to consume adequate calories is limited to pathophysiological justification, descriptive studies and expert opinion (evidence grade IV). It appears likely that assisted feeding can reverse mal-

nutrition in some patients and improve their quality of life. However, RCCTs using well-defined health-related quality-of-life scoring parameters are needed to validate the benefits and risks of assisted feeding in patients with CKD and better identify those patients who would benefit most from this form of management.

MEDICAL MANAGEMENT OF CKD

Fluid therapy

CKD is characterised by progressive reduction in GFR, worsening azotaemia and ultimately uraemia. Chronic administration of subcutaneous balanced electrolyte solutions has been advocated to prevent dehydration, maintain renal blood flow and GFR, increase urine output and ameliorate clinical manifestations of uraemia resulting from prerenal azotaemia, which could exacerbate primary renal azotaemia (Adams 2004, Polzin and others 2005a). A study in normal dogs confirmed that dehydration decreases GFR and both intravenous fluid therapy and water gavage cause significant increases in GFR (Tabaru and others 1993). Additional studies are required to assess physiological and clinical parameters in dogs with naturally occurring CKD. Although clinical impression suggests that some dogs with CKD may benefit from long-term subcutaneous fluid therapy, no controlled clinical studies exist to determine whether such therapy prolongs survival or improves quality of life. Overzealous fluid therapy and use of fluids with increased sodium chloride concentrations may promote systemic hypertension and oedema. In addition, some pet owners and dogs may find frequent subcutaneous administration of fluids to be unacceptable.

In summary, evidence supporting long-term, owner-administered subcutaneous fluid for managing chronic or recurrent dehydration in dogs with CKD is limited to pathophysiological justification and expert opinion (evidence grade IV). Subcutaneous fluid therapy should theoretically be most beneficial for dogs with stages 3 to 4 CKD that are unable to maintain normal hydration status without supplemental fluid therapy. RCCTs are necessary

to identify the benefits and risks attendant of this therapy. Seemingly, many or most dogs with CKD do not require this form of therapy.

Alkalinisation therapy

Metabolic acidosis appears to be a common complication of CKD in dogs. In one recent report, 6 of 38 dogs with CKD had metabolic acidosis of sufficient severity to warrant therapy (Jacob and others 2002). Alkalinisation therapy has been justified on pathophysiological grounds as well as extrapolation from clinical recommendations in human beings with CKD. Potential benefits may include (a) ameliorating clinical signs caused or enhanced by uraemic acidosis, (b) preventing the catabolic effects of metabolic acidosis on protein metabolism, thereby promoting adaptation to dietary protein restriction, (c) limiting skeletal changes resulting from bone buffering and (d) modifying progression of kidney disease (Mitch 1998, Allen and others 2000, Polzin and others 2005a). However, no controlled clinical trials have been performed to confirm that appropriate alkalinisation therapy significantly improves clinical outcomes or alters progression of CKD in dogs.

In summary, evidence supporting use of alkalinising drugs in dogs with CKD is limited to pathophysiological justification and expert opinion (evidence grade IV). Since foods designed for patients with CKD typically have a neutralising effect on acidosis, alkalinisation therapy is probably only warranted in affected dogs consuming typical maintenance foods or when metabolic acidosis persists once the patient is consuming a therapeutic renal food. RCCTs are necessary to identify the benefits and risks attendant of this therapy and better identify those canine patients most likely to benefit from use of oral alkalinising agents. This is especially important in light of the fact that drugs used for alkalinisation are often not well accepted by dogs and must be given multiple times per day for the remainder of the pet's life.

Angiotension-converting enzyme inhibitor therapy

Systemic and glomerular changes observed in dogs with kidney disease may contribute to the progression of renal injury.

Factors frequently implicated in promoting progression of CKD include systemic hypertension, glomerular hypertension, glomerular hypertrophy and proteinuria (Polzin and others 2005a, Lees and others 2005). Initial urine protein:creatinine ratio (UP:C) 1.0 or more in dogs with CKD is associated with greater risk of development of uraemic crisis and death compared with dogs with UP:C less than 1.0 (Jacob and others 2005). Evidence from experimental studies in animals and clinical studies in human beings suggest that therapy with angiotension-converting enzyme inhibitors (ACEIs) preserves glomerular structure and function and reduces proteinuria in CKD. Administration of ACEIs to rodents with reduced renal mass lowers glomerular capillary and systemic blood pressures, prevents glomerular hypertrophy and limits renal impairment (Anderson and others 1986, Yoshida and others 1989). Systematic reviews and meta-analysis of clinical studies using ACEI in human beings have shown benefit in slowing progression of both diabetic and non-diabetic kidney disease (Jafar and others 2001, Casas and others 2005). The beneficial effect of ACEI in patients with renal disease seems to be mediated by factors in addition to decreasing blood pressure and urinary protein excretion and is greater in patients with proteinuria (Jafar and others 2001). Although ACEI therapy has been shown to reduce the magnitude of proteinuria in cats with spontaneous CKD, weak evidence exists to support a recommendation for or against the use of ACEI therapy for the purpose of slowing progression and prolonging survival of cats with CKD (Roudebush and others 2009).

Long-term administration of enalapril has been shown to alter glomerular haemodynamics, blood pressure, proteinuria and structural progression of renal injury in a remnant kidney model of canine CKD when dogs were consuming a therapeutic renal food (Brown and others 2003). Use of the ACEI enalapril in dogs with spontaneous proteinuric CKD has been shown to reduce proteinuria and systemic arterial blood pressure (Grauer and others 2000). Similarly, renoprotective effect of ACEIs has been reported in a canine model of hereditary nephritis and

a model of drug-induced diabetes mellitus (Brown and others 1993, Grodecki and others 1997). While ACEI treatment of dogs with hereditary nephritis did not lower systemic blood pressure, it delayed onset of an increase in serum creatinine concentration and treated dogs survived significantly (1.36 times) longer than untreated dogs (Grodecki and others 1997). A recent clinical trial of 26 dogs with spontaneous CKD evaluated effects of the ACEI benazepril alone, benazepril plus short-term heparin therapy and placebo in a 6-month clinical study (Tenhüdfeld and others 2009). Administration of benazepril reduced proteinuria in dogs with CKD compared with placebo administration. Unfortunately, the severity of proteinuria was not the same at baseline between the benazepril-treated groups and the dogs receiving placebo, such that the improvement of proteinuria with benazepril administration in this study must be cautiously interpreted. In this study, the addition of short-term heparin to benazepril appeared to have no effect on proteinuria.

In summary, there is strong evidence from RCCTs that ACEIs are effective in reducing the magnitude of proteinuria in dogs with proteinuric CKD (evidence grade I). However, reducing proteinuria is a surrogate end point that may or may not translate to clinically important outcomes (e.g. improved survival or quality of life). There is also good evidence from a laboratory study on dogs with a spontaneous form of hereditary nephritis that ACEI may delay loss of renal function and prolong survival (evidence grade II). In contrast to the RCCT's end point of reducing proteinuria, this laboratory study provides evidence of a favourable impact on the clinically important outcome of survival. Evidence from a clinical trial using an ACEI in dogs with spontaneous CKD also showed improvement in some clinical parameters (health status score, GFR and proteinuria) compared with placebo. Several of the studies evaluating ACEI therapy were performed while the dogs were consuming therapeutic renal foods. It is unknown if similar benefits would be achieved with dogs consuming foods not formulated for the management of CKD. Further RCCTs are needed to confirm

the apparent renoprotection provided by ACEI to dogs with proteinuric and non-proteinuric CKD.

Antihypertensive therapy

Hypertension is a well-recognised complication of CKD in dogs and has been shown to be a risk factor for shortened survival times (Jacob and others 2003, Wehner and others 2008). Using a systolic blood pressure value of more than 160 mmHg to indicate hypertension, recent clinical data suggest that the prevalence of hypertension in dogs with CKD may be about 30% (Jacob and others 2003). Sustained systemic hypertension can result in hypertensive retinopathy with retinal detachment, haemorrhage and blindness. However, dogs with such severe ocular manifestations probably reflect only a small percentage of patients with hypertension (Henik 1997, Littman 2000, Brown and others 2007). More subtle ocular lesions such as retinal oedema, retinal vessel tortuosity or papilloedema may be much more common. Hypertension-related CNS disorders (e.g. seizures, loss of balance, abrupt changes in personality and obtundation) have also been observed (Henik 1997, Littman 2000, Brown and others 2007). Hypertension may also damage other organs including the kidneys, heart and blood vessels (Henik 1997, Brown 2005).

Initiation of therapy for hypertension has been advocated in dogs with clinical signs consistent with pressure-related end-organ damage and/or blood pressure values more than 150 to 160 mmHg (Jacob and others 2003, Brown and others 2007). However, the potential renoprotective benefit of antihypertensive therapy in dogs is largely extrapolated from observations in human beings and experimental studies in animals. The potential benefits of antihypertensives in dogs without clinical evidence of hypertensive organ injury might include retarding progression of CKD, reduction in proteinuria, prolonging survival and reducing the incidence of hypertensive retinopathy and encephalopathy.

Well-controlled clinical trials on the effectiveness of managing hypertension in dogs with CKD have not been reported. Administration of the ACEI enalapril to

dogs with induced CKD for 6 months lowered systemic mean arterial pressure and resulted in fewer glomerular and tubulointerstitial lesions compared with a placebo (Brown and others 2003). However, enalapril is thought to have additional renoprotective benefits unrelated to its antihypertensive effects. As a consequence, it is not possible to ascribe the apparent renoprotection observed in this study to antihypertensive therapy alone. Use of other antihypertensive agents (calcium channel blockers, beta-blockers and aldosterone inhibitors) in dogs with CKD is reported but no clinical studies of efficacy with these drugs have been published (Acierno 2009).

In summary, evidence supporting antihypertensive therapy for dogs with CKD is limited to pathophysiological justification, descriptive studies and expert opinion (evidence grade IV). It is often difficult to achieve satisfactory blood pressure reductions in hypertensive dogs with CKD, and the relative effectiveness of various therapeutic strategies designed to control hypertension in dogs have not been adequately investigated. However, it appears rational to initiate therapy with an ACEI for hypertension in dogs. RCCTs are needed to confirm the clinical value of ACEI and other antihypertensive therapies in dogs with CKD.

Erythropoietic hormone replacement therapy

Low packed cell volume, erythrocyte count and haemoglobin are characteristics of dogs with moderate to advanced (stages 3 to 4) CKD (Cowgill 2004, Polzin and others 2005a). The principal cause is hypoplasia of erythroid elements of the bone marrow secondary to inadequate renal production of erythropoietin. Shortened erythrocyte lifespan, erythropoietic inhibitor substances in plasma, chronic gastrointestinal blood loss, nutritional abnormalities (e.g. iron deficiency) and bone marrow fibrosis may contribute to anaemia in some patients with CKD (Cowgill 2004, Polzin and others 2005a). Recent studies in human beings indicate that hypoxia from anaemia of renal disease may contribute to progression of CKD because the anaemia reduces oxygen delivery within the kidney, further promoting hypoxia and progressive renal

damage from oxidative stress (Rossert and Froissart 2006).

Hormone replacement therapy using recombinant human erythropoietin (rHuEPO; Epogen® Amgen, Thousand Oaks, CA, USA) has been shown to be effective in correcting anaemia of CKD in dogs. A clinical trial using dogs with anaemia of CKD as their own controls provided evidence of normalisation of haematocrit values along with substantial improvement in appetite and quality of life with rHuEPO therapy (Cowgill and others 1998). Unfortunately, development of antibodies directed against rHuEPO has limited usefulness of this therapy in a substantial number of dogs. As a consequence, it has been recommended that erythropoietin therapy should be limited to dogs with packed cell volume values less than 20 to 22% and clinical signs attributable to anaemia (Cowgill 2004).

Although unproven, darbepoietin alpha (Aranesp® Amgen, Thousand Oaks, CA, USA) may be less immunogenic in dogs than erythropoietin (Epogen® Amgen); however, studies on the clinical effectiveness and safety of this product in dogs with CKD have not been published. Evidence concerning its effectiveness in dogs with CKD is limited to unpublished case descriptions and personal communication (Cowgill 2009).

The effectiveness and safety of recombinant canine erythropoietin (rcEPO) in dogs with anaemia of CKD has been reported (Randolph and others 2004). Most dogs developed erythroid hyperplasia, reticulocytosis, increased haematocrit and improved quality of life with the treatment. The immunogenicity problems observed with rHuEPO administration to dogs were not observed with use of rcEPO. Although mean blood pressure values did not change with rcEPO therapy, five dogs had elevations of systolic blood pressure during therapy (Randolph and others 2004). Systemic hypertension is a recognised complication of erythropoietin therapy in human beings receiving rHuEPO. The recombinant canine erythropoietin used in this study is not currently available.

In summary, there is evidence from non-randomised, self-controlled clinical trials that rHuEPO and rcEPO are effective in

correcting anaemia of CKD and improving some measures of quality of life in these canine patients (evidence grade III). However, development of anti-erythropoietin antibodies limits application of rHuEPO in dogs. Should rEPO become commercially available, it may improve the overall success of therapy for anaemia of CKD in dogs. Recommendation for use of darbepoietin in dogs with anaemia of CKD is based on anecdotal evidence and personal communication. Factors such as the degree of azotaemia, expected rate of progression of CKD and anaemia, appetite and willingness to eat therapeutic renal foods may also be considered in the risk-benefit analysis of when to start therapy. In addition, factors that may be promoting the anaemia, such as gastrointestinal bleeding or iron deficiency, should also be addressed.

Calcitriol therapy

Calcitriol is the major renal hormone responsible for calcium metabolism. The kidneys convert 25-hydroxycholecalciferol to its active metabolite, 1,25-dihydroxycholecalciferol, also known as calcitriol. Among calcitriol's important functions is modulation of parathyroid hormone (PTH) activity (Brody 1999). Because CKD may be associated with impaired production of 1,25-dihydroxycholecalciferol, calcitriol deficiency may promote renal secondary hyperparathyroidism. Supplementing calcitriol may ameliorate a variety of adverse effects attributed to excess PTH in patients with CKD. It has been reported that 27 of 40 dogs with CKD had serum 1,25-dihydroxycholecalciferol concentrations within the normal reference range (Gerber and others 2003). However, serum concentrations of PTH were increased in these dogs, suggesting a relative deficiency of calcitriol.

Uncontrolled clinical observations suggest that calcitriol therapy may prolong survival of dogs with CKD (Chew and Nagode 1992, Nagode and Chew 1992, 1996). In these reports, dogs with CKD receiving calcitriol therapy (1) were brighter and more alert, (2) had improved appetites, (3) were more physically active and (4) lived longer (Nagode and Chew 1996). A recent double-masked RCCT tested the hypothesis that calcitriol therapy reduces

Table 2. Summary of evidence grades supporting recommendations for therapy of canine CKD

Grade I evidence
Therapeutic renal foods (stages 3 and 4 CKD) * Calcitriol therapy (hyperparathyroidism in dogs with CKD)
Grade II evidence
Angiotensin-converting enzyme inhibitors (proteinuric CKD) Therapeutic renal foods (proteinuric CKD)
Grade III evidence
Recombinant human erythropoietin (suitably anaemic dogs with CKD) Dietary phosphorus restriction (stages 3 and 4 CKD) Omega-3 PUFA supplementation (stages 3 and 4 CKD) Antioxidant supplementation (stages 2 and 3 CKD)
Grade IV evidence
Fluid therapy (chronically dehydrated dogs with CKD) Angiotensin-converting enzyme inhibitors (non-proteinuric CKD) Antihypertensive therapy (renoprotection in dogs with CKD and proven hypertension) Alkalinising therapy (acidaemic dogs with CKD) Assisted feeding (anorexia and malnutrition in dogs with CKD) Therapeutic renal foods (stages 1 and 2 CKD)

CKD, chronic kidney disease; PUFA, polyunsaturated fatty acid.
*See International Renal Interest Society (2009) for details of CKD grading system.

mortality in dogs with CKD (Polzin and others 2005b). In the unpublished study of 37 dogs, calcitriol therapy was associated with a significant reduction in all-cause mortality and median survival time was longer for dogs receiving calcitriol than for dogs receiving placebo. All-cause mortality was 63% in the placebo group and 28% in the calcitriol group, while median survival time was 365 days for dogs receiving calcitriol and 250 days for dogs receiving placebo.

In summary, based on one unpublished RCCT, calcitriol appears to be effective in prolonging survival in dogs with stages 3 and 4 CKD (evidence grade I), although publication of the data will allow further interpretation of results and potential benefits. Uncontrolled clinical observations also suggest that quality-of-life parameters may be improved in dogs with CKD treated with calcitriol.

CONCLUSIONS

Evidence scores for various treatment recommendations for managing dogs with CKD are summarised (Table 2). The concepts of EBM can be readily applied to management of CKD in dogs. 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. Using this system, grades I and II evidence is the most reliable predictor of results likely to be seen in clinical practice. Grades III and IV evidence provide substantially less robust support for recommendations. However, it would be inappropriate to conclude that treatments supported by weaker forms of evidence should not be recommended. Strength of evidence should be used primarily to prioritise recommendations for therapy. As a general rule, treatments with the strongest evidence supporting their effectiveness should be recommended first. Prioritisation of treatment options is particularly relevant when resource issues or client preferences limit application of all appropriate therapy recommendations. In addition, the impact of providing unnecessary or unproven treatments on the pet-owner relationship should be considered. Treatments which the pet or owner find undesirable may be disruptive to the pet-owner relationship. Since providing high-quality health care to pets is based on the pet-family bond, it is important to avoid inadvertently disrupting this relationship when recommending therapy.

Conflicts of interest

P. Roudebush, T. Towell and S. D. Forrester are employees of Hill's Pet Nutrition, Inc., Topeka, Kansas, USA

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