Managing Renal Disease for Improved Patient Outcome

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Introduction

Chronic kidney disease (CKD) is the most commonly recognized form of kidney disease in dogs and cats, and is both irreversible and progressive, requiring life-long treatment. While we have to accept that no treatment can correct the irreversible kidney lesions of CKD, the clinical and biochemical consequences of reduced kidney function can frequently be well managed with the correct supportive therapy. Therefore both dogs and cats can often survive for months to years with a good quality of life. The inevitable progressive course of CKD may be slowed by therapeutic intervention. Nutrition is central to this intervention, helping to slow CKD progression as well as ameliorate the associated clinical signs and therefore nutrition plays a pivotal role in a multi-modal approach for optimal patient care.

These proceedings come in two complementary parts and are aimed at providing both the clinician, and the veterinary nurse, with some of the latest knowledge and practical clinical advice on optimal CKD patient care for companion animals.

The first part, '**Managing renal disease for improved patient outcome**', comes from four recognized experts in the United States of America and covers essential aspects of patient care. CKD of both the dog and cat are discussed. At the end of this first section there are a number of case presentations that provide additional practical examples of case management.

In the second part, '**Chronic kidney disease in the cat: tricks, tips and treatment: Practical advice on the diagnosis, assessment and optimal management of the renal patient**' we have four clinical articles by our European guest author Dr Sarah Caney. In this section Dr Caney has focused just on the cat and once again practical day to day advice on patient management has been shared.

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Part 1

Managing Renal Disease for Improved Patient Outcome

Part 2

Chronic kidney disease in the cat: tricks, tips and treatment

Practical advice on the diagnosis, assessment and optimal management of the renal patient

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Author's biography

Dr Sarah Caney

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Dr Caney, Chief Executive Officer of Vet Professionals, has worked as a feline-only vet since 1994. She is internationally recognised as one of only fourteen veterinary specialists in feline medicine in the UK. In addition to her popular 'Caring for a cat' series of books, she has published widely in prestigious international journals and has been an invited speaker to veterinary conferences worldwide. Dr Caney has worked for many years with the UK cat charity International Cat Care (ICC) and the International Society of Feline Medicine.

A Blueprint for Successful Renal Care: Diagnosing and Staging Kidney Disease

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Most chronic kidney disease (CKD) in dogs and cats is not reversible, but the clinical course varies dramatically among patients. Although congenital disease causes a transient increase in the prevalence of CKD in animals aged <3 years, the prevalence of CKD increases with advancing age starting at 5 to 6 years. In geriatric populations at referral institutions, CKD affects up to 10% of dogs and 35% of cats.[1,2] Estimates of the prevalence of CKD in the general small animal population have varied widely (e.g., 0.37%[3] to 3.7%[4] in dogs), but it is clear that this is a common and important clinical problem in cats and dogs.

The proposed IRIS staging system can be used to facilitate the earlier diagnosis and prospective management of canine and feline patients with CKD.

Animals with CKD should be managed in a multistep process. The initial step ("**Find 'em**") is strategic evaluation of history, physical examination, blood work, and urinalysis to establish a diagnosis of CKD. The next step ("**Stage 'em**") focuses on the use of clinical chemistry values and physical findings to stage animals using the classification scheme of the International Renal Interest Society (IRIS).[5] The final step ("**Manage 'em**") provides individualized diagnostic and therapeutic plans for each animal with CKD based on the disease stage. Focusing on the diagnosis and staging of CKD, this discussion emphasizes important differences in establishing a diagnosis of CKD and individualized management of animals at various IRIS stages.

CKD in dogs and cats generally progresses along a continuum from an initial nonazotemic stage to end-stage uremia. As veterinarians, we are obligated to address the specific problems and patient needs that characterize each animal's disease, which vary from stage to stage. IRIS has proposed a classification system for CKD that facilitates this staged approach in dogs and cats (Table 1). This classification scheme is based on the use of serum creatinine concentration to estimate the degree of decline of glomerular filtration rate (GFR) caused by the kidney disease. The IRIS proposal recognizes that the degree of azotemia in cats is not synonymous with that in dogs. This classification system employs 4 stages: stage 1, nonazotemic CKD; stage 2, mild renal azotemia; stage 3, moderate renal azotemia; and stage 4, severe renal azotemia.

Find 'em (The diagnosis of CKD is not always simple!)

The term *CKD* refers to any disease process in which there is a loss of functional renal tissue caused by a prolonged (generally >2 months in duration), usually progressive, process. CKD generally produces dramatic changes in kidney structure as well, although the correlation between structural and functional changes in this organ is imprecise. This is partly because of the tremendous renal functional reserve; cats can survive for long periods with only a small fraction of initial renal tissue, perhaps 5% to 8%. Thus, CKD often smolders for many months or years before it becomes clinically apparent. Once the GFR falls enough to cause the blood urea nitrogen and serum creatinine concentrations to increase, the diagnosis is generally straightforward. Usually, at this time, the urine specific gravity (USG) is <1.030 and plasma inorganic phosphate levels are increased. Classically, we were taught that CKD was diagnosed as the presence of renal azotemia accompanied by low USG (<1.030). Unfortunately, these diagnostic criteria are incredibly insensitive, identifying the presence of CKD only after three-quarters of functional renal mass has been destroyed. It is a valid diagnostic approach, but it identifies only the tip of the iceberg: animals with marked renal injury in the late stages of CKD. The proposed IRIS staging system can be used to facilitate the earlier diagnosis and prospective management of canine and feline patients with CKD.

When GFR is measured, the presence of a reduced GFR is a generally reliable indicator, although reductions of GFR can also be caused by renal, prerenal, and postrenal factors, and GFR is not commonly measured in clinical medicine. A more readily available clinical approach to early identification of CKD is serial measurement of serum creatinine concentrations. The presence of serial increases in serum creatinine concentration, where each increase is

>0.3 mg/dL (>25 µmol/L), that occur over several months or years suggests the presence of CKD.

In contrast to acute kidney injury or acute renal failure, CKD typically causes renal structural changes that can be palpated or documented by imaging studies. In early CKD, when azotemia and clinical signs are absent, the diagnosis is sometimes made inadvertently, occurring as a result of physical examination (irregular, firm, or small kidneys), imaging studies, or laparotomy.

Routine complete urinalyses are very important (Figure 1). The presence of CKD should be suspected if the USG is < 1.030 despite dehydration. It should also be suspected if the USG is < 1.020, regardless of hydration status. Although measuring USG is a simple and readily available test, interpretation of a finding of a low USG can be complicated because the polyuria caused by CKD must be differentiated from diseases that cause primary polydipsia (e.g., hyperadrenocorticism, hyperthyroidism). Sensitive, specific tests for identification of proteinuria in veterinary patients have recently been developed.[6] They include the urine protein:creatinine ratio and species-specific albuminuria tests. The ability to identify persistent renal proteinuria with these tests offers promise as being clinically useful for identifying early CKD. Persistent proteinuria that cannot be attributed to a systemic disease (prerenal proteinuria) or to protein leak in the lower urinary tract (postrenal proteinuria) suggests that renal proteinuria is present. The presence of persistent renal proteinuria for >2 months suggests the presence of CKD.

Figure 1. A complete urinalysis is a particularly important step in the identifi cation of animals with CKD. In addition to dipstick tests and measurement of USG, urinalysis should always include a sediment examination. An aerobic bacterial urine culture test should be performed annually in animals with CKD and any time a urinary tract infection is suspected.

Although renal azotemia with a fixed low USG is the most reliable marker of CKD, it occurs only very late in the disease process, perhaps too late to have a major impact in many of our patients. Earlier diagnosis is important. The presence of a low USG, renal structural changes, renal infection, serial increases in serum creatinine concentration of >0.3 mg/dL (>25 µmol/L), or persistent renal proteinuria should all be considered as suggestive of the diagnosis of CKD.

We now recognize that proteinuria is associated with an increased risk of developing end-stage CKD and that there may be an increased risk of mortality even in nonazotemic animals.

Stage 'em (Not all animals with CKD are the same!)

For all animals with CKD, a thorough history and physical examination should be accompanied by complete clinical pathology testing, including a biochemistry panel, hematology, and urinalysis with specific proteinuria tests and aerobic bacterial culture. Survey radiography ± abdominal ultrasonography and blood pressure measurements should be performed. This initial battery of tests allows the veterinarian to evaluate the severity of the disease, establish a prognosis, follow the response to subsequent therapy, and identify complicating factors. The IRIS stage is based on serum concentration of creatinine in a hydrated, stable patient (Table 1).

Approximately 20% of animals with CKD have high arterial blood pressure (systemic hypertension) and are, therefore, susceptible to target organ damage from this high pressure.[7] Target organ damage of concern includes progression of CKD, exacerbation of proteinuria, ocular injury (including sudden onset of blindness), and neurologic and cardiovascular complications. Based on IRIS recommendations, all animals with CKD should have their arterial blood pressure measured (Figure 2) and their disease process substaged on the basis of these measurements (Table 2).

Recent findings have suggested that renal protein leak is not only a marker of severity of renal disease but also

TABLE 1. IRIS CKD Staging [5] Based on Serum Creatinine Measurement*

	IRIS CKD Stage 1	IRIS CKD Stage 2	IRIS CKD Stage 3	IRIS CKD Stage 4
	Nonazotemic CKD	Mild renal azotemia	Moderate renal azotemia	Severe renal azotemia
DOGS Creatinine				
(μmol/L)	<125	125–180	181–440	>440
(mg/dL)	<1.4	1.4–2.0	2.1–5.0	>5.0
CATS Creatinine				
(μmol/L)	<140	140–250	251–440	>440
(mg/dL)	<1.6	1.6–2.8	2.9–5.0	>5.0

*All values are for a hydrated animal with stable kidney function.

TABLE 2. IRIS Substaging of CKD in Dogs and Cats Based on Blood Pressure [5]

	Risk of Future Target Organ Damage*			
	Minimal risk (AP0)	Low risk (AP1)	Moderate risk (AP2)	High risk (AP3)
BLOOD PRESSURE (mm Hg)				
Systolic	<150	150–159	160–179	≥180
Diastolic	<95	95–99	100–119	≥120
SUBSTAGE				
No complications (nc) present	AP0nc	AP1nc	AP2nc	AP3nc
Complications (c) present	AP0c	AP1c	AP2c	AP3c

*If blood pressure is not measured, the patient is classified as risk not determined (RND).

TABLE 3. IRIS Substaging of CKD Based on Proteinuria [5]

	IRIS Substage		
	Nonproteinuric (NP)	Borderline proteinuric (BP)	Proteinuric (P)
DOGS Urine protein:creatinine ratio	<0.2	0.2–0.5	>0.5
CATS Urine protein:creatinine ratio	<0.2	0.2–0.4	>0.4

potentially a cause of renal injury.[6] We now recognize that proteinuria is associated with increased risk of developing end-stage CKD in dogs[8] and cats[9,10] and that there may be an increased risk of mortality even in nonazotemic animals. Further, studies have shown that therapies that reduce the magnitude of proteinuria are often renoprotective. Based on IRIS recommendations, CKD should be substaged on the basis of the result of the urine protein:creatinine ratio (Table 3). If proteinuria of this magnitude is persistent and renal in origin in an animal with CKD, the clinician should consider proceeding to the third step of the paradigm (Manage 'em) by employing antiproteinuric therapy (e.g., angiotensin-converting enzyme inhibitor, low-protein diet, and/or omega-3 polyunsaturated fatty acid supplementation).

Manage 'em (Individualized care is the key to success!)

Although beyond the scope of this overview, the purpose of the IRIS staging system is to allow the veterinarian to individualize a proper management scheme for a dog or cat with CKD.[5] This requires a clear understanding of the diagnostic and therapeutic priorities in the stage of disease at the time a patient is being managed. For example, early in the disease process (IRIS CKD stage 1), a careful evaluation of the kidneys to identify the primary disease process and specific therapy to eliminate this disease is critical. In the middle stages (IRIS CKD stages 2 and 3), it is imperative to carefully monitor the rate of progression of CKD while providing renoprotective therapy to slow this progression. In IRIS CKD stage 4, more frequent and thorough evaluations of the patient with institution of appropriate symptomatic therapy become the primary considerations of the veterinarian.

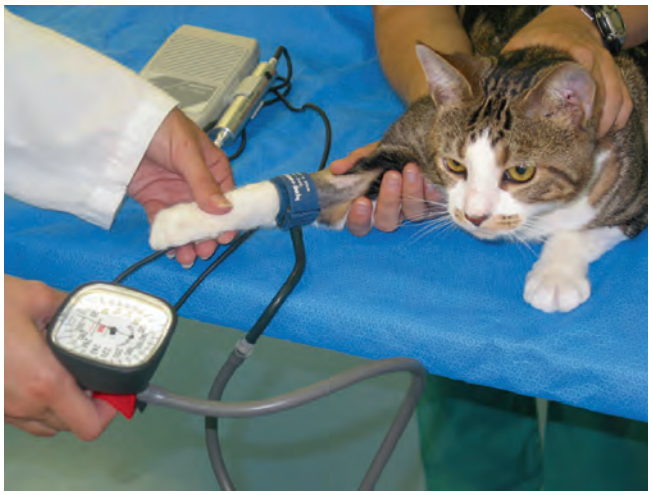

Figure 2. Measurements of arterial blood pressure should be performed to identify animals with CKD that are at risk for future target organ damage.

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Finding the right balance: medical management of renal patients

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Although most cases of chronic kidney disease (CKD) are progressive and irreversible, survival can be relatively long. With appropriate medical management, many affected animals will die of other causes. The International Renal Interest Society (IRIS) staging system can facilitate decisions regarding medical management. As the animal transitions from late stage 2 into stage 3, it is important to address factors affecting progression: appropriate nutrition as well as identification and control of proteinuria, hypertension, hyperparathyroidism, and anemia. When animals transition from late stage 3 into stage 4, factors affecting morbidity must also be addressed: early recognition and treatment of urinary tract infections, acidosis, dehydration, hypokalemia (primarily cats), uremic gastropathy, and ureteroliths (primarily cats).

A reduction in the magnitude of proteinuria is believed to be renoprotective.

Reducing Proteinuria

Patients with persistent renal proteinuria have a greater frequency of renal morbidity and mortality as well as all-cause mortality when compared to those without proteinuria. Any renal disease in which there is functional or structural alteration of the glomeruli, tubules, or interstitium may be associated with renal proteinuria. The magnitude of proteinuria should be assessed by serial urine protein:creatinine (UPC) ratios. Dogs and cats with glomerular proteinuria may eventually progress to have a UPC ratio >2.0; however, in the early stages of disease, the magnitude of proteinuria may be lower than this. Because most glomerular diseases occur secondary to noninfectious inflammatory, infectious, and neoplastic diseases, any animal with persistent renal proteinuria should be evaluated thoroughly for these disorders. Specific treatment should be implemented for any identified underlying disease.

A reduction in the magnitude of proteinuria is believed to be renoprotective. Angiotensin-converting enzyme inhibitors (ACEIs; Table 1) reduce proteinuria and preserve renal function by several possible mechanisms and are currently recommended as the first line of treatment when renal proteinuria causes the UPC to be >0.5 in a dog or >0.4 in a cat. If severe hyperkalemia develops or if proteinuria is not adequately controlled with an ACEI, an angiotensin-receptor blocker (ARB) can be substituted or added. Combination therapy with an ACEI and an ARB may lead to a greater reduction in proteinuria than monotherapy with either an ACEI or an ARB. Losartan is the ARB that I have used most often. If an ACEI is not tolerated, an ARB can be used instead of the ACEI.

With either ACEI or ARB therapy, the drug should be given for 2 to 3 months before it is determined that there has not been an adequate reduction in proteinuria. An adequate response is considered to be either a UPC <0.5 or a reduction in UPC of >50% from baseline. The serum potassium should be maintained <6.0 mEq/L, and the systolic blood pressure should remain >120 mm Hg. Increases in serum creatinine <30% of baseline due to ACEI or ARB therapy are tolerable in CKD stages 1 through 3. Ideally, there is no increase in serum creatinine in stage 4 CKD.

Use of immunosuppressive drugs should be considered in dogs with evidence of immune complex–mediated disease as determined via renal biopsy.

Controlling Hypertension

Hypertension is common in dogs and cats with CKD, and systolic pressures >160 to 180 mm Hg have been associated with a more rapid rate of progressive decline in renal function. Blood pressure control should be considered a cornerstone of appropriate management of dogs and cats with CKD. The current recommendation is to use ACEIs as the first-line antihypertensive agents for dogs and cats, with a calcium channel blocker (e.g., amlodipine besylate) used as a second agent when needed. Animals with systolic pressures >200 mm Hg or evidence of target organ damage (e.g., choroidopathy) should be given both an ACEI and a calcium channel blocker because ACEI monotherapy is unlikely to provide adequate control. Both of these agents are vasodilators and can cause a decrease in glomerular filtration rate. If renal function worsens after initiating

TABLE 1. Drugs Used in the Management of CKD

Drug	Dose Range*	Frequency	Route	Drug Class or Indications
Aluminum hydroxide	30–90 mg/kg/day	Give divided with meals	PO	Phosphate binder
Calcium carbonate	90–150 mg/kg/day	Give divided with meals	PO	Phosphate binder
Calcium acetate	60–90 mg/kg/day	Give divided with meals	PO	Phosphate binder
Sevelamer	400 mg**	Give with meals 2–3 times/day	PO	Phosphate binder
Epakitin (Ipakitine®, Vétoquinol)	1 scoop/5 kg	Give with meals 2–3 times/day	PO	Phosphate binder
Lanthanum	200 mg	Give with meals 2–3 times/day	PO	Phosphate binder
Calcitriol	2.0–2.5 ng/kg, not to exceed 5.0 ng/kg; adjust based on iCa and PTH concentrations	q24h given on an empty stomach	PO	Control of hyperparathyroidism
Famotidine	0.5 mg/kg	q12–24h	PO, IV (dogs only), SC	H_2 blocker Uremic gastropathy
Cimetidine†	2.5–5 mg/kg	q12h	PO, IV, SC	H_2 blocker Uremic gastropathy
Ranitidine†	1–2 mg/kg	q12h	PO, IV, SC	H_2 blocker Uremic gastropathy
Omeprazole†	Dogs: 0.5–1 mg/kg Cats: 0.7 mg/kg	q24h	PO	Proton pump inhibitor Uremic gastropathy
Sucralfate	Dogs: 0.5–1 g Cats: 0.25 g	q8–12h	PO	Gastric protectant Gastric ulceration
Metoclopramide†	0.2–0.5 mg/kg	q6–8h	PO, IV, SC	Control of vomiting
Ferrous sulfate	Dogs: 100–300 mg Cats: 50–100 mg	q24h	PO	Iron deficiency
Iron dextran	50–300 mg/dog 50 mg/cat	Once/month	IM	Iron deficiency
Darbepoetin	0.45 mcg/kg	Induction: once/week Maintenance: q2–4wk	SC	Moderate to severe anemia
Potassium gluconate	Dogs: 0.5 mEq/kg Cats: 1–4 mEq/cat	Dogs: q12–24h Cats: q12h	PO	Hypokalemia
Potassium citrate	0.3–0.5 mEq/kg	q12h	PO	Hypokalemia or metabolic acidosis
Sodium bicarbonate	8–12 mg/kg	q8–12h	PO	Metabolic acidosis
Enalapril‡	0.5–1.0 mg/kg	q12–24h	PO	ACEI Hypertension or proteinuria
Benazepril ‡	0.5–1.0 mg/kg	q12–24h	PO	ACEI Hypertension or proteinuria
Losartan	0.5–1.0 mg/kg	q24h	PO	ARB Hypertension or proteinuria
Amlodipine ‡	Starting doses: Dogs: 0.1 mg/kg Cats: 0.625 mg/cat	q24h	PO	Hypertension

iCa = ionized calcium; PTH = parathyroid hormone.
*Doses listed are for both dogs and cats unless otherwise indicated.
**Should be used cautiously in small dogs; dosage modification may be required.
†Dosage modification may be required in animals with moderate to severe renal failure.
‡Should be used cautiously in animals with severe renal failure; frequent monitoring is required.

treatment with an antihypertensive agent, the drug should be temporarily withdrawn and reinstituted at a lower starting dose.

Controlling Renal Secondary Hyperparathyroidism

Animals with CKD are less able to excrete phosphates through the kidneys. Phosphate retention may contribute to the progression of CKD through the development of renal secondary hyperparathyroidism, nephrocalcinosis, or both. Parathyroid hormone has been described as a uremic toxin that contributes to the progression of CKD. However, increased concentrations of parathyroid hormone may simply be a marker of vitamin D deficiency, which may be the culprit in uremia. Low doses of calcitriol administered orally reduce parathyroid hormone concentrations in dogs with CKD. Preliminary results of a controlled clinical study suggest that calcitriol is effective in prolonging survival in dogs with stages 3 and 4 CKD[1]; the benefits have not been as clear in cats. Calcitriol should not be given until hyperphosphatemia is controlled and the calcium-phosphorus product is <60. Parathyroid hormone concentrations should be monitored to document that renal secondary hyperparathyroidism is adequately controlled during calcitriol administration.

Renal diets are often effective in reducing serum phosphate to the target ranges in dogs and cats with stage 2 and early stage 3 CKD; however, additional control with an intestinal phosphate binder may be needed when animals progress to late stage 3 or stage 4 CKD.

Renal diets are often effective in reducing serum phosphate to the target ranges in dogs and cats with stage 2 and early stage 3 CKD; however, additional control with an intestinal phosphate binder may be needed when animals progress to late stage 3 or stage 4 CKD (Table 2). Aluminum hydroxide has been the phosphate binder of choice for many years but may become relatively less available because of concerns about aluminum toxicity. Calcium carbonate and calcium acetate are effective alternatives, but both carry the risk of causing hypercalcemia and should be used with caution in dogs or cats when the serum calcium-phosphorus product is >60. Epakitin (in Europe Ipakitine® is available from Vétoquinol) is an intestinal phosphate binder that contains chitosan and calcium carbonate and appears to be effective at reducing serum phosphorus concentrations. However, it also has the potential to increase the calcium-phosphorus product. Furthermore, chitosan is marketed as an intestinal fat absorber, leading to weight loss in people. The patient's weight should be closely monitored while receiving this medication. Sevelamer is an intestinal phosphate binder that is a polymer, is not absorbed systemically, and does not promote hypercalcemia. Dogs given sevelamer at 100 times the recommended dosage did not develop any apparent toxicosis. However, the use of this agent in dogs and cats has not been studied and recommended doses have not been established. Lanthanum is another new phosphate binder that can be used in dogs and cats with resistant hyperphosphatemia.

TABLE 2. Target Ranges for Serum Phosphate Concentrations Based on the IRIS CKD Stage

IRIS CKD Stage	Target Serum Phosphate Range	
	mg/dL	mmol/l
2	2.7 to 4.6	0.9 to 1.5
3	2.7 to 5.0	0.9 to 1.6
4	2.7 to 6.0	0.9 to 1.9

Managing Anemia

Moderate to severe anemia may lead to anorexia, cold intolerance, lethargy, and weakness. Sources of ongoing blood loss (e.g., gastrointestinal hemorrhage), infection, or inflammation should be eliminated; iron deficiencies should be corrected; and blood sample collection should be minimized in animals with CKD and anemia. Transfusions of whole blood or packed red blood cells may be used for short-term control of anemia but are less suited for long-term control. Animals requiring repeat transfusions to maintain a packed cell volume (PCV) >20% to 25% benefit from administration of darbepoetin, a synthetic form of erythropoietin. Blood pressure should be adequately controlled before instituting darbepoetin therapy. Iron supplementation is needed to prevent iron deficiency during treatment. Darbepoetin appears to be less antigenic and can be given less frequently than recombinant human erythropoietin and is now considered the standard for managing anemia in dogs and cats. Increased PCV from these therapies results in increased alertness, appetite, energy, playfulness, strength, and weight gain.

Administering Fluid Therapy

Dogs and particularly cats with CKD may be susceptible to volume depletion, which can exacerbate clinical signs and contribute to further renal damage. The goals of fluid therapy should be to restore the patient to euvolemia and alleviate clinical signs of uremia. Attention should be given to the well-being of the patient rather than achieving a "magic" number for serum urea nitrogen or creatinine. The patient's volume status must be assessed before initiation and during administration of fluid therapy.

Some animals with stage 4 CKD subjectively appear to have fewer uremic episodes and improved appetites when given subcutaneous fluid intermittently; others do not appear to benefit from this therapy. Fluids should be administered in the smallest volume and the lowest frequency needed to help improve clinical signs. Chronic sodium administration may be harmful to the kidneys and exacerbate hypertension. Ideally, fluids formulated for maintenance therapy should always be used to minimize the amount of sodium given to these patients.

Managing Acid-Base and Potassium Disturbances

Metabolic acidosis may be associated with progressive renal injury, loss of lean muscle mass, and the development of osteodystrophy and contributes to anorexia, lethargy, and nausea in patients with CKD. Alkalinization therapy should be considered in animals with CKD and metabolic acidosis. Sodium bicarbonate is commonly used for alkalinization therapy. Potassium citrate may have an added advantage in cats with CKD and concurrent hypokalemia because correction of the hypokalemia may lead to improved renal function. Because hypokalemia is usually correctable by increasing potassium intake, potassium content is increased in feline renal diets. Potassium supplementation should be considered in cats that do not maintain a serum potassium >4.0 mEq/L while consuming a renal diet. Potassium supplementation may also be needed in dogs with Fanconi syndrome.

Attention should be given to the well-being of the patient rather than achieving a "magic" number for serum urea nitrogen or creatinine.

Controlling Uremic Gastropathy

Anorexia, nausea, and vomiting may be signs of uremic gastropathy in dogs and cats with CKD. The frequency of these signs may decrease when the patient consumes a renal diet. When these signs are not controlled by diet alone, histamine type 2 (H_2)-receptor antagonists (i.e., cimetidine, ranitidine, and famotidine) are often used to reduce gastric acid secretion. Proton pump inhibitors (e.g., omeprazole) are more effective than H_2-receptor antagonists at reducing gastric acid secretion. Proton pump inhibitors should be tried in dogs and cats that have persistent signs of uremic gastropathy despite appropriate administration of an H2-receptor antagonist. If gastric ulceration is suspected, sucralfate should also be given. Centrally acting antiemetics (e.g. metoclopramide, or maropitant [Cerenia®, Zoetis] is licensed for cats in some countries) may be needed to control vomiting during a uremic crisis.

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Suggested Reading

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Enhancing Quality of Life: Nutritional Management of Renal Patients

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Renal disease is a common cause of morbidity and mortality in older dogs, and it occurs in approximately 20% of dogs over 5 years of age, with a mean age of 10.2 years.[1] Chronic kidney disease (CKD) is the most common cause of renal disease in dogs. The most successful treatment of CKD requires a multimodal approach that involves identifying and eliminating exacerbating factors combined with appropriate dietary and medical management.[2–4]

Dietary management is one of the few current recommendations for management of CKD that has grade 1 evidence for support; thus, it remains the cornerstone of therapy.

Many therapeutic interventions have been developed or advocated for the management of CKD in dogs; however, evidence of efficacy or effectiveness is often lacking or highly variable for many of these treatment recommendations. If therapeutic recommendations currently advocated for the management of CKD were to undergo the scrutiny of evidence-based medicine, very few of our current recommendations meet the criteria to receive a grade I, a recommendation based on the highest quality of evidence. Evidence-based medicine designates four different grades (I–IV), where grade I means that evidence for a recommendation is based on results from one or more properly designed, randomized, controlled clinical studies performed in clinical patients of the target species, and grade IV, which is the lowest recommendation, is based on 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.[2] Dietary management is one of the very few current recommendations for management of CKD that has grade I evidence for support. As a result, dietary management remains the cornerstone of therapy for the management of this condition in both dogs and cats.[5]

Veterinary Therapeutic Renal Diets Versus Standard Maintenance Diets

Research has shown that veterinary therapeutic renal diets are superior to maintenance diets for managing CKD.[3,4] One study evaluated whether there was a benefit of feeding a therapeutic renal diet versus a standard maintenance diet to dogs with spontaneous CKD.[3] Thirty-eight dogs with spontaneous CKD were enrolled in a double-blind, randomized, controlled clinical trial; 17 dogs were fed a therapeutic renal diet, and 21 dogs were fed a standard maintenance diet. There were no statistical differences in baseline parameters between diet groups, and the primary study end point was a diagnosis of uremia established by two clinicians unaware of the diet being fed and uninvolved in patient management. Results showed that on average, it took 252 days for the dogs consuming the maintenance diet to be diagnosed with a uremic crisis, while those consuming the veterinary therapeutic renal diet took on average 615 days to develop a uremic crisis. In addition, dogs consuming the renal diet had a lower mortality rate. Therefore, this study showed that therapeutic renal diets are superior to maintenance diets for minimizing uremic episodes and death in dogs with spontaneous CKD. However, the two diets fed in this study varied in many of the key nutrients for the management of CKD, including dietary protein, phosphorus, and fatty acid composition, so it was uncertain what component(s) of the therapeutic renal diet resulted in the benefits observed in this study. Another retrospective clinical study that was done to determine whether there was an association between body condition score and survival in dogs with CKD also observed that dogs that were fed a veterinary therapeutic diet had a significantly longer survival time compared to dogs not consuming a renal diet (P=0.03).[4]

Key Nutrients in the Management of CKD in Dogs

Phosphorus

A study was conducted in dogs to determine the effects of high (H) and low (L) levels of dietary phosphorus and protein on renal function and survival in adult dogs with induced CKD.[6] Forty-eight dogs divided into four diet groups (n=12)

were fed one of four experimental diets for 24 months after surgical reduction of renal mass. The experimental diets contained varying levels of protein (Pr) and phosphorus (Ph) listed on a percent dry matter basis:

- Diet 1: HPr:HPh (32% Pr and 1.4% Ph)
- Diet 2: HPr:LPh (32% Pr and 0.4% Ph)
- Diet 3: LPr:HPh (16% Pr and 1.4% Ph)
- Diet 4: LPr:LPh (16% Pr and 0.4% Ph)

Diet 4 is most consistent with many commercially available veterinary therapeutic renal diets. Results showed that when renal function was reduced to the point that moderate azotemia (serum creatinine: 3–4 mg/dL) occurs, dietary phosphorus restriction was beneficial, with a longer period of stable glomerular filtration rate (GFR) and improved survival. However, dogs fed 32% dietary protein had neither functional nor morphologic evidence of adverse effects of increased protein intake, compared to dogs fed 16% dietary protein. As a result, this study showed that survival was enhanced by phosphorus restriction but not by protein restriction.

However, therapeutic renal diets vary in their nutritional composition, and it is currently unknown which component(s) of these diets benefit patients. In addition, although dietary protein restriction has been a mainstay in the management of this condition for many years, recent research has called into question whether this is necessary or even the best approach for our patients. This paper discusses some newer research evaluating dietary components of therapeutic renal diets and discusses a clinical study using two dietary approaches for managing CKD in dogs.

Omega-3 Polyunsaturated Fatty Acids (PUFAs)

Dogs lack the ability to synthesize omega-6 (n-6) and omega-3 (n-3) PUFAs, which is why these are considered dietary essential fatty acids.[7] Dogs have a dietary requirement for linoleic acid (LA), which is an n-6 PUFA, but they have the enzyme capability to convert LA into arachidonic acid (AA), another n-6 PUFA, and therefore do not have a dietary requirement for AA. However, dogs are unable to convert n-6 PUFAs into n-3 PUFAs, and therefore have a dietary requirement for n-3 PUFAs as well.

Among the n-3 PUFAs, differences exist depending on whether the source is terrestrial plant or marine in origin, and not all n-3 PUFAs are metabolically equivalent. Plant-based sources of n-3 PUFAs, such as flaxseed, linseed, and canola oil, are rich in alpha-linolenic acid (ALA), while oily cold water fish and marine algae are good sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although the n-6 PUFA LA is readily converted to AA, the conversion of n-3 PUFA ALA to EPA and DHA occurs much more slowly. This conversion rate is <10% in humans, and it is believed to be rather limited in dogs as well.[8] While dietary ALA does have some benefits in healthy dogs and in the management of some dermatologic disease,[9] the majority of therapeutic benefits that we see with n-3 PUFAs, such as anti-inflammatory and prostaglandin effects, occur from EPA, while central nervous system development and retinol function, which are critical during pregnancy and early in life, occur from DHA. Therefore, when using diets supplemented with n-3 PUFAs to manage medical conditions, such as cardiovascular disease, idiopathic hyperlipidemia, inflammatory and immune diseases, kidney disease, and osteoarthritis,[7,8,10] it is important that the source of n-3 PUFAs be one that already contains EPA and DHA, because the conversion rate of ALA to EPA and DHA may be too slow to be of much benefit to the patient.

In one study, survival in dogs with CKD was enhanced by phosphorus restriction but not by protein restriction.[6]

When nephrons are destroyed in CKD, the remaining viable nephrons hypertrophy in an attempt to compensate for nephron destruction, and this process results in a maladaptive increase in glomerular capillary pressure (GCP). Dietary n-3 fatty acid supplementation can have beneficial effects in reducing GCP.[11–13] In a study by Brown,[13] the effects of various dietary n-6:n-3 ratios on glomerular hypertension in a remnant kidney model in dogs were evaluated. Eighteen dogs were equally divided into three diet groups consisting of n-6:n-3 ratios of 50:1, 25:1, and 5:1. The source of n-3 PUFA supplementation in the diets was in the form of fish oil, which is rich in EPA and DHA, and the diets were fed to the dogs for 10 weeks. Results showed that the n-6:n-3 diet with the 5:1 ratio normalized GCP in dogs with reduced kidney function to a level consistent with what is found in dogs with normal kidney function.

Antioxidants

A free radical is any atom or molecule that has a single unpaired electron. Normal aerobic metabolism, along with many environmental factors, contributes to the formation of reactive oxygen species (ROS) in the body. ROS can damage membrane lipids, nucleic acids, and proteins in the body that in turn contribute to disease processes. Normally, antioxidant defense mechanisms adequately remove ROS as they are formed; however, endogenous antioxidant defense mechanisms become inadequate as animals age, and progressive oxidative damage is a consistent feature of

aging unless adequate dietary sources of antioxidants are provided. It is also important to keep in mind that there are optimal levels of dietary antioxidant supplementation, and oversupplementation of dietary antioxidants might be as detrimental as a deficiency of dietary antioxidants. Because CKD occurs most commonly in older dogs, oxidative stress can also be a contributing factor to the decline in GFR associated with this disease. Additionally, renal oxidative stress is a problem in CKD because surviving hypertrophied nephrons become adaptively hyperfunctional, which leads to a dramatic increase in cellular oxidative phosphorylation. In a study by Brown,[13] the effects of n-3 fatty acid supplementation and antioxidant supplementation were evaluated separately and in combination in 6- to 8-year-old beagles with induced CKD. Thirty-two dogs were divided into four equal groups (n=8) and fed one of four diets:

- Diet 1 was a high n-3 PUFA diet (from fish oil).
- Diet 2 was a high n-3 PUFA plus antioxidants (vitamin E, carotenoids, lutein) diet.*
- Diet 3 was a high n-6 PUFA diet (from vegetable oil).
- Diet 4 was a high n-6 PUFA plus antioxidant diet.

Results showed that when compared to the control diet (diet 3), the diet supplemented with n-3 fatty acids (diet 1) and the diet supplemented with antioxidants (diet 4) both slowed the rate of decline in GFR (Figure 1).

*Similar to Iams Veterinary Formula Renal Plus for Dogs (USA product)

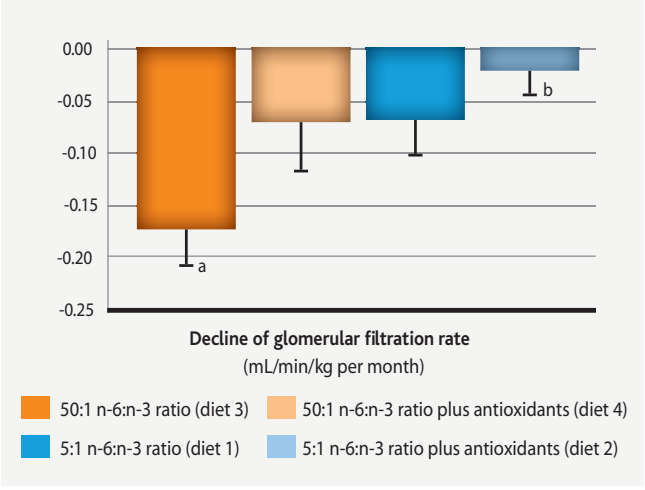

FIGURE 1. Omega-3 fatty acids from fish oil and antioxidants independently reduce the decline in GFR in dogs with CKD when compared to a control diet not supplemented with either n-3 fatty acids or antioxidants. However, when both n-3 fatty acids and antioxidants are added to a diet simultaneously, there is a statistically significant reduction in the decline in GRF when compared to the control diet. Adapted from Brown SA. Oxidative stress and chronic kidney disease. Vet Clin North Am Small Anim Pract 2008;38:164.

However, when n-3 fatty acids were combined with antioxidants (diet 2), the effects on slowing down the rate of decline in GFR were additive and statistically significant when compared to the control diet (Figure 1). In addition, dietary antioxidants have been shown to reduce the magnitude of proteinuria, glomerulosclerosis, and interstitial fibrosis in dogs with CKD. Therefore, veterinary therapeutic renal diets that are supplemented with both n-3 fatty acids from fish oil in combination with antioxidants appear to be better at slowing down the progression of CKD than diets that are supplemented with only one or the other or not at all.

Protein

The traditional approach to management of CKD in dogs is to reduce protein intake to less than the Association of American Feed Control Officials (AAFCO)-recommended minimum levels for adult maintenance (18% on a dry matter basis). The benefits and rationale for this approach is that reduced-protein diets decrease the production of nitrogenous waste products in the body that must be excreted by the kidneys. In addition, protein is one of the major contributors to phosphorus in the diet, and by reducing dietary protein, dietary phosphorus levels can also be reduced, which has been shown to be beneficial in the management of CKD in dogs.[6]

The downside to reduced-protein diets for the management of CKD in dogs is that this is generally a condition diagnosed in older dogs, and older dogs may actually require more dietary protein than their younger counterparts to maintain protein reserves and maximize protein turnover rates because they are less efficient in metabolizing dietary protein.[14,15] In a study by Kealy,[16] 26 healthy pointers 7 to 9 years of age were assigned to diets based on gender and body weight and fed either a 16.5% or 45.6% protein diet. After 2 years of study, the percent lean body mass was directionally higher and the percent lean body fat was directionally lower on the 45.6% protein diet than on the 16.5% protein diet. The dogs fed the 16.5% protein diet had an average percent lean body mass and body fat of 71.1 and 24.8, respectively, whereas the dogs fed the 45.6% protein diet had an average percent lean body mass and body fat of 76.2 and 19.6, respectively. In people, loss of lean body mass that often accompanies dietary protein restriction can also result in loss of physical strength and motor coordination, as well as impair immune function.[17,18] Loss of lean body mass has also been associated with increased rates of morbidity and mortality in people, and a similar result was observed in dogs in the Kealy study. In addition, the work by Finco and colleagues showed that dietary phosphorus restriction, but not dietary protein restriction, was beneficial in dogs with CKD.[6]

Facilitating Higher-Protein Intake in Dogs with CKD

Protein Source

Levels of dietary phosphorus are generally closely associated with levels of dietary protein, and it has already been established that dogs with CKD benefit from a phosphorus-restricted diet.[6] However, it is possible to formulate diets for management of CKD in dogs that are phosphorus restricted but higher in protein than what is traditionally used by choosing protein sources that are naturally lower in phosphorus content; soy isolate is one of those protein sources.

Nitrogen Trap Fiber System (Enteric Dialysis)

When dietary protein is metabolized, the kidneys are responsible for excreting some of the metabolites from the body. The major nitrogen-containing metabolites that must be excreted by the kidneys include primarily urea, followed by creatinine, ammonia, and uric acid,[19] and the reduced ability of the kidneys to excrete nitrogenous protein catabolites is one of the major causes of uremic signs. Urea is formed in the liver via the urea cycle when two molecules of ammonia combine with one molecule of carbon dioxide, and urea is a much less toxic waste product from protein metabolism to be transported in the body than is ammonia. The primary benefit of monitoring blood urea nitrogen (BUN) values in dogs with CKD is that they are an indicator of retention of harmful nitrogenous waste products in the body. However, whenever urea is excreted by the kidneys, water comes with it. Therefore, relying solely on the kidneys to excrete urea in patients with CKD that have elevated levels of BUN is not a desirable situation, and feeding these patients higher-protein diets only exacerbates this problem. However, adding certain fiber types to the diet can direct some of the nitrogenous waste product excretion from the body to the colon in a process known as *enteric dialysis*. In addition, enteric dialysis allows more dietary protein to be fed without increasing the nitrogenous excretion burden on the kidneys.

Adding certain fiber types to a higher-protein diet can direct some of the nitrogenous waste product excretion from the body to the colon in a process known as *enteric dialysis*.

The mechanism by which certain types of fermentable dietary fiber can be used to promote enteric dialysis is multifactorial. Normally, a small amount of urea is transported from the blood supplying the colon into the lumen of the gut, where intestinal bacteria hydrolyze urea into ammonia by producing the enzyme urease. This ammonia is subsequently incorporated into bacterial protein and excreted from the body when the animal defecates. However, this process can be enhanced by adding certain types of fermentable fiber to the diet. Fermentable fiber is a fuel source for certain types of intestinal bacteria, and when these bacteria ferment dietary fiber, they produce short-chain fatty acids (SCFA), which provide about 70% of the energy needs for the large intestinal epithelial cells. Therefore, provision of dietary fermentable fiber not only increases bacterial numbers but also increases the production of SCFA and health and surface area of the colonic mucosa. SCFA in turn increase the blood flow to the colon and urea presentation to the intestinal tract. Increased bacterial proliferation maintains urea concentration gradient and allows continued flow of urea from blood into the lumen, and excretion via the intestine when the animal defecates. This process allows some of the wasteful products from protein metabolism to be excreted from the body by a nonrenal mechanism.

A study was conducted in 12 healthy adult dogs divided into two groups that were fed either a normal maintenance diet or the same diet supplemented with a fermentable fiber blend for 14 days.[20] The fiber blend included beet pulp, fructooligosaccharide (FOS), and gum arabic. Results showed that when dogs were fed the diet containing the fermentable fiber blend, fecal nitrogen excretion increased by 34% ($P<0.05$) and urinary nitrogen excretion decreased (Figure 2). Therefore, the body was able to increase nitrogenous waste product excretion via a nonrenal mechanism, and this mechanism could be used to potentially increase dietary protein intake in dogs with CKD without increasing the buildup of uremic toxins.

Clinical Outcome Measures in Dogs With Naturally Occurring CKD

A multicenter clinical study involving six veterinary teaching hospitals was conducted in dogs with naturally occurring CKD.[21] After baseline evaluation, dogs were randomly and blindly assigned to be fed one of two diets formulated for dogs with CKD and followed for 24 months. Both diets were phosphorus restricted and had similar energy content but varied in their protein levels. The control diet was a protein-restricted diet, while the treatment diet had protein levels 45% higher and approximately 23% above the AAFCO-recommended minimum levels for adult maintenance. In addition, the treatment diet was supplemented with a prebiotic fiber blend that was previously shown to enhance enteric dialysis,[20] as well as supplemented with n-3 PUFAs and antioxidants.

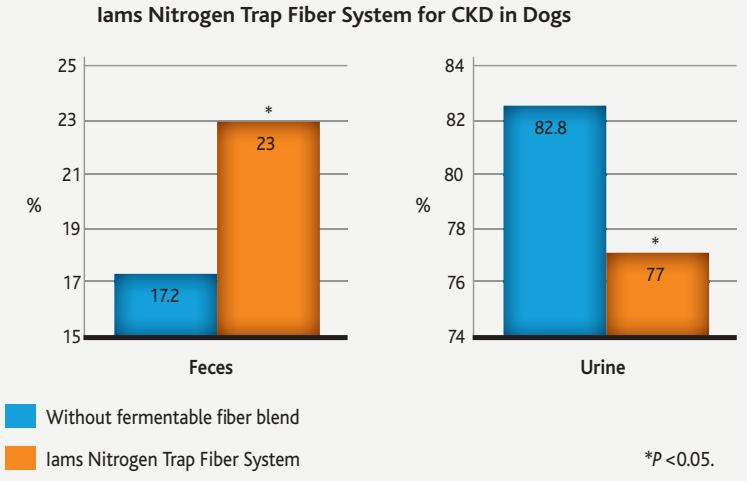

FIGURE 2. The Nitrogen Trap Fiber System resulted in a 34% increase in fecal nitrogen excretion in healthy dogs.

There was no difference in baseline parameters between diet groups. Results showed that despite feeding more protein with the treatment diet versus control diet, survival and clinical markers of renal function, including serum creatinine and iohexol clearance, were not significantly different between diet groups. However, preliminary data shows that body condition score was significantly higher 2 months into the study for the dogs consuming the higher-protein diet compared to those consuming the protein-restricted diet. In addition, although BUN was higher in the higher-protein group after 2 months, there was no statistical difference in BUN levels between diet groups for the remainder of the study, confirming that the prebiotic fiber blend effectively allowed more dietary protein to be fed without causing the buildup of nitrogenous waste products in the blood. Therefore, this study shows that dietary protein restriction does not enhance survival in dogs with CKD as long as the diet is phosphorus restricted. In addition, higher dietary protein levels in combination with a prebiotic fiber blend that enhances enteric dialysis, n-3 PUFAs, and antioxidants is advantageous in maintaining a better body condition score in dogs with CKD.

Dietary Recommendations for CKD and IRIS Staging

The International Renal Interest Society (IRIS) has developed four stages of CKD based on serum creatinine levels (Table 1).[22] A common question is: When in the course of CKD should a veterinary therapeutic renal diet be initiated for the management of this condition? Based on the clinical study discussed above,[21] as well as other research that has been conducted evaluating nutritional management of this condition, it is appropriate to recommend a therapeutic renal diet to patients that are diagnosed with IRIS stages 2 to 4 CKD. Now that research documents that it is unnecessary to protein-restrict these patients, as long as other nutritional components are included in the diet, there is less concern about feeding a higher-protein therapeutic renal diet to a patient in earlier stages of CKD on a long-term basis, especially in aging patients where dietary protein requirements may actually be higher than in younger patients. However, because IRIS stage 1 for CKD incorporates a number of different conditions, it is still best to make dietary recommendations on a case-by-case basis for patients that fall within this stage of renal disease.

TABLE 1. IRIS Staging of CKD Based on Serum Creatinine Concentration

Stage	Serum Creatinine Levels*		Comments
	Dogs	Cats	
–	<125 µmol/L <1.4 mg/dL	<140 µmol/L <1.6 mg/dL	**At risk of CKD** For patients identified as "at risk," consider regular screening and taking steps to reduce risk factors.
1	<125 µmol/L <1.4 mg/dL	<140 µmol/L <1.6 mg/dL	**Nonazotemic** Some other renal abnormality present (e.g., inadequate concentrating ability without identifiable nonrenal cause; abnormal renal palpation and/or abnormal renal imaging findings; persistent proteinuria of renal origin; abnormal renal biopsy results, progressively elevating creatinine levels).
2	125–180 µmol/L 1.4–2.0 mg/dL	140–250 µmol/L 1.6–2.8 mg/dL	**Mild renal azotemia** Lower end of the range lies within the reference range for many labs, but the insensitivity of creatinine as a screening test means that animals with creatinine values close to the upper limit of normality often have excretory failure; clinical signs are usually mild or absent.
3	181–440 µmol/L 2.1–5.0 mg/dL	251–440 µmol/L 2.9–5.0 mg/dL	**Moderate renal azotemia** Systemic clinical signs may be present.
4	>440 µmol/L >5.0 mg/dL	>440 µmol/L >5.0 mg/dL	**Severe renal azotemia** Systemic clinical signs are usually present.

Adapted from the International Renal Interest Society (IRIS). *IRIS 2009 Staging of CKD.* www.iris-kidney.com/pdf/IRIS2009_Staging_CKD.pdf.
*These serum creatinine levels apply to average-sized dogs; levels of dogs of extreme size may vary.

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Putting it all together: Renal Clinical Case Discussions

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Chronic kidney disease (CKD) is a common problem that affects an estimated 1% to 3% of all cats.[1–3] Its prevalence increases with age, with up to 30% to 35% of geriatric cats in hospital populations having CKD.[1,3,4] Nephron damage with CKD is usually irreversible and can be progressive. Most feline CKD is associated with tubulointerstitial lesions, although a primary etiology is often not determined. Whether the underlying CKD primarily affects glomeruli, tubules, interstitial tissue, or renal vasculature, irreversible damage to any portion of the nephron renders the entire nephron nonfunctional. Healing of irreversibly damaged nephrons occurs by replacement fibrosis. CKD occurs over a period of months or years and is an important cause of death in cats. It is often not possible to improve renal function in CKD; therefore, treatment is aimed at stabilizing renal function. Importantly, there is increasing evidence that dietary and antiproteinuric treatments are renoprotective and can decrease the progressive nature of CKD.

The irreversible, often progressive nature of CKD emphasizes the need for early diagnosis and intervention.

Etiology and Pathophysiology OF CKD

The cause of feline CKD is usually difficult to determine because the end point of irreversible nephron damage is the same, regardless of etiology. Morphologic heterogeneity between nephrons exists in chronically diseased kidneys, with changes ranging from severe atrophy to marked hypertrophy. The more common renal diseases associated with the development of CKD in cats include amyloidosis, feline infectious peritonitis, neoplasia, nephrolithiasis, polycystic kidney disease, pyelonephritis, and tubulointerstitial disease. In some cases, the initial underlying renal insult remains undetected/untreated and continues to damage nephrons. It is also possible that progressive kidney dysfunction can become "self-perpetuating" even after the initial underlying insult is resolved (Figure 1).

Progressive kidney disease that destroys nephrons at a slow rate allows remaining intact nephrons to undergo compensatory hypertrophy, which delays the onset of renal failure. Renal azotemia usually does not occur until >75% of the cat's nephrons are lost. When renal failure finally occurs, nephron hypertrophy can no longer maintain adequate renal function. By the time the disease progresses to International Renal Interest Society (IRIS) stage 4 CKD, cats usually have <5% to 10% of their original nephron population intact. The irreversible, often progressive nature of CKD emphasizes the need for early diagnosis and intervention.

Clinical Signs and Diagnosis OF CKD

Clinical signs of CKD may not be present in early stages and, when present in later stages, are usually nonspecific (anorexia, dehydration, depression, gastroenteritis, and lethargy). Unique signs of CKD (versus acute renal disease) include a long history (weeks to months) of weight

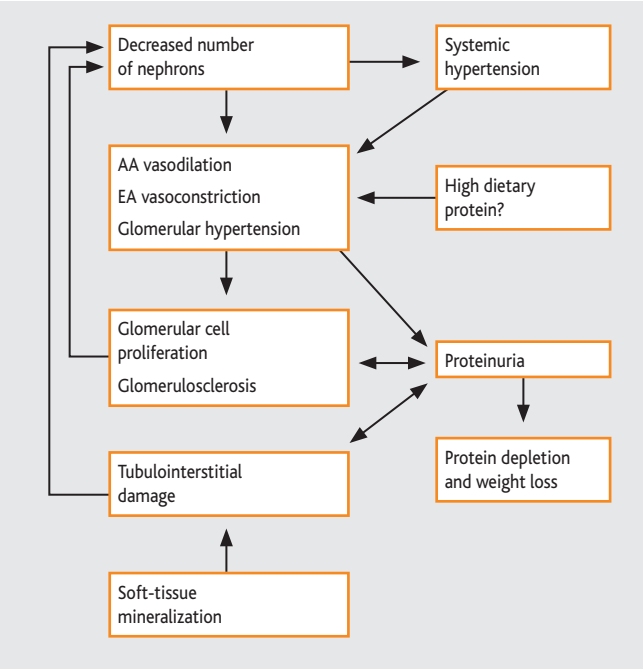

FIGURE 1. Some of the potential mechanisms involved in the progression of feline CKD. AA = afferent arteriole; EA = efferent arteriole.

loss and polydipsia/polyuria and poor body condition. Unique physical examination and clinicopathologic findings include nonregenerative anemia, renal secondary hyperparathyroidism, and small and irregular kidneys. The classic diagnosis of renal failure based on renal azotemia (persistent azotemia superimposed on the inability to concentrate urine) corresponds to IRIS CKD stages 2 (late stage 2) through 4. IRIS stage 1 and early stage 2 CKD (nonazotemic CKD) can be diagnosed in cats with persistent proteinuria, abnormal renal palpation or renal imaging findings, urine concentrating deficits, or increases in serum creatinine over time, even if the values remain in the normal range (e.g., serum creatinine that increases from 0.6 to 1.2 mg/dL could indicate a 50% reduction in glomerular filtration rate if pre- and postrenal causes of the increased creatinine are ruled out).

In general, the diagnostic approach to patients in which CKD has been identified and staged is focused on three areas: (1) characterization of the primary renal disease, (2) characterization of the stability of the renal disease/function, and (3) characterization of the patient's problems associated with the decreased renal function. Further definition of the primary renal disease (beyond a standard minimum database) could include, for example, quantitation of proteinuria, measurement of blood pressure, urine culture, kidney imaging, and kidney fine-needle aspiration or biopsy. The stability of the renal function is assessed by serial monitoring of abnormalities identified during the initial characterization of the renal disease. This monitoring should always include serum biochemistry profiles, urinalyses, quantitation of proteinuria, and measurement of blood pressure but may also include follow-up urine cultures and ultrasonography. Characterization of the renal disease and its stability is most important in the earlier stages of CKD, when appropriate treatment has the greatest potential to stabilize renal function. Characterization of patient problems becomes more important in the later stages of CKD, when clinical signs tend to be more severe. In the later stages of CKD, diagnostic (and subsequent therapeutic) efforts should be directed at patient problems caused by the decreased renal function.

Characterization of the renal disease and its stability is most important in the earlier stages of CKD, when appropriate treatment has the greatest potential to stabilize renal function. Characterization of patient problems becomes more important in the later stages of CKD, when clinical signs tend to be more severe.

Management OF CKD

Similar to the diagnostic approach to CKD, the therapeutic approach should be tailored to fit the patient's stage of disease. For example, disease-specific treatments for nephroliths and bacterial pyelonephritis, as well as treatments designed to slow the progression of renal disease (so-called *renoprotective treatments*) are of most value in the early to middle stages of CKD. Examples of potentially renoprotective treatments include dietary changes designed to reduce serum phosphorus concentrations and administration of angiotensin-converting enzyme inhibitors (ACEIs) to normalize systemic and intraglomerular blood pressures and reduce proteinuria. In the later stages of CKD, treatment tends to be focused on relieving the patient's clinical signs and improving abnormalities associated with decreased renal function, such as acidosis, anemia, anorexia, hypertension, potassium depletion, and vomiting. See the case presentations on pages 23 and 24 for specific examples of managing cats with CKD.

Acute Decompensation of CKD

The cause of "acute on chronic" decompensation usually falls into one of three categories: prerenal, renal, or postrenal (see box). The most common prerenal cause is dehydration and decreased renal perfusion. Decreased renal perfusion can also be associated with decreased cardiac output and thromboembolic disorders. Renal causes of acute decompensation include ascending urinary tract infections (i.e., pyelonephritis that may or may not be associated with nephroliths), renal neoplasia, and precipitous progression of the underlying renal disease (rare). Postrenal causes include obstructive uropathy, most commonly a nephrolith that migrates into a ureter and results in a partial or complete obstruction.

Most Common Causes of Acute Uremic Crisis in Cats With Previously Stable CKD (Along With Rule-Outs)

- Prerenal dehydration (response to fluid therapy)
- Ascending infection resulting in pyelonephritis (urine cultures, pyelocentesis)
- Renal neoplasia (ultrasonography ± fine-needle aspiration with cytology)
- Obstructive uropathy (imaging ± contrast studies)
- Hypertensive crisis (indirect measurement of systolic BP)
- Primary disease progression (diagnosis of exclusion)

Case Presentations

Lab Test Abbreviations

BP = blood pressure	Phos = phosphorus	K^+ = potassium	T_4 = thyroxine
Ca^+ = calcium	TCO_2 = total carbon dioxide	PCV/TP = packed cell volume /total protein	UPC = urine protein:creatinine (ratio)
KCl = potassium chloride	BUN = blood urea nitrogen		

Case 1:

"**Willie**" was an 11-year-old neutered, male domestic shorthaired cat presented for an annual health examination. Physical examination was unremarkable; body condition score was 2.5/5.

Clinicopathologic Data

BUN	28 mg/dL	(10 mmol/l)
Serum creatinine	1.9 mg/dL	(168 µmol/l)
K^+	4.2 mEq/L	
TCO_2	13.8 mmol/L	
Ca^+	10.4 mg/dL	(2.6 mmol/l)
Phos	4.6 mg/dL	(1.5 mmol/l)
Urine specific gravity	1.028	
Urine dipstick protein	2+	
Microalbuminuria assay	Negative	
UPC	0.15	
Urine sediment	No bacteria observed	
Systolic BP	140 mm Hg	

Further Diagnostics

- T_4 was normal.
- Urine culture was negative.
- Renal ultrasonography was unremarkable.

Assessment

IRIS stage II, nonproteinuric, nonhypertensive CKD.

Treatments

- Transition to a renal diet.
- Administer enteric phosphate binders?
  (depends on response to the renal diet)
- Administer ACEI?
  (no indication without hypertension and/or proteinuria)

Monitoring Plan

Document the stability of the azotemia; then perform serial biochemistry profiles/UPCs/urine cultures/BP assessments every 6 to 12 months.

Case 2:

"**Sarah**" was a 13-year-old spayed, female domestic shorthaired cat with a 4-month history of weight loss, decreased activity, and polyuria/polydipsia.

Within the previous 2 weeks, Sarah had become anorexic and had started vomiting. On physical examination, she was bright, alert, and responsive, with a rectal temperature of 100.8°F (38.2°C), pulse of 160 bpm, and respiration rate of 24 bpm. Her heart and lungs auscultated normally, and her pulses were strong and regular. Her body condition score was 2/5, and her kidneys were small, firm, and irregular. There was no palpable thyroid enlargement, a fundic exam was normal, and she was assessed to be 6% to 8% dehydrated. Indirect systolic BP was 170 mm Hg. Case continues overleaf.

Clinicopathologic Data

T_4	Normal	
BUN	86 mg/dL	(31 mmol/l)
Serum creatinine	4.4 mg/dL	(389 µmol/l)
K^+	2.4 mEq/L	
TCO_2	12.8 mmol/L	
Ca^+	10.2 mg/dL	(2.5 mmol/l)
Phos	8.6 mg/dL	(2.8 mmol/l)
Urine specific gravity	1.021	
Urine dipstick protein	+2	
Microalbuminuria	Med/High +	
UPC	0.8	
Urine sediment	No bacteria observed	

Initial Treatment (Case 2 continued)

Intravenous fluid therapy (supplemented with KCl) was given to correct dehydration. Amlodipine treatment was started at 0.625 mg/cat PO once daily for the hypertension.

Clinicopathologic Data After Fluid Therapy

BUN	67 mg/dL	(23 mmol/l)
Serum creatinine	3.9 mg/dL	(345 µmol/l)
K^+	2.8 mEq/L	
TCO_2	13.2 mmol/L	
Ca^+	10.2 mg/dL	(2.5 mmol/l)
Phos	8.0 mg/dL	(2.6 mmol/l)

Further Diagnostics

- Follow-up systolic BP was 155 mm Hg.
- Urine culture yielded *Escherichia coli*.
- Renal ultrasonography showed mild pyelectasia with mineral densities in both kidneys.

Assessment

IRIS stage III, proteinuric, hypertensive CKD.

Additional Treatments

- Fluid therapy (rehydration already accomplished; need for routine subcutaneous fluid therapy to be determined).
- Long-term (4 to 6 weeks) antibiotic treatment based on urine culture and sensitivity.
- Oral potassium supplementation.
- Address gastrointestinal irritation (anorexia and vomiting).
- Transition to a renal diet.
- Enteric phosphate binders.
- ACEI/calcium channel antagonist (hypertension and proteinuria).
- Feeding tube?

Monitoring Plan

Perform serial biochemistry profiles/UPCs/urine cultures/BP assessments every 1 to 2 months.

Follow-Up on "Sarah"

Four months after initial diagnosis, Sarah presented for acute-onset anorexia, depression, and lethargy. On physical examination, she was quiet, alert, and responsive with normal temperature, pulse, and respiration; her heart and lungs auscultated normally; there were no pulse deficits; and her body condition score and body weight were stable.

Clinicopathologic Data

PCV/TP	34%/7.8 g/dL (stable)
BP	165 mm Hg (stable)
BUN	79 mg/dL [28 mmol/l] (increased from 67 mg/dL [23 mmol/l] at most recent recheck)
Serum creatinine	6.4 mg/dL [566 µmol/l] (increased from 3.9 mg/dL [345 µmol/l] at most recent recheck)
Urine culture	Negative
UPC	0.3 (stable)

Treatment Plan

Administer 2× maintenance fluids overnight to correct any subclinical dehydration.

Further Diagnostics/Assessments

- BUN 72 mg/dL (25.7 mmol/l) and serum creatinine 6.5mg/dL (575 µmol/l) were stable 24 hr after fluid therapy (helps rule out prerenal dehydration)
- Negative urine culture (ascending urinary tract infection less likely).
- Stable BP (helps rule out hypertensive crisis).
- No change in UPC.
- Previously observed mineral densities in kidneys along with cystic calculi and possible ureterolith on radiographs; ultrasonographic changes suggestive of right-sided obstructive uropathy; no evidence of renal infiltrative disease.

Updated Treatment Plan

Right-sided ureterotomy and cystotomy. Several calcium oxalate stones/blood clots were removed from the ureter and bladder.

Outcome

Postoperative outcome was uneventful. Sarah began eating and was discharged 4 days later. BUN was 49 mg/dL (17.5 mmol/l) and serum creatinine was 3.2mg/dL (283 µmol/l).

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Notes

Diagnosis and assessment of patients with chronic kidney disease

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Abstract
Early diagnosis of chronic kidney disease (CKD) is desirable so that appropriate treatment and monitoring can be implemented. Unfortunately, early diagnosis is difficult without proactive diagnostic testing. A thorough history and physical examination is helpful in detecting subtle and non-specific signs of illness such as weight loss which may be seen in patients with CKD. Urine specific gravity testing is a simple and effective screening test for identifying patients that may be suffering from renal disease and has the advantage of being possible in the absence of the cat! Blood tests, specifically urea and creatinine levels, are required to confirm a diagnosis of CKD. Care should be taken to interpret blood creatinine and phosphate levels using the International Renal Interest Society (IRIS) guidelines (www.iris-kidney.com) rather than in-house or commercial laboratory reference ranges. Early diagnosis facilitates early, appropriate interventions which can make a huge difference to both quality and length of life.

Background
Chronic kidney disease (CKD) is one of the most common causes of morbidity and mortality in older cats – estimated to affect more than 30% of cats over the age of 10 years. Unfortunately a diagnosis of this illness is often only made following the appearance of clinical signs associated with azotaemia (raised urea and/or creatinine). By this stage, at least 75% of the renal function has been lost. Diagnosis at an earlier stage is an advantage to the patient and owner, allowing earlier interventions and monitoring which help to prolong life and aid quality of life.

How can an earlier diagnosis be made?
Diagnosing CKD before the appearance of clinical signs is a challenge. To make an earlier diagnosis, attention should be taken to:

(i) Assess 'at risk' patients more frequently. Since older cats are more vulnerable to developing CKD, these patients should be targeted for assessment. The author recommends that practices embrace International Cat Care's Wellcat guidelines which provide life-stage appropriate recommendations for care. These guidelines are outlined in more detail later on (page 30) and their web site is at end of this article.

(ii) Detailed history and thorough physical examination: many clues of CKD are non-specific. Attention should be paid to looking for indicators of ill health such as reduced appetite, increased thirst, weight loss, dehydration and abnormal renal palpation (microrenale, renomegaly, abnormal renal contours, pain etc). It is important to note that physical examination of patients with renal disease is often normal.

(iii) Bodyweight assessment (fig 1): weight loss is a valuable, although non-specific, indicator of ill health. Bodyweight and body condition score should be assessed on every occasion that the cat visits the clinic. For cats over the age of 11 years, weight checks every 3-6 months are justified. The author finds it helpful to calculate percentage weight loss as outlined in Table 1. Translating percentage weight changes into 'human' values can also be helpful when explaining the significance to a pet owner. For example a 10% weight loss (e.g. a cat that previously weighed 4kg now weighing 3.6kg) equates to a 64kg person losing 6.4kg in weight. Unless that person is on a weight loss regime, this degree of weight loss is extremely concerning.

Figure 1. Weight checks are a valuable component of the health assessment. Weight loss can be a valuable although non-specific indicator of ill health.

Harry is a 17 year old male neutered DSH. One year ago, he weighed 4.7 kg. Today he weighs 4.1 kg. His owners have not noticed any weight change in him at home (this is not unusual in the author's experience) although they reported an increased thirst and some stiffness. Further investigations revealed IRIS Stage 2 chronic kidney disease.	
Calculation of percentage weight loss:	
Step 1: Calculate the amount of weight lost by subtracting today's weight from the previous weight: 4.7 - 4.1 = 0.6 kg	
Step 2: Divide the number obtained in Step 1 by the original weight. 0.6 ÷ 4.7 = 0.128	
Step 3: Multiply the number obtained in Step 2 by 100%: 0.128 × 100 = 12.8%	
Assessment:	
Harry has lost 12.8% bodyweight over the past year	
Interpretation of percentage weight loss figures – author's recommendations:	
> 10% weight loss	Severe weight loss, immediate action justified
5 – 10% weight loss	Significant weight loss, further investigations justified
< 5% weight loss	May or may not be significant, further monitoring justified if concerned

Table 1: Calculation of percentage weight loss: Case example

(iv) Urine screening (Table 2 and fig 2): renal disease is typically associated with a reduction in the ability to produce concentrated urine. For cats, this means a urine specific gravity (USG) below 1.035. Unless there is another reason for this 'low' USG such as a cat that receives a very liquid diet or enjoys drinking cat milk, further investigations are recommended. Renal disease is not the sole cause of reduced USG, other common conditions that can cause this include hyperthyroidism and diabetes mellitus. Dipstick testing for glucose is helpful to rule out diabetes mellitus. In those cats where renal disease is confirmed, further urinalysis (ideally using a cystocentesis collected sample) is indicated. This should include a sediment examination, bacterial culture and protein estimation (ideally urine protein to creatinine ratio, UPC) to further characterise the severity of disease and identify complications. Free catch samples can be used for these further tests but interpretation of results may be complicated by contamination from the urethra, genital tract and litter tray.

The author considers a USG of 1.035-1.040 to be 'borderline' and closer monitoring is justified (Table 2 and fig 3).

Figure 2. Screening of free catch urine samples is helpful in identifying several common conditions affecting older cats such as chronic kidney disease, hyperthyroidism and diabetes mellitus.

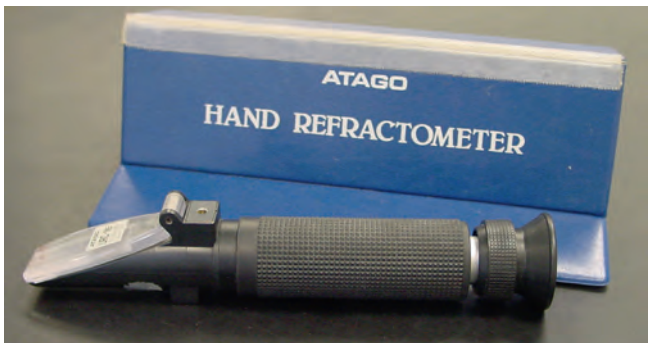

Figure 3. Urine specific gravity should always be assessed using a refractometer and not a dipstick!

(v) Blood screening: Many cats in early renal disease show few or no clinical signs. Blood screening allows the identification of azotaemia (raised urea and/or creatinine) in addition to looking for complications associated with

USG Value	Interpretation	Immediate recommendations	Advice for the cat owner
Less than 1.035	Abnormal result	• Ensure that a detailed history has been taken to: • Rule out non-renal causes of producing dilute urine such as feeding a very liquid diet, drinking lots of 'cat milk', receiving diuretics (e.g. furosemide) or other medications which can cause polyuria/polydipsia (e.g. corticosteroids), receiving other fluids (e.g. on a drip) • Obtain as many clues of illness as possible – e.g. weight loss, reduced appetite, increased thirst • Dipstick testing to check for presence of glucose (rule out diabetes mellitus)	Further investigations are recommended unless a 'benign', non-renal cause of the low USG can be elucidated from the history and the cat seems otherwise healthy. The major differential diagnoses are chronic renal disease, hyperthyroidism and diabetes mellitus. Further investigations should include urine dipstick and haematology, serum biochemistry (including renal and hepatic parameters plus proteins and electrolytes) and total thyroxine. Blood tests should be done after an 8 hour fast (water intake should not be limited during this period). In cats with USG < 1.035 there is also justification for performing a urine sediment examination, protein estimation (ideally performing a urine protein:creatinine ratio) and urine bacterial culture and sensitivity testing.
1.035-1.040	Borderline result		A USG greater than 1.035 indicates significant concentration of the glomerular filtrate as is expected in cats with good renal function. However, renal disease cannot be completely excluded on this basis so further investigations should be performed as discussed for cats with USG<1.035 if there is any concern based on patient history or physical examination (if performed). The author considers a USG of 1.035-1.040 to be 'borderline' and closer monitoring is justified. So long as the cat is considered otherwise healthy, further testing is not necessary at this stage. However, repeat testing is recommended within 6 months, sooner if the owner or clinician has any concerns.
More than 1.040	Normal result		A USG greater than 1.035 indicates significant concentration of the glomerular filtrate as is expected in cats with good renal function. However, renal disease cannot be completely excluded on this basis so further investigations should be performed as discussed for cats with USG<1.035 if there is any concern based on patient history or physical examination (if performed). Otherwise, repeat urine specific gravity testing is recommended annually in cats aged 7-10 years, once or twice yearly in cats aged 11-14 years and twice yearly in cats aged 15 years or over.

Table 2: Interpretation of urine specific gravity in routine screening of elderly cats

renal disease such as hyperphosphataemia, hypokalaemia and anaemia.

(vi) Additional recommendations for older cats: blood pressure measurement is to be encouraged in all older cats since systemic hypertension is a common entity in these patients. Cats with renal disease are especially vulnerable to developing systemic hypertension - at least 20% of patients suffer from this potentially life-threatening complication.

How frequently should I assess my patients and what testing is recommended?

The author recommends that clinicians follow the International Cat Care (formerly Feline Advisory Bureau, FAB) WellCat guidelines for assessment of older cats in order to diagnose illness promptly. iCatCare's WellCat guidelines advocate that:

- Cats of all ages should be assessed at a veterinary practice at least once a year and their weight and body condition score recorded in addition to a general physical examination and discussion of appropriate preventative health care
- In addition to this:
  - 'Mature' cats – those aged ≥ 7 years - should have their blood pressure (BP) checked once a year and a urinalysis performed.
  - 'Senior' cats – those aged ≥ 11 years - should have blood tests done (haematology, serum biochemistry, total T_4) once a year. Consideration should be given to increasing the frequency of BP and urinalysis check-ups to every 6 months in these cats.
  - 'Geriatric' cats – those aged ≥ 15 years - should be assessed at a veterinary practice every 6 months at which time a clinical examination, weight check, body condition score, BP and urinalysis should be performed. Blood tests should continue to be done annually unless there is any clinical indication to increase the frequency of these.

The author prefers to see 'Senior' patients every 6 months and 'Geriatric' patients every 3 months, checking blood pressure and urinalysis every 6 months in both groups (see Table 3 page 51).

How is a diagnosis of kidney disease confirmed?

Cats with significant kidney disease have both an azotaemia (increased blood urea and/or creatinine) and a reduction in their urine specific gravity (USG < 1.035). For cats in the earlier stages of disease, a reduction in USG may be the only abnormality – in these patients it is important to rule out other causes of reduced USG such as hyperthyroidism and diabetes mellitus.

IRIS Stage	Description	Plasma creatinine results		Clinical signs?	Comments
		Conventional units	SI units		
1	Non-azotaemic	< 1.6 mg/dl	< 140 µmol/l	Absent	Patients have some other renal abnormality – for example: • reduced urine concentrating ability (USG < 1.035) without an identifiable non-renal cause • abnormal feeling kidneys on palpation • persistent proteinuria of renal origin • abnormal renal ultrasound • abnormal renal biopsy results • progressively increasing creatinine levels
2	Mild renal azotaemia	1.6 – 2.8 mg/dl	140 – 250 µmol/l	Mild or absent	The lower end of the creatinine range for Stage 2 patients lies within the reference range for many laboratories but is recommended to identify patients suffering from CKD
3	Moderate renal azotaemia	2.9 – 5.0 mg/dl	251 – 440 µmol/l	May be present	
4	Severe renal azotaemia	> 5.0 mg/dl	> 440 µmol/l	Usually present	

Table 3: IRIS staging of kidney disease

What is the IRIS system for classification of renal disease?

The International Renal Interest Society (IRIS) was formed in 1998 and aims to help veterinary practitioners to better understand, diagnose and treat renal disease in cats and dogs. Patients are primarily staged according to their blood creatinine levels (Table 3). It is important to use creatinine values obtained after the cat has been re-hydrated since dehydration increases creatinine levels and may give a false impression that the kidney disease is worse than it actually is. Some cats with CKD will pass through all of the IRIS stages as their kidney disease progresses; other cats will remain stable for years in the same stage.

What other tests are important in cats with kidney disease?

Further testing in confirmed cases of chronic kidney disease is helpful in finding complications and learning more about the cause of the renal disease. Treatment of complications often provides an immediate benefit to quality of life and may, in some cases, improve survival (Table 4).

What diagnostic pitfalls should I be aware of?

As with all aspects of medicine, no diagnostic tests are completely uncontroversial!

(i) Urea and Creatinine: accumulation of urea and creatinine is used to diagnose renal disease with azotaemia (increased blood levels of urea and/or creatinine) found in cats with IRIS Stage 2, 3 or 4 renal disease. Azotaemia is not specific to renal disease so care should be taken to rule out pre-renal causes such as dehydration (USG should be > 1.040 in these cats) and post-renal causes such as bladder rupture and urethral obstruction. Levels of urea tend to be disproportionately higher than creatinine levels in dehydrated patients since urea is able to passively diffuse back into the circulation from the glomerular filtrate in the proximal tubule. Since creatinine cannot be reabsorbed into the circulation, blood levels more accurately reflect renal function and there is an inverse correlation between creatinine levels and glomerular filtration rate (GFR). Levels of urea and creatinine are affected by a number of non-renal factors such as those summarised in Table 5.

Test	Comment
Detailed history	Look for evidence of clinical signs that would benefit from symptomatic treatment; e.g. appetite stimulants, anti-emetics. Look for potential cause/s of the kidney disease such as intoxication (e.g. plants such as lilies).
Physical exam	Look for clinical complications such as dehydration, anaemia, presence of additional concurrent disease
Blood creatinine	Stage renal disease (Table 3)
Haematology	Look for anaemia, leucocytosis (infection)
Serum biochemistry including proteins, electrolytes (Na, K, Ca, P), glucose, liver enzymes, total thyroxine	Look for hypokalaemia, hyperphosphataemia, hypoproteinaemia, hypercalcaemia, evidence of additional concurrent diseases which may affect management (e.g. hyperthyroidism)
Urine dipstick	Identify marked proteinuria, concurrent diabetes mellitus. NB dipsticks are unreliable for assessment of specific gravity, leucocytes, nitrites and urobilinogen.
Urine culture	Identify bacterial urinary tract infections
Urine protein (UPC)	Look for evidence of renal proteinuria and quantify severity
Urine sediment	May help identify cause of the renal disease e.g. pyelonephritis
Blood pressure	Identify patients suffering from systemic hypertension
Acid-base status ?	Selected renal patients, look for metabolic acidosis
Parathyroid hormone ?	Selected renal patients, confirm renal secondary hyperparathyroidism
Ionised calcium ?	Relevant in hypercalcaemic renal patients
Imaging (if possible)	May help identify cause of the renal disease: e.g. polycystic kidney disease, renal stones, neoplasia, FIP
Biopsy ?	May be indicated in renomegaly patients (e.g. lymphoma possible) and those with marked renal proteinuria (UPC > 2.0)

Table 4: Further testing recommendations for cats with renal disease

Factor	Effect on blood urea	Effect on blood creatinine
High protein diet, feeding within 8-12 hours of sampling	⇧	+/- ⇧
Gastrointestinal haemorrhage	⇧	-
Catabolic conditions e.g. starvation, infection, fever, necrosis	⇧	
Glucocorticoid therapy	+/- ⇧	-
Tetracycline therapy	+/- ⇧	-
Low protein diet	⇩	-
Anabolic states e.g. anabolic steroid therapy	⇩	-
Hepatic insufficiency, portosystemic shunt	⇩	-
Non-renal causes of polyuria	⇩	-
Severe exercise	⇧	⇧
Lab artefact: presence of cephalosporins or ketones	-	⇧
Young cats, cats with poor muscle mass	-	⇩
Male cats, well muscled cats	-	⇧

Table 5: Important non-renal/urinary factors affecting blood urea and creatinine levels

Most common are:

- A post-prandial (after eating) increase in blood urea levels of around 1-4 mmol/l which could result in azotaemia and falsely indicate renal disease in a normal cat (or indicate more significant renal disease in patient already diagnosed with this condition).
- A reduction in creatinine levels associated with lack of muscle mass (i.e. very thin cats) which could mislead the clinician into thinking that renal function was normal in a cat with CKD.

(ii) Phosphate levels: hyperphosphataemia is extremely common in cats with CKD, estimated to affect around two thirds of patients. Hyperphosphataemia is a potent trigger for development of renal secondary hyperparathyroidism which has negative consequences on both quality and length of life. Although all hyperphosphataemic patients will be suffering from renal secondary hyperparathyroidism, absence of hyperphosphataemia does not rule this out.

Unfortunately most diagnostic laboratory's reference ranges for normal blood phosphate levels, typically ranging from around 0.95 mmol/l to 2.0 mmol/l, are unsuitable for assessing cats with CKD – mainly since the upper limit of normal is above that recommended by IRIS for stages 2, 3 and 4 CKD (see values at the top of the next column). In fact, IRIS recommends that blood phosphate levels should be kept at the bottom of the reference range in cats with CKD (ideally 1-1.2 mmol/l) and has published guidelines on target phosphate levels for cats, according to the severity of their renal disease:

- Iris Stage 2: target blood phosphate levels 0.9-1.5 mmol/l
- Iris Stage 3: target blood phosphate levels 0.9-1.6 mmol/l
- Iris Stage 4: target blood phosphate levels 0.9-1.9 mmol/l

Clinicians are advised to be aware of the discrepancy between in-house/commercial laboratory reference ranges and IRIS guidelines when reviewing lab results. Having a highlighter pen and the IRIS guidelines to hand can help to avoid missing significant results! Management of hyperphosphataemia is discussed in the Treatment notes (pages 48-49).

(iii) Blood pressure measurement (fig 4) and interpretation: cats are very susceptible to stress-associated or 'white coat' hypertension (increased blood pressure) so care should be taken to measure blood pressure in as calm and quiet a location and manner as possible. Examination of the eyes is recommended in all cats to look for ocular evidence of high blood pressure such as retinal oedema, detachment and haemorrhage. If present, the diagnosis of systemic hypertension is confirmed. In the absence of ocular abnormalities, consideration must be given to the possibility of 'white coat' hypertension and repeat measurements are recommended before prescribing anti-hypertensive therapy.

Further information on how to measure and interpret blood pressure and how to examine the eyes to look for evidence of systemic hypertension is available in the Free Downloads section of the author's website: http://www.vetprofessionals.com/catprofessional/free_downloads.html. See also separate notes on measurement of blood pressure (pages 40-45).

Figure 4. Blood pressure measurement – ideally using Doppler methodology – is recommended in all cats with chronic kidney disease.

(iv) Urine protein estimation: it is now known that presence of protein in the urine (proteinuria) is useful both diagnostically and prognostically. Unfortunately urine dipsticks are insensitive and unreliable for documenting proteinuria and do not take into account the concentration of the urine – for example, most cats will produce urine with a trace/+ reading on the dipstick. For a cat with very dilute urine, this could be misleading as a small amount of protein in a very dilute urine sample generally equates to significant amounts of protein loss overall. For this reason, dipsticks are not recommended for the assessment of proteinuria. The urine protein to creatinine (UPC) ratio is recommended in all cats with known renal disease or where protein assessment is required. Idexx laboratories manufacture UPC strips suitable for in-house analysis of the UPC, otherwise a urine sample should be sent to a diagnostic laboratory. Normal cats can have a UPC of less than 0.3-0.6. Some entire male cats can have a value of 0.6, even approaching 1.0 (see the proteinuria text in these proceedings for more information). It is important to remember that proteinuria can be present due to pre-renal disease (e.g. hyperproteinaemia due to multiple myeloma), renal disease (e.g. glomerulonephropathy) and post-renal disease (e.g. cystitis).

More information on proteinuria classification and interpretation can be found in the accompanying notes on proteinuria (pages 34-39).

(v) Other problems with urine dipsticks: readers should be aware that urine dipsticks are unreliable for the assessment of USG, nitrite, urobilinogen and leucocytes in cats.

What other challenges are there to making an early diagnosis?

Renal compensatory mechanisms make early diagnosis a challenge in that typically two thirds of nephrons must be lost before a reduction in USG is seen and three quarters of functional nephrons must be lost before azotaemia (increased blood urea and/or creatinine) develops. Cats are very good at hiding signs of illness, adapting their lifestyle and behaviour to hide any evidence of disease and this too, makes early diagnosis a challenge. Owners should be educated to report any change in their cat's behaviour, however insignificant they feel that this is, in case it facilitates early diagnosis of an illness. Barriers to owners bringing their cats in to the clinic include concerns that

- A veterinary examination is a stressful and unpleasant experience for their cat
- Nothing can be done to help their cat so what is the point of consulting the vet?
- Tests will be costly and invasive
- It's normal for an older cat to be thin and in poor condition
- Many owners worry that their vet will recommend euthanasia of the cat

Asking owners to bring in urine samples collected at home is one way around some of these concerns – assessment of USG and a dipstick test is quick, easy, inexpensive and can be done in the absence of the cat. If a USG result < 1.035 is found, owners should be encouraged to bring the cat in for more detailed assessment including collection of blood samples (complete haematology, biochemistry, T_4) and more detailed urinalysis (sediment, culture, UPC).

Conclusions

Early diagnosis of CKD is a challenge but is worthwhile in facilitating early and effective interventions such as phosphate restriction and prompt treatment of complications such as systemic hypertension. Treatment interventions not only improve quality of life, but in some examples such as phosphate restriction have the ability to increase lifespan. Education and support of all practice staff helps to ensure that everyone is 'on board' and that these strategies are as successful as possible.

Further reading

» Free downloads are available on the Cat Professional website http://www.vetprofessionals.com/catprofessional/free_downloads.html on a number of relevant topics including:
  - Doppler blood pressure measurement
  - Ocular manifestations of systemic hypertension
  - Collecting urine samples from cats

» IRIS website: www.iris-kidney.com

» Wellcat guidelines and further information: http://www.icatcare.org/vets/wellcat-life

Proteinuria – what is this and why do we worry about it?

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Proteinuria is the term used to describe the presence of protein in the urine. Albumin, the major blood protein is at the upper size limit of proteins which are filtered by the basement membrane of the normal glomerulus (molecular weight 69 kilodalton [kDa]). Albumin is also negatively charged and so naturally repelled by the basement membrane (fig 1). Small proteins, especially those less than 7 kDa in molecular weight, are readily filtered at the level of the glomerulus but are reabsorbed into the circulation at the level of the proximal tubules using a process called pinocytosis (fig 2). In this process, the cells of the proximal tubule reabsorb the protein, break it down into the constituent amino acids and pass these back into the circulation. Albumin is too large to be reabsorbed using the pinocytosis mechanisms and therefore is the main protein present in the urine (fig 2). Normal cats do not lose more than 30 mg of albumin per kg bodyweight per day. Presence of very small amounts of albumin in the urine is termed microalbuminuria.

Urine also normally contains proteins lost from the tubules (Tamm Horsfall protein), lower urinary and genital tracts.

Before assuming that any proteinuria is of renal origin, it's important to exclude pre- and post-renal causes:

- Pre-renal causes: proteinuria caused by filtration and excretion of proteins that are not normally present in the circulation e.g. haemoglobin, myoglobin, Bence Jones proteins (in patients with multiple myeloma).
- Post-renal causes: entry of protein into the urine after it has passed through the renal pelvis e.g. lower urinary tract disease (cystitis, urolithiasis, bacterial urinary tract infection, haemorrhage), diseases affecting internal or external genitalia

Renal proteinuria can be seen because of physiological and pathological reasons:

- Physiological causes; e.g. pyrexia, strenuous exercise, seizures, stress. These are usually a cause of mild, transient proteinuria.
- Pathological reasons; e.g. glomerular disease, tubular disease, interstitial disease

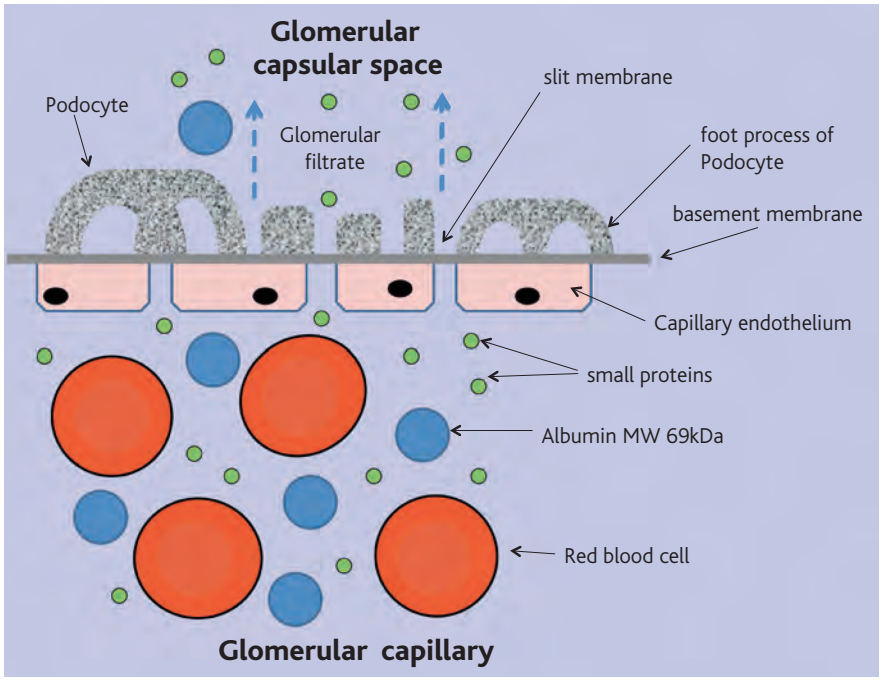

Figure 1. Small proteins can pass through the endothelial cells, and basement membrane and into the glomerular capsular space (start of the nephron). The glomerulus' capillary membrane helps to partly prevent larger molecules like albumin from passing into the capsular space resulting in a normal albumin loss of <30mg/kg/day.

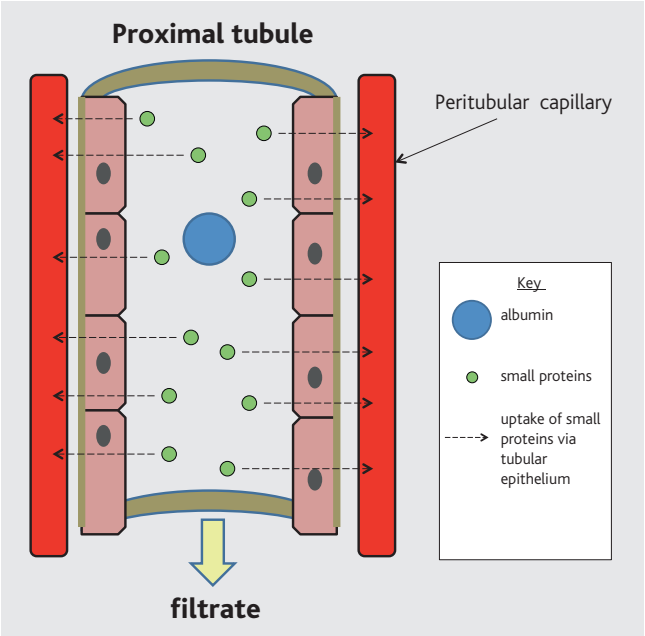

Figure 2. The small proteins that enter the glomerular filtrate are reabsorbed in the proximal tubule by pinocytosis.

Proteinuria is an important potential complication of renal disease and may be mediated by Angiotensin II as discussed later in this text. It is now recognised that presence of proteinuria is not only a marker of renal injury but also an important independent mediator of progressive renal injury. Proteinuria can worsen renal damage by:

- Overwhelming the ability of the proximal tubule cells to resorb protein from the glomerular filtrate
- Protein leaking into the interstitial space and triggering inflammatory cascades
- Blocking tubules leading to their loss

Proteinuria has a negative consequence on survival. Studies have shown that in azotaemic cats with chronic kidney disease (CKD) a urine protein:creatinine (UPC) ratio >0.4 (normal cats can have a UPC of less than 0.3-0.6. Some entire male cats can have a value of 0.6, even approaching 1.0) is an indicator of poor prognosis, and may warrant treatment (Lees et al 2005). One study found that mean survival times were 449 days in cats with a UPC <0.2, 224 days in cats with a UPC 0.2-0.8, and only 117 days in cats with a UPC >0.8 (King et al 2006). A separate study found that mean survival times were ~700 days with a UPC <0.43, but ~270 days with a UPC >0.43 (Syme et al 2006). IRIS, the International Renal Interest Society now recommend that each cat is assessed for proteinuria by UPC and classified into the ranges <0.2 [non-proteinuria], 0.2-0.4 [borderline proteinuric] and >0.4 [proteinuria] (Elliott and Syme 2006; IRIS Guidelines).

How is proteinuria best assessed?

Before interpreting proteinuria results, urine sediment should be examined to look for obvious evidence of lower urinary tract infection/inflammation. Sediment examination in cases of renal proteinuria may reveal presence of hyaline casts and causes of the underlying disease (e.g. bacteria in the case of bacterial pyelonephritis). A bacterial urine culture is recommended in all CKD patients to rule out urinary tract infection (UTI) which will also increase the protein content of the urine. Interpretation of proteinuria results should also give consideration to the method of sample collection – for example free catch samples risk contamination of the urine with genital secretions which may affect results. The ideal sample for protein assessment in CKD is therefore a cystocentesis sample.

Dipstick tests:

Dipsticks (fig 3) are relatively insensitive in documenting proteinuria and do not take into account the concentration of the urine – most cats with CKD will produce urine with a trace/+ reading on the dipstick. These subjective colorimetric tests are designed for human samples and have a detection range of 0.3 to 10 g protein per litre. It is important to remember that urine pH can affect dipstick protein results (false increase in very alkaline samples, false decrease in very acidic samples). Dipstick tests only measure the amount of protein in a spot sample and so interpretation has to take the concentration of the sample into consideration. For example, low levels of protein in a very dilute urine sample may well be significant. In general, guidelines for interpretation include:

- Protein >2 g/l (++++) is likely to be significant whatever the urine concentration: UPC test recommended to quantify the magnitude of the proteinuria
- Protein >0.3 g/l (+) and urine specific gravity <1.030 warrants further investigation - UPC test recommended to quantify the magnitude of the proteinuria

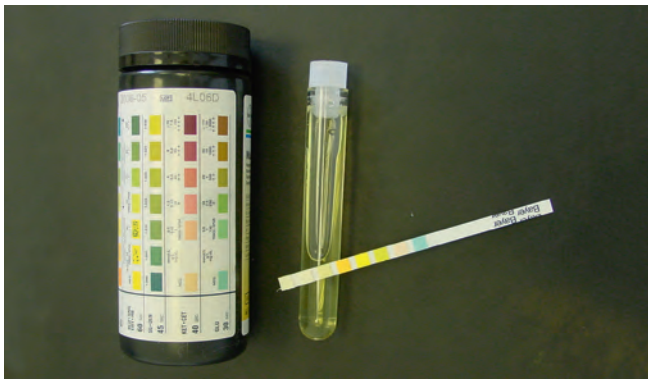

Figure 3. Dipsticks are insensitive in assessing protein levels and the urine protein to creatinine (UPC) ratio is recommended, where possible.

Quantitative protein assessment:

Some laboratories measure protein amounts in mg per litre (or dl) of urine sampled (fig 4). This technique has many of the disadvantages of the dipstick test but in quantifying protein levels is a little more helpful and is less affected by urine pH and the subjectivity of dipstick interpretation. Normal cat urine samples contain less than 200 mg protein per dl of urine (0.2 g/l). A UPC test is recommended when a protein of >200 mg/dl is identified to quantify the magnitude of the proteinuria.

Figure 4. Proteinuria should not be assessed on grossly haematuric samples as levels will be affected by the presence of blood. The patient should be reassessed once the haematuria has resolved.

24 hour protein excretion:

The 'gold standard' technique for assessment of proteinuria is to collect all of the urine passed in a 24 hour period and measure the amount of protein lost in mg protein in urine/kilogram bodyweight. Practical limitations mean that this is not generally used outside a research setting.

UPC test:

The urine protein:creatinine (UPC) ratio offers the best means of assessing the severity of proteinuria and correlates well with 24 hour protein loss. This test aims to give an accurate reflection of the 24 hour protein loss by testing a spot sample of urine. The amount of creatinine and protein is measured by a laboratory and the ratio of protein to creatinine then derived. Normal neutered cats have a UPC ratio of less than 0.3-0.6. It is normal for entire male cats to have a UPC ratio of up to 1.0.

IRIS guidelines for interpretation of results in cats with CKD:

< 0.2	Not proteinuric
0.2 – 0.4	Borderline proteinuria
> 0.4-2.0	Mild proteinuria
> 2.0	Severe proteinuria (e.g. glomerular disease)

Repeat assessment is indicated within 2-4 weeks to confirm that any proteinuria documented is persistent and of similar magnitude. If this remains the case then treatment with an ACEI is indicated.

Microalbuminuria tests:

While the above tests measure protein, microalbuminuria tests (e.g. the semi-quantitative Early Renal Damage [ERD] test, Woodley®) measure levels of albumin. In normal cats, the amount of albumin lost in the urine is very small. Increased loss, even at small levels – microalbuminuria - is thought to be a significant indicator of glomerular damage and can be used to identify early renal disease. Technically this means levels lower than 0.3 g/l (the lower level of detection by a dip stick). Microalbuminuria may indicate glomerular capillary hypertension (increasing the filtration pressure and hence increasing protein loss), glomerular basement membrane pathology (increasing permeability to protein), proximal tubule pathology (leading to problems with pinocytosis) or a combination of all of these. There is some evidence to suggest that microalbuminuria tests may be more sensitive as an indicator of renal damage than UPC ratios (i.e. microalbuminuria levels rise before the UPC is affected). Studies performed by the Royal Veterinary College, London have shown that the ERD semi-quantitative microalbuminuria test correlates well with UPC ratio results.

Microalbuminuria tests are species specific (i.e. human tests cannot be used in cats) and are commonly recommended in people to assess for development of early renal disease. Levels of microalbuminuria also correlate with systemic blood pressure – elevated levels are seen in people with chronically elevated blood pressure and the same may be true in cats. In people, microalbuminuria levels are used to monitor successful management of systemic hypertension.

In cats, presence of persistent or increasing microalbuminuria is an indication for intervention with an angiotensin-converting-enzyme inhibitor (ACEI).

How is proteinuria treated?

For around ten years now, benazepril (Fortekor®, Novartis Animal Health) has been a licensed treatment for cats with chronic kidney disease (CKD). Several studies have shown that benazepril is effective in lowering urine protein to creatinine ratios. More recently, an angiotensin receptor blocker telmisartan (Semintra®, Boehringer Ingelheim Animal Health) has been licensed for treatment of renal disease in cats.

Understanding the Renin angiotensin aldosterone system – RAAS

The RAAS involves a number of hormones and plays an important role in regulating salt and water balance within

the body. Renin is released from the juxtaglomerular cells in response to a number of physiological stimuli including hypovolaemia, hypotension, hyponatraemia, reduced renal perfusion and activation of the sympathetic nervous system. Renin catalyses the conversion of Angiotensinogen (produced by the liver or locally) to Angiotensin I. Angiotensin I is converted to Angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II has a number of actions including:

- Arterial vasoconstriction and an increase in systemic blood pressure
- Increased thirst and water intake
- Enhanced sodium and water resorption by the kidneys resulting in increased blood volume and blood pressure
- Stimulation of aldosterone release which also encourages sodium and water resorption by the kidneys
- Vasoconstriction of the efferent arteriole leading to increased glomerular pressure and filtration. NB: The afferent arteriole and mesangium are unaffected as these produce prostaglandins which counter the effect of Angiotensin II. However in patients receiving non-steroidal anti-inflammatory agents, production of these prostaglandins is inhibited leaving the afferent arteriole and mesangium also susceptible to Angiotensin II.

At low renal perfusion pressures (<70 mm Hg), glomerular filtration is very dependent on the presence of Angiotensin II. This is an important consideration in anaesthetised cats where systemic and renal blood pressure can fall markedly. Angiotensin II helps to maintain renal perfusion and GFR in these patients.

What is the relationship between Angiotensin, ACEI and renal disease?

ACE inhibitors (ACEI) have been proposed as a component for management of human kidney disease for around 30 years. At this time, researchers in the human field proposed that renal compensatory mechanisms designed to support renal function following loss of nephrons in fact contributed towards progression of disease. Following loss of nephrons there is activation of the RAAS and hypertrophy of residual nephrons with reduced arteriolar resistance and increased glomerular blood flow. As renal disease progresses, the afferent arteriolar tone decreases more than the efferent arteriole tone resulting in glomerular hypertension and hyperfiltration – sometimes also referred to as an increased 'single nephron GFR'. Glomerular hypertension and hyperfiltration results in proteinuria and this further contributes towards progression of renal disease. Angiotensin II is an important mediator of glomerular hypertension and hyperfiltration by:

- Causing vasoconstriction of the efferent arteriole. Vasoconstriction of the efferent arteriole results in an increase in glomerular pressure and filtration.
- Angiotensin II may have additional direct effects on glomerular pore size and perm-selectivity contributing to proteinuria
- Angiotensin II is a modulator of renal cell growth and may contribute towards proliferation of glomerular cells and fibroblasts leading to renal damage and fibrosis
- Angiotensin II stimulates macrophage activation and phagocytosis which may increase the inflammation associated with some forms of renal disease

ACEI therapy has been shown to significantly reduce progression of renal disease in people primarily through its effects to reduce proteinuria and systemic and glomerular blood pressure. ACEI are especially recommended for people with diabetic kidney disease and those with proteinuric kidney disease.

ACE inhibitors such as benazepril prevent the conversion of Angiotensin I to Angiotensin II with the following net effects:

- Reduction in systemic and glomerular blood pressure. Most cats with renal disease suffer from glomerular hypertension and sometimes systemic hypertension. Glomerular hypertension is believed to be damaging and known to be an important contributor to progression of renal disease in people
- Reduction in proteinuria (anti-proteinuric effects). This is mediated in particular via the reduction in intra-glomerular pressure seen as a result of vasodilation of the efferent arteriole.
- Reduction in glomerulosclerosis, tubulointerstitial lesions and progression of disease in those patients with renal disease
- Increased concentrations of bradykinin (ACEI inhibit degradation of these substances). Bradykinin is a vasodilator with hypotensive effects contributing to the reduction in blood pressure seen with ACEI.
- Benazepril has been shown to increase appetite and weight gain in healthy cats which may be an advantageous additional effect in cats with CKD!

Benazepril is converted to the active metabolite, Benazeprilat, following administration. Benazeprilat is excreted 85% via the biliary and 15% via the urinary route in cats. The clearance of benazeprilat is not affected in dogs or cats with impaired renal function and therefore no adjustment of dose is required in either species in cases of renal insufficiency.

Although ACEI inhibit conversion of Angiotensin I to Angiotensin II via angiotensin converting enzyme, they

do not inhibit other non-ACE mechanisms of conversion such as conversion by chymase and serine proteases. 'Angiotensin escape' is the phenomenon which explains production of Angiotensin II in some patients receiving ACEI. In these patients, other beneficial effects of ACEI may still be experienced.

Which patients benefit most from ACEI therapy?

ACEI have been shown to have a number of effects in cats with CKD and benazepril is licensed for the treatment of CKD. Main benefits are:

- Reduction of systemic and glomerular blood pressure, normalising filtration within the kidney
- Reduction of proteinuria
- Reduction of other negative consequences of Angiotensin II such as renal scarring and fibrosis

Overall, when one blinded study assessed 192 pet cats with CKD that were either receiving placebo or benazepril treatment, the results were (King et al, 2006):

- No overall difference in survival between the two treatment groups
- Significant reduction in proteinuria in those cats treated with benazepril
- Improved quality of life in those cats treated with benazepril

A separate study indicated that benazepril was effective in slowing progression of renal disease (Mizutani et al 2006).

ACEI are especially proven to be beneficial for cats with proteinuric renal disease. In one study of cats with naturally occurring CKD, those with a UPC of >1.0 especially benefitted from ACEI treatment with prolonged lifespan, improved quality of life, reduced proteinuria and weight gain reported (King et al 2006). Cats with persistent renal proteinuria (identifiable on at least two occasions and having ruled out pre- and post-renal causes) benefit from benazepril treatment at 0.5-1.0 mg/kg.

The anti-hypertensive effects of ACEI make these suitable for treatment of hypertensive cats. However, ACEI are generally considered to have relatively weak potency and are unlikely to be effective as the sole treatment in cats with systolic blood pressure readings above 180-190 mm Hg. In these cats, an alternative agent such as amlodipine (0.625-1.25 mg/cat/day) is recommended alone or in combination with benazepril.

In cats with CKD that are non-proteinuric and normotensive, there may be some benefits still to be gained from using an ACEI:

- Improved quality of life was reported by owners using benazepril in their cats with CKD versus those using a placebo treatment
- Benazepril may improve appetite and weight gain in some cats
- Although survival times may not be altered, benazepril may have some benefits on renal pathology through reducing levels of Angiotensin II and increasing levels of bradykinin
- Reduction in proteinuria (from normal to lower!) may still be of some benefit in terms of renal pathology and progression

How do angiotensin receptor blockers work?

Telmisartan, the new veterinary licensed angiotensin receptor blocker (ARB) has a high affinity for the angiotensin receptor-1 (AT-1). The net effect of an ARB is to block the actions of Angiotensin and hence the potential negative consequences associated with this substance. So far, there is very little information on the use of ARBs in cats although one field study showed non-inferiority to an ACEI in terms of reduction of proteinuria associated with CKD. In human medicine, ARBs are a popular choice in people suffering side-effects to ACEI such as development of a cough. ARBs have been used in combination ACEI in some people although there is still controversy as to whether this enhances efficacy or just potentiates side-effects! ARBs may be more potent anti-hypertensives and therefore could be useful in cats with hypertension although their efficacy is still thought to be much less than that seen with calcium channel blockers such as amlodipine.

Summary

In conclusion, assessment of proteinuria is of value in the diagnosis and management of patients with renal disease. A good understanding of the mechanisms of proteinuria is important to ensure that physiological and non-renal causes are ruled out. Where an excessive proteinuria is identified, then further diagnostics (e.g. renal ultrasound, blood tests, urine culture) are indicated to localise the proteinuria and identify any underlying disease. Intervention is generally recommended in azotaemic cats with renal disease when the UPC ratio is persistently above 0.4 or if there is a persistent/worsening microalbuminuria. In these patients, ACEI or ARB therapy is indicated. The UPC ratio can be used to assess response to treatment.

Patients should be re-hydrated (where necessary) and stabilised before starting ACEI or ARB treatment. In normotensive, non-proteinuric cats with CKD, ACEI and ARB

may provide some benefits although survival may not be increased.

Cautions regarding ACEI or ARB and understanding of the RAAS

- Anaesthetised cats and hypovolaemic (e.g. dehydrated) cats are very dependent on Angiotensin II to maintain renal blood flow and GFR at low perfusion pressures. ACEI therapy risks decompensating these patients and tipping them into an overt renal crisis. Patients therefore should be rehydrated first before starting ACEI treatment
- Cats receiving non-steroidal anti-inflammatory drugs (NSAIDs): protective prostaglandins in the afferent arteriole and mesangium are inhibited leaving these cats vulnerable to Angiotensin II. For example dehydrated cats receiving NSAIDs are vulnerable to renal crises as a result of loss of protection of renal blood flow associated with NSAID treatment

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» IRIS guidelines are available on www.irisi-kidney.com

Assessment and management of systemic hypertension

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Systemic hypertension – a persistent increase in the systemic blood pressure - is now commonly recognised in feline practice. There are several reasons for this including an increased awareness of hypertension as a feline problem, increased access to diagnostic facilities and possibly an increased prevalence of this condition related to the increasing age of the cat population.

Idiopathic hypertension (also referred to as primary or essential hypertension) accounts for less than 20% of cases and most reported cases occur secondary to other medical problems. The most common secondary causes of hypertension are chronic kidney disease (CKD) and hyperthyroidism. Prevalence rates quoted have been highly variable – for example from 20-65% of CKD cats, and 9-23% of newly diagnosed hyperthyroid cats. Other diseases that have been associated with hypertension in cats include primary hyperaldosteronism (Conn's syndrome), phaeochromocytoma, chronic anaemia and erythropoietin therapy. A link between systemic hypertension and other feline endocrinopathies such as diabetes mellitus, acromegaly and hyperadrenocorticism has not yet been demonstrated. Since most of the diseases commonly associated with hypertension are seen in older cats this explains why most hypertensive disease is seen in this age group.

Clinical findings in hypertensive cats

Unfortunately, hypertension is often only suspected very late in the course of disease – typically once target organ damage (TOD or end-organ damage) has already occurred. The target organs most vulnerable to hypertensive damage are the brain, heart, kidneys and eyes. Table 1 summarises the typical changes seen.

Organ affected	Pathology	Clinical findings	Reported approximate prevalence
Brain	Hyperplastic arteriosclerosis of cerebral vessels, oedema of the white matter and microhaemorrhage development resulting in hypertensive encephalopathy +/- stroke	Many changes possible including behavioural changes (e.g. night vocalisation, signs of dementia), ataxia, seizures, coma	15%
Heart	Left ventricular hypertrophy, cardiac failure	New murmur and/or gallop rhythm. Signs of congestive heart failure.	50-80%
Kidneys	Glomerular hypertrophy and sclerosis, nephrosclerosis, tubular atrophy and interstitial nephritis resulting in progression of CKD	Reduced urine specific gravity, proteinuria, increasing creatinine levels, decreasing GFR	
Eyes	Hypertensive retinopathy/choroidopathy resulting in many changes including intra-ocular haemorrhage, retinal oedema, retinal detachment, arterial tortuosity, variable diameter of retinal arterioles, papilloedema, glaucoma. Foci of retinal degeneration (hyper-reflectivity) may develop where damage has previously occurred.	Visual deficits, blindness, mydriasis	60-80%

Table 1: Target organ damage seen with systemic hypertension

Cats with systemic hypertension may be presented with signs referable to their underlying systemic disease such as inappetence and weight loss in the CKD patient.

Diagnosis

Blood pressure should be evaluated as a routine part of check-ups of all cats of 7 years of age or older, and in younger cats if there is any reason to suspect they may be vulnerable to developing hypertension.

Blood pressure should be assessed in cats presented with:

- Visual deficits
- Ocular disease – particularly where findings are consistent with hypertension
- Any disease reported to have an association – particularly CKD and hyperthyroidism
    - Three to six monthly blood pressure assessment is recommended in order to detect an increase in blood pressure prior to development of TOD
- Unexplained proteinuria
- Auscultable cardiac abnormalities consistent with systemic hypertension (murmur, gallop)
- Left ventricular hypertrophy
- Behavioural or neurological signs (especially older cats)
- As a component of 'well cat' clinics, particularly in cats aged > 7 years. The Wellcat guidelines and further information can be found at: http://www.icatcare.org/vets/wellcat-life

Ideally, diagnostic evaluation should include systolic (SBP) and diastolic (DBP) blood pressure measurement. As yet we have little information on diastolic hypertension. However, in other species it is known to be an important cause of vascular damage. The author recommends Doppler measurement of blood pressure (fig 1) since oscillometric techniques have been shown to be unreliable in conscious cats. Oscillometric machines fail to give a reading in a proportion of conscious cats and tend to overestimate low blood pressure and underestimate high blood pressure.

A detailed ophthalmic examination is essential both in the diagnosis and assessment of the extent of ocular disease. A thorough ocular examination is most easily done by using distant indirect ophthalmoscopy. This requires the following:

- A dark room (no windows or black-out blinds). If a dark room is not available it may be necessary to dilate the pupils using tropicamide drops. These take up to 15 minutes to exert their effect which will typically last for several hours.
- Hand held lens – e.g. 2.2 Dioptre, Pan Retinal lens – held at arms distance, just in front of the eye
- A light source held by the side of your head: best is a focussed light source (e.g. Finhoff transilluminator attached to your otoscope/ophthalmoscope body) but good working alternatives would be your standard ophthalmoscope set to a small circle or, failing that, a pen torch. Shine the light into the cat's eye; once a tapetal reflection can be seen, insert the lens just in front of the eye and an upside down image of the fundus will be seen

Figure 1. Blood pressure measurement – ideally using Doppler methodology – is recommended in all cats with chronic kidney disease.

This is an ideal way to visualise large portions of the retina very quickly. Gross abnormalities including retinal oedema and detachment, intraocular haemorrhage and vessel changes can be seen. Direct ophthalmoscopy can be used to have a closer look at any lesions identified.

Measuring blood pressure using a Doppler machine in conscious cats

Blood pressure measurement should be performed in a quiet room, away from barking dogs and telephones, ideally allowing the cat 10 minutes to acclimatise to these surroundings before the measurements are taken. This 'acclimatisation' period helps to reduce the incidence of 'white coat hypertension' – stress and anxiety stimulate the sympathetic nervous system leading to falsely high blood pressure readings. For some cats, having the owner present limits the effect of stress on blood pressure readings. After the acclimatisation period, the cat is restrained as gently as possible for the procedure to be done – usually all that is required is gentle steadying of the cat whilst the cuff is placed and readings are taken. The forelimb is used most commonly (fig 1), but care should be taken not to over-extend the elbow as this is a common site for osteoarthritis in older cats. Some cats do not like their paws to be held; when this is the case it can be simplest to use the base of the tail (coccygeal artery) instead.

Many Doppler units are suitable and available for veterinary use (see end of notes for more information on where to buy). An inflatable cuff (2.5cm wide cuff for most cats, with the width being ~40% of the limb circumference [30-40% is fine]) is placed just below the elbow. Surgical spirit can be used to wet the area over the common digital artery which is located on the palmar surface of the forelimb between the carpal and metacarpal pads. A liberal quantity of ultrasound coupling gel is then applied over this area to ensure that a good signal can be obtained. Ultrasound coupling gel is then also applied to the Doppler probe. The Doppler probe is placed over the common digital artery, maintaining the Doppler crystals perpendicular to the limb axis and therefore the blood vessel. To avoid excessive noise it is preferable not to switch the Doppler unit on until after the probe has been placed on the skin. Alternatively, headphones can be worn so that the cat does not hear any of the noise associated with measurement of blood pressure. If pulsatile blood flow cannot immediately be heard it may be necessary to gently move the probe over the skin between the carpal and metacarpal pads until a signal is detected. Additional ultrasound coupling gel is often useful if blood flow still cannot be detected. It is important to hold the probe gently over the skin, and to not apply excessive pressure such that blood flow could be impeded.

Once regular pulsatile blood flow is heard, the cuff should be inflated, using the hand-pump sphygmomanometer, to a pressure of around 20-30 mm Hg above that which is required to occlude the flow of blood – i.e. 20-30 mm Hg above the point at which the sound of blood flow is obliterated. Air is then allowed to *slowly* bleed through the valve at the back of the sphygmomanometer, and the point at which blood flow can *first* be detected clearly and consistently again in the artery is taken as the SBP. The procedure should be repeated 5 times over 2-3 minutes and the SBP taken as an average of these readings. Some cats show a sharp drop (20-30 mm Hg) in SBP over the first 2-3 readings (due to stress) and where this occurs the initial readings are discarded. The DBP is the pressure at which the pulsatile flow becomes a more continuous sound. Unfortunately, it is not always possible to determine this using the Doppler technique.

Top Tips for success

- Be patient, allow a minimum of 20 minutes for the procedure
- Ask the owner to gently restrain the cat using as minimal restraint as possible. The cat should feel comfortable and as un-restrained as possible
- Record who did the procedure, the equipment used, cuff size and location, animal attitude and position as well as the readings obtained. For continuity, the same person should repeat measurements using the same protocol
- The animal should be positioned in such a way that the cuff is at the level of the right atrium
- Use plenty of gel!
- Make sure that your equipment is well maintained: any cuffs that inflate unevenly or need securing with tape should be replaced

Interpretation of SBP results

A number of different 'reference ranges' have been published for normal cats citing normal SBP readings from 107 to 181 mm Hg in healthy cats. When it is possible to measure it, the DBP of normal cats should be <95 mm Hg. 'White coat' hypertension or stress-induced increases in the SBP are a significant issue when interpreting blood pressure results in cats. On average, the 'white coat' effect increases SBP by 15-20 mm Hg. However, the effect is highly variable between cats and can be as much as 75 mm Hg.

The American College of Veterinary Internal Medicine has published a classification system according to risk of TOD (Table 2).

SBP ≥ 180 mm Hg: severe risk of TOD

In general, cats with SBP in excess of 180 mm Hg are genuinely hypertensive and therapy is justified. However, some healthy cats may transiently have SBP above 180 mm Hg. Hypertension should therefore never be treated solely on the basis of a single abnormal blood pressure reading. If evidence of TOD is present, the diagnosis of hypertension is confirmed and treatment can be instituted. In the absence of TOD it is prudent to re-check the SBP on another occasion before pursuing treatment. The author recommends the following

Risk Category	Systolic BP	Diastolic BP	Risk of future TOD
I	< 150	< 95	Minimal
II	150 – 159	95 – 99	Mild
III	160 – 179	100 -119	Moderate
IV	≥ 180	≥ 120	Severe

Table 2. Classification of blood pressure in cats (in mm Hg) based on the risk of future target organ damage (TOD)

Figure 2. Sudden onset blindness is a potential complication of un-treated systemic hypertension. In this patient, bilateral mydriasis is present due to complete retinal detachment. Areas of retinal haemorrhage can be seen on the retina of the left eye.

steps are taken in cats with SBP readings >180 mmHg:

- Ensure that measurements are taken correctly allowing at least 5-10 minutes for acclimatisation before readings are taken
- Perform a clinical and ocular examination: if evidence of TOD (fig 2), the diagnosis of systemic hypertension has been confirmed
- If no evidence of TOD: repeat measurements on one or two separate occasions within 1-2 weeks. If readings remain high, anti-hypertensive treatment is justified. Further investigations aimed at finding secondary causes of hypertension should be pursued.

SBP 160-179 mm Hg: moderate risk of TOD

SBP readings that are persistently between 160-180 mm Hg are believed to pose a moderate risk of TOD. Persistence is defined as being present on several occasions over a two month period. If there is evidence of TOD (e.g. hypertensive retinopathy), or if the cat is known to have CKD or any other condition known to be associated with hypertension, then anti-hypertensive therapy is justified. In the absence of either of these, it might not be possible to rule out 'white coat' hypertension and further monitoring might therefore be more appropriate.

SBP 150-159 mm Hg: mild risk of TOD

Cats in this group may have mild hypertension but many normal cats will also give blood pressure readings in this range due to the 'white coat' effect. Treatment is not normally recommended unless there is evidence of TOD. For those cats with conditions known to predispose to hypertension, 1-3 monthly monitoring of blood pressure and evaluation for evidence of TOD is recommended once readings >150 mm Hg are obtained.

SBP less than 150 mm Hg

Most normal cats have SBP readings of 120-149 mm Hg. This should be viewed as the ideal 'target range' following treatment for hypertension.

Management of hypertensive cats

The goals of management are to

- Identify and treat potential underlying causes of the hypertension
- Identify TOD and characterise severity
- Reduce SBP to an 'ideal' reference range: 120-150 mm Hg

In any hypertensive cat, investigations for secondary causes should include serum thyroxine (T_4), blood urea and creatinine and urinalysis including specific gravity, assessment of urine protein to creatinine ratio and bacterial culture. Where possible, cardiac and renal ultrasound are helpful. A degree of left ventricular hypertrophy is a common echocardiographic finding in hypertensive cats and generally does not require specific treatment. Additional diagnostic tests which may be considered include:

1. More thorough laboratory evaluation: e.g. looking for hypokalaemia (common in cases of primary hyperaldosteronism, also present in around 20-25% cases of CKD)
2. Abdominal ultrasound: e.g. looking for an adrenal mass(es) (common in cases of primary hyperaldosteronism)
3. Endocrine assays: e.g. serum aldosterone (elevated in cases of primary hyperaldosteronism), free T_4 and cTSH (elevated free T_4 in combination with undetectable levels of canine TSH are consistent with hyperthyroidism, especially if the total T_4 is 30 nmol/l or more)

Periodic blood and urinalysis including creatinine levels and assessment of proteinuria. Once stable, these assessments should be done every 6-12 months according to the individual patient's needs

Class of agent	Agent/s and oral dosage regime	Effective?	Comments
Ca channel blocker	Amlodipine 0.625-1.25 mg/cat q12-24h (maximum suggested dose 0.5 mg/kg/day)	Very - typically reduces SBP by 30-50 mm Hg	Often effective as sole therapy. Benazepril (or other agents) can be added if ineffective at the stated doses.
ACE inhibitors (ACEI)	Benazepril 0.25-0.5 mg/kg q12-24h; enalapril 0.25-0.5 mg/kg q24h; ramipril 0.125-0.25 mg/kg q24	Mild to moderate: typically reduce SBP by 10-20 mm Hg	Reduce systemic and glomerular blood pressure, hence of benefit in proteinuric cats. ACEI may provide some additional benefits in cats with chronic kidney disease. Benazepril is often ineffective as a sole therapy, especially in cases of marked hypertension (SBP>190 mm Hg). In these cases, a combination of benazepril and amlodipine is usually very successful. A recent abstract reported successful use of ramipril as a monotherapy in 69% of hypertensive cats (Van Israel et al 2009). Benazepril is commonly used in combination with amlodipine, there is currently no information on combining ramipril with amlodipine.
Beta-blocker	Propranolol 2.5-5 mg/cat q8h; atenolol 6.25-12.5 mg/cat q12-24h	Mild?	Often ineffective as sole therapy.

Table 3. Anti-hypertensive agents commonly used in cats

Irrespective of the nature of the underlying disease, specific management with anti-hypertensive agents is required, at least in the short term.

There is no veterinary licensed treatment available for treating feline hypertension. A number of different agents have been used - most effective and extremely well tolerated is amlodipine and this is considered the most appropriate first line treatment by most clinicians (Table 3). Response to therapy should ideally be monitored after 7-10 days of treatment by measuring SBP and monitoring TOD. In successfully treated cases, the blood pressure should drop to levels between 120 and 149 mm Hg within 7-10 days of initiating therapy. Post-treatment blood pressure readings between 150 and 160 mm Hg are acceptable as long as there is no evidence of continued TOD. In some cases, it may be necessary to use a combination of amlodipine and benazepril in order to achieve an adequate response. Once blood pressure is stable, patients should be assessed every 1-2 months, reducing the frequency to a minimum of once every 3-4 months in very stable patients. Follow-up assessments should include:

- Measurement of blood pressure
- Assessment for evidence of TOD

Emergency treatment of hypertension may be indicated in some cases – for example cats with very high blood pressure or where there is acute onset of TOD such as retinal detachment. In most of these cases, oral amlodipine is effective in safely but rapidly lowering blood pressure within 24 hours, other options for emergency treatment are listed in Table 4.

Sodium restriction is not specifically recommended but high-salt diets should probably be avoided.

Prognosis

The long-term prognosis is very dependent on the presence, nature and extent of any underlying disease. In primary hypertensive cases it is usually possible to manage the hypertension and prevent future complications such as ocular haemorrhage.

Agent	Dosage regime	Comments
Hydralazine	0.2 mg/kg IV or IM repeated every 2 hours, as needed	Blood pressure should be monitored frequently (e.g. every 20-30 minutes or using a continuous oscillometric monitor) and the drug dose and/or interval adjusted accordingly. Evidence of TOD should also be monitored at least daily.
Enalaprilat	0.2 mg/kg IV or IM repeated every 1-2 hours, as needed	
Esmolol	50-75 µg/kg/minute constant rate infusion	

Table 4. Emergency treatment of hypertension

Further information on blood pressure monitors:

» Doppler models are recommended for use in conscious cats and there are now several models available:

» Thames Medical makes an excellent veterinary model (CAT Doppler Blood Pressure Kit, www.thamesmedical.com). The back-up support is provided from the UK manufacturer. Telephone: +44 1903 522911. info@thamesmedical.com

» The Parks (www.parksmed.com) Doppler machine, (811-B model), with an infant flat probe, is available via Burtons Medical Equipment Ltd. (www.burtons.uk.com) Telephone: +44 1622 832919. The machine was designed for use in people so second hand models may be available.

References

» Van Israel N, Desmoulins PO, Huyghe B, Burgaud S and Horspool LJI (2009). Ramipril as a first line monotherapy for the control of feline hypertension and associated clinical signs. *Journal of Veterinary Internal Medicine* 23:1331-1332 [abstract]

Gold standard management of chronic kidney disease

Dr Sarah Caney
BVSc, PhD, DSAM(Feline), MRCVS

Key points:

- Thorough assessment of patients is needed to ensure that appropriate therapy is being provided
- Phosphate restriction and use of prescription diets have been shown to prolong survival and improve quality of life in cats with CKD
- Treatment of specific complications such as systemic hypertension is also important and improves quality of life
- Regular and frequent check-ups are essential to ensure that the best level of care is being provided
- Management of renal disease is not difficult and can be very rewarding for the cat, owner and veterinary professional

Chronic kidney disease (CKD) is one of the most common diagnoses made in clinical practice. Treatment of CKD patients can seem daunting on first inspection. Kidneys are complex organs so there are a large number of potential complications which might need to be addressed in the individual patient. A key to successful management is seeing your patients regularly and ensuring that you allow sufficient time to perform a thorough evaluation. For many cats, once stabilised, their care is not difficult, time-consuming or stressful and it is possible to provide a good quality of life for months or years.

Healthy Kidney	Potential complication in CKD	Approximate frequency in cats with IRIS Stage 2, 3 or 4 disease*
Excretion of protein breakdown products including urea and creatinine	Azotaemia, clinical signs of uraemia such as poor appetite, nausea and vomiting	99%
Excretion of drugs, toxins and hormones	Accumulation of drugs and toxins can cause adverse effects; accumulation of gastrin (the hormone which regulates gastric acidity) can cause gastritis and gastric ulceration	
Regulation of acid-base status	Metabolic acidosis	65%
Regulation of normal hydration status	Dehydration	65-70%
Regulation of normal electrolyte status	Hyperphosphataemia and hypokalaemia are the most common electrolyte disturbances	60-65% have hyperphosphataemia 20-25% have hypokalaemia
Regulation of normal systemic blood pressure	Systemic hypertension	20%
Production and activation of various hormones including rennin, erythropoietin, calcitriol (Vitamin D_3)	Reduced erythropoietin can contribute to causing anaemia Reduced production of calcitriol is a contributory factor to development of renal secondary hyperparathyroidism	80-85% have renal secondary hyperparathyroidism

Table 1: functions performed by healthy kidneys; complications encountered in CKD
** International Renal Interest Society (IRIS) guidelines (www.iris-kidney.com), blood creatinine level > 140 µmol/l (> 1.6 mg/dl)*

In recent years there have been many advances in treatment options and long-term home care can be very rewarding for all involved. Treatment aims to help the patient to compensate for their renal disease allowing them to live for as long as possible with as good a quality of life as possible. The most proven treatment is feeding a prescription renal diet but there are many other treatments that can be helpful to individual patients.

What treatments are available for kidney disease and what is the aim of treatment?

Treatment should be focussed on:

- Identifying and treating any underlying cause of the disease: e.g. bacterial pyelonephritis, renal stones, exposure to nephrotoxins
- 'Proven' general therapies for CKD such as prescribing renal diets and ensuring that the cat maintains normal hydration as far as possible
- Additional supportive and symptomatic treatments for complications of CKD, according to the individual's specific needs

Initial hospital care may be needed to correct dehydration, acidosis and other severe complications of the renal disease. In most cases, it is possible to stabilise the patient allowing subsequent home care by the owner. Treatment needs to be tailored to the individual according to their specific needs and also those of their owner. Since CKD is a progressive condition, the needs of an individual patient are expected to change with time.

What complications are possible in cats with CKD?

Kidneys perform many complex functions – Table 1 summarises the most common complications that can be seen in patients with CKD.

Prescription renal diets

Prescription renal diets are the single most beneficial proven treatment for cats with renal disease and are especially proven to benefit cats in IRIS Stage 2, 3 and 4 CKD (fig 1). Several studies have now shown emphatically that cats with significant CKD that will eat these diets will live much longer, healthier lives. The diet should be introduced gradually to encourage acceptance by the cat and all efforts should be concentrated on persuading the cat to eat the diet – even if it takes months to achieve this aim!

Renal diets are modified in several ways including:

- Phosphate restricted: cats with kidney disease are vulnerable to developing hyperphosphataemia which contributes towards development of renal secondary hyperparathyroidism and soft-tissue mineralisation. Phosphate restriction has been shown to prolong survival and improve quality of life in cats with CKD.
- Protein restricted: Limiting the amount of nitrogenous waste products for the ailing kidneys to excrete reduces clinical signs associated with uraemia (e.g. anorexia and vomiting).
- Potassium and B vitamin supplemented: helping to prevent hypokalaemia and vitamin deficiency that can occur with CKD.
- Non-acidifying: helping to protect CKD patients from development of metabolic acidosis.
- Palatable and high in calories: helping cats with CKD to maintain a normal bodyweight.

Figure 1. Eukanuba Veterinary Diets Renal for Cats.

Renal diets should be introduced gradually – over a period of weeks or months - to encourage long-term acceptance by the cat. It is always more important that the cat eats than that it eats a kidney diet, so if they are not interested in the prescription diet, they should be offered a cat food which they will eat. Senior diets are preferable to routine cat food as these have lower levels of protein and phosphate in them.

Maintaining normal hydration status

Dehydration is associated with reduced renal perfusion which causes a worsening in renal function. Acutely decompensated cats require intravenous fluid therapy at a veterinary clinic but maintaining adequate fluid intake at home is of prime importance. Cats with CKD should be encouraged to drink as much as possible through tactics such as:

- Feeding moist rather than dry foods, where possible

- Adding extra water to the cat food (wet or dry!). If tolerated, this is an excellent way of increasing a cat's water intake
- Offering broths such as the liquid used to poach chicken or fish, or prawns liquidised in water. Owners should be advised not to offer salty broths (e.g. fish in brine) since this may increase the risk of hypertension, and avoid offering milk as this contains lots of phosphate.
- Offering water fountains or slowly dripping taps. These are helpful in some cats.

In cats that fail to maintain adequate voluntary fluid intake, some owners may be willing to administer subcutaneous fluids (fig 2) at home. Subcutaneous fluid therapy is indicated in those cats suffering from recurrent episodes of dehydration. The sole aim of this therapy is to maintain normal hydration status and prevent dehydration (i.e. not to diurese the patient). A typical regime involves giving 50-100 ml of Hartmann's daily.

Managing hyperphosphataemia

Hyperphosphataemia is present in around two thirds of CKD cats and is a major trigger for the development of renal secondary hyperparathyroidism (R2HP). R2HP is a cause of clinical signs of CKD and also contributes to progression of disease.

Phosphate restriction is believed to be a key reason why cats eating renal diets live so much longer. In cats that won't eat a renal diet, phosphate binders are especially important to help treat/prevent hyperphosphataemia. Oral phosphate binders should be mixed with the food – they work by binding to phosphate present in the diet, retaining this in the bowel and hence limiting the amount of phosphate that can be absorbed by the body. It can take several months for the total body excess phosphate levels and hence blood phosphate levels to normalise.

The International Renal Interest Society (IRIS) recommends phosphate restriction for all cats in Stage 2, 3 or 4 renal disease and has devised target levels for blood phosphate according to severity of renal disease (Table 2). IRIS recommend

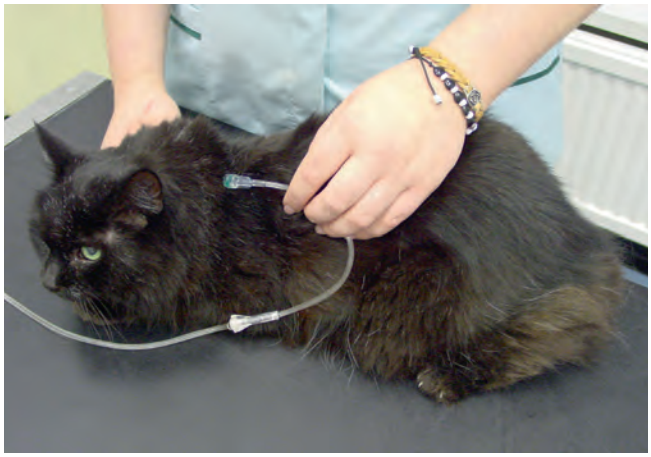

Figure 2. Owners can be trained to give subcutaneous fluids to their cat at home. This treatment is especially helpful for cats in advanced renal disease that struggle to maintain normal hydration.

that blood phosphate levels are kept at the bottom of the reference range (1 – 1.2 mmol/l) as far as possible. Phosphate restriction can be achieved through feeding a phosphate-restricted diet (renal prescription diet, fig 1) and/or mixing intestinal phosphate binders with the food offered. Veterinary phosphate binders include calcium carbonate (Ipakitine®, Vétoquinol) and lanthanum carbonate (Renalzin®, Bayer Animal Health). Intestinal phosphate binders should be mixed with the food; starting at a low dose before gradually increasing to the recommended doses usually ensures good tolerance and compliance. In those patients with blood phosphate results higher than the IRIS targets (Table 2), both a phosphate-restricted diet and intestinal phosphate binders may be required to attain adequate control and it may take several months to achieve this.

Choosing a phosphate binder

In the past, aluminium hydroxide, aluminium carbonate or aluminium oxide were most commonly used at doses between 30-90 mg/kg/day, adjusted according to the response. Long-term use of aluminium hydroxide can, in rare instances, be associated with side-effects such as weakness, tremors and seizures due to aluminium accumulation. Doses above 100 mg/kg/day are especially risky with respect to

IRIS Stage	Blood creatinine	Target phosphate level
1	< 140 µmol/l	N/A
2	140-250 µmol/l	0.9 – 1.5 mmol/l
3	251-440 µmol/l	0.9 – 1.6 mmol/l
4	> 440 µmol/l	0.9 – 1.9 mmol/l

Table 2. Target blood phosphate levels according to the severity of renal disease

side effects. Microcytosis (small red blood cells) is usually the first consequence of toxicity and usually precedes neurological side effects. The side-effects seen are reversible upon stopping treatment. As a result of human concerns over adverse effects, some of these compounds are no longer readily available so may not be accessible to all clinicians.

Alternatives include calcium-based agents (e.g. calcium carbonate – for example Ipakitine®, Vétoquinol, which also contains chitosan). Ipakitine® has been shown to be effective in lowering blood phosphate levels in treated cats. There are a few, rare situations in which calcium containing phosphate binders should not be used (or used with extreme caution):

- Calcium based agents should not be used in hyper-calcaemic cats as they may have the potential to worsen this.
- Similarly they should not be used in cats that are receiving calcitriol (Vitamin D_3) since this increases intestinal absorption of calcium and may increase the risk of soft tissue mineralisation.

More recently, lanthanum containing agents such as Renalzin® (Bayer Animal Health) have become available as alternative intestinal phosphate binders. Lanthanum based compounds are often used as first-line phosphate binders in human medicine since they have the advantages of:

- not containing calcium therefore do not have any of the calcium concerns that might exist with other agents
- being free of adverse effects, even at high doses. Unlike aluminium, lanthanum is not absorbed into the body.

Managing poor appetite, nausea and vomiting

Many cats with CKD suffer from uraemic gastritis contributing significantly to their inappetence and weight loss. General nursing techniques such as feeding warm food by hand may help (fig 3). In other cases, it is worth trying antacids (e.g. H_2-antagonists such as famotidine 0.5 mg/kg daily or on alternate days) anti-emetics (e.g. maropitant 0.5 mg/kg once daily) and/or appetite stimulants (e.g. cyproheptadine 1 mg/cat once or twice daily, mirtazipine 1.75 mg/cat every 3-4 days). In those cats that are bright and relatively well but where appetite remains poor, one long-term possibility includes placing a feeding tube such as an oesophagostomy or gastrostomy tube.

Managing hypokalaemia

Hypokalaemia (potassium < 4.0 mmol/l), caused by inappropriate loss of potassium in the urine and inadequate intake due to inappetence, is present in around 25% of cats with CKD. The cardinal sign of severe hypokalaemia is polymyopathy, with generalised muscle weakness and ventroflexion of the neck. However, more mildly affected cats will only suffer from non-specific signs such as lethargy, weakness and loss of appetite. Hypokalaemia is not only a cause of clinical signs but it also adversely affects renal function. Potassium gluconate (e.g. Tumil K®, Kaminox®, Amino B+K®) at a dose of 1-4 mmol twice daily is the preferred oral supplement as it is the least gastric irritant. Renal diets which are supplemented in potassium but also are non-acidifying and low in protein help to maintain normal serum potassium concentrations.

Figure 3. Hand-feeding and general nursing tactics can help to encourage appetite in cats with chronic kidney disease.

Managing systemic hypertension

Systemic hypertension affects at least 20% of CKD patients. Hypertension can have serious consequences including blindness, neurological signs (such as seizures), cardiac changes (most commonly a systolic heart murmur due to cardiac remodelling) and renal damage. Blood pressure should be evaluated as a routine part of all check-ups of CKD cats and anti-hypertensive therapy prescribed to those where the mean systolic blood pressure readings, taken with the cat in a calm state, are persistently above 160-170 mm Hg or where there is evidence of hypertensive retinopathy. Ocular manifestations of systemic hypertension include retinal oedema, haemorrhage and detachment (fig 4, next page).

The most commonly used drugs for treatment of feline hypertension are the calcium channel blocker amlodipine besylate (0.625-1.25 mg/cat once or twice daily; available as generic preparations and Istin®, Pfizer in the UK) and the ACE inhibitor benazepril (0.5 mg/kg once or twice daily; available as Fortekor®, Novartis Animal Health and others). In general, amlodipine is more effective in lowering blood

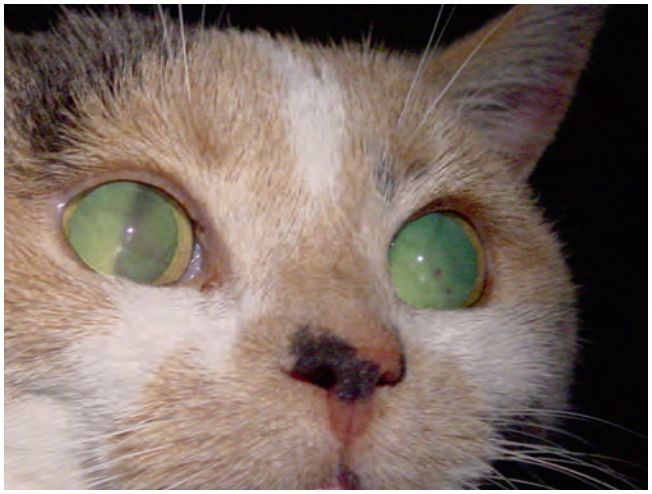

Figure 4. Sudden onset blindness is a potential complication of un-treated systemic hypertension. In this patient, bilateral mydriasis is present due to complete retinal detachment. Areas of retinal haemorrhage can be seen on the retina of the left eye.

pressure than the ACE inhibitors. In some cats, a combination of these drugs may be required to achieve adequate control.

Managing proteinuria

Proteinuria is common in cats with CKD and is associated with a worse prognosis. ACE inhibitors such as benazepril or an angiotensin receptor blocker (ARB) such as telmisartan (Semintra®, Boehringer Ingelheim Animal Health) are indicated in cats with a urine protein to creatinine ratio persistently greater than 0.4 where pre- and post-renal causes of proteinuria have been excluded. ACE inhibitors and ARBs should only be used in clinically stable, normally hydrated cats. See also separate notes in these proceedings on proteinuria (pages 34-39).

Managing urinary tract infections

Around 25% of cats with CKD suffer from a bacterial cystitis at some point in the course of their disease – probably since the urine they are producing is so dilute. Bacterial cystitis may pose a risk of ascending infection and pyelonephritis or may represent bacterial seeding of the urine from pre-existing pyelonephritis. Unfortunately, in many cases the bacterial infection does not cause any clinical signs of cystitis – in other words, the infection is clinically 'silent'. A course of antibiotics, ideally chosen on the basis of bacterial culture and sensitivity results, is often needed for several weeks (or months) in order to successfully eliminate the bacterial infection.

Managing metabolic acidosis

Metabolic acidosis is commonly encountered in patients with CKD and may contribute to a number of clinical signs including anorexia, vomiting and weight loss. Maintaining normal hydration and feeding a renal diet help to reduce the incidence of acidosis although a small number of cats may require further treatment with oral sodium bicarbonate (dose 15-45 mg/kg/day).

If the cat is receiving a urinary acidifying diet, this should be stopped and, ideally, a low-protein diet instituted.

Managing anaemia

Progressive anaemia (fig 5) is common in CKD and can contribute to lethargy, inappetence, weakness and weight loss. In some cats, iron deficiency can contribute to the anaemia both through inadequate dietary intake and gastro-intestinal blood loss. Treatment options which may be considered include iron supplementation (50-100 mg ferrous sulphate daily), anabolic steroids and recombinant human erythropoietin.

Figure 5. Anaemia is common in chronic kidney disease and contributes to poor clinical status.

ACE inhibitors and CKD

ACE inhibitors are prescribed to people with CKD as they prolong lifespan, reduce proteinuria and reduce blood pressure. Reduction of blood pressure *and* proteinuria are both believed to be important in reducing the progression of renal disease in people.

Data from clinical trials has shown that CKD cats receiving benazepril (e.g. Fortekor®, Novartis Animal Health) have a better quality of life (as assessed by their owners) and a reduction in proteinuria. Cats with significant proteinuria and Persian cats with CKD did especially well in one trial of this treatment with prolonged survival times reported. Proteinuria is believed to contribute to the progression of renal disease since filtered proteins present in the glomerular filtrate are renotoxic. Azotaemic cats with a urine protein to creatinine (UPC) ratio of greater than 0.4 are considered to be proteinuric.

	Tests done	Aim of tests	Frequency of check-up			
			Once a month	Every 3 months	Every 6 months	Every 12 months
History	Full clinical history and discussion with client	- assess progress - look for complications of CKD - provide client support for treatment recommendations				
Clinical examination	Complete physical examination including body-weight (calculate % weight changes), body condition score and eye examination	- identify and treat complications of CKD promptly: e.g. dehydration				
Blood pressure (once stable or if nor-motensive)	Eye examination and Doppler blood pressure measurement	- identify and treat high blood pressure promptly - monitor stabilised hypertensive patients in case a change in the medication dose is required				
Urine tests	USG, sediment, dipstick, culture and UPC	- assess progression of CKD - identify and treat complications of CKD: e.g. proteinuria, UTI				
Blood tests	Full haematology and biochemistry including proteins, urea, creatinine, sodium, potassium, phosphate, calcium, liver enzymes. Total T_4 and others (e.g. acid-base status, iron status) if indicated clinically.	- assess progression of CKD - assess management of previously diagnosed complications: e.g. does the dose of phosphate binder need to be increased? - identify and treat complications of CKD promptly: e.g. hypokalaemia				

Table 3: A guide to check-ups in stable cats with CKD.

Key	Colour in table above
Initial recommendation	
Recommendation in very stable cases – for example those that have been stable when monitored for 6-12 months	
Not to be recommended – too infrequent	

ACE inhibitors are indicated for treatment of CKD cats in stable disease and especially those with proteinuria and/or systemic hypertension. As discussed earlier ACE inhibitors alone may not be sufficient to control high blood pressure and amlodipine may be needed as an additional treatment to manage the hypertension.

One study has also shown that benazepril increases appetite and body weight in healthy cats – a potentially useful effect in cats with CKD!

Other treatments

Other treatments not discussed in these notes may be needed in the individual patient according to their needs.

Check-ups

Monitoring visits are very important to ensure that owners are supported and that clinical problems are identified and treated promptly. The required frequency of check-ups varies according to the patient's needs but should initially be at least once a month. All check-ups should include weighing the patient (and calculating percentage weight changes) and assessing for clinical problems (such as dehydration). Blood pressure and laboratory monitoring should be checked according to the patient's needs and owner's concerns – I measure blood pressure every 3-6 months and reassess blood and urine tests every 6-12 months, depending on the individual patient's needs. A summary of check-up guidelines is outlined in Table 3. Check-ups should be performed more frequently than advised in those patients where additional concerns are present – for example if physical examination

reveals pale mucous membranes then haematology is indicated as soon as possible.

The long-term outlook for cats with CKD is very variable ranging from a few weeks post diagnosis to many years. Although CKD is a progressive condition the rate of progression varies considerably according to the cause of the disease and other individual factors. For many cats, once stabilised, their care is not difficult, time-consuming or stressful and it is possible to provide a good quality of life for months or years.

Useful additional resources

» Free downloads are available on the Cat Professional website (http://www.vetprofessionals.com/catprofessional/free_downloads.html) on a number of relevant topics including:
  - Potassium supplementation
  - Doppler blood pressure measurement
  - Ocular manifestations of systemic hypertension
  - Giving subcutaneous fluids to your cat
  - Encouraging your cat to take in more fluids

» www.iris-kidney.com for guidelines and information from the International Renal Interest Society (IRIS).

» For more detailed information on proteinuria (pages 34-39) and systemic hypertension (pages 40-45) please refer to their specific text in these proceedings.

Addendum

Renal for Cats

Nutritional management of renal function in cats

Renal for Cats is formulated to support renal function in case of chronic renal insufficiency.

PRODUCT AVAILABILITY AND PACKAGING

Dry Formula
1.5kg

Canned Formula
170g

NUTRITIONAL PROFILE

Renal for Cats contains a restricted amount of high quality protein and low phosphorus.

- **Reduced phosphorus level (0.35%)*** – soy protein isolate (reduced phosphorus) helps nutritionally manage hyperphosphataemia
- **Moderate level (28%)* of high quality animal-based protein** – help to maintain the glomerular filtration rate
- **Omega-3 fatty acids** – helps to support the glomerular filtration rate
- **Added potassium citrate** – helps to manage the normal acid-base balance of the body

ADDITIONAL BENEFITS

- **Nitrogen Trap Fibre System (beet pulp, FOS, Gum Arabic)** – helps to increase excretion of nitrogenous waste via the faeces and reducing urinary nitrogen excretion. This helps allow for the feeding of a moderate protein level of 28%*
- **Dry and canned formulas, can be mixed if needed** – helps maximize pet and client compliance

*Renal for Cats dry formula

NUTRIENTS TO HELP MANAGE OVERALL HEALTH AND WELL-BEING

- **Vitamin E** – an antioxidant to support strong natural defenses
- **Beet pulp** – a moderately fermentable fibre that produces butyrate, a short-chain fatty acid (SCFA), which is a preferential energy source for the colonocytes. Helps maintain intestinal health and optimal stool consistency
- **FOS (fructooligosaccharides)** – the prebiotics fructooligosaccharides (FOS) and clinically proven beet pulp to maintain digestive health and support nutrient absorption

COMPOSITION

Dry: Maize grits, animal fat, soya protein isolate, corn gluten meal, dried beet pulp, Dried Chicken and Turkey, fructooligosaccharides, fish oil, calcium carbonate, chicken digest, potassium chloride, sodium chloride.

Canned: Beef liver, chicken, beef by-products, maize, animal fat, maize starch, dried whole egg, dried beet pulp, fish oil, fructooligosaccharides, brewer's dried yeast, calcium carbonate, potassium chloride, sodium chloride.

ANALYTICAL CONSTITUENTS

Nutrient/Ingredient	Dry	Canned	Nutrient/Ingredient	Dry	Canned
Protein:	28.0%	8.0%	Vitamin A:	12000IU/kg	10000IU/kg
Fat content:	23.0%	6.0%	Vitamin D_3:	1000IU/kg	125IU/kg
Omega-6 fatty acids:	3.35%	1.20%	Vitamin E (α-tocopherol):	220mg/kg	25mg/kg
Omega-3 fatty acids:	0.50%	0.20%	Magnesium:	0.08%	0.02%
Crude Ash:	4.60%	1.50%	Potassium citrate:	0.55%	0.07%
Crude Fibres:	3.30%	0.80%	Beet pulp:	6%	1.5%
Moisture:	8.00%	77.00%	FOS:	1.5%	0.37%
Calcium:	0.60%	0.22%	Gum Arabic:	2.1%	0.5%
Potassium:	0.65%	0.23%	kcals/kg: *	4114	1115
Sodium:	0.45%	0.14%	MJ/kg: *	17.2	4.7
Phosphorus:	0.35%	0.18%			

*Metabolizable Energy (Atwater)

FEEDING GUIDELINES

Weight	Dry Feeding (grams per day)	Canned Feeding (cans per day)
2kg	25-35g	½ - ⅔
3kg	35-55g	
4kg	50-70g	1 - 1⅓
5kg	60-85g	
6kg	75-100g	1½ - 2
8kg	95-135g	2 - 2¾
10kg	120-170g	2½ - 3½

TRANSITION PRODUCTS

Renal for Cats is formulated for long-term feeding under veterinary supervision

EUKANUBA VETERINARY DIETS

Renal for Dogs

Nutritional management of renal function in dogs

Renal for Dogs is formulated to support renal function in case of chronic renal insufficiency.

PRODUCT AVAILABILITY AND PACKAGING

Dry Formula
12kg bag

NUTRITIONAL PROFILE

Renal for Dogs contains a restricted amount of high quality protein and low phosphorus.

- **Reduced phosphorus level (0.4%)** – soy protein isolate (reduced phosphorus) helps nutritionally manage hyperphosphataemia
- **Moderate levels (18.8%) of high quality animal-based protein** – helps to maintain the glomerular filtration rate
- **Omega-3 fatty acids** – helps to support the glomerular filtration rate
- **Added potassium citrate** – helps to manage the acid-base balance of the body

ADDITIONAL BENEFIT

- **Nitrogen Trap Fibre System (beet pulp, FOS, Gum Arabic)** – helps to increase excretion of nitrogenous waste via the faeces and reducing urinary nitrogen excretion. This helps allow for the feeding of a moderate protein level of 18.8%

NUTRIENTS TO HELP MANAGE OVERALL HEALTH AND WELL-BEING

- **Vitamin E** – an antioxidant to support strong natural defenses
- **Beet pulp** – a moderately fermentable fibre that produces butyrate, a short-chain fatty acid (SCFA), which is a preferential energy source for the colonocytes. Helps maintain intestinal health and optimal stool consistency
- **FOS (fructooligosaccharides)** – the prebiotics fructooligosaccharides (FOS), and clinically proven beet pulp, to maintain digestive health and support nutrient absorption

COMPOSITION

Maize, maize grits, rice, animal fat, fish meal, dried beet pulp, soya protein isolate, dried whole egg, chicken digest, poultry liver meal, fructooligosaccharides, brewer's dried yeast, calcium carbonate, sodium chloride, potassium chloride, linseed.

ANALYTICAL CONSTITUENTS

Nutrient/Ingredient		Nutrient/Ingredient	
Protein:	18.8%	Phosphorus:	0.40%
Fat content:	13.0%	Vitamin A:	5400IU/kg
Omega-6 fatty acids:	2.15%	Vitamin D_3:	325IU/kg
Omega-3 fatty acids:	0.35%	Vitamin E (α-tocopherol):	100mg/kg
Crude Ash:	4.70%	Potassium citrate:	0.2%
Crude Fibres:	3.70%	Beet pulp:	6%
Moisture:	8.00%	FOS:	1.45%
Calcium:	0.70%	Gum Arabic:	1.7%
Potassium:	0.60%	kcals/kg:: *	3596
Sodium:	0.48%	MJ/kg: *	15.1

*Metabolizable Energy (Atwater)

FEEDING GUIDELINES

Weight	Feeding (grams per day)
2kg	45-50g
5kg	80-90g
10kg	130-145g
20kg	205-230g
30kg	270-300g
40kg	325-360g
50kg	380-420g
60kg	430-475g
70kg	475-525g

TRANSITION PRODUCTS

Renal for Dogs is formulated for long-term feeding under veterinary supervision

EUKANUBA VETERINARY DIETS

Notes

Managing Renal Disease for Improved Patient Outcome

P&G Pet Care

Procter and Gamble Pet Care
47 Route de Saint-Georges
1213 Petit-Lancy 1
Geneva
Switzerland

Manufacturers of Eukanuba® and Iams® premium dog and cat foods and the veterinary exclusive Eukanuba Veterinary Diets®

EUKANUBA VETERINARY DIETS