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CLINICAL REVIEW

FELINE CKD
Current therapies – what is achievable?

Rachel Korman and Joanna White

Practical relevance: Treatment of feline chronic kidney disease (CKD) tends to focus on minimising the adverse effects of reduced renal function, rather than addressing an underlying cause. Despite this, and the progressive nature of CKD, treatment can improve quality of life and enable many cats to have long survival times.

Evidence base: Strong evidence supports the provision of renal diets, which are protein and phosphorus restricted; compliance is improved by gradual dietary transition. Additional phosphorus restriction is achieved by the use of phosphate binding agents, although it is unknown if these yield similar survival benefits to those provided by renal diets. Interventions to control hypokalaemia and hypertension in affected cats are important to prevent serious complications. Administration of benazepril to cats with proteinuric kidney disease has been shown to significantly improve their appetite but not their survival. As CKD progresses, many cats will benefit from treatment to control clinical signs of uraemic gastroenteritis and anaemia.

Therapy for CKD – what are the aims?

The ideal treatment for feline chronic kidney disease (CKD) would correct or reverse the underlying cause of CKD, identify and address factors associated with progressive CKD and minimise signs of reduced renal function. Unfortunately, the cause of feline CKD is usually unknown and treatments that slow CKD progression in other species (eg, calcitriol, benazepril) have not been proven effective in cats.[1–4] The irreversible and progressive nature of CKD can be disheartening; however, treatment can improve quality of life and survival, providing fulfilling experiences for veterinarians and owners.

Figure 1 Easy administration is an important consideration to aid owner compliance

CKD causes retention of renally excreted wastes (eg, phosphorus) and loss of compounds (eg, potassium) that should be retained. Most therapy is aimed here, consisting of supportive and symptomatic treatments to correct hydration and address endocrine, metabolic and nutritional disturbances. Treatment is lifelong, highlighting the importance of easy medication administration to aid owner compliance (Figure 1).

Evidence-based medicine (EBM) integrates available research, clinical expertise, patient and owner preferences, and resource availability to tailor treatments in order to optimise outcome. Veterinary classification of EBM guidelines exists, and is summarised, together with the strength of evidence for currently available interventional therapeutics in feline CKD, in the box on page 30. Guidelines for CKD staging established by the International Renal Interest Society (IRIS) (www.iris-kidney.com) provide the classification system used throughout this article.

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Strength of evidence supporting current interventional therapies in feline CKD

Veterinary classification of EBM guidelines

Grade I
Evidence obtained from one or more properly designed, randomised, controlled, clinical trials performed in cats with spontaneous disease.

Grade II
Evidence obtained from properly designed, randomised, controlled studies performed in cats with spontaneous disease in a laboratory or research animal colony setting.

Grade III
Evidence obtained from appropriately controlled studies without randomisation, appropriately designed cohort or case control studies, studies using acceptable models of disease or simulations in cats, case series or dramatic results from uncontrolled studies.

Grade IV
Evidence obtained from studies conducted in other species, reports of expert committees, descriptive studies, case reports, pathophysiological justification and clinical experience of recognised experts.

Adapted from Roudebush et al[5,6]

Grade I
- Provision of renal diets in stages 2–3 to minimise uraemic episodes and improve survival
- Use of benazepril to reduce proteinuria and improve appetite in proteinuric cats

Grade II
- Use of chitosan or lanthanum-containing phosphate binding agents to reduce hyperphosphataemia

Grade III
- Use of potassium supplementation to treat hypokalaemia
- Use of vitamins E and C, and β-carotene to reduce oxidative damage
- Use of erythropoietin-stimulating agents to treat anaemia of CKD and improve quality of life
- Use of amlodipine to reduce hypertension

Grade IV
- Use of antiemetic and/or gastroprotective agents to treat uraemic gastroenteritis
- Use of fluid therapy to treat chronic dehydration
- Use of appetite stimulating agents and enteral feeding to treat malnutrition
- Supplementation with calcitriol to reverse renal hyperparathyroidism (grade I evidence fails to support use)
- Use of alkalinisation therapy to treat metabolic acidosis
- Use of essential fatty acids in renal diets to improve survival and reduce uraemic episodes
- Use of benazepril in non-proteinuric CKD

Dietary modification

Of all the CKD treatments used to date, dietary modification has the most positive long-term effect on outcome.[7–9] Cats with CKD receiving renal diets instead of normal food survived significantly longer (20.8 months versus 8.7 months;[7] 16 months versus 7 months[8]). Additionally, a randomised, controlled, clinical trial (RCCT) compared feeding maintenance diets with renal diets in spontaneous CKD stages 2 and 3.[9] Cats fed the renal diet developed fewer uraemic episodes (0% versus 23%) and none died from renal disease. Thus, strong evidence exists to support the use of renal diets to prolong survival and improve the quality of life for cats with CKD.

There is no evidence supporting dietary modification in stage 1 CKD, although, in the authors' experience, introducing a dietary change in a clinically well cat improves diet acceptance. Over 90% of cats with CKD accepted renal diets when a very gradual transition was used.[9] Attempting changes in sick, hospitalised, anxious patients can result in food aversion. Dietary modification should not be attempted until patients are well and discharged from hospital. There will always be some cats defiant of diet change. Although home-prepared renal diets are attractive to some owners, dietary assessment identified numerous nutritional inadequacies.[10] Therefore, in cats refusing renal diets, use of senior diets with phosphate binding agents (PBAs) if hyperphosphataemia is present, while not ideal, may be better than provision of maintainence diets alone.

Of all the CKD treatments used to date, dietary modification has the most positive long-term effect on outcome.

Renal diets are restricted in protein, phosphorus and sodium and supplemented with potassium, omega-3 fatty acids, B vitamins and fat content, and are alkalinising. It is unknown which alterations are responsible for survival benefits, although studies in experimental models support phosphate restriction,[11] and essential fatty acid (EFA) supplementation as potential mechanisms.[12]

Table 1 Recommendations for serum phosphate concentration in cats with CKD by IRIS stage

IRIS stage	Target serum phosphate concentration mmol/l (mg/dl)
2	0.81–1.45 (2.5–4.5)
3	0.81–1.61 (2.5–5)
4	0.81–1.94 (2.5–6)

IRIS = International Renal Interest Society
Adapted from Kidder et al[16] and Elliott et al[18]

Table 2 Commonly used phosphate binding agents in cats

Drug	Dosage	Comments
Aluminium hydroxide	30 mg/kg PO q8h 45 mg/kg PO q12h	May cause constipation Aluminium toxicity possible
Calcium acetate	60–90 mg/kg PO q24h	Monitor for hypercalcaemia
Calcium carbonate	30 mg/kg PO q8h 45 mg/kg PO q12h	Monitor for hypercalcaemia
Chitosan and calcium carbonate	1 g /4.5 kg (10 lb) PO q8h	Monitor for hypercalcaemia
Lanthanum carbonate	6.25–12.5 mg/kg PO q12h	
Lanthanum carbonate octahydrate	400–800 mg/cat q24h divided with meals	Also contains kaolin for possible uraemic toxin binding effects and vitamin E for antioxidant effects. Should be given 1 h prior to or 3 h after other medications
Sevelamer hydrochloride	30–50 mg/kg PO q8h 50–80 mg/kg PO q12h	Safety and efficacy in cats unknown

NB All drugs must be given with food

Phosphate restriction

Strong evidence supports dietary phosphate restriction in animals with kidney disease. Serum phosphate is an independent predictor of disease progression in cats with CKD.[11,13] In rodent models, phosphate restriction was associated with reduced tissue mineralisation and reduced glomerular hypertension.[14] Cats with induced renal disease fed phosphate-restricted diets had less severe histological renal changes than cats fed normal diets.[15]

Renal diets restrict serum phosphate, and subsequently parathyroid hormone (PTH) concentrations, by limiting phosphorus-containing proteins,[7,16,17] and are effective in controlling hyperphosphataemia and renal secondary hyperparathyroidism (RHPTH) and increasing survival in cats with CKD.[7] The goal of dietary therapy is to reduce phosphate concentration within 2–4 weeks of complete diet change. Target phosphate concentrations exist based solely on expert opinion (Table 1).[16,18] Dietary modification alone can often control phosphate concentrations up to stage 3 CKD.[17,19] In stage 4, diet alone may be insufficient. If after 4 weeks of dietary modification hyperphosphataemia (or increased PTH) persists, use of a PBA should be considered (Table 2). Regular monitoring of phosphate concentration every few months is recommended.

Sodium restriction

Studies on dietary sodium intake in cats with and without CKD have produced variable results. High dietary sodium has been shown not to alter systolic blood pressure (SBP)[20,21] or kidney function in healthy cats or cats with induced CKD.[20,22,23] In contrast, serum creatinine concentration increased when cats changed from a low sodium to a high sodium diet. Notably, the increase in creatinine concentration was most marked in cats with higher initial creatinine concentrations.[21] However, dietary sodium restriction is not without potential risk. Cats receiving sodium-restricted diets have been shown to have renin–angiotensin–aldosterone system activation, hypokalaemia and reduced glomerular filtration rate (GFR).[20] Additionally, a case control study found that cats receiving higher sodium diets were less likely to develop CKD, although confounding factors may have affected this study.[24]

In people, dietary sodium intake has been proposed to cause progressive kidney injury by mechanisms unrelated to hypertension, such as increased oxidative stress.[25]

While results of the above studies indicate that hypertension is not salt sensitive in cats, the conflicting results, small study sizes and short study durations mean that the ideal dietary salt intake for cats with CKD that would minimise progressive renal damage remains unknown. There is currently no indication to alter the sodium intake of cats with CKD beyond the relatively low amounts found in renal diets.

Renal diets restrict serum phosphate and subsequently parathyroid hormone concentrations, and are effective in increasing survival in cats with CKD.

Essential fatty acid supplementation

Feeding dogs with induced CKD diets enriched with omega-3 fatty acids decreased intraglomerular hypertension, maintained GFR and improved survival.[12,26] No data is available in cats. A retrospective study reported longer survival times for cats receiving renal diets with the highest omega-3 fatty acid content,[8] and cats receiving renal diets that contain omega-3 fatty acid supplementation had fewer uraemic crises than those on maintenance diets alone.[9]

Vitamins and antioxidants

Oxidative stress contributes to progression of CKD in people,[27] and has been identified in cats with CKD.[28,29] A cross-over study in cats with spontaneous CKD found that vitamin E, C and beta-carotene supplementation reduced oxidative stress.[30] Studies assessing survival benefits are required.

Treatment of hyperphosphataemia and renal secondary hyperparathyroidism

Approximately 60% of cats with CKD are hyperphosphataemic.[31] The aetiopathogenesis of hyperphosphataemia and RHPTH has been described.[16,17,32] Serum phosphorus concentration is a negative prognostic indicator in CKD and potentially contributes to progressive renal dysfunction.[11,13,33] Methods for controlling hyperphosphataemia include rehydration, dietary phosphorus restriction and PBAs for cats with stage 2 or higher CKD.[17]

In people, PTH is a major uraemic toxin, increasing intracellular calcium and resulting in neurotoxicity, immune dysfunction and exacerbation of anaemia.[34] If PTH is similarly toxic in cats, another treatment goal would be to normalise or prevent PTH increases by dietary phosphate restriction, use of PBAs and calcitriol administration.[16] In general, PTH concentrations parallel serum phosphate concentrations and the prevalence of RHPTH increases with the severity of renal disease,[31] although some cats develop RHPTH before overt azotaemia or hyperphosphataemia.[35]

Phosphate binding agents

PBAs bind dietary phosphorus in the gastrointestinal tract, producing insoluble compounds that are excreted in faeces. Safety and efficacy data for some PBAs in cats are available; however, little data exist regarding their effects on survival.[36–38] PBAs must be given with food and can be poorly accepted, causing inappetence that negates any potential benefits of both PBAs and renal diets. Treatment response should be assessed with regular phosphate monitoring. Obtaining fasted blood samples avoids post-prandial hyperphosphataemia.[32] Commonly used PBAs are described in Table 2.

Chitosan and calcium carbonate administration reduces hyperphosphataemia in cats.[36,38] Plasma phosphate and blood urea nitrogen (BUN) concentrations decreased within 35 days in six cats with CKD receiving the supplement with a maintenance diet.[38] A RCCT in cats with induced CKD identified decreased serum phosphate and PTH concentrations and reduced urinary fractional excretion of phosphorus in animals receiving the supplement compared with maintenance diets alone.[36] No differences in BUN, creatinine, GFR or renal plasma flow were found. These studies suggest that for cats in stages 1 and 2 CKD, administration of chitosan-containing PBAs decreases phosphate concentration. Whether the survival benefit differs from that provided by dietary phosphate restriction is unknown. Calcium-containing PBAs can cause hypercalcaemia if used with calcitriol.[32]

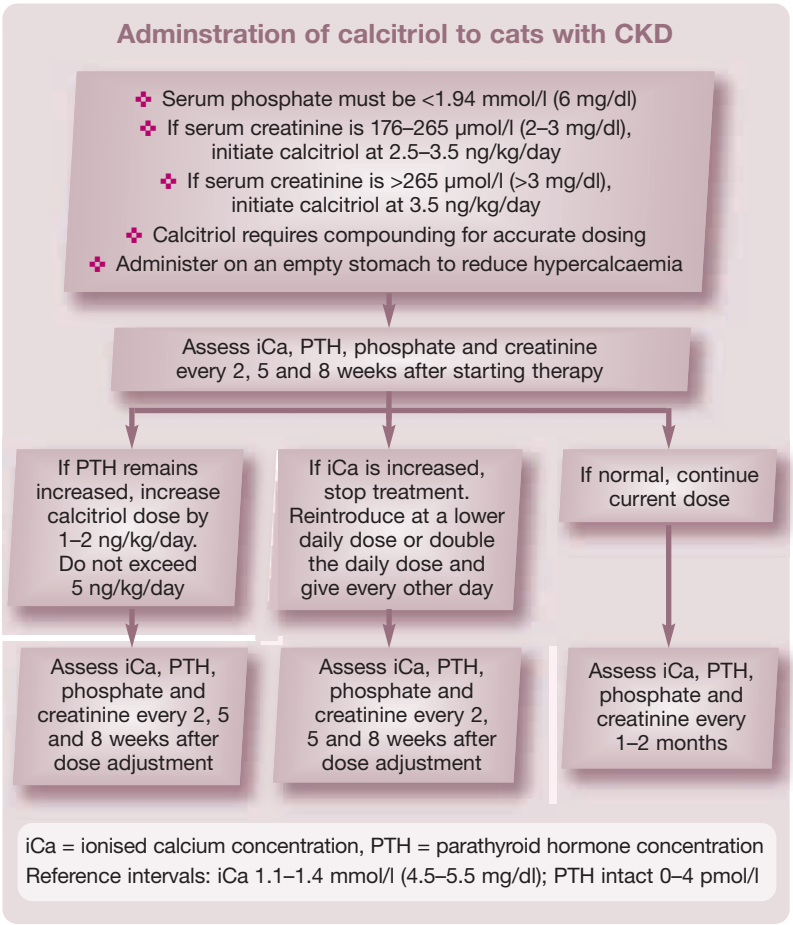
In people with renal failure, lanthanum appears efficacious with few adverse effects,[39] although tissue accumulation is reported in rats.[40] Vomiting occurs in cats at high dosages.[37] Preliminary results of lanthanum use in cats with CKD showed decreased serum creatinine and phosphate concentrations.[41]

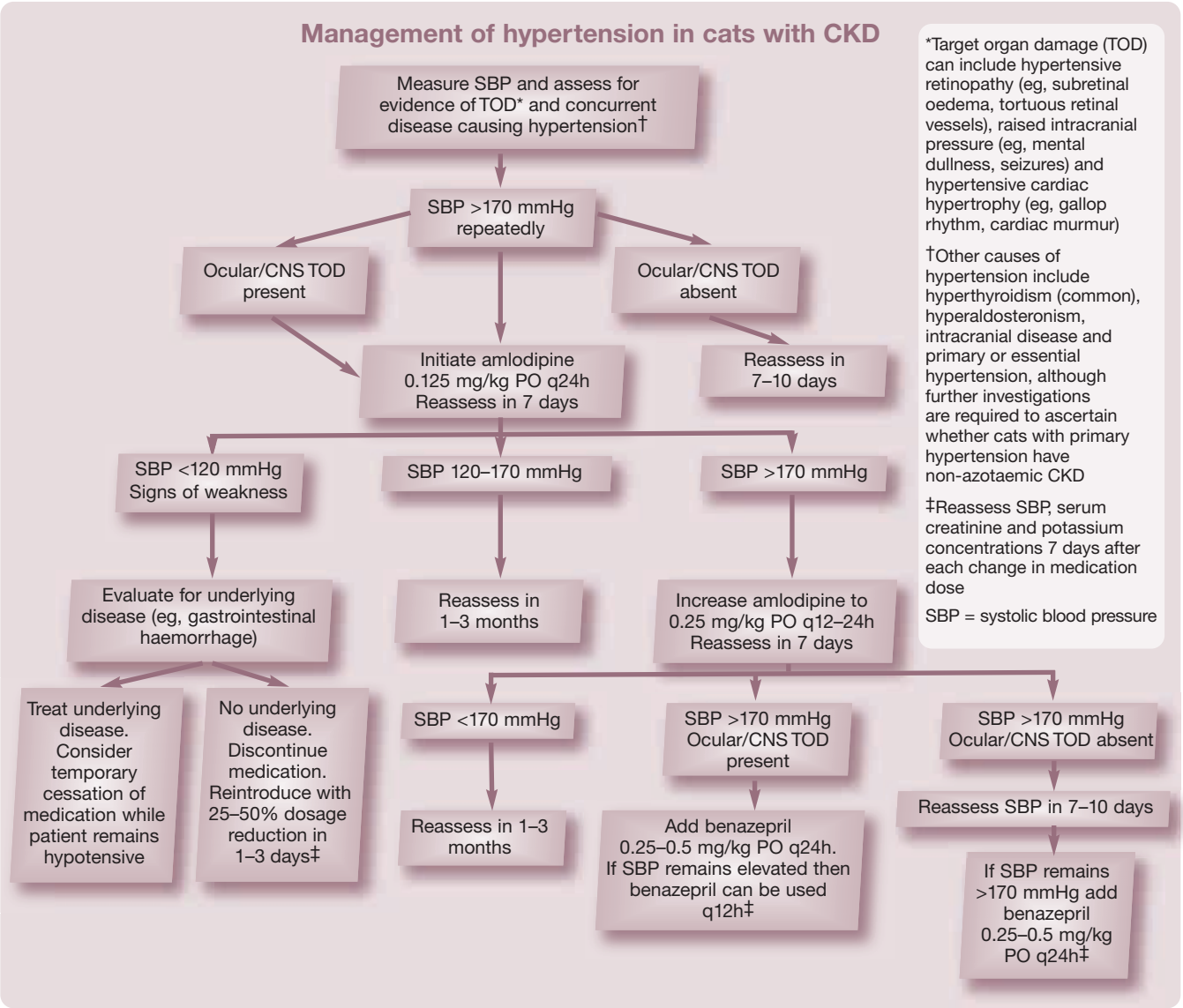
Aluminium toxicity has been demonstrated in people and dogs with renal failure.[42,43] However, as aluminium hydroxide is effective, inexpensive and readily available, use has continued. Constipation occurs commonly in cats and can be addressed by conservative doses (to avoid dehydration) of lactulose (eg, 0.5–1 ml PO q12h).

Another phosphate binder widely used in humans, sevelamer, contains neither calcium nor aluminium but may bind additional vitamins and thus vitamin supplementation is required.[44]

Calcitriol

Calcitriol supplementation can theoretically ameliorate excess PTH and early intervention may prevent parathyroid gland hyperplasia.[2] An uncontrolled survey reported that calcitriol administration to cats with CKD improved activity levels and appetite;[45] however, neither daily nor intermittent calcitriol





administration reduced PTH concentration,[1] and a 1 year RCCT of calcitriol administration in cats with CKD failed to show any benefits.[2] Details of this last study have not been published and benefits of calcitriol have been identified in dogs[46] and people,[47,48] so it remains possible that the dose, study duration or a type II study error (false-negative results) limited the ability of the study to detect a genuine effect of calcitriol. Based on current evidence, however, it is difficult to justify routine administration of calcitriol to cats. Additional RCCTs would be valuable.

If serum phosphate levels are above 1.94 mmol/l (6.0 mg/dl), calcitriol administration can cause soft tissue mineralisation.[44] Calcitriol should only be considered after dietary phosphorus restriction and PBA use (see box on page 32). In stages 1 and 2 CKD, dietary phosphate restriction may be sufficient to combat declining calcitriol levels.[17]

TOD aside, hypertension is associated with proteinuria, and proteinuria is associated with survival in CKD, which may justify antihypertensive treatment.

Controlling hypertension

Hypertension occurs in 20–60% of cats with CKD,[49,50] causing target organ damage (TOD)[49,51,52] and potentially contributing to CKD progression.[53] Guidelines for diagnosis of hypertension are detailed elsewhere.[54,55] No association between hypertension and survival has been identified;[56–58] however, hypertension is associated with proteinuria,[57] and proteinuria is associated with survival in CKD,[58] which may provide justification for antihypertensive treatment in addition to the amelioration of TOD. The risk of TOD justifies screening for and treating hypertension in cats with CKD (see box above).

Amlodipine, a calcium channel blocker, is effective in reducing hypertension, proteinuria and the risk of TOD, and improving quality of life in cats.[51,57,59,60] Few side effects, rapid onset and easy administration make this

the first choice for hypertension control. Transdermal amlodipine is available; however, bioavailability is reduced.[61]

Angiotensin-converting enzyme (ACE) inhibitors reduce both systemic and glomerular hypertension,[62,63] but provide only modest antihypertensive effects,[64,65] making them generally unsuitable for monotherapy. ACE inhibition may increase potassium and creatinine concentrations due to GFR reduction following efferent arteriole dilation. Increases in serum creatinine concentration of 30% above pre-treatment baselines, or inappetence associated with ACE inhibitor administration, warrant treatment cessation.[66] Benazepril (0.25–0.5 mg/kg PO q12–24h) may be better tolerated than enalapril (0.2–0.7 mg/kg q12–24h) as biliary excretion compensates for reduced renal clearance, although the potential adverse effect of reduced GFR exists for both.[67]

Treatment of proteinuria

Proteinuria is a negative prognostic marker for people, dogs and cats with CKD.[13,58,68–71] ACE inhibitor treatment improves survival in people with proteinuric renal disease,[68] but is not recommended in early stage CKD.[72] Treatments reducing proteinuria, specifically benazepril, have been trialled in cats with the aim of improving survival. Although benazepril reduced proteinuria, a RCCT of 61 cats with spontaneous CKD receiving benazepril or placebo failed to identify significant survival benefits,[4] a result confirmed in another study of 192 cats with spontaneous CKD.[3] In the latter study, administration of benazepril to proteinuric cats (urine protein:creatinine ratio [UPC] >1) was associated with increased appetite (and a trend towards prolonged survival, although this was not statistically significant) compared with placebo-treated cats.

Consensus recommendations to reduce renal proteinuria suggest introducing dietary protein restriction and ACE inhibitor therapy in stages 2–4 CKD when UPC >0.4.[73] ACE inhibitors cause efferent arteriolar dilation, the potential benefit of which is to reduce glomerular hypertension. The use of these agents in cats with induced CKD maintained GFR while reducing glomerular hypertension.[62,63] However, in cats with severe CKD or concurrent hypovolaemia, glomerular hypertension is a mechanism for maintaining total GFR, and marked deteriorations in renal function have been associated with the use of ACE inhibitors in dogs and cats.[66]

In patients with moderate to severe CKD, dose titration of ACE inhibitors should be performed cautiously, with regular monitoring, due to the risk of GFR reduction. A mild increase (10–15%) in creatinine concentration in a hydrated, appetent cat is not an indication to stop treatment but cats should be monitored for inappetence, dehydration and progressive increases in creatinine concentration. As mentioned, increases of 30% or more above pre-treatment baselines, or inappetence associated with ACE inhibitor administration, warrant treatment cessation.[66]

Proteinuria is a negative prognostic marker for people, dogs and cats with CKD.

EFA supplementation reduces renal proteinuria in dogs.[12,26] If supplementation above that provided by renal diets is required, fish oil (10–200 mg/kg PO q24h) may be useful.[74]

Therapy for uraemic gastroenteritis

Gastrin is excreted by the kidneys and the concentration increases with CKD progression, increasing gastric acidity and the risk of ulceration.[75] Cats in CKD stages 3–4 often demonstrate gastrointestinal signs of uraemia (eg, inappetence, nausea, vomiting, stomatitis, gastrointestinal ulceration, diarrhoea, colitis) and addressing these may improve quality of life. Commonly used antiemetic and gastroprotective agents are detailed in Table 3.

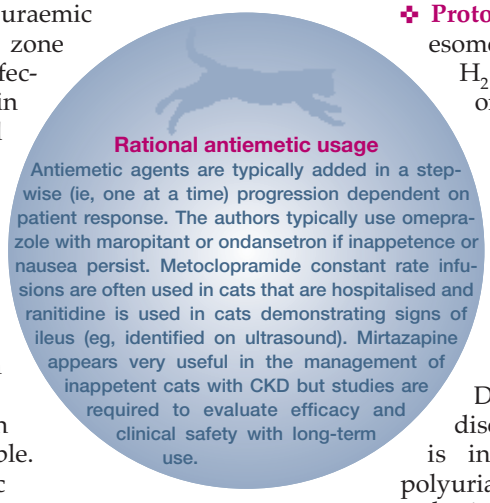
Table 3 Commonly administered antiemetic and gastroprotective agents in cats

Drug	Dosage	Comments
Cimetidine	2.5–5 mg/kg PO, IV or IM q12h	Numerous drug interactions No prokinetic effects
Dolasetron	0.6–1 mg/kg IV or PO q24h	Cost often prohibitive Compounding required for accurate dosing
Esomeprazole	0.7 mg/kg IV q24h	S-enantiomer of omeprazole
Famotidine	0.5–1 mg/kg PO q12–24h	30% dosage reduction recommended in CKD stages 3–4
Maropitant	1 mg/kg IV, SC or PO q24h	A 2 day rest period after 5 days of treatment is recommended. Antiemetic effects remain during the rest period Pain on injection may be reduced by refrigeration
Metoclopramide	0.1–0.5 mg/kg PO q6–12h 1–2 mg/kg/24h CRI	Useful prokinetic agent administered as CRI CRI may be more efficacious 50% dosage reduction in CKD and concurrent fluid therapy recommended
Mirtazapine	1.88–3.75 mg/cat PO q24–72 h to effect	Antiemetic effect possible Known appetite stimulant Dose-dependent adverse effects include hyperexcitability and muscle tremors
Ondansetron	0.5–1 mg/kg PO q12–24h	Wafers are convenient to administer
Omeprazole	0.5–2.0 mg/kg PO q12–24h	Possible adverse effects from prolonged administration not yet identified in cats Very useful as once daily administration effective
Ranitidine	1–2.5 mg/kg IV q12h 1–3.5 mg/kg PO q12h	Useful prokinetic agent Avoid rapid IV administration due to risk of hypotension and collapse 30% dosage reduction recommended in CKD stages 3–4 Oral liquid often unpalatable
Sucralfate	250 mg PO q8–12h	Potential phosphate-binding action Compliance may be problematic Can affect absorption of other agents and should not be given within 1–2 h of other medications

CRI = constant rate infusion

Vomiting is mediated via effects of uraemic toxins on the chemoreceptor trigger zone and gastrointestinal irritation. The effectiveness of many antiemetic agents in cats is established[76–78] (and reviewed by Trepanier 2010).[79] However, few studies have evaluated these drugs in uraemic cats.[80]

- **Maropitant** inhibits neurokinin-1 receptors and is an effective, once daily antiemetic in cats with few adverse effects. The parenteral formulation is associated with pain on injection.[76] Refrigeration reduces pain in dogs,[81] and the same appears true in cats. Oral formulations are also available.
- **Metoclopramide** is a dopaminergic antagonist, prokinetic and antiemetic agent. A short elimination half-life in other species and clinical experience suggest that constant rate infusions are substantially more effective than other routes of administration.[79] In people with renal failure, metoclopramide reduces renal plasma flow and renal failure is associated with impaired metoclopramide clearance.[82,83] Dose reduction and concurrent fluid therapy should be considered in cats with CKD.
- **Mirtazapine** has often marked appetite-stimulating properties and potential antiemetic effects via 5-HT_3 receptor antagonism. Its antiemetic efficacy in cats with CKD is unknown. Pharmacokinetic studies in cats with stage 2–4 CKD found prolonged renal clearance and doses at the lower end of the range (see Table 3) are recommended.[80,84]
- **Ondansetron** and **dolasetron** are potent antiemetic agents, mediated via 5-HT_3 receptor antagonism.[78] No studies have investigated their use in cats with CKD; however, experience with ondansetron suggests efficacy, although costs can be prohibitive.
- In CKD stages 3–4, addressing gastric hyperacidity and subsequent mucosal irritation may be beneficial. **H_2 receptor blockers** (famotidine, ranitidine, cimetidine) reduce gastric acidity. Famotidine is more potent than ranitidine, with a similar duration of action;[79] however, famotidine was no more effective than placebo in normal dogs.[85] Studies in cats are required. Uraemic gastroenteritis alters gastrointestinal motility in people,[86] and as ranitidine also has prokinetic actions, it may be the better choice. Elimination of H_2 receptor blockers is reduced in people with renal failure and dose reduction should be considered in CKD.[87,88] Cimetidine has a veterinary market authorisation but provides no prokinetic action and is associated with a range of drug interactions via its effects on hepatic microsomal enzymes.[89]
- **Proton pump inhibitors** (omeprazole, esomeprazole) are more potent than H_2 receptor blockers and are effective once daily agents in cats.[90]
- **Sucralfate** is an aluminium compound that forms a barrier over ulcers and stimulates bicarbonate and prostaglandin E_2 production,[91] which may be beneficial in stage 4 CKD.



Rational antiemetic usage

Antiemetic agents are typically added in a stepwise (ie, one at a time) progression dependent on patient response. The authors typically use omeprazole with maropitant or ondansetron if inappetence or nausea persist. Metoclopramide constant rate infusions are often used in cats that are hospitalised and ranitidine is used in cats demonstrating signs of ileus (eg, identified on ultrasound). Mirtazapine appears very useful in the management of inappetent cats with CKD but studies are required to evaluate efficacy and clinical safety with long-term use.

Treatment of dehydration is essential in cats with pre-existing CKD experiencing a uraemic crisis or in newly diagnosed CKD patients that are clinically unwell.

Correcting dehydration

Dehydration occurs due to concurrent disease, inappetence or water intake that is inadequate to compensate for the polyuria that consistently accompanies CKD. Dehydration can potentiate progression of CKD – and in cats with pre-existing CKD experiencing a uraemic crisis or the newly diagnosed CKD patient that is clinically unwell, treatment of dehydration is essential. Treatment goals are to correct dehydration, restore GFR and reduce uraemia.[6,44] Hydration status must be assessed regularly (Table 4) but interpreted with care. Elderly or emaciated cats have reduced skin elasticity and uraemia may cause dry mucous membranes independent of hydration.[93] Overzealous intravenous fluid therapy contributes to systemic hypertension and congestive heart failure in patients with concurrent disease (eg, hyperthyroidism) and should be avoided (see box on page 36).

Water intake is encouraged by improving water access, adding water to food, using fountains and via feeding tubes. Oral intake of water avoids the sodium increase that is associated with parenteral fluids. Where oral intake is inadequate, however, alternative methods of hydration are required.

For cats with stages 3–4 CKD, subcutaneous

Table 4 Clinical assessment of hydration status

% Dehydration	Clinical findings/status
<5	No detectable signs; dehydration may be suggested by history (eg, inappetence, vomiting)
5	Subtle loss of skin elasticity
6–10	Definite delay in return of skin tent to normal position when testing skin turgor Eyes may be sunken in orbits Slightly prolonged capillary refill time Mucous membranes may be dry
10–12	Tented skin stands in place Prolonged capillary refill time Eyes sunken in orbits Dry mucous membranes Possible signs of shock (tachycardia, weak pulses) Dull mentation
12–15	Signs of shock present Death imminent

Adapted from Chew et al[92]

Guidelines for administering intravenous fluid therapy to cats with CKD and chronic dehydration

Select a balanced electrolyte solution and consider parenteral potassium supplementation*

- Lactated Ringer's
- Plasmalyte-14
- Normosol R

Calculate dehydration deficit

- Body weight (kg) x estimated % dehydration = fluid deficit (l)

Determine deficit replacement rate

- Gradual (eg, over 24 h) replacement in chronically dehydrated patients minimises risk of overperfusion

Calculate maintenance fluid requirements

2–2.75 ml/kg/h

Add estimated losses (eg, vomiting)

eg, 5 ml replaced over 1 h

Ongoing monitoring

- Reassess hydration status, physical examination, body weight and fluid rate plans twice daily
- Anorexic patients lose 0.5–1% body weight daily
- Excess loss may be caused by alterations in fluid status
- Monitor trends in PCV/TP in the absence of gastrointestinal bleeding
- Monitor for signs of overperfusion – eg, nausea, serous nasal discharge, chemosis, tachypnoea, pulmonary crackles, peripheral oedema, pulmonary oedema, pleural effusion

Assess BUN/creatinine every 24–48 h

- Return to baseline concentration is rare. Monitor for plateau development (typically within 3–5 days)
- Gradually reduce rate over 24–48 h

Reassess patient after 2–4 days to determine stability

- Hydration status
- Physical examination
- Body weight
- PCV/TP
- BUN/creatinine

*See Table 5 for further details. BUN = blood urea nitrogen, PCV = packed cell volume, TP = total protein

Overzealous intravenous fluid therapy contributes to systemic hypertension and congestive heart failure in patients with concurrent disease.

fluid therapy may help to prevent dehydration. Once daily, alternate day or twice weekly subcutaneous fluid therapy using a balanced electrolyte solution (eg, lactated Ringer's) appears to be helpful clinically, but has yet to be assessed with RCCTs. Dosage depends on patient size (30–100 ml per cat q24–48h to twice weekly, as required, to maintain hydration). For a step-by-step guide, owners can be directed to icatcare.org/advice-centre/cat-care/how-give-subcutaneous-fluids-your-cat.

Subcutaneous indwelling catheters (Figure 2) provide permanent ports for administration of fluids. General anaesthesia is required for placement, which could potentiate further deterioration in renal function, and catheters may increase the risk of infection. For owners who cannot otherwise manage subcutaneous fluid therapy, this may, however, be a useful option.

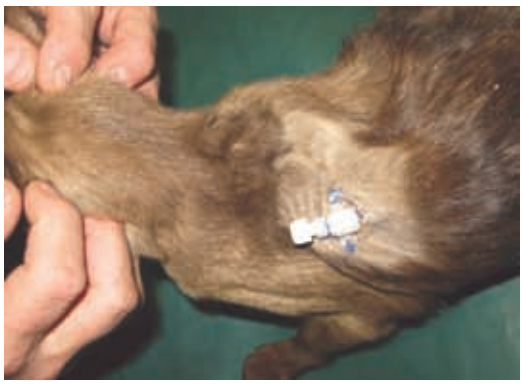


Figure 2 Subcutaneous fluid catheters provide an alternative method for fluid administration in the home

Addressing malnutrition

Malnutrition can result from inappetence secondary to uraemic gastroenteritis, dehydration, azotaemia, anaemia and concurrent disease. Dogs with CKD that are underweight have shorter survival times,[94] and malnutrition likely has similar negative effects in cats. Renal diets improve survival,[7–9] so it is vital to address any causes of inappetence that could contribute to failure to implement a dietary change. Estimating resting energy requirements (70 x $BWkg^{0.75}$ or 30[BWkg] + 70) determines daily calorie requirements. Dietary intake is improved by providing highly palatable, warmed food. Treatment goals are to maintain body weight and a body condition score of 5/9 or 2.5–3/5.

Mirtazapine is a useful appetite stimulant, with effects occurring within 30 minutes of administration (Table 3). Food should be offered around this time. Cyproheptadine and diazepam stimulate appetite; however, their effects are short-lived and can be unpredictable. While side effects associated with cyproheptadine (eg, sedation) are mild, oral diazepam has been associated with idiosyncratic liver failure in a small number of cats.[95,96] Importantly, use of these agents does not typically result in adequate and predictable food intake and, therefore, they are not recommended.[97]

Assisted enteral nutrition should be considered in cats that are inappetent or anorexic for more than 3 days.[98] Naso-oesophageal tubes allow short-term nutrition, but only limited diets can be administered. Oesophagostomy tubes allow provision of adequate nutrition and water, plus easy administration of medication (Figure 3); they can remain in situ for long periods (eg, 3–6 months). Feeding tube placement is discussed elsewhere.[97] While insertion site infection, tube migration and CKD progression following anaesthesia are potential risks, the advantages of oesophagostomy tubes tend to outweigh complications. In the authors' experience, the ability to easily provide nutrition and medications improves quality of life.

Figure 3 An oesophagostomy tube allows provision of adequate nutrition and water, plus easy medication administration

Treatment for hypokalaemia

Hypokalaemia has been identified in 20–30% of cats with CKD and is more common in hypertensive cats.[50,99,100] The exact cause is unknown but assumed to be a combination of reduced intake, increased urinary losses and renin–angiotensin activation.[101] Hypokalaemia can cause weakness due to myopathy (Figure 4) and potentially contributes to progressive renal injury.[102,103] Potassium supplementation in hypokalaemic cats with muscle weakness often results in clinical improvement of weakness within a week. Parenteral and oral potassium administration is detailed in Table 5.

Total body potassium deficits may occur before hypokalaemia;[104] however, no evidence exists to suggest that potassium administration to normokalaemic cats with CKD is beneficial. In one study, potassium gluconate administration in cats with spontaneous disease did not alter SBP, aldosterone concentration, creatinine or UPC, although studies of longer duration are needed.[105]

Table 5 Guidelines for parenteral and oral potassium supplementation in cats

	Serum potassium concentration (mEq/l or mmol/l)	Amount of potassium chloride to add to lactated Ringer's solution (mEq/l or mmol/l)	Maximum fluid rate (ml/kg/h)*
PARENTERAL potassium chloride	<2.0	80	6
	2.1–2.5	60	8
	2.6–3.0	40	12
	3.1–3.5	28	18
	3.6–5.0	20	25
	Assess potassium concentration q12–48h, titrating dose to maintain concentration within the middle to upper half of the reference interval (RI) Higher supplementation rates necessitate more frequent monitoring 20–30 mmol/l potassium chloride may be added to subcutaneous fluids *Do not exceed 0.5 mEq/kg/h		
	Compound	**Dose**	**Comments**
ORAL potassium	Potassium gluconate	2–6 mEq/cat/day divided q8–12h	
	Potassium citrate	40–60 mg/kg/day divided q8–12h	Potential benefits of alkalinisation
	Assess potassium concentration every 7–14 days, titrating dose to maintain concentration within the middle to upper half of the RI		

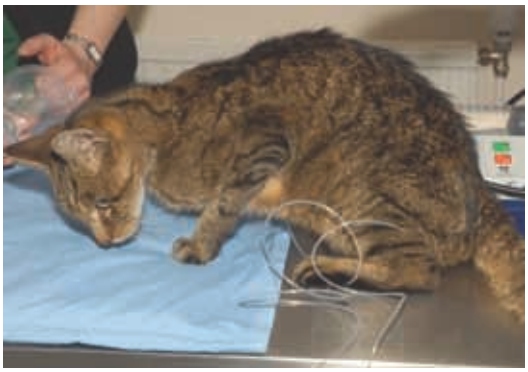


Figure 4 A cat with CKD demonstrating cervical ventroflexion, which is typical of hypokalaemic myopathy

Addressing metabolic acidosis

Metabolic acidosis affects 15% of cats in stage 3 and 52.6% of cats in stage 4 CKD.[106] Acidosis and hypokalaemia could have additive adverse effects on kidney function.[103] Whether additional alkalinisation above that provided by renal diets is required is unknown. It seems reasonable to provide additional alkalinisation in stage 3–4 CKD where blood pH is <7[22] and bicarbonate concentration <15 mmol/l in a hydrated patient.[32] Treatment options include sodium bicarbonate and potassium citrate. Unfortunately, sodium bicarbonate tends not to be palatable. Potassium citrate (Table 5) also provides additional potassium.

Monitoring by blood gas analysis should be performed every 10–14 days during stabilisation, with blood collected just prior to drug administration and pH determined within 1 h.[107] Bicarbonate concentration should be maintained between 15 and 22 mmol/l and blood pH between 7.2 and 7.4.

Treatment for anaemia

Anaemia of CKD results from insufficient renal erythropoietin (EPO) production and is often exacerbated by gastrointestinal haemorrhage, malnutrition and reduced red cell life span (reviewed by Chalhoub et al 2011).[108] It is typically normocytic, normochromic and poorly regenerative. Approximately 30–65% of cats with CKD develop anaemia, with severity proportional to disease stage.[99,100,109] Whether anaemia severity affects survival is unclear;[11,69,110] however, moderate to severe anaemia is likely to have a negative impact on quality of life.

All potential causes of anaemia should be addressed. Gastrointestinal haemorrhage without melaena or hypochromia occurs,[110] and should be suspected if the severity of anaemia outweighs the degree of renal dysfunction present or if urea concentration is disproportionately increased compared with serum creatinine in the absence of dehydration. Therapeutic trials with gastroprotective agents (Table 3) can be helpful.

Recombinant human erythropoietin (R-HuEPO) products, including epoetin and darbepoetin, have been used in cats with CKD, resulting in improvements in appetite and quality of life. Both products are identical to the naturally occurring hormone in people and relatively similar (83.3%) to feline erythropoietin, with darbepoetin having a prolonged half-life and, therefore, requiring less frequent administration than epoetin.[108] As R-HuEPO differs structurally from feline EPO, a major obstacle is anti-EPO antibody development; cross-reaction with the R-HuEPO agent and EPO causes pure red cell aplasia, a severe, non-regenerative anaemia that occurs in 25–30% of cats receiving R-HuEPO.[111] It is theorised that the prolonged half-life of darbepoetin compared with epoetin reduces the antigen load administered and thus the likelihood of treated cats developing antibodies.[108]

Whether anaemia severity affects survival is unclear. However, moderate to severe anaemia is likely to have a negative impact on quality of life.

There is limited published information on the efficacy and safety of R-HuEPO administration in cats with CKD and that which is available comes from uncontrolled case series.[111–113] In a study of 25 cats treated with darbepoetin, most (56%) responded to treatment and responders lived significantly longer than non-responders.[112] Concurrent disease was identified more often in non-responders than in responders.[112] Notably, however, cats were only included in this study if they survived longer than 56 days after treatment was instituted. R-HuEPO may be less effective in cats with concurrent disease causing anaemia or with more severe renal disease. Further work is required to evaluate the effect of treatment with R-HuEPO on survival and the optimal time to institute treatment.

R-HuEPO agents should only be considered in cats with advanced CKD and haematocrit <22%, plus clinical signs of anaemia (eg, weakness, tachycardia, tachypnoea, pallor) without an obvious underlying cause. Additional adverse effects of R-HuEPO treatment include polycythaemia, vomiting, iron deficiency, injection site discomfort, skin reactions, fever and

Table 6 Guidelines for recombinant human erythropoietin agent administration in cats

	Darbepoetin	Epoetin
Induction dosage	1 µg/kg SC once weekly	100 IU/kg SC three times weekly (50 IU/kg if hypertensive)
Iron supplementation	Iron dextran (50 mg/cat IM monthly) or Oral iron (10–20 mg/cat elemental iron daily; 50–100 mg/cat ferrous sulfate daily)*	
Initial monitoring	Weekly physical examination, SBP and PCV measurement until target achieved	
Target PCV	Target PCV 25–35%, with 1–3% increase weekly Avoid rapid PCV increases due to risk of hypertension	
Maintenance dosage	Reduce dose by 20–25% or extend dose interval to fortnightly (darbepoetin) or twice weekly (epoetin)	
Ongoing monitoring	Physical examination, SBP and CBC/PCV every 1–3 months	
Investigating treatment failure	Perform physical examination, CBC, serum biochemistry, serum cobalamin measurement and iron panel, and consider diagnostic imaging and bone marrow sampling to identify PRCA and/or underlying causes of anaemia If there is no underlying concurrent disease, treatment failure is likely due to anti-EPO antibody formation and R-HuEPO therapy should be stopped	

CBC = complete blood count, EPO = erythropoietin, PCV = packed cell volume, PRCA = pure red cell aplasia, R-HuEPO = recombinant human erythropoietin agent, SBP = systolic blood pressure
*Oral iron supplements can be bitter, poorly absorbed and associated with gastrointestinal complications. For these reasons some authors recommend injectable iron dextran[108]

arthralgia.[111,112] Hypertension occurred in 41–50% of cats receiving R-HuEPO agents and seizures in 16% receiving darbepoeitin.[112,114,115] In human medicine, the use of epoetin has been largely replaced by darbepoetin because of its increased potency and duration of action.[116] Table 6 presents guidelines for administration of R-HuEPO agents (darbepoetin and epoetin).

Iron deficiency can occur in cats with CKD due to gastrointestinal haemorrhage and reduced absorption or intake.[108] Ideally, true iron deficiency should be differentiated from the anaemia of inflammatory disease (iron sequestered in bone marrow monocytes) because iron supplementation of the latter is ineffective and may result in iron overload. Serum iron status is difficult to assess; however, true iron deficiency should result in low serum iron, ferritin and transferrin saturation. Iron supplementation is recommended with true iron deficiency and when commencing R-HuEPO treatment (Table 6).

Other treatments considered in CKD

- Intermittent haemodialysis has limited availability for feline CKD. Peritoneal dialysis is possible but technically difficult.[119]
- Renal allografting also has limited availability, and severe complications may occur.[120,121]
- Theoretically, pre- and probiotics redistribute nitrogen into the gastrointestinal tract for elimination, reducing azotaemia and selecting for bacteria that promote intraluminal nitrogen utilisation and reduce colonic absorption; however, there was no efficacy demonstrated in one study evaluating probiotics administered with food.[122]

Anabolic steroids (eg, nandrolone cypionate, stanozolol) produce effects that are potentially beneficial in cats with CKD, including improved haematocrit, appetite and muscle mass.[117] However, results are generally mild or inapparent and stanozolol is hepatotoxic in cats.[118] The use of anabolic steroids in general is no longer recommended in cats with CKD.

Treatment of concurrent disease

Urinary tract infections

Urinary tract infections (UTIs) (Figure 5) are common in cats with CKD,[100,123,124] and are often asymptomatic.[125,126] A UTI is not a marker for increasing CKD severity.[124,126] Optimal treatment strategies remain undetermined. While treatment of asymptomatic UTIs may promote antibiotic resistance,[127] untreated UTIs could result in pyelonephritis and exacerbation of renal injury. It appears sensible to treat UTIs if clinical signs are present or there is evidence of CKD progression. If possible, antibiotic selection should be determined by bacterial culture and sensitivity profiles. Pending these results, amoxicillin or related antimicrobials are a rational first choice.

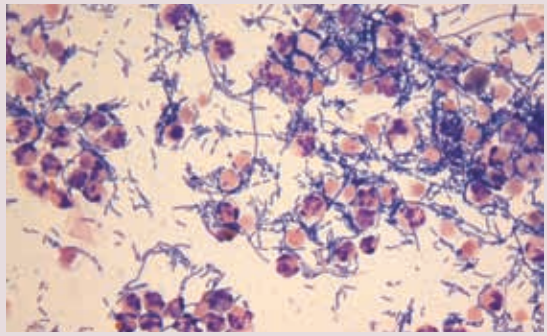


Figure 5 Photomicrograph of direct urine sediment findings in a cat with CKD and a UTI with *Escherichia coli.* x 500

Osteoarthritis

Many cats with CKD have osteoarthritis, affecting quality of life and requiring analgesia.[128] Hypovolaemia and hypotension increase the risk of adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs),[129] and use of COX-2 selective drugs may not improve the safety profile of NSAIDs.[130] However, meloxicam (0.01–0.05 mg/kg PO q24h) has been administered long term to well-hydrated, clinically stable, closely monitored cats without clinically apparent complications.[131,132] Titration to the lowest effective dose is recommended. Alternatively, buprenorphine (0.01–0.02 mg/kg sublingually q8–24h) or tramadol (2–4 mg/kg PO q8–12h) can provide good analgesia alone or permit a reduction in NSAID dosage.

Diabetes mellitus

In a study of 104 cats with diabetes mellitus, 13% had concurrent CKD.[133] The dietary modifications required for each disease are conflicting – the high protein, low carbohydrate diets recommended for diabetes are contraindicated in cats with CKD. Generally, dietary treatment of CKD takes precedence, with insulin dosage adjusted to achieve glucose regulation.

Hyperthyroidism

Management of cats with hyperthyroidism and CKD is challenging. Hyperthyroidism increases GFR, potentially masking underlying CKD. Development of CKD following hyperthyroid treatment is difficult to predict. A therapeutic trial with methimazole or carbimazole is recommended prior to permanent (eg, thyroidectomy or radioactive iodine) treatment. If renal azotaemia does not develop in a cat that has been euthyroid for over 30 days, permanent treatment options are likely to be safe. While pre-existing CKD has been shown to have an adverse effect on survival post-hyperthyroid treatment,[134] mild to moderate azotaemia is not a contraindication to continued treatment of an otherwise well cat, as the post-treatment decline in GFR was non-progressive over 6 months in one study,[135] and post-treatment azotaemia did not correlate with survival in another.[136] If clinical signs of CKD occur, titrating anti-thyroidal medications to allow a more thyrotoxic state supporting GFR may be required.

Dental disease

Dental disease is common in CKD patients, and has implications for the anaesthesia required for treatment. Perioperative hypotension reduces GFR, potentiating CKD progression. There is no consensus on the best method to address these patients; however, ensuring adequate CKD management and possibly administering systemic antimicrobials prior to anaesthesia appears sensible. Anaerobic cover is important (eg, metronidazole 10 mg/kg q12h, clindamycin 10 mg/kg q12h).[137] Patients are likely to be sensitive and to resent handling for tablet administration, so consideration of owner compliance is important. Normal hydration (Table 4) should be achieved prior to anaesthesia. Perioperative intravenous fluid therapy, SBP monitoring and minimising anaesthesia time are suggested. If anaesthesia is contraindicated (eg, stage 4 CKD), pulse-dose antibiotic therapy and analgesia is reasonable.

The frequency of monitoring for CKD is determined by disease severity, client compliance, treatment response and financial constraints.

Ongoing monitoring and treatment prioritisation

CKD is a progressive condition requiring monitoring with a frequency determined by disease severity, client compliance, treatment response and financial constraints. Following diagnosis, patients should be monitored every 2–4 weeks until disease stability is established and persistent changes (eg, hypertension, proteinuria) identified. Patients in stage 1–2 could be monitored 6-monthly, and stage 3–4 every 1–3 months. Monitoring recommendations are detailed in the box on the right.

Treatment is prioritised based on the strength of evidence available (see box on page 30), together with consideration of cat and owner compliance, ease of administration, resource availability and financial constraints. Given the strong evidence supporting renal diets, ensuring successful dietary modification should be a treatment priority.

Table 7 details survival estimates for cats categorised by CKD stage. Survival times at lower stages can be long and cats receiving effective treatment often die from other diseases.[9] Currently, treatment of CKD is about management rather than cure, centred on diagnosis and staging followed by multimodal treatments to correct hydration and address endocrine, metabolic and nutritional discrepancies. With a considered approach, it is possible to improve both quality and quantity of life.

Recommendations for long-term monitoring of cats with CKD

Minimum parameters
- Thorough history, including nutritional status
- Body weight and body condition score
- Physical examination findings
- Hydration status

Standard parameters
As above, plus:
- SBP
- PCV/TP
- Fasted serum biochemistry including urea, creatinine, potassium and phosphate
- Urine specific gravity
- Urine sediment examination
- UPC if proteinuria is present on dipstick as ≥2+ in the absence of a UTI

Ideal parameters
As above, plus:
- Complete blood count
- Urine bacterial culture
- PTH and iCa concentrations
- Venous blood gas
- UPC

Home monitoring parameters
- Body weight
- Nutritional intake
- Water intake (estimate)
- Observation for altered micturition behaviour
- Activity levels

Table 7 Survival estimates for cats classified by IRIS stage

IRIS stage	Survival time estimate in years (days)		
	Boyd et al[11]	Syme et al[58]	King et al[3]
1	Not assessed	0.97 (357) 1 (365) BP	Not determined
2b*	3.1 (1151)	1.4 (504) 0.51 (187) BP	Not determined
3	1.9 (679)	0.42 (154) 0.77 (281) BP	1.3 (475)
4	0.1 (35)	0.16 (57) 0.05 (21) BP	0.16 (60)

IRIS = International Renal Interest Society, BP = survival estimate for hypertensive cats
*Stage 2b azotaemic stage: creatinine concentration 200–250 µmol/l (2.26–2.82 mg/dl)

With a considered approach, it is possible to improve both quality and quantity of life for cats with CKD.

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Conflict of interest

The authors do not have any potential conflicts of interest to declare.

KEY POINTS

- Renal diets prolong survival and improve quality of life. Which dietary component is responsible for survival benefits is unknown, although experimental models support phosphorus restriction and fatty acid supplementation.
- It is vital to address any causes of inappetence that could contribute to diet change failure.
- Phosphate binding agents reduce hyperphosphataemia. Whether survival benefits differ from those provided by dietary phosphate restriction is unknown.
- A significant benefit to justify routine administration of calcitriol has not yet been identified.
- Amlodipine is effective in reducing hypertension, proteinuria and the risk of target organ damage, and is the treatment of choice in hypertensive cats.
- Benazepril may not prolong survival in proteinuric cats (UPC >1); however, quality of life is improved.
- Recombinant human erythropoietin agents (eg, darbepoietin, epoetin) should be considered in cats with advanced CKD that are demonstrating clinical signs of anaemia. Darbepoetin is less antigenic, more potent and longer acting than other available agents.
- Survival times for cats at lower stages of CKD can be long and patients receiving effective treatment often die from other diseases.

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