



ISFM Consensus Guidelines on the Diagnosis and Management of Feline Chronic Kidney Disease



Practical relevance: Chronic kidney disease (CKD) is one of the most commonly diagnosed diseases in older cats. In most cats, CKD is also a progressive disease and can be accompanied by a wide range of clinical and clinicopathological changes. These ISFM Consensus Guidelines have been developed by an independent panel of clinicians and academics to provide practical advice on the diagnosis and management of this complex disease.

Clinical challenges: Although CKD is a common clinical problem in cats, the manifestations of disease vary between individuals. Thus there is a need for careful and repeat evaluation of cats with CKD and adjustment of therapy according to individual needs. In addition to addressing problems arising from CKD and improving quality of life (QoL) for the patient, therapy may also target slowing the underlying progression of disease and hence prolonging life. While maintaining QoL is of paramount importance in our patients, this can be challenging when multiple therapies are indicated. In some cases it is necessary to prioritise therapy, given an understanding of what is likely to most benefit the individual patient.

Evidence base: In preparing these Guidelines, the Panel has carefully reviewed the existing published literature, and has also graded the quality of evidence for different interventions to help to provide practical recommendations on the therapeutic options for feline CKD. This is a field of veterinary medicine that has benefited from some excellent published clinical research and further research findings will undoubtedly modify the recommendations contained in these Guidelines in the future.

INTRODUCTION

Chronic kidney disease (CKD) is a common feline disease. Its prevalence will vary between populations, but a large UK study estimated that the prevalence of feline renal disease in first opinion practices was ~4% (CKD was the seventh most common specific diagnosis made).¹ CKD is more common in older cats,^{2–4} and may affect ≥30–40% of cats over 10 years of age.⁴ Renal disease was the most common cause of mortality in cats ≥5 years of age in a UK study, being the cause of death of >13% of cats at a median age of 15 years.⁵

The underlying aetiology of CKD often remains obscure. Most cats investigated have chronic tubulointerstitial nephritis and renal fibrosis on histology (Figure 1)^{6,7} – lesions thought to be the end phase of a variety of potential underlying aetiologies that may include toxic insults, hypoxia, chronic glomerulonephritis, chronic pyelonephritis,

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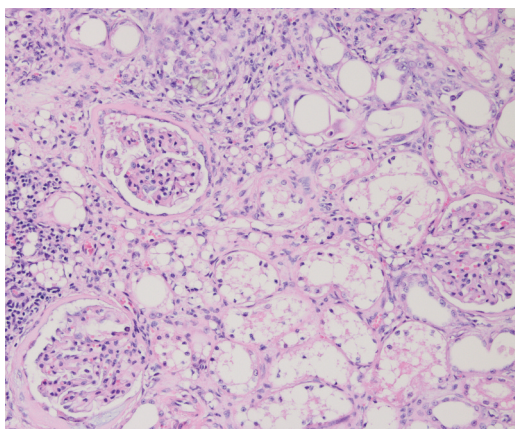
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Figure 1 Typical histopathology of a kidney from a cat with chronic kidney disease (CKD), characterised by inflammatory infiltrate, tubular loss, increase in extracellular matrix and fibrosis x 20. Courtesy of Jessica Quimby



A good relationship and good communication between the clinic and the cat's owner is vital for successful management of CKD.



upper urinary tract obstructions, and potentially viral infections involving retroviruses as well as a recently recognised morbillivirus.⁸⁻¹² Other specific causes of CKD sometimes recognised include amyloidosis, polycystic kidney disease, renal lymphoma, hypercalcaemic nephropathy and congenital disorders – some of these have breed associations.^{4,8,13}

Other than age, clear risk factors for development of CKD have not been identified in cats,¹⁴⁻¹⁷ but weight loss or poor body condition, polyuria/polydipsia (PU/PD), higher creatinine concentrations, dehydration and potentially lower urine specific gravity (USG) may indicate the presence, or predict development, of CKD.¹⁴⁻¹⁷

The purpose of these Guidelines is to give practitioners an up-to-date, critically assessed overview of the current diagnostic and treatment options to guide in the practical management of CKD.

Quality of evidence as an intervention

The Panel has provided guidance on the current quality of evidence for different therapeutic interventions based on peer-reviewed published data – summarising (as 'GOOD', 'POOR' or 'NONE') any evidence that a therapy improves longevity, and also that a therapy improves quality of life (QoL). However, it should be noted that many interventions have not yet been adequately evaluated.



Figure 2 Blood pressure measurement should be part of the routine evaluation of all cats with proven or suspected CKD. Courtesy of Sarah Caney



Figure 3 Ocular examination (in this case distant indirect ophthalmoscopy) is valuable, given the strong association between CKD and hypertension. Courtesy of Sarah Caney

DIAGNOSIS AND ASSESSMENT OF CKD IN CATS

Routine diagnosis of CKD in cats

CKD in humans is defined as a sustained (≥ 3 months) reduction in glomerular filtration rate (GFR, $< 60 \text{ ml/min/1.73 m}^2$) or evidence of sustained (≥ 3 months) kidney damage (eg, structural damage, proteinuria).¹⁸ Although CKD has not been clearly defined in cats, similar principles should apply; notably there should be evidence of sustained functional or structural kidney damage (eg, ≥ 3 months' duration).

As CKD is more common in older cats, these patients should be targeted for more detailed and frequent health assessments. Recommendations from International Cat Care/International Society of Feline Medicine, the American Association of Feline Practitioners and the American Animal Hospital Association suggest health checks every 6 months for cats > 7 years of age (including evaluation of body weight, body condition score and blood pressure), together with selected diagnostic testing (including haematology, serum biochemistry screening and routine urinalysis) at least annually.^{19,20}

Historical and clinical findings suggestive of CKD, such as weight loss, altered kidney size, unexplained dehydration, PU/PD, systemic hypertension or an unexplained low USG ($< 1.035-1.040$), also justify further investigation.

A simple, accurate biomarker to assess renal function does not currently exist. Thus in clinical practice the combination of azotaemia (increased serum creatinine and/or urea) and an inappropriately low USG are routinely used to diagnose CKD. However, their interpretation is not always straightforward.^{21,22}

- ❖ Although often measured together, creatinine is preferred over urea as a marker of GFR as its concentration is inversely related to GFR, and is affected by fewer non-renal factors.
- ❖ Creatinine is an imprecise marker of GFR though; it lacks specificity if reference intervals are set low enough to detect early stage disease, but lacks sensitivity if reference intervals are set higher.
- ❖ Creatinine concentration is affected by lean tissue mass and hydration.
- ❖ Creatinine concentrations (and reference intervals) vary between different assays, analysers and laboratories.
- ❖ The exponential relationship between GFR and creatinine means that substantial early declines in GFR may be accompanied by only small changes in creatinine, while in the latter stages of disease large changes in creatinine may reflect only small changes in GFR.

Bearing in mind these limitations, in clinical practice feline CKD is often diagnosed on the basis of:

- ❖ An increased serum creatinine concentration >140 µmol/l (>1.6 mg/dl); *together with*
- ❖ An inappropriately low USG (<1.035); *and*
- ❖ Evidence that these changes are sustained (over several weeks or months) or with a history suggesting sustained clinical signs consistent with CKD.

However, not all cats with CKD will meet these criteria:

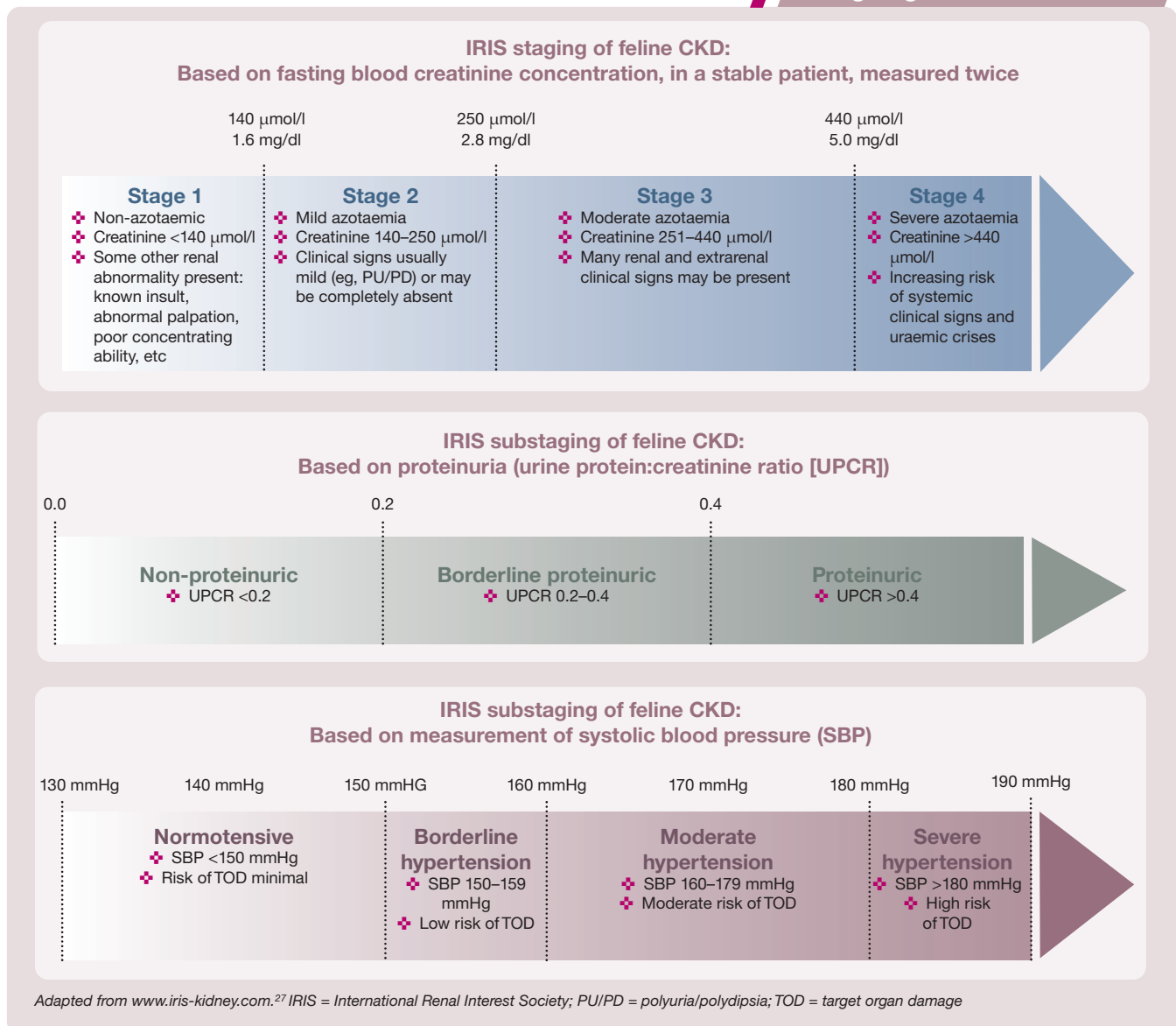
- ❖ Chronic kidney damage evidenced by structural changes to the kidney recognised on diagnostic imaging or persistent renal-origin elevated proteinuria may be present in the absence of azotaemia or an inappropriate USG.
- ❖ While relatively few healthy cats will

produce a USG <1.035, this can be affected by diet,²³ and occasionally some cats with azotaemic CKD will produce a USG ≥1.035.^{24,25}

- ❖ Some cats have reduced urine concentrating ability before they develop overt azotaemia.
- ❖ A persistent and substantial (>15%) increase in serum creatinine from previously determined baseline values in a cat is also likely to indicate reduced renal function.

For these reasons, serial (eg, annual or bi-annual) assessment of serum creatinine or symmetric dimethylarginine (SDMA – see later) and USG may be helpful in older cats (>7 years of age) to determine changes over time, as this may facilitate earlier or more certain diagnosis of CKD.^{22,26} Additionally, if there is doubt over the diagnosis, additional testing (see page 222) may be desirable.

Staging of feline CKD



Routine investigation and staging of CKD in cats

Where CKD is suspected, a minimum routine database should ideally include:

- ❖ Full history and physical examination;
- ❖ Routine urinalysis (to include USG, 'dipstick' analysis, urine sediment analysis, urine protein:creatinine ratio [UPCR], and culture where indicated);
- ❖ Routine serum biochemistry, to include a minimum of proteins, urea, creatinine, electrolytes (Na^+ , K^+ , Ca^{2+} , Cl^- , PO_4^-), and other analytes (eg, thyroxine in an older cat) as relevant;
- ❖ Routine haematology;
- ❖ Systolic blood pressure (SBP);
- ❖ Diagnostic imaging (renal ultrasonography is generally more valuable than radiography);
- ❖ In some situations (eg, unexplained renomegaly) a kidney biopsy or fine-needle aspiration may be desirable.

These investigations are aimed at:

- ❖ Identifying potential underlying aetiologies of the CKD (which may require specific therapy);
- ❖ Identifying complications that are arising from the CKD;
- ❖ Identifying concomitant disease that may affect management (eg, hyperthyroidism).

The International Renal Interest Society (IRIS) has established a CKD staging system²⁷ based on the cat's fasting creatinine concentration (see box on page 221). This is valuable as the stage (severity) of disease is related to the prognosis for the patient (see later) and can help to focus attention on appropriate treatments. Staging is applicable in cats with confirmed, stable CKD that are well hydrated, and IRIS substaging is based on UPCR and SBP, two important prognostic and therapeutic parameters.

Advanced and emerging tests for feline CKD

Estimation of GFR

The gold standard in renal function testing is direct determination of GFR. Limited- and single-sample plasma clearance methods (eg, using iohexol, inulin, exogenous creatinine or radiolabelled markers) have made GFR assessment easier to undertake in clinical practice, but the reduced numbers of blood samples may yield greater inaccuracy.^{21,28} Clinical measurement of GFR is mainly used to confirm suspected CKD in non-azotaemic cats.

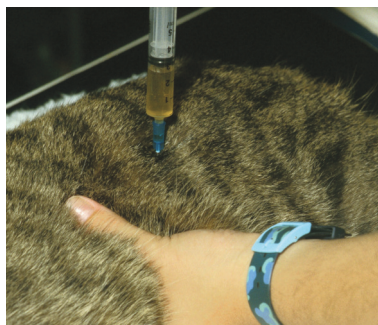


Figure 4 Collection of a urine sample by lateral cystocentesis for routine monitoring of CKD. Courtesy of Sarah Caney



Figure 5 Collection of blood for routine monitoring of CKD (note the no restraint technique). Courtesy of Jessica Quimby

Symmetric dimethylarginine (SDMA)

SDMA has become available in the veterinary marketplace as a surrogate marker of GFR and, like creatinine, its reciprocal has a linear relationship with GFR.²⁹ It appears to offer greater sensitivity than creatinine for detection of early CKD³⁰ and does not appear to be affected by muscle mass. However, further studies are required to fully evaluate its accuracy in clinical patients as SDMA may also be affected by non-renal factors.³¹ Although it cannot currently be recommended as a single screening test for CKD, its measurement may be helpful in supporting a diagnosis of CKD or in staging CKD, especially in cats with marked loss of muscle mass.²⁷

Serum cystatin C

Serum cystatin C is a useful surrogate marker of GFR in human patients. However, in cats its diagnostic value appears compromised by overlap in values between healthy cats and cats with CKD, and the interference of non-renal factors.^{32,33}

Microalbuminuria

Detection of microalbuminuria is important in the diagnosis of CKD in human patients where there is a high prevalence of glomerular disease, but its clinical significance in cats remains unclear. It is measured using a species-specific assay but a benefit of measuring urine albumin:creatinine ratio (UACR) over UPCR in predicting which cats will develop azotaemia has not been demonstrated.¹⁷

Other assays

Studies have demonstrated that development of renal secondary hyperparathyroidism³⁴ and increased fibroblastic growth

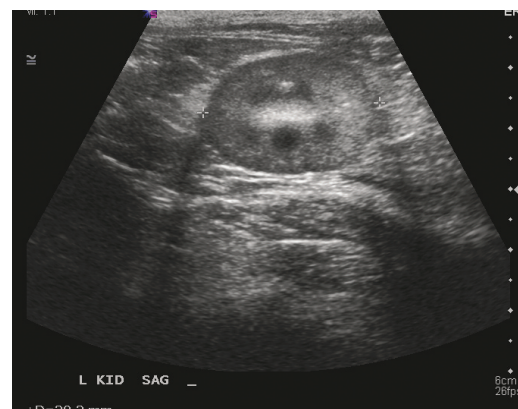


Figure 6 A small kidney and loss of corticomedullary distinction are ultrasound findings consistent with feline CKD. Courtesy of Jessica Quimby

Recommended monitoring of cats with CKD

Optimal monitoring strategies for cats with CKD have not been systematically evaluated and the extent of monitoring will vary depending on the owner, the patient, disease stability, the number and severity of secondary complications and the presence of concomitant disease(s). However, in addition to monitoring the clinical signs and clinical condition of the patient, regular assessment for the occurrence of hypertension,³⁶ proteinuria,³⁷ hypokalaemia,³⁸ hyperphosphataemia,³⁸ urinary tract infections (UTIs),³⁹ anaemia and CKD-associated mineral bone disorder^{34,40} is important, given that these complications are common and

In the long-term, even if stable, cats should be re-evaluated at least every 3–6 months.

often associated with disease progression or a poor QoL. Suggested routine evaluations are outlined in Table 1.

Following diagnosis (and stabilisation, if necessary), initial re-evaluations should typically be undertaken every 1–4 weeks, according to clinical needs. Full monitoring (Table 1) will not be necessary at each visit (and not all evaluations are needed in all cats and at all times), but should be performed sufficiently frequently to allow good patient management. Even in cases of early and apparently stable CKD, initial monthly revisits can be helpful in supporting the diagnosis, providing support to the owner, and in monitoring progression and therapy. In the long term, even if stable, cats should be re-evaluated at least every 3–6 months. Particular attention should be paid to appropriate monitoring of the efficacy of interventions to ensure that therapeutic targets are being met. In advanced disease, care may be needed to avoid exacerbating anaemia by too frequent blood collection.

Routine monitoring of cats also permits assessment of disease progression and repeat IRIS staging. Deterioration of disease (progression from one IRIS stage to the next, a substantial

increase in serum creatinine or a consistent rise in serial blood samples, a substantial increase in UPCr, a consistent reduction in body weight and body condition, etc) changes the prognosis for the patient and should prompt more detailed re-evaluation.

Veterinary nurses and technicians can play a very valuable role in the ongoing assessment of CKD patients and in supporting owners.

Table 1 Routine evaluation of feline CKD patients

| Assessment | To include: |
|---------------------------|--|
| Full history | Evaluation of progress, complications and owner concerns Evaluation of changes since last assessment |
| Full clinical examination | Body weight, % change in body weight and body condition score Hydration status |
| Blood pressure assessment | Systolic blood pressure (Figure 2) and ocular examination (Figure 3) |
| Urinalysis | USG, UPCr, 'dipstick' and sediment analysis Bacterial culture if indicated (Figure 4) |
| Routine haematology | Full haematology may not always be required but haematocrit or PCV should be regularly assessed (Figure 5) |
| Serum biochemistry | Proteins, urea, creatinine and electrolytes (Na ⁺ , K ⁺ , Ca ²⁺ , Cl ⁻ , PO ₄ ⁻) Other analytes should be measured as necessary, including thyroxine, liver enzymes and acid-base status |
| Diagnostic imaging | Ultrasonography or radiography (Figures 6 and 7) – to assess for structural changes, obstructions or other lesions – should be part of the initial investigation and may be worth repeating, especially with unexpected deterioration |

USG = urine specific gravity; UPCr = urine protein:creatinine ratio; PCV = packed cell volume

factor-23 (FGF-23)³⁵ may precede azotaemia in feline CKD. However, whether there is any diagnostic utility in these assays remains to be determined.



Figure 7 Radiographs are helpful for identifying abnormalities such as stones within the urinary tract. Courtesy of Jessica Quimby

Prognosis

The prognosis for cats with CKD at the time of diagnosis depends on the severity of the disease, which can be determined according to their IRIS stage²⁷ (Table 2).

Additional clinical parameters that are significantly associated with prognosis include:^{37,41–45}

- ✦ Level of proteinuria
- ✦ Level of hyperphosphataemia
- ✦ FGF-23 concentration
- ✦ Presence of progressive CKD
- ✦ Lower packed cell volume

Table 2 Studies evaluating IRIS stage and prognosis

| Study | Reported median survival time (days) | | |
|----------------------------|--------------------------------------|--------------|--------------|
| | IRIS stage 2 | IRIS stage 3 | IRIS stage 4 |
| Boyd et al ⁴¹ | 1151 | 778 | 103 |
| King et al ⁴² | Not reached | ~500 | ~70 |
| Syme et al ³⁷ | 504 | 154 | 57 |
| Geddes et al ⁴³ | 490 | 263 | 20 |

Management of CKD is largely focused on supportive and symptomatic therapy.

APPROACH TO MANAGEMENT

Management of CKD is largely focused on supportive and symptomatic therapy with the aim of improving the quality of life (QoL) of affected cats (especially those in CKD stages 3 and 4) and, where possible, slowing the progression of disease (especially in CKD stages 2 and 3). Although beyond the scope of these Guidelines, careful evaluation of cats (as outlined earlier) should also allow identification of certain underlying aetiologies that permit specific intervention such as renal lymphoma, UTIs, nephroliths and ureteroliths.

Because of the chronic nature of the disease, the need for regular monitoring and the potential for various interventions, establishing a good relationship and good communication between the clinic and the cat's owner is vital. This will facilitate individualised management plans to be created that take into consideration the wishes and ability of the owner, as well as the needs of the cat.

Issues that should be considered are outlined in the box below.



General considerations

- ❖ **Full evaluation of the patient** – often when CKD is diagnosed the disease has actually been present for a long time and thus careful and full patient evaluation is important
- ❖ **Initial stabilisation of the cat** – eg, hospitalisation for investigations and for initial fluid therapy to correct dehydration
- ❖ **Detection and management of concomitant diseases** – this may also help CKD management, especially if concurrent disease is associated with persistent fluid loss or reduced appetite
- ❖ **Assessment of the stage, substage and complications of CKD (when the cat is stable)** – this allows a more meaningful prognosis to be given, and may identify therapeutic interventions that are required
- ❖ **Therapeutic priorities** – administering multiple medications, potentially several times a day, can be a daunting prospect for many owners and stressful for many cats. Importantly, palatable and easy to administer medications make this easier, and it may be possible to combine medications (eg, placing small tablets together in a single gelatine capsule). However, in some cases optimum therapy may not be achievable, in which case it is important to assess carefully what treatments are practical and likely to have the most impact on improving QoL
- ❖ **Potential for 'acute on chronic' CKD** – cats may present with acute exacerbations of CKD due to concomitant disease, dehydration, etc. Careful assessment and management of these patients is required (including fluid therapy and management of complications)
- ❖ **Progression of CKD** – this often occurs in a stepwise rather than a linear manner. The patient should be thoroughly re-evaluated each time significant progression has occurred to ensure treatable complications are not being overlooked

MANAGEMENT OF CKD PATIENTS

Managing hydration in CKD^{46,47}

Quality of evidence as an intervention

- ❖ Increased longevity: No data
- ❖ Improved QoL: No data, but Panel considers the impact of preventing dehydration is likely GOOD

CKD is associated with variable obligatory diuresis, and affected cats may be predisposed to dehydration, especially in CKD stages 3 and 4.

Panel recommendations: hydration

Although studies confirming the clinical benefit of maintaining hydration in CKD are lacking, the Panel considers it a crucial part of management. It is likely to be important for maintaining QoL, and could affect progression, as dehydration may compromise renal blood flow. In addition to maintaining hydration, fluid therapy may be beneficial in addressing electrolyte and acid–base disturbances, and diluting uraemic toxins.

Correcting dehydration^{46,47}

Cats with unstable or decompensated CKD may require hospitalisation and intravenous fluid therapy, typically with lactated Ringer's solution or Hartmann's. Consideration should also be given to concomitant electrolyte and acid–base disturbances that may need addressing.

The fluid required to correct dehydration (in ml) is calculated from: body weight (kg) × estimated dehydration (%) × 1000, and this (along with maintenance fluids, eg, 50 ml/kg/24 h) is typically provided over 24–48 h, although some cats may tolerate more rapid rehydration.

After rehydration, maintenance fluids can be administered but cats should be monitored carefully to avoid fluid overload. When azotaemia is stable, fluids should be tapered over 2–3 days before the patient is discharged.

Long-term maintenance of hydration

- ❖ **Voluntary water intake** Free access to good quality water should be provided at all times (Figure 8), and owners should be advised to offer a variety of water sources (including flavoured waters and running water – eg, a 'pet fountain') to encourage drinking. Feeding a wet diet rather than dry diet where possible is important, as it will also increase water intake.⁴⁸ Additional water can be added to the food where



Figure 8 Multiple sources of fresh water are important for maintaining hydration. Courtesy of Jessica Quimby

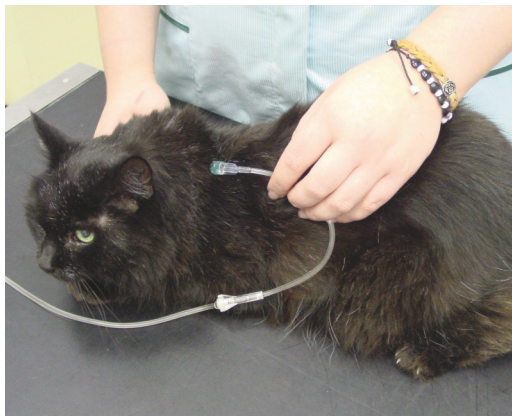


Figure 9 Subcutaneous fluid therapy can be used on an outpatient basis or by owners at home. Courtesy of Sarah Caney

dehydration is a concern, but it is important to ensure intake of other nutrients is maintained.⁴⁹

❖ **Use of feeding tubes** Water can also be administered via a feeding tube, and this may be preferable to subcutaneous fluids (see below) in many cases. A feeding tube is suitable for long-term maintenance of hydration and is a more physiological approach. It also allows for nutritional support when needed.

❖ **Subcutaneous fluid therapy** Repeated subcutaneous fluid therapy (75–150 ml every 1–3 days) can be used on an outpatient basis (Figure 9) or by owners at home to maintain hydration. This is most commonly employed in cats with advanced (stages 3 and 4) CKD, but should be considered on a case-by-case basis. Cats should be carefully monitored to ensure there is clinical benefit and to avoid overhydration.

Although a balanced electrolyte solution such as lactated Ringer's solution is often used, a hypotonic solution (half-strength lactated Ringer's or 0.45% saline, with added potassium as needed) may be preferable to reduce the sodium load. Fluids can be administered via a needle and giving set, or through an indwelling subcutaneous catheter, although there is the risk of the latter becoming blocked or infected.

Managing diet and mineral/bone disease in CKD

Dietary manipulation is a mainstay of CKD therapy in human⁵⁰ and veterinary patients. Renal formulated diets are restricted in both protein and phosphorus, but other features include an increased calorie density, sodium restriction, potassium supplementation, alkalisation, and supplementation with B vitamins, antioxidants and omega-3 fatty acids.

Renal diets have been shown to significantly prolong longevity of cats with CKD.



Figure 10 Muscle wasting and dehydration in a cat with CKD. Careful attention to body condition, muscle mass and caloric intake is important. Courtesy of Jessica Quimby

Protein and phosphate restriction

Quality of evidence as an intervention

- ❖ Increased longevity: GOOD
- ❖ Improved QoL: GOOD

Protein restriction and phosphate restriction are considered together as they are the main features of commercial renal diets, and are thought to confer the major benefits seen. Feline renal diets typically contain 6–7 g of protein per 100 kcal (above the 5 g/100 kcal recommended allowance for adult cats,⁵¹ but below the 9–10 g/100 kcal commonly seen in maintenance diets). Energy requirements of older (>13 years) cats may increase and severe protein restriction may lead to loss of lean tissue;⁵² thus moderate protein restriction is recommended in CKD, together with monitoring of lean body mass, weight and caloric intake (Figure 10). In addition to protein restriction, renal diets contain much less phosphate compared with typical maintenance diets.^{53,54}

In cats with CKD, renal diets have been shown to reduce clinical signs of uraemia,^{55–57} and to significantly prolong longevity (see Table 3), providing a strong rationale for their use.

Table 3 Studies evaluating effect of renal diets on longevity

| Study | Reported median survival time (days, all cause mortality) | |
|-------------------------------|---|-------------|
| | Normal diet | Renal diet |
| Elliott et al ⁵⁵ | 264 | 633 |
| Plantinga et al ⁵⁴ | 210 | 480 |
| Ross et al ⁵⁶ | ~730 | Not reached |

Differentiating the effects of protein and phosphate restriction is complex and not always possible, but while moderate protein restriction is thought to help reduce signs of uraemia, there is little evidence that this alone has a major effect on progression of CKD.^{58–60} Conversely, hyperphosphataemia is known to be associated with progression of CKD,^{42,44,45} and phosphate restriction may reduce the severity of renal pathology in CKD,^{53,61} thus phosphate restriction is thought to be mainly responsible for the improved longevity seen. Furthermore, renal secondary hyperparathyroidism (which may contribute to uraemia and disease progression) can be seen prior to the development of overt hyperphosphataemia or azotaemia,³⁴ and phosphorus-restricted diets reduce hyperphosphataemia, hyperparathyroidism and FGF-23 (which may indirectly promote hyperparathyroidism).^{55–57,62,63}

Panel recommendations: dietary intervention

The Panel strongly recommends the feeding of a commercial renal diet in all cats with azotaemic (stages 2–4) CKD. Where possible, this diet should be fed exclusively but the overall nutrition of the cat should not be compromised. Feeding a wet rather than dry diet to increase water intake is also recommended. Appropriate home-prepared diets⁶⁴ (see box below) may be an alternative if a commercial diet is not accepted.

Changing and transitioning diets

Renal diets are generally less palatable than maintenance diets (probably at least partially due to their lower protein content). This can lead to poor acceptance of these diets,^{24,65} a problem that may be exacerbated by inappetence in cats with more advanced CKD.

Panel recommendations: transitioning cats to a renal diet

- ❖ Although the point at which dietary intervention produces benefits has not been determined, the diet should be introduced as early as possible in stage 2 CKD (before the cat's appetite is affected by the disease)
- ❖ Gradual transition to the new diet will increase its acceptance – this may be achieved by providing the new diet in the same bowl, side by side, next to the old food,⁶⁶ or by mixing the old and new food together. The amount of the old food is then gradually decreased while the new food is increased over several (eg, 4–8) weeks
- ❖ To avoid food aversion, medications should be administered via an alternative, palatable food
- ❖ Feeding home-prepared diets can improve palatability, but these must be balanced for the desired nutrient requirements by a veterinary nutritionist⁶⁴
- ❖ A diet change should not be introduced to the cat while it is hospitalised or clinically unwell (eg, nauseous), to avoid development of food aversion
- ❖ Maintaining caloric intake is the highest priority in CKD and the preferred choice of diet is generally in the following order: wet renal > dry renal > home-prepared renal diet > wet senior > dry senior > wet maintenance > dry maintenance. Senior diets generally have lower protein (and phosphate) than adult maintenance diets but, in the absence of a renal diet, earlier intervention with a phosphate binder may be necessary (see Table 4).
- ❖ Feeding tubes (oesophagostomy or gastrostomy) can be valuable in both short- and long-term maintenance of nutrition and hydration in some cats with CKD

Table 4 Some common oral phosphate binders used in cats

| Medication | Initial total daily dose* | Possible adverse effects |
|-------------------------------|---------------------------|---|
| Aluminium hydroxide/carbonate | 90 mg/kg | Constipation |
| Calcium carbonate | 90 mg/kg | Hypercalcaemia |
| Calcium acetate | 60–90 mg/kg | Hypercalcaemia |
| Iron, starch, sucrose complex | 0.25–0.5 g/day | Little data available |
| Sevelamer | 90–160 mg/kg | Constipation, impaired vitamin absorption, metabolic acidosis |
| Lanthanum | 30–90 mg/kg | Vomiting |

*For all phosphate binders, it is important to split the daily dose and give it mixed with food or at the same time that the cat eats. Doses may have to be increased to achieve the desired effect

Use of phosphate binders

Quality of evidence as an intervention

- ❖ Increased longevity: No data, but likely to be GOOD, based on dietary phosphate restriction
- ❖ Improved QoL: No data

As CKD progresses, serum phosphate tends to increase and may become more refractory to control with dietary phosphate restriction. Where diet alone is insufficient, the use of intestinal phosphate binders is important. Several agents can be used for this purpose (see Table 4).^{53,67–69} There are no studies comparing different phosphate binders in cats with CKD, but all are likely to be efficacious.⁵³ Offering alternative binders when needed may be appropriate, as palatability of the phosphate binders varies.^{69,70} If calcium-containing phosphate binders are used, monitoring of serum calcium (ideally ionised) is recommended, as hypercalcaemia is occasionally seen as an adverse event.⁵³

Where cats cannot be transitioned to a commercial or home-prepared renal diet with restricted phosphate, phosphate binders can be used with a maintenance diet, but their efficacy is likely to be compromised by the quantity of phosphate in the diet.

Panel recommendations: phosphate binders

Serum phosphate should be monitored in cats with CKD, and a phosphate-restricted diet should be used in all cats with azotaemic CKD (stages 2–4). If a commercial or home-prepared renal diet cannot be used, or is insufficient to control serum phosphate, phosphate binders should be used (given with food), the response monitored (eg, 1 month after medication change), and the dose adjusted accordingly. Although not subjected to clinical testing, the Panel suggests adopting the target serum phosphate concentrations recommended by IRIS:⁷¹

- ❖ Stage 2 disease: 0.9–1.45 mmol/l (3–4.5 mg/dl)
- ❖ Stage 3 disease: 0.9–1.6 mmol/l (3–5 mg/dl)
- ❖ Stage 4 disease: 0.9–1.9 mmol/l (3–6 mg/dl)

Managing serum calcium

Hypercalcaemia is a recognised cause of renal injury, but CKD can also cause changes in serum calcium, although these are generally mild. Ionised hypocalcaemia appears to be most common, and tends to be seen in advanced CKD.⁷² An increased calcium–phosphorus product has been linked with disease severity in cats.⁷³

Panel recommendations: serum calcium

An increased calcium–phosphorus product in CKD is usually caused by hyperphosphataemia, but cats at risk of hypercalcaemia (eg, those receiving calcium-containing phosphate binders or calcitriol) should have serum calcium monitored, ideally by measuring ionised calcium. If ionised hypercalcaemia develops, maintaining hydration is important and it may be necessary to reduce the dose of any phosphate binder.

Calcitriol therapy

Quality of evidence as an intervention

- ❖ Increased longevity: No evidence of benefit
- ❖ Improved QoL: No evidence of benefit

Calcitriol (active vitamin D) deficiency may occur with CKD due to various mechanisms including hyperphosphataemia-mediated

Dietary intervention is a mainstay therapy, and should be introduced early in stage 2 CKD.



inhibition of hydroxylation and loss of renal tissue. Calcitriol supplementation can potentially help suppress renal secondary hyperparathyroidism and has been shown to be beneficial in dogs and humans;⁷⁴ but despite anecdotal reports of improved QoL, low dose calcitriol has not been shown to have the same benefits in feline CKD.⁷⁵ Additionally, formulations of calcitriol can make accurate dosing difficult in cats. Hyperphosphataemia should also be carefully controlled when using this therapy to avoid increasing the serum calcium–phosphate product.

Panel recommendations: calcitriol

Based on current evidence (a single published study⁷⁵), calcitriol therapy cannot be recommended for cats with CKD, but further studies are needed as therapy has been shown to be helpful in other species.

Managing potassium

Quality of evidence as an intervention

- ❖ Increased longevity: No data
- ❖ Improved QoL: GOOD, if symptomatic with hypokalaemia

Feline CKD can lead to excessive kaliuresis, which may be compounded by reduced potassium intake, vomiting and transcellular shifts.^{55,76} Hypokalaemia may cause or contribute to clinical signs such as lethargy, inappetence, constipation and muscle weakness, and may contribute to development of acidosis, but has not been identified as a risk factor for disease progression or outcome.^{42,44,45}

Although renal diets are typically supplemented with potassium, hypokalaemia may still be seen in some cats. Conversely, hyperkalaemia may occasionally be seen in advanced CKD.

Panel recommendations – potassium

Serum potassium (K) should be routinely monitored in cats with CKD. Supplementation with potassium gluconate (or citrate) is recommended if serum K <3.5 mmol/l (<3.5 mEq/l), at a typical starting dose of 1–4 mmol (1–4 mEq) K per cat q12h, adjusted according to response. Supplementation may be started earlier, when serum K is 3.5–3.9 mmol/l (3.5–3.9 mEq/l), but the clinical benefits of this are uncertain.

Managing acid–base balance

Quality of evidence as an intervention

- ✦ Increased longevity: No data
- ✦ Improved QoL: No data

Metabolic acidosis is multifactorial in CKD⁷⁷ and bicarbonate therapy has been shown to improve nutrition (calorie and protein intake, lean body mass) and slow progression in humans with CKD.⁷⁸ Metabolic acidosis has been reported to occur in over half of cats with advanced (stage 4) CKD.^{79,80} However, cats fed commercial renal diets may have higher serum bicarbonate concentrations.⁵⁶

Panel recommendations: acid–base balance

Feeding a renal diet formulated to minimise acidosis, and maintaining good hydration, are likely to be beneficial in preventing clinically significant metabolic acidosis in cats with CKD. Additional therapy is rarely needed, but if clinical concerns exist and blood bicarbonate or total CO₂ concentrations are <16 mmol/l, oral supplementation with potassium citrate (40–75 mg/kg q12h as starting dose) may be used, aiming to maintain a blood bicarbonate or total CO₂ in the range of 16–24 mmol/l.

Other nutrients

Quality of evidence as an intervention

- ✦ Increased longevity: No data
- ✦ Improved QoL: No data

One retrospective study suggested that renal diets with the highest omega-3 fatty acid content were associated with the longest survival times.⁵⁴ However, a causal relationship could not be established, and feeding a renal diet may not alter fatty acid profiles.⁸¹

Dietary sodium restriction is recommended for people with CKD to mitigate hypertension and other effects,⁸² but evidence for a beneficial effect in older cats, with and without CKD, is generally lacking, and very restricted sodium intake may be deleterious.^{83–86}

Cats with CKD have evidence of increased oxidative stress compared with healthy cats,^{87,88} and dietary antioxidant therapy (with vitamins E, C and beta-carotene) may reduce this.⁸⁹ Whether this results in any renoprotective effect remains to be determined.

Other dietary supplements, including Chinese rhubarb (*Rheum officinale*) and a prebiotic/probiotic combination, have not shown any beneficial effects.^{90,91}

Panel recommendations: other nutrients

The feeding of commercial renal diets to cats with CKD may have benefits beyond protein and phosphate restriction including minimising risks of hypokalaemia, acidosis and oxidative stress, and increasing essential fatty acid and water-soluble vitamin intake. The potential benefits of some of these effects in CKD have not been critically assessed.

Managing hypertension in CKD

Quality of evidence as an intervention

- ✦ Increased longevity: No evidence of benefit
- ✦ Improved QoL: GOOD, if symptomatic with hypertension

Systemic hypertension associated with CKD has a reported prevalence of 19–40%^{36,92} in primary care practices, and as high as 65% in referral populations.⁹³ The pathogenesis is not entirely clear, with some cats demonstrating activation of the renin–angiotensin–aldosterone system (RAAS),^{94–96} and some having apparent autonomous hyperaldosteronism.^{96,97}

Doppler and high-definition oscillometry are the most reliable non-invasive blood pressure measurement techniques in conscious cats.^{98–105} However, even when cats are calm and a standardised protocol is followed,¹⁰⁵ measurements will vary with the equipment, the operator, the cat and the circumstances.^{36,106–111} Current non-invasive techniques are inaccurate for assessing diastolic blood pressure in cats.^{101,104}

Within these limitations, hypertension is usually defined as a SBP persistently >160–180 mmHg,^{36,112} but has also been defined according to the perceived risk of target organ damage (TOD) (see box on page 221 and Table 5).^{27,105} Target organs are those particularly susceptible to hypertensive damage – the eyes,^{93,107,113} heart,^{114–116} cerebrovascular tissue^{113,117} and kidneys. While hypertension is an independent risk factor for progressive CKD in dogs and people,^{118,119} this has not been proven in cats.^{37,116,117,120} However,

Table 5 Blood pressure categories according to risk of target organ damage (TOD)^{27,105}

| SBP (mmHg) | Risk of TOD | Treatment |
|------------|-------------|--|
| <150 | Minimal | No treatment advised |
| 150–159 | Mild | No treatment advised |
| 160–179 | Moderate | Treatment advised if TOD is present. Cats with CKD are assumed to have TOD |
| ≥180 | Severe | Treatment indicated |

SBP = systolic blood pressure

Table 6 Suggested oral therapy for systemic hypertension

| Drug | Dose | Comments |
|--|---|--|
| Amlodipine (calcium channel blocker) | 0.0625–0.25 mg/kg q24h | Licensed for feline use in some countries. Good efficacy in several studies. Licensed dose in Europe is 0.125–0.25 mg/kg q24h; dose can be doubled (up to 0.5 mg/kg q24h) if needed ¹²⁷ |
| Telmisartan (ARB) | 1–3 mg/kg q24h | Licensed for feline use in some countries as an antiproteinuric agent. Clinical efficacy as antihypertensive uncertain and best currently considered as adjuvant therapy in refractory cases |
| Benazepril (ACEI) | 0.25–0.5 mg/kg q24h | Limited effect on blood pressure used alone; best considered as adjuvant therapy in refractory cases. Dose can be doubled to 0.5–1.0 mg/kg q24h if needed |
| Propranolol Atenolol (beta-blockers) | 2.5–5.0 mg/cat q8h 6.25–12.5 mg/cat q12h | Limited effect on blood pressure used alone; best considered as adjuvant therapy in refractory cases |

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

hypertension is associated with the severity of proteinuria (as in people and dogs),^{37,120–122} which can be reduced with successful antihypertensive therapy.^{37,120,123}

Management of hypertension is aimed at preventing TOD, although the current perceived risk categories (Table 5) are imprecise as data are lacking, risks may vary between individuals and may, for example, depend on how rapidly blood pressure rises. In general, treatment aims to reduce SBP to <150–160 mmHg.^{27,105}

Monotherapy with angiotensin-converting enzyme inhibitors (ACEIs) or atenolol is not effective in most hypertensive cats.^{95,105,112,124,125} There is some experimental data to suggest the ARB telmisartan at 3 mg/kg q24h may be more effective than benazepril as an anti-hypertensive agent,¹²⁶ but further clinical studies are needed. Conversely, the calcium channel blocker amlodipine is an effective monotherapy for most (but not all) cats,^{97,112,113,115,120,127,128} and may be combined with other drugs if adjuvant therapy is needed (Table 6).

Panel recommendations: hypertension

There is a strong association between CKD and hypertension, and cats diagnosed with CKD may subsequently develop hypertension.³⁶ As hypertension has important clinical implications, blood pressure assessment should be part of the routine evaluation of all cats with suspected or proven CKD. Currently amlodipine is the treatment of choice in cats, but other drugs may be helpful, especially in cats refractory to amlodipine therapy. Cats with hypertension (eg, sustained SBP >160 mmHg) should be treated and monitored, with the aim of reducing SBP to <150–160 mmHg.



Complications such as hypertension, anaemia and proteinuria are common and often associated with disease progression or a poor quality of life.



Figure 11 Anaemia is a recognised risk factor for progression of CKD. Courtesy of Cathy Langston

Managing anaemia in CKD

Quality of evidence as an intervention

- ✦ Increased longevity: POOR
- ✦ Improved QoL: GOOD, if symptomatic with anaemia

Anaemia of varying severity is seen in 30–65% of cats with CKD³⁸ (Figure 11). A relative lack of erythropoietin (EPO) in CKD produces a non- or poorly-regenerative anaemia, which may be exacerbated by blood loss and/or shortened red blood cell (RBC) survival.¹²⁹ Anaemia has been identified as a dependent or independent risk factor for progression of CKD,^{42–45} and there is evidence that treatment with erythrocyte-stimulating agents (ESAs) may improve QoL and potentially survival in some cats with CKD.¹²⁹

Blood transfusions and haemoglobin-based oxygen carrying solutions (eg, Oxyglobin; Dechra Veterinary Products) have limited value for the chronic anaemia associated with CKD,^{130,131} and the use of anabolic steroids is not recommended due to lack of evidence of efficacy and potential adverse events.^{132,133} In contrast, the use of ESAs (EPO or EPO analogues) has become the standard of care in human medicine.

ESA therapy is designed to elevate the packed cell volume (PCV) to around the lower limit of the reference interval – sufficient to meet tissue oxygen demand. Iron supplementation alone is not effective in managing CKD-associated anaemia, but it enhances the efficacy of ESA therapy in humans,¹³⁴ and anecdotal evidence suggests the same is true in cats.

Table 7 Clinical use of human epoetin alfa or darbepoetin alfa in cats with CKD

| Drug | Initial therapy | Maintenance therapy | Efficacy studies in CKD anaemia | Adverse events ^{135,136} |
|------------------|---|--|--|--|
| Epoetin alfa | 100 U/kg SC 3 x weekly Until PCV \geq 25% | 50–100 U/kg SC 1–2 x weekly Based on PCV | Effective for cats and dogs ¹³⁷ | Systemic hypertension (40–50%) Seizures (2–10%) Polycythemia (unlikely) Injection site discomfort Skin reactions (redness) PRCA (25–40%)* |
| Darbepoetin alfa | 1 μ g/kg SC 1 x weekly Until PCV \geq 25% | 1 μ g/kg SC q2–3 weeks; <i>or</i> Lower dose (eg, 0.5 μ g/kg) weekly Based on PCV | Effective in cats Response tends to occur in 2–3 weeks ¹³⁵ | Similar adverse event profile to EA but lower incidence of PRCA (<10%)*, so a better choice for therapy in cats |

*Anti-erythropoietin antibodies are produced and PRCA manifests as worsening anaemia, lack of erythrocytosis, and no response to ESA therapy. Diagnosis is supported by a bone marrow aspirate/core and cats become transfusion-dependent for months.¹³⁷ SC = subcutaneously; PCV = packed cell volume; PRCA = pure red cell aplasia

Treatment with erythrocyte-stimulating agents may improve quality of life and potentially survival.



The two ESAs most widely used in cats are recombinant human epoetin alfa (EA, ~80% homology to feline EPO) and darbepoetin alfa (DA, a hyperglycosylated recombinant human EPO analogue). Although often successful, in one study, >40% of cats with CKD-associated anaemia failed to respond or failed to develop a sustained response to ESA therapy.¹³⁵ Potential reasons for this include:^{129,135}

- ❖ Concurrent illnesses (present in most cats that fail to respond to ESA);
- ❖ Infections or inflammation;
- ❖ Gastrointestinal bleeding;
- ❖ Iron deficiency;
- ❖ Pure red cell aplasia (PRCA) from production of anti-EPO antibodies (Table 7).

Hypertension is also recognised as an adverse effect of ESA therapy, affecting up to 50% of treated cats.^{129,135}

Panel recommendations – anaemia

ESA therapy should be considered in cats:

- ❖ With persistent CKD-associated anaemia that is symptomatic; *or*
- ❖ If the PCV is persistently <20%.

The use of DA is preferred over EA as it appears significantly less likely to induce PCRA.¹³⁵ The target for therapy should be a PCV of \geq 25%. Irrespective of the ESA used, iron supplementation is generally recommended to ensure iron deficiency does not contribute to the anaemia:

- ❖ Iron dextran: 50 mg IM per cat at the start of ESA therapy, repeated monthly as needed; *or*
- ❖ Oral iron supplements (ferrous sulfate): 50–100 mg/cat per day (less ideal)

For cats receiving ESA therapy, PCV, reticulocyte count and blood pressure should be routinely monitored:

- ❖ Weekly until target PCV is reached;
- ❖ At every tapering of ESA dosage;
- ❖ Every 1–3 months once lowest effective dosage is reached¹²⁹

If response to therapy is poor, iron status (serum iron, ferritin and total iron binding capacity) should be verified and the patient reassessed for concomitant disease.^{129,135}

Managing proteinuria in CKD

Quality of evidence as an intervention

- ❖ Increased longevity: No evidence of benefit, although magnitude of proteinuria linked to survival
- ❖ Improved QOL: POOR

In human medicine, regardless of the cause of CKD, the severity of proteinuria at the time of diagnosis is an important prognostic indicator, and controlling proteinuria results in slower progression of CKD, largely irrespective of the underlying cause of the CKD.¹³⁸ CKD is generally associated with increased intraglomerular capillary pressure and other changes that impair glomerular permselectivity, leading to increased loss of albumin (and other proteins) into tubular fluid; this appears to directly contribute to disease progression by promoting tubular inflammation and fibrosis.¹³⁸

Although there may be species differences in pathophysiology, increased proteinuria in cats with CKD (assessed with UPCr and not routine dipsticks, which are inappropriate for assessment of feline proteinuria^{139,140}) is also known to carry a poorer prognosis.^{37,42,44,120,123} In one study,³⁷ cats with a UPCr <0.2 were reported to have a median survival time of ~1000 days compared with around 500 days for those with a UPCr of 0.2–0.4, and ~400 days for those with a UPCr >0.4. Very similar findings have also been reported elsewhere.¹²⁰ Currently, there is no evidence that measurement of UACr rather than UPCr offers any benefits in cats,^{37,141} but the urinary proteome in healthy cats and cats with CKD is complex and more studies are needed.^{142–146}

In humans, treatment with angiotensin receptor blockers (ARBs) or ACEIs is effective in blocking RAAS activation, decreasing glomerular capillary pressure, restoring

glomerular permselectivity, reducing proteinuria and slowing the progression of CKD.^{138,147–149} These effects are partly as a result of haemodynamic changes and partly through modifying non-haemodynamic remodelling in the kidney.¹⁵⁰

The existing IRIS²⁷ CKD (see box on page 221) and American College of Veterinary Internal Medicine (ACVIM) proteinuria¹⁵¹ guidelines suggest cats should be classified as:

- ❖ Overtly proteinuric: UPCr >0.4
- ❖ Borderline proteinuric: UPCr 0.2–0.4
- ❖ Non-proteinuric: UPCr <0.2

Using these criteria, around 50–66% of cats with CKD are likely to be non-proteinuric and around 20% overtly proteinuric.^{37,42}

In cats with CKD, RAAS inhibition with the ACEI benazepril has been shown to significantly reduce the severity of proteinuria.^{152–154} More recently, the ARB telmisartan has been licensed in some countries for the management of proteinuric CKD in cats and has been demonstrated to be at least as effective as benazepril.¹⁵⁵ However, a survival benefit from RAAS blockade in cats has not been demonstrated.^{152,153} The reasons for the lack of effect on survival are uncertain but may include:

- ❖ Underpowered clinical trials;
- ❖ Inadequate duration of clinical trials;
- ❖ Differences in the pathophysiology between humans and cats with CKD (eg, proteinuria could be a marker of tubular dysfunction in cats rather than a cause of progressive disease);
- ❖ Differences in the prevalence or severity of proteinuria between humans and cats with CKD;
- ❖ Inadequate control of proteinuria and/or inappropriate targets for antiproteinuric therapy (while benazepril therapy significantly reduced UPCr in CKD cats compared with placebo in clinical trials, these studies also showed little overall reduction in the UPCr from baseline values within the treatment group^{152,153}).

Further investigations are needed to assess the role of RAAS inhibition in feline CKD and to determine optimal therapy, but currently both ARBs and ACEIs are available and used in cats, and are licensed in some countries (Table 8). There is some (weak) evidence that RAAS blockade may have more beneficial

Panel recommendations: proteinuria

Based on their ability to significantly reduce proteinuria in feline CKD, their modification of renal haemodynamics¹²⁵ and the potential (though yet unproven) beneficial effect this may have, the Panel suggests RAAS inhibition should be considered in non-dehydrated cats with stable CKD where the UPCr is persistently >0.4. Note that:

- ❖ As CKD cats with a UPCr of 0.2–0.4 have a much poorer prognosis than those with a UPCr <0.2, there is also a logical rationale in the decision of some clinicians to institute therapy where UPCr is persistently >0.2;
- ❖ Because the benefits of RAAS blockade have not yet been proven in cats, currently other treatments with proven benefits should have a higher priority if treatment choices need to be made.

As treatment of hypertension can reduce proteinuria,¹²⁰ the need for additional antiproteinuric therapy should be assessed after appropriate antihypertensive therapy in cats with high blood pressure.

Adverse effects of RAAS inhibition are uncommon in cats with stable, well-compensated CKD, but greater care should be taken in patients with more advanced (eg, stage 4) CKD. Potential complications include worsening of azotaemia, reduced blood pressure and (rarely) hyperkalaemia.¹²⁵ The Panel recommends that in addition to clinical signs, urea, creatinine and blood pressure should be monitored 5–7 days after starting therapy or following dose adjustments, and any increase in creatinine of >15–20% should prompt further evaluation and/or cessation of or reduction in therapy. Additionally, the higher risks of acute kidney injury with the concomitant use of both an ACEI or ARB and a non-steroidal anti-inflammatory drug (NSAID) means this combination should be used with caution or avoided in cats with CKD based on a risk:benefit analysis.

effects (possibly on survival, QoL and appetite) in CKD cats with more severe proteinuria (eg, UPCr ≥1.0),¹⁵² and currently IRIS and ACVIM guidelines suggest^{71,151} antiproteinuric therapy should be instituted in CKD cats with a UPCr >0.4.

Managing inappetence, nausea and vomiting in CKD

Quality of evidence as an intervention

- ❖ Increased longevity: No data
- ❖ Improved qQoL: Likely to be GOOD if cat is symptomatic

Cats with CKD can suffer from nausea, vomiting and inappetence as a result of uraemic toxins affecting the central chemoreceptor trigger zone. Inappetence is a significant QoL concern for owners,¹⁵⁶ and in the CKD patient could result in protein and calorie malnutrition with its many adverse consequences.¹⁵⁷ A reduced appetite should therefore be actively managed, along with complications of CKD that can contribute to inappetence, such as dehydration, hypokalaemia, acidosis and anaemia. Centrally acting antiemetics such as

Table 8 Suggested oral therapy for managing proteinuria

| Drug | Dose |
|-------------------|---------------------|
| Telmisartan (ARB) | 1 mg/kg q24h |
| Benazepril (ACEI) | 0.25–0.5 mg/kg q12h |

ARB = angiotensin receptor blocker;
ACEI = angiotensin-converting enzyme inhibitor

Table 9 Suggested therapy for managing inappetence, nausea and vomiting

| Drug | Dose |
|--|--|
| Maropitant (neurokinin-1 receptor antagonist) | 1 mg/kg q24h SC/IV 2 mg/kg q24h PO |
| Mirtazapine (tetracyclic antidepressant, alpha-2 antagonist) | ~0.5 mg/kg (or 1.88 mg/cat) q48h PO |
| Ondansetron (5-HT ₃ receptor antagonist) | 0.5–1.0 mg/kg q6–8h PO |
| Dolasetron (5-HT ₃ receptor antagonist) | 1.0 mg/kg q24h PO |
| Famotidine (H ₂ blocker) | 0.5–1 mg/kg q12–24h PO |
| Omeprazole (proton pump inhibitor) | 0.5–1 mg/kg q12–24h PO |

SC = subcutaneously; IV = intravenously; PO = orally

maropitant, mirtazapine, ondansetron and dolasetron^{158–160} should be considered for management (Table 9). In placebo-controlled trials of cats with stage 2 or 3 CKD, maropitant (given orally for 2 weeks) was shown to reduce vomiting,¹⁶⁰ and mirtazapine (given orally for 3 weeks) reduced vomiting and also increased appetite and weight.¹⁵⁸ Mirtazapine may therefore be a useful adjunct to the nutritional management of cats with CKD.

There are anecdotal reports of H₂ blockers or proton pump inhibitors alleviating inappetence in some feline CKD patients, but the presence and degree of gastric hyperacidity and efficacy of these medications remain unproven. Additionally, although hypergastrinaemia has been reported in feline CKD,¹⁶¹ gastric ulceration has generally not been observed or reported.^{73,162} If therapy for hyperacidity in cats is considered, omeprazole appears to be superior to famotidine.¹⁶³



Figure 12 Enteral (oesophagostomy) tube in place to support food and fluid intake. Courtesy of Isuru Gajanayake

Panel recommendations: inappetence, nausea and vomiting

Vomiting should be actively managed in cats with CKD and nausea should always be considered as a potential contributory cause in cats with inappetence. Based on available evidence, centrally acting antiemetics are likely to be most valuable, and the use of mirtazapine may have additional benefits.

If cats remain too nauseous or unwell to maintain sufficient voluntary food intake despite appropriate treatment, placement of an enteral feeding tube (eg, oesophagostomy [Figure 12] or gastrostomy) should be considered, and anecdotal reports suggest these can be valuable in maintaining food and fluid intake in some cats with CKD.

Managing UTIs in CKD

Quality of evidence as an intervention

- ✦ Increased longevity: No evidence of efficacy
- ✦ Improved QoL: Likely to be GOOD if cat is symptomatic

Bacterial UTIs in cats with CKD occur at a reported frequency of around 15–30%,^{39,164–166} with older female cats having an increased risk.³⁹

Most (>70%) of these UTIs appear to be subclinical (ie, without lower urinary tract signs [LUTS]), although >85% show changes on urine sediment analysis (>5 white blood cells [WBCs]/hpf, and/or >5 RBCs/hpf, and/or microscopic bacteriuria).³⁹ *Escherichia coli* represents 60–75% of isolates, while other organisms include *Enterococcus*, *Streptococcus*, *Staphylococcus*, *Enterobacter*, *Pseudomonas* and *Klebsiella* species.

The presence of LUTS or detection of pyuria (≥5 WBCs/hpf) in routine urinalysis of CKD patients are indications for bacterial culture of a cystocentesis sample, but whether routine culture of all urine samples should be recommended is controversial, as the significance of subclinical bacteriuria is uncertain. While some clinicians advocate routine treatment of all CKD-associated UTIs (as cats may be at risk for pyelonephritis and deterioration of CKD), recurrent or recrudescing UTIs are common after treatment,³⁹ the presence of subclinical UTIs has not been associated with disease severity or apparent survival,³⁹ and unnecessary treatment may risk development of bacterial resistance.

When treated, UTIs should be managed according to international guidelines,¹⁶⁷ selecting antibacterials based on sensitivity testing (note that boric acid tubes should be avoided for urine cultures¹⁶⁸) that are excreted unchanged in urine and have a wide therapeutic index (Table 10). If initial empirical therapy is needed, amoxicillin (11–15 mg/kg PO q8h)¹⁶⁷ or potentiated amoxicillin¹⁶⁹ are appropriate choices; 2–4 weeks' therapy has been

Panel recommendations: UTIs

Treatment of UTIs in cats with CKD should be considered when there is a positive urine culture and where:

- ✦ LUTS are present *and/or*
- ✦ Systemic signs are present (eg pyrexia, neutrophilia, left shift, abdominal pain) *and/or*
- ✦ Pyuria is present (>5 WBC/hpf) *and/or*
- ✦ When there is an unexplained deterioration in renal function

Whether other subclinical UTIs should be treated remains controversial and requires further investigation, but it may be more appropriate to monitor cats than intervene at initial diagnosis.

Table 10 Considerations when selecting an antibacterial to treat urinary tract infections in cats with CKD

| Consideration | Action | Antibacterials |
|------------------------------|---|---|
| Probably safe | No dose adjustment required, due to wide therapeutic index or excretion via extrarenal routes | Chloramphenicol Penicillins (including clavulanate) |
| Consider dosage adjustment | Adjust dose in moderate or severe CKD (IRIS stages 3 and 4) | Cephalosporins (most)* Fluoroquinolones† Sulphonamides (± trimethoprim) |
| Hazardous, avoid if possible | Accumulation of drug or its metabolites in CKD can increase risk of adverse events | Nalidixic acid Nitrofurantoin Tetracyclines‡ (except doxycycline) |
| Nephrotoxic | Avoid – high-risk drugs will exacerbate CKD | Aminoglycosides Polymyxins |

*Some cephalosporins accumulate in renal tubular cells and can cause damage
†Avoid enrofloxacin in cats with CKD due to increased risk of retinopathy at standard therapeutic doses
‡Water soluble tetracyclines (eg, oxytetracycline) depend partly on renal excretion. Tetracyclines also increase protein catabolism, and breakdown products of oxytetracycline have been shown to be nephrotoxic
IRIS = International Renal Interest Society

recommended,¹⁶⁷ although optimum duration of therapy for CKD-associated UTIs is uncertain.¹⁷⁰ Response to treatment should be monitored with repeat culture 7 days after cessation of treatment.

Other treatments

Anabolic steroids

Information regarding the efficacy of anabolic steroids for cats with CKD is lacking and, as hepatotoxicity has been reported,¹³³ their use is not currently recommended.

Stem cell therapy

Pilot studies investigating stem cell therapy for feline CKD have not to date demonstrated beneficial effects; and with some techniques adverse effects occur.^{171,172}

Consequently, this treatment is not currently recommended.

Renal transplantation

Kidney transplants from living donors may be available to treat cats with CKD at specialist centres in some regions. This procedure has numerous implications including ethical, financial, welfare and monitoring considerations.^{173–176} While it may be viable in some patients, kidney transplantation is beyond the scope of these Guidelines.

Dialysis therapy

Haemodialysis or peritoneal dialysis are techniques that can be successfully applied to cats, although complications may arise. Their main indications are for management of acute kidney injury or acute on chronic kidney disease.^{177,178}

Specific therapeutic issues in cats with CKD

Adverse drug effects

Nephrotoxic drugs (eg, aminoglycosides, NSAIDs, antineoplastic agents) should be used with great care in cats with CKD and, depending on the drug and the stage of CKD, their use may be contraindicated. Decisions on therapy should be made on a case-by-case basis, assessing risks and benefits. There is, however, evidence that low dose (0.01–0.03 mg/kg) meloxicam, for example, is well tolerated long-term for the management of osteoarthritis and pain in cats with stages 1–3 CKD.^{179–181}

Drugs that are primarily excreted in urine may accumulate in patients with CKD, leading to higher risks of adverse events; thus drugs primarily biotransformed by the liver or excreted by extrarenal routes (eg, benazepril,¹⁸² telmisartan¹⁸³) are preferred where possible. Nevertheless, the risk:benefit ratio of each treatment should be assessed,¹⁸⁴ and dose adjustments may help to mitigate risks.

Hyperthyroidism

Hyperthyroidism may contribute to the progression of CKD, and can also mask coexisting CKD as GFR increases in cats with hyperthy-

roidism.¹⁸⁵ Mild to moderate renal azotaemia becomes apparent after treatment of hyperthyroidism in ~15–40% of cats,¹⁸⁵ and hyperthyroid cats with pre-existing CKD have a much higher risk of renal decompensation than non-azotaemic cats.^{185,186} Hyperthyroidism is also frequently associated with significantly elevated parathyroid hormone concentrations that may potentially complicate existing CKD.¹⁸⁷ Conversely, iatrogenic hypothyroidism is also associated with a higher risk of azotaemia and reduced survival times.^{188,189}

In cats with pre-existing CKD or where there are significant concerns over renal function, a thioureylene (methimazole, carbimazole) is the preferred initial treatment for hyperthyroidism, as its effects can be titrated and are reversible. Close monitoring of the cat's clinical condition, serum creatinine and thyroxine is required to tailor the dose for each patient. Starting doses can be titrated upward if the initial control of hyperthyroidism is inadequate, or downward if there is worsening of clinical signs of CKD or marked worsening of azotaemia.¹⁸⁶ In cats that can be successfully stabilised, definitive treatment for hyperthyroidism may be undertaken (eg, radioiodine therapy).

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CONFLICT OF INTEREST

Catherine Langston is a paid consultant for Bayer and for Abaxis. Hervé Lefebvre has received grants/research contracts and/or performs consulting for Royal Canin, Novartis Animal Health, CEVA Animal Health and Bayer. Jonathan Elliott has acted as a paid consultant for CEVA Animal Health, Boehringer Ingelheim, Pfizer (now Zoetis), Bayer, Idexx, Novartis Animal Health, Waltham Centre for Pet Nutrition and Royal Canin; he has research grant funding and contracts to work on kidney disease in cats from CEVA Animal Health, Orion, Zoetis and Royal Canin.

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