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Updates on management of chronic renal disease (including IRIS staging)

Rachel Korman

Iris Staging of Chronic Renal Disease

Chronic kidney disease (CKD) is the most common kidney disease in cats, estimated to affect 0.5-1.5% of the general population and 30% of cats over 15 years. The term CKD or chronic renal disease is non-specific, but preferred to "chronic renal failure" or "chronic renal insufficiency" as owners understand the terminology and the negative context imbued by "failure" is avoided.
Staging

Guidelines for staging cats with CKD were established by the International Renal Interest Society (IRIS)(http://www.IRIS-kidney.com) and provide a useful classification system for ongoing monitoring and information on expected outcome. CKD staging is based on serum/plasma creatinine concentration and recently, symmetric dimethylarginine (SDMA) has also been included in the guidelines. It is important to note that the specificity of SDMA has not been tested in large scale prospective studies. A recent study compared SDMA, creatinine and glomerular filtration rate in 49 cats that were normal or had CKD or diabetes mellitus (Brans et al JVIM2020). SDMA was a reliable marker of reduced GFR but superiority of SDMA over creatinine could be demonstrated.

Staging is undertaken following the diagnosis of CKD to guide treatment and monitoring.

Staging is based on fasting blood creatinine and/or SDMA, assessed ideally on at least two occasions in the stable patient. Cats must be hydrated prior to staging, otherwise any pre-renal component of the azotaemia may misclassify cats into a higher stage, which carries a poorer prognosis.

Further substaging is based on the presence of proteinuria and hypertension. Proteinuria should be confirmed renal in origin and persistent, being identified on two separate occasions, ideally a few weeks apart. Urine sediment and urine bacterial culture are performed to exclude haematuria, inflammation or infection as the source of the proteinuria. Urine samples obtained with non-absorbable cat litter are often suitable for follow-up.
Likewise, systolic blood pressure (SBP) measurements should be assessed on multiple occasions and care taken to reduce "white coat" hypertension.

Based on stage and substages, empirical recommendations can be made about treatment.

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IRIS staging of feline chronic kidney disease

STAGE BASED ON SERUM OR PLASMA CREATININE CONCENTRATION		
Stage	Plasma Creatinine umol/l (mg/dl) *Plasma SDMA ug/dl*	Comments
1	<140 (<1.6) *<18*	Nonazotaemic or mild increase in SDMA Some other renal abnormality is present e.g. inadequate urine concentrating ability without identifiable non-renal cause; abnormal renal palpation and/or abnormal renal imaging findings; proteinuria of renal origin; abnormal renal biopsy Persistent elevation in blood SDMA concentration >14ug/dl maybe used to diagnose early CKD
2	140-250 (1.6-2.8) *18-25*	Mild renal azotaemia Clinical signs usually mild or absent
3	251-440 (2.9-5.0) *26-38*	Moderate renal azotemia Many systemic clinical signs maybe present
4	>440 (>5.0) *>38*	Severe renal azotemia Many systemic clinical signs and uraemic crises

SUBSTAGE BASED ON PRESENCE OF PROTEINURIA DETERMINED BY UPC	
Substage	UPC value
Nonproteinuric	<0.2
Borderline proteinuric	0.2-0.4
Proteinuric	>0.4

SUBSTAGE BASED ON PRESENCE OF SYSTEMIC ARTERIAL HYPERTENSION AND RISK OF SYSTEMIC ARTERIAL HYPERTENSION-RELATED COMPLICATIONS		
Substage	Systolic blood pressure (mm Hg)	Risk of Future Target Organ Damage
Normotensive	<140	Minimal
Prehypertensive	140-159	Low
Hypertensive	160-179	Moderate
Severely hypertensive	>180	High

CKD: Chronic kidney disease, UPC: Urine protein: creatinine ratio
For full details of the IRIS staging system, see the International Renal Interest Society's website: www.iris-kidney.com

Cats in IRIS stage 2 may have creatinine concentrations within the reference range for many laboratories. The insensitivity of creatinine means that cats with creatinine concentrations close to the upper limit often have excretory failure.

Management of Chronic Renal Disease
Ideally, treatment for chronic kidney disease (CKD) would correct or reverse the underlying cause, identify and slow factors associated with progressive disease and relieve signs of kidney dysfunction.

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Unfortunately, the cause of CKD is often unknown and treatments slowing progression in other species (e.g. calcitriol, benazepril) don't appear effective in cats. CKD is currently irreversible and progressive, however treatment can improve quality of life and survival, yielding fulfilling experiences for veterinarians and owners.

CKD results in retention of excreted wastes (e.g. phosphorous) and loss of compounds (e.g. potassium) that should be retained. Most therapy targets these changes, consisting of supportive and symptomatic treatments to correct dehydration and address endocrine, metabolic and nutritional disturbances. Treatment is life-long, thus medication must be easy to give to ensure owner compliance.

Of all treatments to date, kidney diets have the most positive effect on outcome. Anything that contributes to inappetance will result in diet failure, negating any positive effects. Many of the treatments in the following discussion also improve appetite, via addressing nausea and discomfort.

Renal therapeutic diets (kidney diets)

Dietary modification using a kidney diet has a positive long-term effect on survival. In two studies, cats with CKD receiving kidney diets instead of normal food survived significantly longer (20.8 months versus 8.7 months; 16 months versus 7 months). Another randomized controlled clinical trial, compared feeding maintainence diets with kidney diets in spontaneous CKD stages 2 and 3. Cats in the kidney diet group had fewer uraemic episodes (0% versus 23%) and none died from kidney disease. Thus strong evidence exists to support the use of kidney diets to prolong survival and improve quality of life for cats with CKD.

There is no evidence supporting dietary modification in stage 1 CKD. Recently a prospective, double blinded randomized, placebo controlled trial assessed a diet with moderate dietary protein and phosphate restriction on calcium-phosphate homeostasis in healthy older cats. The diet was well tolerated and increased urinary fractional excretion of phosphate. There was no significant change in plasma PTH concentration in cats receiving the test diet, but increased plasma PTH was seen in cats on the control diet. There was no significant effect of the test diet on the development of azotemic CKD over the 18 month period of the study.

In the author's experience, introducing a diet change in a clinically well cat improves the likelihood of a dietary transition. Over 90% of cats with CKD accepted the kidney diets when a very gradual transition was used in one retrospective study. Attempting a diet change in a sick, hospitalized, anxious cat is unlikely to be successful and may prevent acceptance of the food at a later date due to the development of food aversion. Diet change is attempted when the patient is well and discharged from hospital.

There will always be cats that refuse all attempts at dietary change. Assessment of home prepared CKD diets has identified numerous nutritional imbalances, therefore feeding a kidney diet mixed with a senior diet and addition of a phosphate binding agent (PBA) if hyperphosphatemia is present, is likely to be better than providing a maintainence diet alone.

Kidney diets are restricted in protein, phosphorous and sodium and are supplemented with potassium, omega 3-fatty acids and B vitamins. They are higher in fat content and are alkalinizing. It is unknown which aspect of the kidney diet is responsible for improvement in survival times, however experimental model studies support phosphate restriction and essential fatty acid supplementation as possible mechanisms.

Hyperphosphataemia and renal secondary hyperparathyroidism (RHPTH)

Approximately 60% of cats with CKD have elevated phosphate concentrations. Serum phosphorus concentration is a negative prognostic factor in CKD. In general, parathyroid hormone (PTH) concentrations parallel serum phosphate and frequency of RHPTH increases with the severity of kidney disease. FGF-23 is a recently identified phosphaturic hormone, that is involved in phosphate regulation in the cat. Hyperphosphatemic cats have higher FGF-23 within a given IRIS stage than normophosphatemic cats and dietary phosphate restriction reduces plasma FGF-23 concentration.

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Phosphate levels are reduced by improving hydration, dietary phosphate restriction and phosphate binding agents (PBAs). Dietary phosphate restriction alone can control phosphate concentration up to IRIS stage 3. In stage 4, phosphate restricted diets are unlikely to reduce phosphate levels sufficiently. If after 4 weeks of dietary modification, phosphate levels remain above target, PBAs are considered.
In people, PTH is a major uraemic toxin, increasing intracellular calcium and resulting in neurotoxicity, immune dysfunction and exacerbating anaemia. If PTH is similarly toxic in cats, another treatment goal would be to normalise or prevent PTH increase by addressing alterations in phosphate levels.

Phosphate binding agents
PBAs bind dietary phosphorous in the GI tract producing insoluble compounds excreted in faeces. PBAs are efficient at reducing phosphate levels, however little data exists regarding effects on survival. PBAs must be given with food and can be poorly accepted, causing inappetance that negates any potential benefits of either PBAs or the kidney diet.

Commonly used phosphate binding agents in cats

Drug	Dosage	Comments
Aluminium hydroxide	30 mg/kg PO q8h	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	1g / 4.5 kg (10lb) PO q8h	Monitor for hypercalcaemia
Lanthanum carbonate	6.25-12.5 mg/kg PO q12h	Not currently available in Australia.
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 or 3 h after other medications
Lenziaren		Not currently available in Australia. No dosage information available.
Sevelamer hydrochloride	30-50 mg/kg PO q8h 50-80 mg/kg PO q12h	Safety and efficacy in cats is unknown

Chitosan and calcium carbonate administration effectively reduced hyperphosphataemia in cats. Whether a survival benefit is different to that provided by dietary phosphate restriction is unknown. Calcium containing PBAs can cause hypercalcaemia if used with calcitriol. One study assessed feeding of a supplement containing calcium carbonate, calcium-lactate gluconate, chitosan and sodium bicarbonate in cats with IRIS 3 and 4 CKD compared with a control group. Cats fed the supplement appeared to tolerate it well and demonstrated reduced serum phosphorus and increased serum bicarbonate concentration.

In people with renal failure, **lanthanum** is efficacious with few adverse effects. Vomiting occurs in cats at high dosages. Lanthanum decreased serum creatinine and phosphate concentration in cats with CKD. Again, survival benefits are unknown.

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Aluminium toxicity has been demonstrated in people and dogs with renal failure. However, as **aluminium hydroxide** is an effective PBA, inexpensive and readily available, use has continued. Constipation in cats is common and can be addressed by conservative doses (to avoid dehydration) of lactulose (e.g. 0.5-1ml PO q 12h) or osmolax (1/4 teaspoon mixed with each meal). Unfortunately, like other PBAs, aluminium hydroxide is unpalatable and administration can be difficult. Sucralfate has been suggested as a possible phosphate binder but in recent research evaluating sucralfate administration as a slurry to cats with CKD, no alterations in phosphate were identified and 15% of cats developed vomiting, with signs severe enough to warrant termination of the study.

Another PBA used in humans, **sevelamer**, does not contain calcium or aluminium. It may bind additional vitamins and vitamin supplementation should be given.

Treatment response to PBA administration is assessed with regular phosphate monitoring. Fasted blood samples (e.g. 12 h) are required to avoid post-prandial hyperphosphataemia. Target recommendations for phosphate restriction are used.

Targets for serum phosphorous concentration assessed by IRIS stage

IRIS stage	Target serum phosphorous 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)

Calcitriol

Calcitriol supplementation theoretically reduces excess PTH and early supplementation may prevent parathyroid gland hyperplasia. In addition to serum phosphate measurements, regular assessment of PTH would be ideal, with consideration of calcitriol administration to patients with elevated PTH despite dietary intervention and use of phosphate binders. Unfortunately, access to the PTH assay in Australia is currently limited.

An uncontrolled survey reported calcitriol administration to CKD cats improved activity levels and appetite. Conversely, in another study, neither daily, nor intermittent calcitriol administration reduced PTH concentration. Additionally, a one year, randomized, controlled clinical trial of calcitriol administration to cats with CKD did not identify any significant benefits. Unfortunately, this study has not been published. Calcitriol administration is beneficial in both dogs and people where it prolonged survival (365 days in dogs with CKD treated with calcitriol, compared to 250 days in placebo treated dogs). It remains possible that the dose, study duration or false negative results affected the ability of the feline study to detect a genuine beneficial effect of calcitriol.

If serum phosphate levels are above 1.93 mmol/l (6.0 mg/dl), calcitriol administration causes soft tissue mineralisation. Nausea, vomiting, anorexia and PUPD are also reported. Calcitriol should only be considered after dietary phosphorous restriction and PBA use. In stages 1-2, dietary phosphate restriction may be sufficient to combat declining calcitriol levels. Based on current evidence and absence of a reliable PTH assay in Australia, it is difficult to justify routine administration of calcitriol to cats. Further studies are required.

Calcitriol administration

1. If serum creatinine is 176-265 µmol/l (2-3 mg/dl), calcitriol is initiated at 2.5-3.5 ng/kg/day
2. If serum creatinine is >265 µmol/l (>3 mg/dl), calcitriol is initiated at 3.5 ng/kg/day
    1. Calcitriol must be compounded for accurate dosing
    2. Administer on an empty stomach to reduce hypercalcaemia
    3. Ionized calcium (iCa), PTH, phosphate and creatinine concentrations are monitored every 2, 5 and 8 weeks after starting therapy
    4. If PTH remains increased, the calcitriol dose is increased by 1-2 ng/kg/day
    5. 5 ng/kg/day must not be exceeded
    6. iCa, PTH, phosphate and creatinine concentrations are monitored every 2, 5 and 8 weeks after dose adjustment

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7. If iCa is increased, treatment is stopped and calcitriol reintroduced at a lower daily dose. Alternatively, the daily dose is doubled and given every other day.
8. If levels are normal, the current dosage is continued.
9. Intermittent rather than daily dosing (or twice weekly dosing given every 3.5 days) is likely to become more common as less hypercalcemia appears to occur with this protocol.

Addressing malnutrition

An older cat with reduced body condition score and chronic kidney disease

Malnutrition in CKD patients occurs secondary to uraemic gastroenteritis, dehydration, azotaemia, electrolyte derangements, anaemia and underlying diseases. Underweight CKD dogs have shorter survival times and malnutrition likely has similar negative effects in cats. Kidney diets improve survival, so it is important to address any causes of inappetance that contribute to diet change failure.

Estimating resting energy requirements (RER =70x $BWkg^{0.75}$ or 30 (BW_{kg}) + 70) determines daily calorie needs. Dietary intake is improved by providing highly palatable, warmed food. Kidney diets are not offered when the patient is sick to avoid dietary aversion. During this time, any calorie intake is beneficial. Treatment goals are to maintain body weight and a body condition score of 5/9.

Appetite stimulants

Mirtazapine is a potent appetite stimulant with effects occurring within 30 minutes of administration. Ideally, food is offered around this time. In a recent study comparing placebo administration to cats with CKD, mirtazapine significantly increased appetite, decreased vomiting and improved body weight gain compared with placebo treated cats. Both oral and transdermal formulations are effective with transdermal preparations providing a more sustained plasma drug concentration over time.

Cyproheptadine and diazepam have appetite stimulant effects, however effects are short-lived and unpredictable. Adverse effects associated with cyproheptadine (e.g. sedation) are mild, however oral diazepam has been associated with idiosyncratic liver failure in a small number of cats. Generally, cyproheptadine and diazepam don't result in sufficient food intake to maintain RER and their use is not recommended.

Assisted enteral nutrition (feeding tube placement) is considered in cats that are inappetant or anorexic for over three days. Naso-oesophageal tubes (NO tubes) allow short-term nutrition, however only limited (e.g. liquid) diets can be administered. Oesophagostomy tubes (O-tube) allow provision of adequate nutrition (including kidney diets), water and facilitate medication administration. Possible complications include stoma site infection, tube migration and CKD progression following anaesthesia for placement, however the advantages of the O-tube tend to outweigh complications. The ability to easily provide adequate nutrition and medications appears to improve quality of life and can be life changing in some patients.

Uraemic gastroenteritis

The hormone gastrin is excreted by the kidneys. As kidney function deteriorates, gastrin concentration increases, increasing gastric acidity and the risk of gastrointestinal (GI) ulceration. Cats in stages 3-4 often demonstrate GI signs of uraemia (e.g. inappetance, nausea, vomiting, stomatitis, GI ulceration, diarrhoea, colitis). It is important to note that although gastrin levels are higher in cats with CKD, gastric ulceration itself appears uncommon. Lesions associated with fibrosis and mineralisation are more readily identified. This should be considered when prioritising medications for cats with CKD.

Stomatitis

Rinsing the oral cavity (0.1-0.2% chlorhexidine solution q 8-12 hr) reduces bacterial contamination associated with uraemic stomatitis and is tolerated in some cats. Providing analgesia (e.g. buprenorphine 0.01mg/kg sublingually, q 6-12 hr) is important.

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Vomiting

Vomiting occurs due to the effects of uraemic toxins on the chemoreceptor trigger zone and GI irritation. Many antiemetic agents are known to be effective in cats.

Maropitant inhibits NK1 receptors and is an effective, once daily antiemetic in cats with few adverse effects. Pain on injection may occur. Refrigeration reduces pain in dogs and this appears true in cats. Oral formulations are also available. Maropitant can be used chronically to effect. In cats with CKD it is safe and effective in reducing vomiting. Dose between 1-2 mg/kg PO q24hrs or 1 mg/kg subcutaneously q24 hrs. One study has evaluated the use of maropitant in cats with CKD compared with placebo. It was administered at a dose of 4mg orally, once daily for 2 weeks. Although cats receiving maropitant had less vomiting, there was no significant different in appetite, activity scores, weight or serum creatinine compared with placebo.

Maropitant can be a useful drug to reduce vomiting in cats with kidney disease

Metoclopramide is a dopaminergic antagonist, prokinetic and antiemetic agent. A short elimination half-life in other species and experience suggests constant rate infusions (CRI) are more effective. A recent prospective study demonstrated effectiveness of metoclopramide given orally as a prokinetic agent in healthy cats. In humans with kidney failure, metoclopramide clearance is reduced and metoclopramide administration reduced renal plasma flow. Dose reduction and concurrent intravenous fluid therapy (IVFT) should be considered in CKD cats.

Mirtazapine has antiemetic and potent appetite-stimulating properties, elicited via 5-HT_3 receptor antagonism. Pharmacokinetic studies in cats with stage 2-4 disease found prolonged renal clearance and lower doses are recommended. The author typically uses 2mg mirtazapine per cat, administered every 2-3 days as required to maintain a good appetite. Recently transdermal mirtazapine has also been shown to be effective as an appetite stimulant and the author has had good responses in cats with CKD and other chronic disease states.

Ondansetron and **dolasetron** are potent antiemetic agents, mediated via 5-HT_3 receptor antagonism. No studies have investigated their use in CKD cats, however experience with ondansetron suggests it is efficacious, albeit expensive. The wafer formulation is easiest to administer.

Gastric hyperacidity and altered GI motility

In CKD stages 3-4, addressing increases in gastric acid secretion and subsequent mucosal irritation is thought to be beneficial, however a recent study identified more changes due to fibrosis and mineralisation than ulceration. H_2 receptor blockers (famotidine, ranitidine, cimetidine) reduce gastric acidity. **Famotidine** is more potent than ranitidine with a similar duration of action. Unfortunately, it was no more effective than placebo in normal dogs. Studies in cats with CKD are required.

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Uraemic gastroenteritis slows GI motility resulting in ileus, which contributes to nausea and inappetance. Although **ranitidine** has a prokinetic action, it is no longer available. **Cimetidine** has a veterinary market authorization but provides no prokinetic action and demonstrates numerous drug interactions via effects on hepatic microsomal enzymes. A recent prospective study demonstrated effectiveness of metoclopramide given orally as a prokinetic agent in healthy cats.

Proton pump inhibitors (**omeprazole, esomeprazole**) are more potent than H_2 receptor blockers and are effective and useful, once daily agents in cats. Omeprazole may cause constipation, nausea and vomiting in a small number of human patients, however this is rarely observed in cats. Long term (over several years) administration may increase serum gastrin levels and predispose to the development of atrophic gastritis, a precursor of gastric carcinoid. These changes are not identified in cats and chronic administration appears safe. Only twice daily administration of omeprazole significantly reduced gastric acid secretion in healthy cats. Once daily omeprazole and standard doses of ranitidine did not reduce gastric acid secretion.

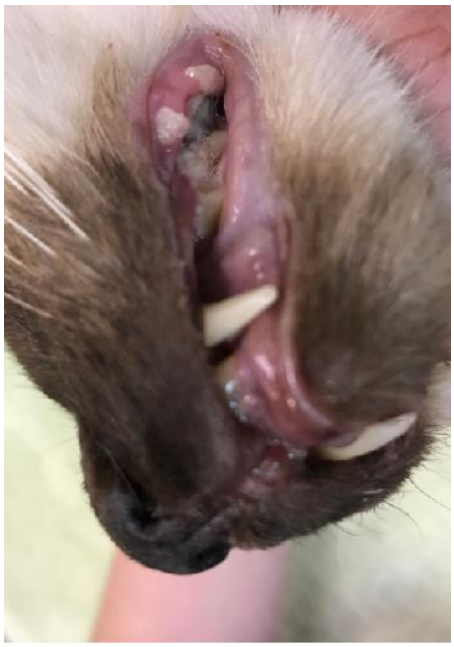
Sucralfate is an aluminium compound that forms a barrier over ulcers and stimulates bicarbonate and prostaglandin E_2 production. Unfortunately, sucralfate is difficult to administer to even the most tolerant of cats and adverse effects including vomiting, dehydration and worsening of azotemia associated with decompensation resulted in a recent study on sucralfate efficacy as a phosphate binder to be discontinued.

A recent retrospective study assessed the effect of acid-suppressant therapy on clinicopathologic parameters of cats with CKD. Cats received other treatments throughout the study period and often had co-morbid disease, so clear evaluation of therapeutic benefit is difficult. A significant increase in blood sodium concentration was found in cats receiving proton pump inhibitor treatment, however this was not associated with a more rapid progression of CKD.

Antiemetic and gastroprotectant agents are added one at a time, dependent on patient response. The author typically uses mirtazapine and maropitant first, with esomeprazole used if the patient is hospitalised and receiving intravenous fluids and IRIS stage 3 or 4. If nausea and/or vomiting persist, a metoclopramide CRI is added. Ondansetron is reserved for cats with refractory vomiting.

When the patient is discharged, mirtazapine and/or maropitant are prescribed for home use in the event of further vomiting or inappetance.

Commonly administered antiemetic and gastroprotective agents



A cat with severe azotemia demonstrating uremic ulceration

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Drug	Dosage	Additional considerations
Cimetidine	2.5-5 mg/kg PO, IV, IM q 12h	Numerous drug interactions No prokinetic effects
Esomeprazole	0.7-1 mg/kg IV q 12h	S-enantiomer of omeprazole
Famotidine	0.5-1 mg/kg PO q12-24h	30% dose reduction recommended in stages 3-4
Maropitant	1 mg/kg SQ, PO q24-48h or 4mg/cat PO q24-48h	A 2 day rest period after 5 days of treatment is recommended Alternate day oral dosing has been used for chronic administration Pain on injection reduced by refrigeration
Metoclopramide	0.1-0.5 mg/kg PO q8-12h 1-2 mg/kg/24 hours CRI	Useful prokinetic agent as CRI or per os CRI maybe more efficacious as anti-emetic 50% dosage reduction in CKD and concurrent fluid therapy recommended
Mirtazapine	2-3.75 mg per cat PO or transdermal daily to every 3 days to effect	Antiemetic effect possible Known appetite stimulant Dose-dependent adverse effects include hyperexcitability and muscle tremors Do not use concurrently with tramadol or ondansetron
Ondansetron	0.5-1 mg/kg PO q12-24h	Wafers are convenient to administer
Omeprazole	0.5-2.0 mg/kg PO q12h	Possible adverse effects from prolonged administration not yet identified in cats

CRI: constant rate infusion

Dehydration

Dehydration occurs due to inappetance, inadequate water intake to compensate for polyuria and underlying disease. Dehydration can potentiate CKD progression and uraemic crises. Addressing dehydration in cats with pre-existing CKD experiencing a uraemic crisis or ill, newly diagnosed CKD patients is important. Treatment goals are to correct dehydration, restore glomerular filtration rate (GFR), increase urine output and reduce azotaemia. Some of these goals are not achievable in patients with severe disease (e.g. restoration of GFR), however correction of dehydration is generally achievable.

Hydration status is assessed regularly but interpreted with care. Elderly or emaciated cats have reduced skin elasticity and uraemia may cause dry mucous membranes independent of hydration (xerostomia). Volume overload due to overzealous IVFT contributes to systemic hypertension and congestive heart failure, particularly in patients with concurrent disease (e.g. hyperthyroidism, occult hypertrophic cardiomyopathy) and should be avoided.

IVFT is administered to CKD cats using the following technique:

- Select a balanced electrolyte solution (e.g. Lactated Ringers/ Hartmanns, Plasmalyte-14, normosol R) and consider the requirement for parenteral potassium supplementation
- Calculate the dehydration deficit

Fluid deficit (mL) = ([(% dehydration)/100] x [body weight (kg)]) x 1000

- Replace the deficit gradually over 24 hours to reduce the risk of volume overload
- Calculate and add maintenance fluid requirements to the dehydration deficit (2.2 ml/kg/h)
- Add ongoing estimated losses (e.g. vomiting 5 ml replaced over 1-2 hours)

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- Ongoing patient monitoring to avoid volume overload is vital
  - 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 due to alterations in fluid status
  - Monitor trends in PCV/TP in the absence of GI haemorrhage
  - Monitor for signs of volume overload e.g. nausea, serous nasal discharge, chemosis, tachypnoea, pulmonary crackles, peripheral oedema, pulmonary oedema, pleural effusion and vocalization
- Assess creatinine and electrolyte concentrations every 24-48 hours
  - A return to normal baseline concentration is rare. Monitor for development of a plateau of creatinine (typically within 3-5 days) then gradually taper the IVFT over 24-48 hours

Reassess the patient again after 2-4 days to determine patient stability of the following:

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

For cats with CKD stages 3-4, **subcutaneous fluid therapy** (SQFT) may help prevent dehydration. Once daily, alternate day or twice weekly SQFT using a balanced electrolyte solution (e.g. Lactated ringers/Hartmann's) is useful in controlling dehydration in chronic patients. Dosage depends on patient size (30-100 ml/dose bid-eod, bi-weekly), as required to maintain hydration. Owners can be directed to http://www.icatcare.org/advice/cat-care/how-give-subcutaneous-fluids-your-cat for a step-by-step guide.

One study has evaluated owner experiences with administration of SQFT to cats. Most (85%) owners found it was an easy/no stress or somewhat easy/no stress experience and 89% reported an easy/no stress or okay experience for their cats. Several strategies appeared to improve tolerance of the procedure including:

- Warming fluids prior to administration
- Keeping time of administration to a minimum
- The use of treats for positive reinforcement and
- Needle size.

Subcutaneous indwelling catheters provide permanent ports for administration of SQFT. General anaesthesia is needed for placement, which could cause progression of kidney disease. Catheters may also provide a portal for bacterial infection. Recently, fibrosarcoma at the site of port insertion was reported in a cat with CKD. For owners who cannot manage SQFT using other techniques, these catheters may be beneficial.

For patients that do not require IVFT/SQFT or where owners decline these options, **increasing oral water intake** maybe beneficial. This can be achieved via improving water access, adding water to food, using water fountains and via O-tube placement. Oral intake of water avoids sodium increases associated with parenteral fluid administration. If oral intake remains inadequate, other methods of addressing hydration are required.

Proteinuria

Proteinuria is a negative prognostic marker for CKD in people, dogs and cats and forms part of the substaging for the IRIS staging scheme. Treatment to reduce the degree of proteinuria in cats maybe beneficial.

Cats with borderline proteinuria (UPC 0.2-0.4) require close monitoring. Cats with proteinuria (UPC >0.4) require investigation for any concurrent disease process (e.g. urinary tract infection, pyelonephritis, urolithiasis) and to confirm that the proteinuria is renal in origin.

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Current recommendations to reduce renal proteinuria are to commence dietary protein restriction and administer an RAAS inhibitor (e.g. ACEi or ARB). Drug therapy is contraindicated in a cat that is clinically dehydrated or showing signs of hypovolemia as a significant drop in glomerular filtration rate may occur. Correction of dehydration should be considered before drug introduction.

The goal is to reduce the UPC back into the normal range, or identify a 50% reduction. Serially increasing creatinine concentrations and/or increasing UPC suggests disease progression.

Patients with severe CKD or concurrent hypovolaemia may be dependent on glomerular hypertension in order to maintain total GFR. Introduction of an angiotensin converting enzyme inhibitors (ACEi) may reduce GFR, thus dose titration of the ACEi is performed cautiously with regular monitoring of creatinine.

A mild increase (10-15%) in creatinine concentration in a bright, hydrated cat with a good appetite is not an indication to stop treatment. Cats should be monitored for inappetance, dehydration and progressive increases in creatinine concentration. Increases 30% above pre-treatment baseline or inappetance or depression associated with ACEi administration warrant stopping treatment.

Angiotensin II receptor blockers

Angiotensin II receptor blockers (ARBs) also block angiotensin II via antagonism of the angiotensin II receptor. Recently **telmisartan** (used in human medicine for hypertension) has demonstrated similar effects to benazepril in reducing proteinuria in CKD cats. Although both telmisartan and benazepril reduced UPC to similar levels in cats with CKD, telmisartan also improved appetite in 17.6% of cats, compared to 10% of cats receiving benazepril. Telmisartan displaces angiotensin II from its binding site at the AT_1 receptor. By preferentially targeting AT_1 receptors, this may help prevent vasoconstriction, aldosterone release, sodium and water retention and glomerular hypertrophy.

Additionally, "ACE-escape", the phenomenon of gradually increasing levels of angiotensin II in patients chronically treated with ACEi, maybe avoided. It appears well accepted by most cats and excretion is independent of kidney function. Treatment results in a dose dependent decrease in mean arterial BP and reduced proteinuria within the first 7 days of treatment. Mild and transient GI signs (e.g. regurgitation, vomiting, diarrhoea) were seen and rarely, liver enzyme elevation was detected. This normalized when treatment was stopped. Telmisartan may also be used in conjunction with amlodipine. It is available as a once daily oral solution in Europe and Australia. It has also recently been demonstrates to be effective in reducing systolic arterial blood pressure (SABP) in hypertensive cats with SABP >160mmHg and <200 mmHg.

Angiotensin-converting enzyme inhibitors

ACEi effectively reduce efferent arteriolar constriction and subsequently glomerular hypertension. Aldosterone production may be reduced and kinin-induced peripheral vasodilation is enhanced. ACEi may also promote nitric oxide and vasodilator prostaglandin production.

Treatment with an ACEi improves survival in humans with proteinuric renal disease, but unfortunately, this has not been found in cats. Although benazepril reduced proteinuria, no survival benefit was found in a randomized controlled clinical trial of 61 cats with CKD receiving benazepril or a placebo. This was similar to findings in 192 CKD cats where administration of benazepril to proteinuric (urine protein: creatinine ratio (UPC) >1) cats increased appetite. A trend towards prolonged survival was identified, but it was not statistically significant.

The ACEi **benazepril** (0.25-0.5 mg/kg PO q 12-24 hr) is predominantly biliary excreted and is used over enalapril. Marked deterioration in kidney function has been associated with starting ACEi in both dogs and cats with CKD.

Dietary protein restriction

Dietary protein restriction is also recommended in proteinuric patients. Protein restriction above that found in kidney diets is likely unnecessary.

Essential fatty acid supplementation

Essential fatty acid supplementation reduces renal proteinuria in dogs. Most renal diets provide additional supplementation, however if more is required, fish oil (10-200 mg/kg per day) may be useful.

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Hypokalemia

Hypokalemia occurs in 20 – 30% of cats with CKD due to reduced intake, increased loss (e.g. urine, vomit) and renin-angiotensin-aldosterone system (RAAS) activation. Potassium supplementation in hypokalaemic cats with muscle weakness (e.g. neck ventroflexion) results in clinical improvement within one week. Total body potassium deficits may occur before hypokalaemia is identified on serum/plasma testing however no evidence exists that providing early potassium supplementation to cats is beneficial.

The findings of hypokalaemia (particularly if refractory to supplementation) and hypertension should prompt consideration for investigation for primary hyperaldosteronism (Conns syndrome).

Parenteral potassium chloride supplementation		
Serum potassium concentration mmol/l (mEq/l)	Concentration of potassium chloride (mmol) added to 500 ml Hartmann's or 0.9% NaCl	Maximum fluid rate (ml/kg/h) (Rate should not exceed 0.5 mEq/kg/h)
< 2	40	6
2-2.5	30	8
2.5-3	20	12
3-3.5	14	18
3.5-5.5	10	25
Oral potassium supplementation		
Potassium gluconate	1-3 mEq per cat q12h	
Potassium citrate	40-75 mg/kg q8-12h	

Potassium supplementation dosages

Metabolic acidosis

Metabolic acidosis is not uncommon in cats with CKD. Whether additional alkalinisation above that provided by kidney diets is required is unknown. It seems reasonable to provide additional alkalinization in stages 3-4 where blood pH is < 7.20 and bicarbonate concentration <15 mmol/l in hydrated patients. Treatment options include sodium bicarbonate and potassium citrate. Sodium bicarbonate is generally unpalatable. Potassium citrate is alkalinizing, provides additional potassium, is available in a liquid formation and is preferred.

Blood gas analysis is monitored every 10-14 days during stabilization with blood collected immediately prior to drug administration and pH determined within one hour. Bicarbonate concentration is maintained between 15-22 mmol/L and blood pH between 7.2-7.4.

Addressing anaemia of renal disease

Anaemia of renal disease results from insufficient kidney erythropoietin (EPO) production and is often exacerbated by GI haemorrhage, malnutrition and reduced red cell (RBC) lifespan due to the effects of uraemic toxins. It is typically normocytic, normochromic and poorly regenerative.

Approximately 30-65% of CKD cats develop anaemia with severity proportional to CKD stage. Whether anaemia severity affects survival is unclear. Moderate to severe anaemia is likely to negatively impact on quality of life.

All possible causes of anaemia should be addressed. GI haemorrhage without melena or hypochromia occurs, and should be suspected if anaemia severity outweighs the degree of renal dysfunction present or if urea concentration is disproportionately increased compared to serum creatinine in the absence of marked dehydration.

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Recombinant human erythropoietin analogues (R-HuEPO), including epoetin and darbepoetin, have been used in CKD cats with improvements in appetite and quality of life identified. Both products are identical to the naturally occurring hormone in people and relatively similar (83.3%) to feline erythropoietin. Darbepoetin has a prolonged half-life, requiring less frequent administration than epoetin, but is more expensive.

Darbopoeitin can be useful in cats with anaemia due to chronic kidney disease

As recombinant human EPO (R-HuEPO) differs structurally from feline EPO, a major obstacle in treatment is anti-EPO antibody development, which cross-reacts with the R-HuEPO agent and EPO, causing pure red cell aplasia (PRCA), a severe, non-regenerative anaemia. PRCA may occur in 25-30% of cats receiving R-HuEPO. The prolonged half-life of darbepoetin may reduce the antigen load administered and possibly reduce antibody development compared to epoietin.

There is limited information on the efficacy and safety of R-HuEPO administration in CKD cats. In one retrospective study, most cats treated with darbepoetin (56%) responded to treatment and responders lived significantly longer than non-responders. Concurrent disease was more common in non-responders. Notably however, cats were only included in the 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 kidney disease. Investigations are required to evaluate the effect of R-HuEPO on survival and the best time to start treatment. R-HuEPOs are considered in cats with advanced CKD and a HCT <22% plus clinical signs of anaemia (e.g. weakness, tachycardia, tachypnoea, pallor) without an obvious underlying cause.

Possible adverse effects of R-HuEPOs include polycythaemia, vomiting, iron deficiency, injection site discomfort, skin reactions, fever and arthralgia. Hypertension occurred in 41-50% of cats and seizures occurred in 16% of cats. The author has used darbopoetin frequently and has not yet experienced seizures as an adverse effect.

In people, the use of epoetin has been largely replaced by darbepoetin because of its increased potency and duration of action.

Guidelines for erythrocyte stimulating agent administration

	Darbepoetin	Epoetin
Induction dosage	1 µg/kg SQ once weekly	100 IU/kg SQ 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; ferrous sulphate 50-100 mg/cat daily)	
Initial monitoring	Weekly physical examination, SBP and PCV until target achieved	
Target PCV	Target PCV is 25-35%, with 1-3% increase per week Avoid rapid increases in PCV 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 a physical examination, CBC, serum biochemistry, serum cobalamin, iron panel and consider diagnostic imaging and bone marrow sampling to identify PRCA and/or underlying causes of anaemia If no underlying co-morbid disease is identified, treatment failure is likely due to anti-EPO antibody formation and ESA treatment should be stopped	

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CBC: complete blood count; EPO: erythropoietin; ESA: erythropoietin stimulating agent; PCV: packed cell volume; PRCA: pure red cell aplasia; SBP: systolic blood pressure

Iron deficiency can occur due to GI haemorrhage and reduced absorption or intake. 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.

Anabolic steroids (e.g. nandrolone cypionate, stanozolol) were thought to improve haematocrit, appetite and muscle mass. Unfortunately, results are generally mild or inapparent and stanozolol is hepatotoxic in cats. Anabolic steroids are no longer recommended for use in cats with CKD.

Other treatments considered in CKD.

Aldosterone receptor antagonists
Aldosterone receptor antagonists (e.g. spironolactone) are used in humans to reduce proteinuria and stabilize kidney function, often in conjunction with ACEi and ARBs. Use in cats with CKD has not been evaluated and cannot be recommended at this time.
Haemodialysis
Intermittent haemodialysis for the treatment of CKD is pivotal in humans, however availability is limited for cats. Peritoneal dialysis is possible but technically difficult and is more likely to be utilized in patients with acute kidney injury.

Other potential treatments for CKD
Renal allograft (renal transplant) has limited availability and severe complications may occur.
Theoretically, **pre- and probiotics** redistribute nitrogen into the gastrointestinal tract for elimination, reducing azotaemia and selecting bacteria to promote intraluminal nitrogen utilization and reduce colonic absorption. However, there was no efficacy in one study evaluating probiotics administered with food.
Intrarenal mesenchymal stem cell injection was assessed in 4 cats with CKD (and 2 healthy cats). Two of the cats with CKD showed a modest improvement in GFR, however numerous sedations and interventions were required to develop and implement the treatment. Further investigations in larger numbers of patients are required.

Ongoing monitoring and prioritizing therapy

CKD is a progressive disease, requiring ongoing monitoring as determined by disease severity, client compliance, treatment response and financial constraints. Following diagnosis, patients are monitored every 2-4 weeks until disease stability is established and persistent changes (e.g. hypertension, proteinuria) identified.
Patients in stages 1-2 could be monitored six monthly and stages 3-4, every one to three months.
Possible parameters for long term monitoring

BCS: body condition score; iCa: ionized calcium concentration; PCV: packed cell volume; PTH: parathyroid hormone concentration; SBP: systolic blood pressure; TP: total plasma protein concentration; UPC: urine protein: creatinine ratio

Treatment for cats with CKD is prioritized based on the likelihood it will be beneficial (e.g. strength of evidence available), together with consideration of cat and owner compliance, ease of administration, resource availability and financial constraints.

Given the strong evidence supporting kidney diets, ensuring successful dietary modification must take priority. Currently, treatment of CKD is all about management rather than cure. Treatment is tailored based 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 for feline patients.

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Prognosis

IRIS staging can provide information regarding prognosis for CKD. Survival times for lower stages can be long and cats receiving effective treatment often die from other diseases. Other factors affecting prognosis include proteinuria (UPC) and serum phosphate concentration. Additionally, weight loss may also indicate deteriorating renal function.

Survival estimates for cats classified by IRIS stage.

IRIS stage	Survival time estimate (years (days)) Boyd et al. 2008	Survival time estimate (years (days)) Syme et al. 2006	Survival time estimate (years (days)) King et al. 2006
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)

* Stage 2b azotaemic stage: creatinine concentration [200-250 µmol/L]
$_{BP}$ Indicates survival estimate for hypertensive cats
IRIS: International renal interest society