



Diagnosis and Management of Chronic Renal Failure in Cats

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Chronic renal failure (CRF) is a common and important cause of morbidity and mortality in cats. The hallmark of CRF is a chronic decline in the population of functional nephrons to a point where the glomerular filtration rate (GFR) is no longer adequate to maintain normal excretory function. This leads to azotemia (elevation in plasma urea and/or creatinine concentrations) and the retention of other plasma solutes and protein catabolic products normally eliminated via the kidneys. Ultimately, renal dysfunction and the retention of these products results in a spectrum of clinical signs associated with CRF, commonly referred to as the “uremic syndrome.” In the early stages of CRF, the declining number of nephrons is compensated for by increased individual (single) nephron GFR (SNGFR). The overall decline in GFR is therefore not proportional to the number of functioning nephrons lost, and this is one reason why early detection of renal disease is difficult.

Although CRF can be seen in young cats and both congenital and hereditary causes are recognized, it is most commonly encountered as an acquired disease in middle-aged to old cats. CRF is thought to be around two to three times more common in the cat than the dog. Furthermore, cats often have more advanced disease than dogs by the time veterinary attention is sought, probably due to the differences in clinical presentation of the disease between the two species (especially polydipsia and polyuria—see later). By the time clinically evident renal failure is present, there is generally a loss of at least 70% of functioning nephrons.

This article will look briefly at the etiology, clinical signs, and diagnosis of feline CRF and then outline approaches to the medical management of this condition.

ETIOLOGY

The underlying etiology of feline CRF is often obscure

although a variety of causes have been documented (Box 1). Histological evaluation of kidneys from affected cats usually reveals chronic interstitial nephritis,¹ but the cause of this is uncertain. It has been speculated that chronic pyelonephritis or glomerulonephritis may account for at least some of these “end stage” cases of chronic renal failure.

CLINICAL SIGNS AND DIAGNOSIS

The clinical manifestations are often nonspecific, with dehydration, anorexia, lethargy, and weight loss being the most common signs (Table 1, data derived from three studies²⁻⁴). Polyuria and polydipsia (PU/PD), which would be regarded as major clinical signs in canine CRF, are reported much less frequently in cats. This is partly, perhaps, because of

BOX 1

Potential etiologies of feline chronic renal failure

- Chronic tubulointerstitial nephritis
- Glomerulonephritis
- Pyelonephritis
- Polycystic renal disease
 - congenital
 - acquired
- Amyloidosis
 - familial
 - acquired
- Nephrotoxins
 - antibiotics
 - ethylene glycol
- Hypercalcemia
- Hydronephrosis
- Renal lymphoma



TABLE 1
Common clinical signs in 337 cases of feline CRF*

Clinical sign	%
Dehydration	67
Anorexia	64
Lethargy/depression	52
Weight loss	47
PU/PD	32
Vomiting	30
Macrorenale	25
Microrenale	19
Pale mucosae	7
Oral ulceration	5
Diarrhea	4
Retinal detachment	4
Also	
Hematuria/dysuria	
Poor coat	
Halitosis	
Osteodystrophy	
Constipation	

*Based on three studies²⁻⁴

their life-style (decreased recognition of PU/PD) but probably mainly because many cats retain much greater urine concentrating ability in the face of CRF than is the case in dogs. Furthermore, although CRF is typically associated with palpably small and irregular kidneys, many cats with CRF have enlarged kidneys reflecting underlying conditions that lead to renomegaly, such as polycystic kidney disease and renal lymphoma. Other common manifestations of the uremic syndrome in cats include vomiting (due to central effects of uremic toxins, hypergastrinemia, and uremic gastric ulceration), pale mucous membranes (due to anemia), and hypertensive retinopathy (including retinal detachments—Figure 1). Systemic hypertension has been reported to occur in up to 60% to 70% of cats with CRF.

Diagnosis of CRF is usually based on clinical signs with the demonstration of azotemia and inappropriately concentrated urine. Because cats often retain some concentrating ability during CRF, isosthenuria is not necessarily observed. In one study, isosthenuria was found in 57% of cats with CRF but degrees of hypersthenuria (SG > 1.015) in 42%. In another study, 60% of cats with CRF had a SG > 1.012. Few cats with advanced CRF can concentrate urine above 1.035 though, and azotemia with a urine SG < 1.035 to 1.040 is usually considered evidence of primary renal failure.^{2,4}

In addition to azotemia, a number of other clinicopathological changes are commonly observed in feline CRF (Table 2,



Figure 1
Sudden onset of blindness with retinal detachment—a severe manifestation of systemic hypertension that can be a complication of chronic renal failure.

data from two studies^{2,4}). Important among these are hyperphosphatemia (due to the decreased GFR), acidosis (inability of the failing kidneys to excrete the normal acid load), hypoproliferative anemia (due to reduced erythrocyte life span, uremic suppression of erythropoiesis, and a relative or absolute deficiency of erythropoietin). Some of the other commonly observed changes (e.g., leukocytosis, lymphopenia, hyperglycemia, and hyperproteinemia) may simply reflect the effects of stress and/or dehydration. With the exception of hyperphosphatemia, severe electrolyte disturbances are generally not encountered until the very late stages of disease. However, in feline CRF an important exception to this is potassium. Hypokalemia is commonly observed in feline CRF, probably due mainly to inappropriate kaliuresis, and is an important complication in this species.

TABLE 2
Common clinicopathological findings in 206 cases of feline CRF*

Finding	%
Elevated urea	99
Elevated creatinine	97
Hypercholesterolemia	73
Decreased TCO ₂	64
Hyperphosphatemia	64
Anemia	37
Hypokalemia	23
Others	
Hyperamylasemia	
Lymphopenia	
Hyperproteinemia	
Hyperglycemia	
Leukocytosis	

*Based on two studies^{2,4}



Figure 2
Intravenous fluid therapy—frequently an important part of stabilization of the patient with chronic renal failure.

reduced renal perfusion, and further impairment of renal function. Some cats are presented in acute decompensation of CRF due to sudden volume depletion, whereas others, particularly as CRF progresses, may experience chronic or recurrent dehydration and renal hypoperfusion. Acutely decompensated cats require intravenous fluid therapy (Figure 2), with reassessment of azotemia after correction of the dehydration to permit accurate assessment of renal function. Maintaining adequate fluid intake is of prime importance, and owners should be made aware of the obligatory polyuria that frequently accompanies renal failure and, therefore, the consequent need for free access to water. Additional water intake can be achieved in a variety of ways (e.g., feeding moist rather than dry foods and by supplementing the diet with water or broth), but, in cats that fail to maintain adequate voluntary fluid intake, many owners may be willing to administer subcutaneous fluids in the home environment (e.g., fluids composed of two parts 5% dextrose to one part lactated Ringer's solution).

ASSESSMENT OF RENAL FUNCTION

Although measurement of GFR is possible and is the standard test of renal function, current methodologies are cumbersome and/or expensive and so are not routinely used in clinical practice. Instead, evaluation of serum urea and creatinine levels are usually used as an indicator of renal function. If nonrenal factors are eliminated, azotemia implies functional loss of around 75% or more nephrons. Care needs to be exercised in interpreting urea and creatinine levels though, particularly in the high-normal to mildly elevated range, as even a quite substantial deterioration in renal function here will result in only relatively small elevations of urea/creatinine. Conversely, late in renal disease a relatively small deterioration in renal function can cause a marked increase in urea/creatinine concentrations. In general, serum creatinine concentrations reflect renal function more accurately than urea concentrations.⁵

MEDICAL MANAGEMENT

Treatment of underlying cause

Identifying and treating reversible causes or contributory factors to CRF is important, although in many cases these may not be present. However, searching for conditions such as pyelonephritis, glomerulonephritis, and urinary tract obstruction or iatrogenic renal damage through administration of non-steroidal antiinflammatory drugs or aminoglycoside antibiotics may allow intervention to arrest further renal damage.

Maintaining fluid balance

Inadequate water intake in CRF is associated with dehydration,

Delaying the progression and managing the complications

Dietary protein restriction

Evidence to support clinical benefit

Good

Evidence to support role in preventing progression

Poor

The clinical benefits of protein restriction in CRF have been supported by studies performed in cats and other species.^{6,7} The products of protein catabolism are thought to contribute significantly to the clinical signs associated with the uremic syndrome, and thus dietary restriction of nonessential protein should reduce nitrogenous wastes and help to ameliorate clinical signs such as vomiting, anorexia, inappetence, weight loss, anemia, and lethargy. Moderate protein restriction in the face of azotemia is therefore a standard recommendation for cats with CRF and is usually best achieved through the use of commercial low-protein diets.

Whether dietary protein restriction has any impact on the progression of renal failure in cats is still very controversial. As in dogs with reduced nephron numbers, the response of the remaining nephrons in cats is an increase in SNGFR achieved by glomerular hyperfiltration, glomerular hypertrophy, and glomerular hypertension and is associated with increased proteinuria.⁸ In some experimental models (most notably in rats), these adaptive changes have been demonstrated to be harmful to the remaining nephrons and, ultimately, to cause or contribute to the progression of CRF.⁷ Restriction of dietary protein can minimize these changes in the experimental models and thus retard the progression of the disease. A recent meta-



analysis of several studies also suggested that protein restriction may slow its progression in humans,⁹ but the same has not been proven in dogs and cats.

Limited studies have been performed in cats, but in one experimental model, protein/calorie restriction resulted in significantly lower proteinuria and glomerular morphological injury, although GFR remained stable in both low- and high-protein/calorie diet groups.¹⁰ Although this study suggested that dietary protein restriction might limit renal morphological damage, the confounding effect of variable calorific intake was not excluded and there is currently no evidence that protein restriction retards the progression of CRF in cats. Furthermore, the reduced palatability of protein-restricted diets to many cats can limit their clinical value, and it is important to avoid protein-calorie malnutrition by using a diet either too restricted in protein or that the animal finds unpalatable.

Dietary phosphorus restriction

Evidence to support clinical benefit **Good**
Evidence to support role in preventing progression **Poor**

Phosphorus retention in CRF is an important factor in the development of renal secondary hyperparathyroidism and also soft-tissue mineralization.¹¹ Dietary phosphorus restriction may therefore blunt renal secondary hyperparathyroidism and, in one study of cats with induced renal failure,¹² was able to prevent renal histological lesions (mineralization, fibrosis, and inflammation) found in cats fed an unrestricted diet. However, neither group of cats in this study had evidence of progressive renal dysfunction.

On the basis of the findings in cats and by extrapolation from studies in dogs and other species, dietary phosphorus restriction is advised in CRF. The use of low-protein diets will achieve a reduced phosphorus intake, but this will not always be sufficient to prevent the hyperphosphatemia encountered in CRF.

If hyperphosphatemia persists (fasting serum phosphorus > 2 mmol/L) despite dietary restriction, oral phosphate binders may be given with meals. Aluminum hydroxide, aluminum carbonate, or aluminum oxide are most commonly used at doses of 30 to 90 mg/kg/day, adjusted according to the response. Calcium-based agents are also available (calcium carbonate and calcium acetate), but their use may induce hypercalcemia.

Calcitriol therapy

Evidence to support clinical benefit **Poor**
Evidence to support role in preventing progression **Poor**

Calcitriol therapy (1.5–3.5 ng/kg/day) has been recommended



Figure 3
Hypokalemia and generalized polymyopathy in a cat secondary to chronic renal failure.

for the treatment of cats with CRF¹³ on the basis that it is an effective treatment for renal secondary hyperparathyroidism and that the latter may have an important role in the pathogenesis of the uremic syndrome and, possibly, progression of renal failure. Although calcitriol has received quite extensive clinical use and is strongly advocated by some clinicians,¹⁴ controlled studies to substantiate a beneficial role for this therapy are lacking. Further studies are necessary before this therapy can receive strong recommendation.

Control of hypokalemia

Evidence to support clinical benefit **Good**
Evidence to support role in preventing progression **Good**

Hypokalemia, probably mainly from inappropriate kaliuresis, is a common finding in feline CRF (Table 2). The cardinal sign of severe hypokalemia is polymyopathy with generalized muscle weakness and ventroflexion of the neck. Furthermore, it appears that hypokalemia may adversely affect renal function and contribute to CRF. Potassium supplementation of hypokalemic cats in CRF often results in improved renal function.¹⁵ In addition, feeding a potassium-restricted acidifying diet to normal cats has been shown to induce renal damage.^{16,17}

Hypokalemic polymyopathy is considered to be the most common cause of generalized muscle weakness in cats, and the majority of these cases are related to CRF (Figure 3). Routine assessment of serum potassium is therefore recommended, with supplementation where necessary (Figure 4). Nonacidifying, low-protein diets help to maintain serum potassium con-



Figure 4
Same cat shown in Figure 3 after 36 hours of supplementation with potassium-enriched intravenous fluids.

centrations, but, if they fall below 4 mmol/L, supplementation with potassium salts is recommended. Potassium gluconate is preferable to potassium chloride, which is unpalatable and may cause gastrointestinal irritation. Initial doses of 1 to 4 mmol potassium twice daily may be given according to the severity of the hypokalemia, with doses of 1 to 2 mmol potassium twice daily usually maintaining normokalemia (serum potassium of 4–5 mmol/L).

Although low-dose oral potassium supplementation has been advocated for all cats with CRF, a recent study showed no benefit from potassium gluconate supplementation of normokalemic cats with naturally occurring CRF.¹⁸

Control of acid-base status

Evidence to support clinical benefit	Good
Evidence to support role in preventing progression	None

Metabolic acidosis is frequently encountered in CRF (Table 2) and may contribute to a number of important features, including anorexia, vomiting, nausea, weight loss, lethargy, hypokalemia, and skeletal muscle demineralization. There are clear potential clinical benefits, therefore, for the management of acidosis in CRF and if total CO₂ (TCO₂) concentrations (or bicarbonate levels) are <15 mmol/L, oral sodium bicarbonate therapy should be considered. This should be administered at an initial dose of 5 to 10 mg/kg given two or three times daily. Dosage needs to be adjusted according to response, with the aim of maintaining TCO₂ concentra-

tions between 18 and 23 mmol/L. If the cat is receiving a urinary acidifying diet, this should be stopped and, ideally, a low-protein diet instituted.

Control of systemic hypertension

Evidence to support clinical benefit	Good
Evidence to support role in preventing progression	Poor

Systemic hypertension is a common finding in feline CRF, although its true prevalence is difficult to determine. Indirect systolic blood pressure (SBP) is readily measured in cats by the Doppler ultrasonic method (Figure 5). Using techniques designed to mimic the situation in an outpatient clinic, we found a mean SBP in healthy cats of 161 mmHg, with some cats having a SBP up to 200 mmHg.¹⁹

In humans, there is unequivocal evidence that control of systemic hypertension retards the progression of CRF.²⁰ Such evidence is lacking in dogs and cats, but, given our current state of knowledge, we would nevertheless recommend instituting antihypertensive therapy for any cat with a SBP consistently >200 mmHg. Furthermore, cats with SBP >180 mmHg require close monitoring, and therapy is indicated for any cat with evidence of hypertensive retinopathy.

The most commonly used drugs for treatment of feline hypertension are the calcium channel blocker amlodipine besylate (0.625–1.25 mg daily administered orally) or the ACE inhibitor enalapril (0.25–0.5 mg/kg once or twice daily administered orally).



Figure 5
Measurement of systolic blood pressure using an indirect Doppler ultrasonic technique.



Management of hypoproliferative anemia

Evidence to support clinical benefit **Good**
Evidence to support role in preventing progression **None**

Progressive anemia is common in CRF (Table 2) and appears to contribute to a variety of clinical signs including lethargy, inappetence, weakness, and weight loss. Hormone therapy with either androgenic steroids or recombinant human erythropoietin (r-HuEPO) is the most widely used treatment for anemia of CRF. In some cats, however, iron deficiency can contribute to the anemia both through inadequate dietary intake and gastrointestinal blood loss. Ferrous sulfate can be given orally at a dose of 50 to 100 mg daily in such cats to correct the deficit. If gastrointestinal bleeding occurs, this also requires attention and the use of sucralfate and/or H₂-receptor antagonists (see below).

Although the administration of androgenic steroids (e.g., nandrolone decanoate at 1–1.5 mg/kg weekly by intramuscular injection) is widespread, there is no substantial evidence to support their use in cats with CRF, and clinical experience suggests that response to therapy, at least in terms of improvement of the anemia, is generally poor.²¹

The value of r-HuEPO has been established in several studies, and it has the capacity dramatically to reverse the anemia and, therefore, to have a significant impact on the clinical condition of the cat. However, possible benefits of treatment have to be weighed against risks of adverse effects and the cost of the drug. Typically, doses of 100 u/kg r-HuEPO (range 50–150 u/kg) are given by subcutaneous injection three times weekly, until the PCV reaches approximately 30%; it is then reduced to a typical maintenance dose of 50 to 100 u/kg given one to three times weekly.²¹ Complications of r-HuEPO therapy include poor response due to iron deficiency (routine iron supplementation may be prudent during therapy), hypertension, polycythemia, and the induction of anti-r-HuEPO antibodies. The latter is potentially the most important side effect and is thought to occur in approximately 30% of treated cats, leading to abrogation of the erythropoietic response and necessitating the withdrawal of treatment. Given the relatively high prevalence of this complication, r-HuEPO therapy is usually reserved for cats with moderate to severe anemia (PCV ≤20%).

Control of nausea and vomiting

Evidence to support clinical benefit **Good**
Evidence to support role in preventing progression **None**

Nausea and vomiting may contribute significantly to the inappetence and weight loss associated with CRF, and attempts

should be made to treat these complications. Uremic gastritis due to hypergastrinemia may be treated with H₂-antagonists (cimetidine, ranitidine), but reduced doses should be used due to the renal excretion of these drugs. Ranitidine may be given intravenously or orally at approximately 2 to 4 mg/kg twice daily. Sucralfate (250–500 mg orally two or three times daily) may also be valuable if there is gastric ulceration.

In addition, centrally acting antiemetics such as metoclopramide (0.2–.5 mg/kg orally three or four times daily) may be helpful in blocking uremic toxin stimulation of the chemoreceptor trigger zone.

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