



Diagnosis and Management of Chronic Renal Failure in Dogs

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ABSTRACT

Chronic renal failure (CRF) in dogs is defined as azotemia of renal origin that has been present for more than 2 weeks. CRF should be distinguished from acute renal failure (ARF); parameters indicative of chronicity include duration of signs, normocytic, normochromic nonregenerative anemia, and bone disease (renal osteodystrophy). The goals of therapy are to maximize the quality and length of life by maintaining adequate nutrient and energy intake, reducing uremia and its complications, and arresting progressive renal injury. Part of the treatment of CRF includes management of secondary factors such as impaired phosphorus homeostasis, glomerular hyperfiltration, hypertension, hypertrophy, systemic hypertension, renal inflammation, and metabolic acidosis. The term *uremic syndrome* is used to describe a variety of clinical abnormalities that occur following the development of marked azotemia and that affect the animal's quality of life; these problems need to be managed, and treatment should be tailored to the individual patient. General recommendations include restricting dietary protein.



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DIAGNOSIS

Chronic renal failure (CRF) in dogs can be defined as azotemia of renal origin that is of more than 2 weeks' duration. Thus a diagnosis of renal failure may be established by identification of azotemia in the absence of pre-renal (e.g., dehydration, systemic hypotension, or hyperproteinemia) or postrenal (e.g., obstruction or rupture) factors. In the dog, the presence of a concentrated urine (specific gravity >1.030, osmolality >900 mOsm/kg) is inconsistent with renal azotemia unless marked proteinuria is present.

Distinguishing acute from chronic renal failure can be of diagnostic, prognostic, and therapeutic significance. The most useful parameters in establishing chronicity are the duration of signs; a normocytic, normochromic nonregenerative anemia; and/or bone disease (renal osteodystrophy). Sequential evaluations of serum creatinine concentration are useful in assessing the rate of change of renal function over time.

The diagnostic tests that are routinely used to establish a diagnosis and full evaluation of a patient with renal failure include urinalysis, urine culture, urine protein-to-creatinine ratio, serum biochemical panel, complete blood count, and, ideally, measurement of systemic arterial blood pressure.

GENERAL THERAPY

The general goals of therapy of dogs with CRF may be summarized as efforts designed to maximize the quality and quantity of life through:

- maintenance of adequate nutrient and energy intake
- reduction of the prevalence and severity of uremia
- reduction of mortality from the complications of uremia
- arresting progressive renal injury.

Careful attention to detail is required in the medical management of dogs with CRF. Clinical problems should be identified, appropriate therapy instituted (Table 1), and the progress of clinical problems carefully and regularly monitored (Box 1).

MANAGEMENT OF PROGRESSIVE CRF

Frequently, animals with renal disease suffer progressive decrements of renal function until terminal uremia ensues (Figure 1). Progression may occur as a result of the ongoing primary renal disease, but secondary factors

BOX 1

Schedule for monitoring of patients with chronic renal failure

<i>Nonazotemic renal failure</i>	Urinalysis, urine culture, serum creatinine concentration (SCr), hematocrit, and blood pressure every 6 months Biochemical panel and complete blood count annually
<i>Azotemic renal failure</i>	Urinalysis, urine culture, SCr, hematocrit, and blood pressure every 3–6 months. More frequently if renal function is unstable
<i>Uremic renal failure</i>	SCr >4 mg/dl or systemic hypertension is documented Biochemical panel and complete blood count annually SCr, BUN, electrolytes, calcium and phosphate every 1–3 days until patient becomes nonuremic Then manage as azotemic renal failure



TABLE 1
Management of abnormalities observed in renal failure

Abnormality	Evaluation method	Therapy
Hyperphosphatemia	Serum phosphorus (P)	Dietary P restriction Intestinal P binders
Hypokalemia	Serum potassium (K)	Dietary K supplements
Acidosis	Serum bicarbonate or total CO ₂	Dietary alkalinizers
Anemia	Complete blood count	Increase caloric intake Erythropoietin Anabolic steroids (?)
Uremia (vomiting, lethargy, inappetence)	History, physical examination	Dietary protein restriction Diagnose and manage all clinical abnormalities
Inappetence	Monitor intake	Change diets Warm food Add palatability enhancers Increase physical activity Cyproheptadine (?) Anabolic steroids (?)
Systemic hypertension	Blood pressure determination	Antihypertensives Dietary sodium restriction
	Ocular examination	(?)
Urinary tract infection	Routine urine cultures Sensitivity testing	Antibiotics Follow-up culture
Progressive renal failure	Serial serum creatinine determinations	Treat primary disease Normalize serum P Antihypertensives (?) Omega-3 PUFA (?)

gression of CRF due to the development of nephrocalcinosis or other effects of hyperphosphatemia, including renal secondary hyperparathyroidism.¹

Renal secondary hyperparathyroidism is common in animals with azotemia of renal origin. Factors that contribute to its development include:

- Phosphate retention, which leads to calcium-phosphate deposition within tissues (often referred to as metastatic mineralization). This, in turn, reduces plasma ionized calcium concentration. The resultant hypocalcemia, although subclinical, stimulates the release of parathyroid hormone (PTH).
- Loss of renal mass, which, in concert with phosphate retention, leads to decreased production and/or activity of the renal 1- α -hydroxylase enzyme, causing reduced generation of 1,25 dihydroxyvitamin D (calcitriol). Hypocalcitraemia results in increased synthesis of PTH and reduced intestinal calcium absorption.

A variety of clinical abnormalities observed in animals with the uremic syndrome have been attributed to the presence of excess PTH. These include uremic osteodystrophy, anemia, arthritis, cardiomyopathy, encephalopathy, glucose intolerance, hyperlipidemia,

have also been implicated in dogs. These factors are believed to be self-perpetuating and operate independently of the primary disease.

They include:

- impaired phosphorus homeostasis
- glomerular hyperfiltration, hypertension, and hypertrophy
- systemic hypertension
- renal inflammation
- metabolic acidosis.

Impaired phosphorus homeostasis

Dietary phosphorus levels are critical for dogs with CRF because phosphorus retention occurs in affected animals as a consequence of impaired renal phosphorus excretion. Excessive intake of dietary phosphate may contribute to the pro-

gression of CRF due to the development of nephrocalcinosis or other effects of hyperphosphatemia, including renal secondary hyperparathyroidism.¹

Therapy

To slow the progression of renal failure, dietary phosphate restriction is advised in all azotemic patients. For dogs, this low-phosphorus diet should contain approximately 0.25% phosphorus on a dry matter basis (supplying 34–42 mg/kg/day). The goal of therapy is normophosphatemia, but, if this has not been achieved after 2 to 4 weeks of phosphate restriction, intestinal phosphorus binders should be added to the diet. Either aluminum- or calcium-containing salts can be employed as phosphorus binders at the same initial dose of 30 to 180

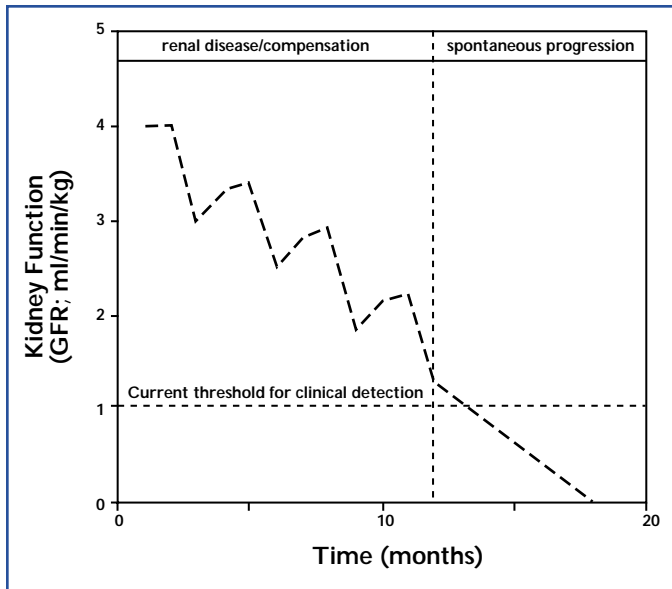


Figure 1

Proposed model of the course of chronic renal disease in dogs. The early stages of renal disease are characterized by a balance between the detrimental effects of renal injury caused by the primary disease process and the apparently beneficial effects of renal compensations. The disease is rarely recognized at this stage. Later, self-perpetuating renal injury predominates and renal function declines progressively, regardless of inciting cause. This latter stage will progress to end-stage uremia even in the absence of a primary renal disease. Early diagnosis of CRF and institution of therapies to slow this spontaneous progression have become pivotal in the proper management of CRF in dogs.

mg/kg/day, but the former may be associated with osteodystrophy or encephalopathy whereas the latter is causally associated with hypercalcemia in some dogs. The phosphorus binder can be mixed with moistened or canned food, but doses should be changed gradually to limit food aversion.

Although it has been argued that PTH is a uremic toxin and responsible for the progression of renal failure, these assertions remain controversial.^{2,3} Dietary phosphorus restriction with or without an intestinal phosphorus binding agent, as outlined above, will generally lower but not normalize serum PTH concentration. At present, there is no clear support for the use of therapy designed to lower PTH further.

Oral calcitriol therapy (0.7–1.4 ng/kg/day given separately from meals) will lower PTH in most, but not all, dogs with CRF.² Treated animals should be monitored every 2 to 4 weeks to avoid hypercalcemia and resultant hypercalcemic nephropathy.

Glomerular hyperfiltration, hypertension, and hypertrophy

These adaptive changes in glomerular function appear to be detrimental to canine glomeruli.^{4–6} The initial rationale for dietary protein restriction was to prevent these maladaptations, but it has proven to be of no apparent benefit in long-term trials in dogs.

Therapy

Dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs) may, however, prove beneficial in lowering intra-glomerular pressure.⁷ Although data are not conclusive, one of the proposed goals is to achieve an omega-6/omega-3 ratio of between 0.2:1 and 5:1. Some manufacturers are changing the fat content of their diets, but commercial diets are already available that lie within or close to this range and manufacturers will generally supply this information on their diets. As an alternative, dietary supplements containing eicosapentaenoic or docosahexaenoic acid (both omega-3 PUFAs) are generally available at health food stores. A general rule of thumb would be 0.5 to 1.0 g of omega-3 PUFA per 100 kcal of food.

The use of an antihypertensive agent, such as an angiotensin-converting enzyme (ACE) inhibitor, may lower glomerular pressure and interfere with a variety of growth factors that appear to play a role in glomerulosclerosis and interstitial fibrosis. Appropriate agents might include enalapril (0.5 mg/kg every 12–24 hours) and benazepril (0.25–0.5 mg/kg every 12–24 hours). Other antihypertensive agents (e.g., amlodipine 0.05–0.25 mg/kg daily or other calcium channel antagonists) may also be renoprotective through antihypertensive or other mechanisms.

Systemic hypertension

Animals with renal diseases frequently have elevated systemic arterial pressure,^{8,10} although the cause-effect nature of this relationship is not always clear. Hypertensive renal injury can result from transmission of these elevated arterial pressures to the vessel wall and endothelium. Although systemic hypertension may be multifactorial in cause, it appears that altered renal handling of sodium, inappropriate vasoconstriction, and/or enhanced generation of angiotensin II may play an important role in dogs.

Severe systemic hypertension can lead to retinal hemorrhages and detachment and resultant blindness, seizures, cardiac hypertrophy, and progressive renal injury. Cardiac arrhythmias and pericardial effusion are rarely observed. Mild to moderate hypertension may be detrimental, but this remains to be established.

Therapy

Some antihypertensive agents (e.g., ACE inhibitors and/or calcium channel antagonists) may be of benefit to any CRF dog with normal or elevated systemic arterial pressure. Generally, however, therapy for hypertension (Table 2) must be based on measurement of blood pressure, with a minimum of five consistent readings obtained. These should be taken by an experienced technician in a quiet setting, using indirect methods, preferably by oscillometry using the coccygeal artery or Doppler ultrasonography using the median artery.

The cutoff point for treatment is controversial. In general,

**TABLE 2****Antihypertensive agents for use in chronic renal failure dogs^{9,10}**

1. Low sodium diet (potential for benefit unknown)
2. Angiotensin-converting enzyme (ACE) inhibitor
Enalapril 0.5 mg/kg orally every 12–24 hours
Benazepril 0.25–0.5 mg/kg orally every 12–24 hours
3. Calcium antagonist
Amlodipine 0.05–0.25 mg/kg orally once daily
4. Alpha₁-antagonist
Prazosin 1 mg/10 kg orally every 8–24 hours
5. Beta antagonist (cardioinhibitory agent)
Atenolol (cardiospecific) 2 mg/kg orally every 12–24 hours
Propranolol (non-specific) 5–80 mg/dog orally every 8–12 hours
6. Diuretic
Hydrochlorothiazide 0.5–5 mg/kg orally every 12 hours
Furosemide 1 mg/kg orally every 12–24 hours
Spironolactone 1–2 mg/kg orally every 12–24 hours

treatment is necessary only if systolic pressure exceeds 200 mmHg and/or diastolic pressure exceeds 110 mmHg (borderline systolic is taken to be 170–200 mmHg). The goal of therapy is to reduce arterial pressure by at least 25 to 50 mmHg while sustaining adequate renal function. The upper limit of the normal range for systolic/diastolic blood pressure is approximately 150/90 mmHg in dogs and cats. Ideally, blood pressure in CRF patients should be maintained within the normal range.

Although a combination of treatments may be required simultaneously, an antihypertensive therapeutic regimen usually starts with a low-sodium diet (Table 2), which may also enhance the effectiveness of the pharmacological agents. There is no contraindication to the co-administration of agents, although two agents from the same class (e.g., atenolol and propranolol) are not generally administered together. Therapy is to effect, with efficacy judged by blood pressure measurements obtained at two weekly intervals. However, it should be noted that some agents, such as diuretics and ACE inhibitors, may cause a decrement in renal function, weakness, and/or syncope. Some may enhance kaliuresis leading to hypokalemia.

Renal inflammation

Renal diseases, including those that are not immune mediated, may lead to glomerular inflammatory injury. These effects seem to be mediated, in part, by local overproduction of growth factors that stimulate glomerular mesangial cells.¹¹ Progressive tubulointerstitial fibrosis is also mediated, in part, by local production of growth factors.

Therapy

Dietary supplementation with omega-3 PUFA, administration of a thromboxane synthase inhibitor, or specific therapy directed at a primary inflammatory disease may prove beneficial in reducing intrarenal inflammation.⁷ As with measures to lower intraglomerular pressure, the aim of dietary omega-3 PUFA supplementation is to achieve an omega-6/omega-3 ratio of between 0.2:1 and 5:1. Nevertheless, clinical trials are needed to assess the efficacy of such maneuvers in dogs with spontaneous CRF.

Metabolic acidosis

Metabolic acidosis is frequently observed in azotemia of renal, prerenal, or postrenal origin. It leads to enhanced renal ammoniogenesis, which can activate the complement cascade, leading to tubulointerstitial injury.¹²

Proteins, particularly those of animal origin, are rich in sulfur-containing amino acids, and the metabolism of these leads to hydrogen ion generation. Consequently, many diets fed to dogs provide a net load of acid that must be excreted by the kidney if acid-base balance is to occur. Vegetable proteins, such as soya protein, may be neutral or alkalinizing.

Reduced renal function leads to a decline in the renal capacity for acid excretion, potentially resulting in metabolic acidosis from acid retention. The acidosis is generally associated with an increased anion gap due to the accumulation of unmeasured anion. This acidosis may contribute to lethargy and inappetence. With metabolic acidosis, enhanced renal ammoniogenesis per unit of residual tissue occurs in acidotic dogs but, apparently, not in cats. The ammonia may be nephrotoxic, contributing to progressive renal injury.

Though uncommon, a normal anion gap metabolic acidosis may be present in an animal with renal tubular acidosis (e.g., Fanconi's syndrome).

Therapy

The serum total carbon dioxide or bicarbonate concentrations should be monitored, with the goal of keeping the value within the normal range; all alkalinizing agents are thus dosed to effect. Oral sodium bicarbonate may be administered at an initial dose of 8 to 15 mg/kg every 8 to 12 hours. Sodium bicarbonate (versus NaCl) is unlikely to exacerbate systemic hypertension but should be used cautiously in hypertensive patients. Alternatively, oral potassium citrate may be used at an initial dose of 30 mg/kg every 12 hours.

A variety of clinical abnormalities may occur in animals once they develop marked azotemia and are commonly referred to as the uremic syndrome. These signs of uremia affect the quality of life of dogs with CRF, and the problems should be managed with therapy individualized for each animal (Table 1).

To reduce the clinical signs of uremia, dietary protein re-

striction should be employed once blood urea nitrogen levels reach 80 mg/dl (28 mmol urea/liter). At that time, the diet should contain approximately 14% to 17% protein on a dry matter basis (supplying 2.0–2.5 g/kg/day). Adequate caloric intake should be ensured by a review of client-maintained records; this can be facilitated by gradual diet changes and trials with each of the various commercially available preparations/formulations.

Dietary phosphorus restriction should be employed earlier in renal failure than dietary protein restriction because of its benefit in slowing the rate of progression of renal failure. However, all low-phosphorus diets are also restricted in protein and sodium content. Until newer diets low in phosphorus but normal in protein and sodium content are formulated, only restricted-protein, low-phosphorus, low-sodium diets will generally be available to veterinarians for azotemic patients.

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