Managing Chronic Renal Failure

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ABSTRACT: Chronic renal failure (CRF) is a common progressive disease in dogs and cats. Although loss of nephrons and associated progressive loss of function in patients with CRF are irreversible, appropriate treatment can slow progression, improve clinical signs, and prolong life. Treatment should be aimed at decreasing clinical signs associated with uremia; minimizing electrolyte, vitamin, and mineral disturbances; supporting nutrition; and slowing progression. Therapy should be individualized based on evaluation of the patient’s historical, physical, and diagnostic findings; response to therapy; and consideration of owner compliance and the patient–owner relationship.

Chronic renal failure (CRF) is an important and common disease. After a diagnosis of CRF has been made, it is important to counsel owners on the progressive and irreversible nature of this disease. Despite its irreversible nature, proper treatment of CRF can alleviate clinical signs and slow progression. With thorough evaluation of each patient, an individualized therapeutic approach can be designed. Staging of patients with CRF is valuable in facilitating an individualized approach and establishing a prognosis (Table 1). Specific therapy designed to address the inciting cause of CRF is most beneficial, but this approach is complicated because the primary cause cannot be found in many patients. Risk factors that may promote progression of renal failure should be identified and eliminated if possible. Such risk factors include dehydration, administration of nephrotoxic drugs, urinary tract infection, nephrolithiasis or ureterolithiasis, systemic hypertension, and proteinuria. Varied therapies have been described in treating CRF. Not all recommended treatments have been proven effective. This article discusses various recommendations in treating patients with CRF (see box on p. 856).

DIETARY THERAPY
For decades, protein modification has been the basis of diet therapy. Studies conducted in humans and rats have suggested a toxic effect of proteins on renal tubular cells and overall damage to renal function. However, canine and feline studies in which investigators created renal failure by removing all but a small fraction of renal tissue (remnant kidney model) have failed to demonstrate an association between dietary protein and lesions in the renal tissue or effects on longevity. The beneficial effects observed in some studies may have been a result of protein or phosphorus restriction or a combination of both. Available data have been interpreted to indicate that dietary protein restriction alone does not profoundly alter the course of CRF and excessive dietary protein intake does not induce renal failure in otherwise healthy humans, dogs, and cats. Current research revealed that a renal diet (modified in protein, phosphorus, sodium, and lipid composition) was superior to an adult
maintenance diet in minimizing uremic episodes and the mortality rate in cats and dogs with spontaneous renal failure. In a study of 38 dogs with spontaneous CRF (creatinine level: 2 to 8 mg/dl) conducted over 24 months, feeding a renal diet reduced the risk for renal causes of death by 69% and the risk for uremic crises by 72% compared with the control group. In addition, the median interval before development of a uremic crisis in dogs fed the renal diet was twice as long as that for the control group.

Investigators also observed that feeding a renal diet to dogs with serum creatinine concentrations of 2 to 3.1 mg/dl delayed the onset of uremic crises by approximately 5 months; this supports early dietary intervention.

An open, nonrandomized study in cats with naturally occurring renal failure suggested that feeding a renal diet and using phosphate binders significantly increase survival time from the initial diagnosis. Once moderate azotemia occurs (blood urea nitrogen [BUN] >75 mg/dl), clinical signs of uremia may be ameliorated by dietary restriction of protein.

In several studies in dogs and cats, investigators have documented that restriction of dietary phosphorus is beneficial in lessening the severity of inflammation and mineralization in the kidneys, decreasing the concentration of parathyroid hormone (PTH), maintaining filtration capacity of the kidneys, and, ultimately, prolonging longevity of animals. Most commercially available renal diets are both protein and phosphorus restricted. However, the level of phosphorus restriction is often not adequate to prevent hyperphosphatemia as renal failure progresses. The concurrent use of phosphate binders to maintain normal phosphorus homeostasis is discussed later.

Recent studies suggest the composition of fat-containing polyunsaturated fatty acids (PUFAs) in the diet is important in preventing progression of renal disease and extending longevity. Dogs with induced renal failure (a remnant kidney model) fed fat containing increased concentrations of ω-3 (ω-3) PUFAs lived significantly longer with better preservation of the glomerular filtration rate and less inflammatory infiltrate than those fed fat containing increased concentrations of ω-6 PUFAs. Most renal diets are supplemented with ω-3 PUFAs. For patients unwilling to consume a renal diet, ω-3 PUFA supplementation can be considered, although further research is necessary to substantiate its efficacy.

Diets with protein and phosphorus restrictions (see box on page 857) should be recommended for all cats and dogs with a diagnosis of CRF regardless of cause. Patients that do not consume an adequate amount of the prescribed diet should either have a feeding tube placed to provide adequate caloric intake of an appropriate diet or be fed any diet that provides sufficient caloric intake.

### Table 1. Chronic Renal Failure Staging and Monitoring Guidelines

<table>
<thead>
<tr>
<th>Definition</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azotemia</strong> (creatinine level [mg/dl])</td>
<td>Dogs</td>
<td>Cats</td>
<td>Dogs</td>
<td>Cats</td>
</tr>
<tr>
<td>&lt;1.4</td>
<td>&lt;1.6</td>
<td>1.4–2</td>
<td>1.6–2.8</td>
<td>2.1–5</td>
</tr>
<tr>
<td>Frequency of monitoring (mo)</td>
<td>Physical examination</td>
<td>6</td>
<td>4–6</td>
<td>3–6</td>
</tr>
<tr>
<td>Chemistry panel</td>
<td>6</td>
<td>4–6</td>
<td>3–6</td>
<td>1–3</td>
</tr>
<tr>
<td>Packed cell volume</td>
<td>6</td>
<td>4–6</td>
<td>3–6</td>
<td>1–3</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>6</td>
<td>4–6</td>
<td>3–6</td>
<td>1–3</td>
</tr>
<tr>
<td>Urine culture</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>3–6</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>3–6</td>
</tr>
</tbody>
</table>


Although loss of nephrons and associated progressive loss of function in patients with CRF are irreversible, appropriate treatment can slow progression, improve clinical signs, and prolong life.
Management of Chronic Renal Failure: Practical Guidelines

Complications that are most likely to be encountered or require treatment in each stage are listed. Clinical judgment should be exercised on a case-by-case basis.

Diet and nutrition (stages 3 and 4 in dogs and middle 2–4 in cats)
- Proven to slow progression, prolong survival, and reduce uremic morbidity
- Characterized by restricted amounts of a high-biologic-value protein and restricted phosphate
- Most commercially available renal diets are also supplemented with ω-3 fatty acids
- Appetite stimulants such as cyproheptadine (2 mg/cat PO bid) or oxazepam (2 mg/cat PO bid) or similar benzodiazepines can be used as needed to treat partial or complete anorexia in cats
- Use feeding tubes if caloric intake is inadequate

Maintenance of serum phosphorus (dogs and cats with hyperphosphatemia in stages 2–4)
- Prescribe intestinal phosphate binders
- Administer 30–90 mg/kg/day divided and given with meals
- Adjust dose based on serial phosphate determinations
- Aluminum-containing binders are most commonly administered
- Monitor for hypercalcemia if administering calcium-containing products

Calcitriol therapy (dogs in stages 3 and 4)
- Administration of low-dose calcitriol to dogs with normal serum phosphorus and calcium concentrations has been shown to decrease PTH levels and prolong survival (calcitriol should not be given to patients with hyperphosphatemia)
- Recommended endpoint: normal PTH level in the absence of hypercalcemia
- Administer a starting dose of 2.5 ng/kg PO sid; adjust based on serum calcium and PTH determinations
- Monitor for hypercalcemia if administering calcium-containing products

Potassium supplementation (dogs and cats with hypokalemia in stages 1–4)
- Treat with a goal of maintaining a serum potassium concentration of >4 mg/dl
- Administer potassium citrate (40–60 mg/kg PO bid or tid)
- Administer potassium gluconate (2 mEq/4.5 kg PO bid in food)

Correction of acidosis (dogs and cats with repeatable serum bicarbonate levels <15 mmol/dl in stages 1–4)
- More frequent in cats; may exacerbate progression
- Renal diets may be sufficient
- If 2–3 weeks of dietary therapy are not sufficient, add one of the following:
  — Potassium citrate (40–60 mg/kg PO bid)
  — Sodium bicarbonate (8–12 mg/kg PO bid or tid); patients may not like the taste

Correction of clinical anemia (dogs and cats in stages 3 and 4)
- Packed cell volume is typically <20%, and patients are symptomatic before treatment is initiated
- Administer r-HuEPO (100 U/kg SC three times weekly) until reaching a target hematocrit of 37%–45% in dogs or 30%–40% in cats, then decrease the dosing interval to once or twice weekly
- Always start iron supplementation concurrently
- Monitor the hematocrit weekly or biweekly for the first 2–3 mo

Antihypertensive therapy (dogs and cats with systolic blood pressure >160 mm Hg in stages 1–4)
- High blood pressure increases the risk for uremic crisis and death
- Canine hypertension
  — ACE inhibitors (e.g., enalapril [0.5 mg/kg PO bid]) are the initial drug of choice
- Feline hypertension
  — Calcium channel blockers (e.g., amlodipine [0.625 mg PO sid in cats <4 kg; 1.25 mg PO sid in cats >4 kg]) are the initial drug of choice

Reduction of proteinuria (dogs and cats in stages 1–4)
- Therapy is indicated when the urine protein:creatinine ratio is >2 in dogs and cats in stage 1 and >0.5 in dogs and >0.4 in cats in stages 2–4
- Proteinuria promotes progression of CRF
- Administer ACE inhibitors (see doses above)
In renal failure, diseased kidneys have a decreased ability to excrete hydrogen ions, often resulting in metabolic acidosis, which is a common complication of CRF in cats, reportedly affecting 60% to 80% of them. Clinical manifestations of acidosis include anorexia, nausea, vomiting, lethargy, weight loss, weakness, and muscle wasting. Severe acidosis (blood pH <7.20) may result in reduced cardiac output, arterial pressure, and hepatic and renal blood flow as well as centralization of blood volume. Acidosis stimulates catabolism of body proteins, which in turn generates more acid. Affected animals catabolize body proteins to meet energy and protein needs when they are not consuming sufficient amounts to maintain body weight and physiologic processes. In this way, acidosis may limit the ability of patients to adapt to protein restriction. Therapeutic diets tend to use combinations of ingredients that alkalize the urine and blood, minimizing dietary contributions to acid load. Although acidifying diets have not been proven to cause CRF or promote its progression in cats, potential adverse effects justify feeding a nonacidifying diet. Medical management of metabolic acidosis is discussed later.

To maximize benefits in patients with CRF, it is best to institute dietary therapy early in the course of the disease and gradually transition to the renal diet over 6 to 8 weeks. At advanced stages of CRF, many patients become anorectic, refusing to consume adequate amounts of any diet to maintain sufficient nutrition. In cats, appetite stimulants such as cyproheptadine (Periactin, Merck; 2 mg PO bid) or oxazepam (Serax, Wyeth Laboratories, Inc; 2 mg PO bid; or similar benzodiazepines) can be used as needed for partial or complete anorexia. Treatment with the anabolic steroid stanozolol has been advocated in dogs and cats with CRF; however, the benefits of stanozolol are questionable, and the risk for hepatotoxicity in cats is documented. Evidence suggests that the use of these drugs leads to clinically important toxicity. Calcium salts have been advocated as phosphate binders to eliminate the risk for aluminum toxicity. Phosphate binders can interfere with absorption of other drugs, and their administration should be separated from that of other

MANAGING HYPERPHOSPHATHEMIA

Phosphorus is retained in patients with CRF, leading to hyperphosphatemia and hyperparathyroidism secondary to dysfunction. Hyperphosphatemia has been detected in approximately 60% of cats with CRF, with the prevalence increasing as renal function declines. Clinical signs attributable to hyperphosphatemia have not been clearly defined in dogs and cats. However, high serum phosphorus levels leads to increased concentrations of PTH, which are believed to damage the kidneys in the long term. Phosphorus retention and hyperphosphatemia have been linked to increased mortality in humans and dogs with CRF.

Dietary phosphate restriction prevents hyperphosphatemia in early stages of CRF; however, the addition of intestinal phosphate binders should be considered when serum phosphorus rises despite dietary restriction. Phosphate binders are not effective at normalizing serum phosphorus levels unless there is concurrent dietary restriction of phosphorus. To maximally suppress PTH secretion, the serum phosphorus level should be kept within the middle to low end of the reference range.

Intestinal phosphate binders should be given orally with meals to reduce intestinal phosphate absorption. Aluminum-containing phosphorus-binding agents include aluminum hydroxide, aluminum carbonate, and aluminum oxide. A starting dose of 30 to 90 mg/kg PO q24h should be adjusted as needed to maintain the serum phosphorus concentration within desired limits. Aluminum toxicity is a potential disadvantage, but little evidence suggests that the use of these drugs leads to clinically important toxicity. Calcium salts have been advocated as phosphate binders to eliminate the risk for aluminum toxicity. However, the lesser efficacy and potential toxicity from hypercalcemia have been cited as disadvantages of using calcium salts. Animals treated with calcium salts must be monitored periodically for the development of hypercalcemia. Phosphate binders can interfere with absorption of other drugs, and their administration should be separated from that of other

Renal Diets (Protein and Phosphorus Restricted)

- Eukanuba Multi-Stage Renal Feline Diet
- Eukanuba Early Stage and Advanced-Stage Canine Diets
- Hill’s Prescription Diet Feline and Canine k/d
- Purina NF Feline and Canine
- Royal Canin Feline Renal LP and Modified Formula
- Royal Canin Canine Renal LP, MP, and Modified Formula
oral medications by an hour. Serum phosphorus concentrations should be serially evaluated every 2 to 4 weeks to ensure efficacy. A number of new phosphate-binding agents (i.e., sevelamer hydrochloride, lanthanum carbonate) have recently become available for humans, but their use in veterinary patients is limited to date.

**CALCITRIOL THERAPY**

Hyperparathyroidism secondary to renal dysfunction occurs in association with multiple factors. Phosphorus retention, which has already been discussed, is only one of multiple factors implicated in the development of hyperparathyroidism. Impaired renal production of calcitriol has been proposed to play a pivotal role in the development of this disease, and oral administration has been shown to reduce the PTH concentration in dogs and cats with CRF.\(^{13,15}\) The clinical benefits of PTH reduction have not been conclusively documented, despite the belief that PTH is a uremic toxin and anecdotal studies suggesting a favorable clinical response in calcitriol-treated patients.\(^{13} \) A controlled clinical trial revealed that calcitriol reduced mortality in dogs with CRF, further supporting calcitriol use.\(^{15} \)

Calcitriol can promote hypercalcemia and renal injury, warranting careful monitoring. The serum phosphorus concentration must be reduced to 6 mg/dl or lower before initiation of therapy, and calcium-containing phosphorus binders should be avoided.\(^{13} \) An initial dose of 2.5 to 3.5 ng/kg/day is recommended; however, the optimum maintenance dose should be determined based on frequent evaluation of calcium, phosphorus, and plasma PTH concentrations.\(^{13} \) The recommended endpoint is PTH level normalization in the absence of hypercalcemia, although reduction of PTH without normalization can also be helpful.\(^{13} \) The development of hypercalcemia after initiation of calcitriol therapy can occur within days to months. Therefore, it is critical to monitor the calcium, phosphorus, BUN, and creatinine levels 1 week after initiating therapy and monthly thereafter.\(^{13} \) The product of the calcium level multiplied by the phosphorus level should not exceed 60. Treatment should be discontinued if hypercalcemia develops and can be reinstituted with a dose reduction when the patient becomes normocalcemic and the phosphorus level is less than 6 mg/dl.\(^{13} \) Calcitriol use in feline CRF is being evaluated.

**MANAGING SECONDARY GASTROINTESTINAL CONDITIONS**

Dogs and cats with uremia may display a variety of gastrointestinal (GI) disturbances, including inappetence, weight loss, vomiting, hematemesis, and, uncommonly, diarrhea.\(^{16} \) Vomiting is a frequent finding and is reported more often in dogs than cats.\(^{9} \) Vomiting is thought to result from both the direct effects of uremic toxins on the chemoreceptor trigger zone and uremic gastritis. It is important to address these GI problems because they make patients more susceptible to dehydration, malnutrition, and anemia and, ultimately, affect disease progression.

Although uremic gastropathy is a common finding affecting over 60% of dogs and up to 75% of humans with renal failure, its pathogenesis is poorly understood.\(^{17,18} \) Hypergastrinemia results secondary to decreased renal gastrin clearance. The increased gastrin concentration is then thought to stimulate parietal cell secretion of hydrochloric acid and lead to chemical erosion and ulceration of the gastric mucosa. A recent investigation\(^{18} \) in cats supported a potential role of high gastrin concentrations on gastric hyperacidity, uremic gastritis, bleeding from the GI tract, and associated clinical signs of hypergastrinemia. GI ulceration was previously thought to be common in canine renal failure based on information extrapolated from studies conducted in rodents and from the human medical literature. However, a recent study\(^{17} \) in dogs showed that gastric histopathology is characterized by mucosal mineralization, edema, and vascular changes, not ulceration, and is more likely to occur in dogs with severe renal failure. No evidence is currently available to support the contention that dogs with renal failure commonly develop gastric hyperacidity and resultant ulceration. Supportive therapy for GI manifestations of CRF includes gastroprotekants, antiemetics, and appetite stimulants. Patients with complete or partial anorexia and/or vomiting can be placed on a histamine (H\(_2\))
blocker (famotidine; 0.5 mg/kg PO, SC, or IM sid or bid) or proton pump inhibitor (omeprazole; 0.7 mg/kg PO sid in cats; 1 mg/kg PO sid in dogs). Patients that continue to vomit daily while receiving an H₂ blocker may receive a centrally acting antiemetic (metoclopramide; 0.2 to 0.4 mg/kg PO or SC tid) or may benefit from an α₂-adrenergic antagonist such as chlorpromazine (0.2 to 0.4 mg/kg SC tid) or prochlorperazine (0.5 mg/kg SC or IM tid). Serotonin type 3 receptor antagonists, such as ondansetron or dolasetron, may also have a role in limiting vomiting, although current evidence of their efficacy is lacking.

Sucralfate (0.25 to 0.5 g PO bid or tid in cats; 0.5 to 1 g PO bid or tid in dogs) can be used if there is evidence of gastric ulceration (i.e., melena, hematemesis, elevated BUN:creatinine [>20]) until signs resolve (usually 1 to 2 weeks). Sucralfate works best in an acid environment and should be administered 30 minutes before H₂ blockers or phosphate binders are.

### MANAGING FLUIDS, ELECTROLYTES, AND ACID–BASE DISORDERS

#### Fluid Therapy

Most patients with CRF have obligatory polyuria. Fluid balance is maintained by increased consumption. With decreased access to water, anorexia, vomiting, or diarrhea in patients, water losses exceed consumption. Volume depletion is commonly recognized in patients with CRF. Dehydration decreases renal perfusion and delivery of oxygen to nephrons. Without rapid correction, dehydration may lead to a rapid and severe decline in renal function. Fluid deficits should be replaced parenterally. Once the deficit has been replaced, the ongoing fluid requirements of patients with CRF are still higher than those of other patients because of polyuria. Patients that develop recurrent dehydration should be considered for long-term subcutaneous fluid therapy. The principal benefits include improved activity and appetite and decreased incidence of constipation. The decision to initiate at-home subcutaneous fluid therapy must be made on a case-by-case basis. A substantial number of cats with CRF benefit from subcutaneous fluid therapy; however, proportionally fewer dogs benefited from this treatment. A typical cat or small dog should receive approximately 75 to 150 ml of fluids every 24 to 48 hours. The amount and frequency should be adjusted based on subjective response to therapy. The risks include volume overload, hypokalemia, and hypertension.

#### Potassium Balance

Hypokalemia may result secondary to decreased intake and/or increased renal losses. The prevalence of hypokalemia in cats with CRF is 20% to 30%, with total body potassium depletion likely to be even higher. Dogs with CRF rarely are notably hypokalemic. Oral treatment is preferred, except in severe cases. Up to 30 mEq/L can be added to subcutaneous fluids when oral therapy is not tolerated. Oral supplementation can be provided as gluconate or citrate salts, with citrate having the additional benefit of alkalinization. Potassium gluconate should be given initially at a dose of 2 to 8 mEq/day/cat PO. Once the serum potassium concentration returns to normal, a maintenance dose of 2 to 4 mEq/day PO is adequate. Potassium citrate is an excellent alternative, especially in the presence of acidosis, and should be initiated at a dose of 40 to 60 mg/kg/day PO divided into two or three doses. The serum potassium concentration should be initially monitored at 7- to 14-day intervals, and the dose should be adjusted accordingly. Hyperkalemia is uncommon but can occur in terminal CRF.

Routine supplementation with 2 to 4 mEq/day PO of potassium has been recommended in all cats with CRF. This recommendation appears to be based on an unproven hypothesis that hypokalemia and potassium depletion might promote a self-perpetuating cycle of declining renal function, metabolic acidosis, and continuing potassium loss. However, results of a recent clinical trial failed to show any benefit to potassium supplementation (4 mEq/day PO for 6 months) in restoring muscle potassium stores in normokalemic feline renal patients compared with a control. This study, however, lacked power because of a small sample size. Although this study did not establish the value of routine potassium supplementation, it did show that cats with CRF are likely to have reduced muscle potassium stores (thereby increasing

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**Cats with CRF are likely to have reduced muscle potassium stores, and potassium supplementation of 4 mEq/day PO for 6 months is unlikely to be associated with adverse side effects.**
their risk for hypokalemia) and that potassium supplementation of 4 mEq/day PO for 6 months is unlikely to be associated with adverse side effects. Based on these data, a recommendation for or against routine potassium supplementation cannot be made.

**METABOLIC ACIDOSIS**

As discussed earlier, metabolic acidosis can be problematic for a multitude of reasons, and although dietary therapy is an appropriate first step, if acidosis persists (plasma bicarbonate <15 mmol/L on more than one determination) after a few weeks of dietary therapy, alkalinization therapy should be considered. Oral sodium bicarbonate is the most commonly used alkalinizing agent. The dose should be individualized for each patient based on response. The initial dose is 8 to 12 mg/kg PO bid or tid. Potassium citrate is an alternative alkalinization agent. Because it can simultaneously treat both hypokalemia and acidosis, it is a particularly advantageous choice in cats. The initial dose is 40 to 60 mg/kg PO bid, unless the serum potassium concentration is above the reference range. In cats with low or low-normal potassium concentrations and metabolic acidosis when 75 mg/kg of potassium citrate is not sufficient to normalize potassium concentration, potassium gluconate (i.e., Tumil K, Virbac Animal Health) can be provided. Regardless of the alkalinization agent, administration of several small doses is preferred to minimize fluctuations in blood pH.

After 10 to 14 days of therapy, the blood bicarbonate or serum total carbon dioxide concentration should be measured just before administration of the next dose.

**USING RECOMBINANT HUMAN ERYTHROPOIETIN TO TREAT NONREGENERATIVE ANEMIA**

Patients with CRF develop hypoproliferative anemia primarily because of inadequate renal production of erythropoietin and secondary erythropoietic bone marrow failure. Treatment with recombinant human erythropoietin (r-HuEPO) has significantly minimized this problem in humans with CRF. r-HuEPO administration has led to complete resolution of anemia, and humans report decreased incidences of depression, lethargy, and weakness and an overall improved quality of life. Because of molecular similarities in dogs and cats, r-HuEPO has cross-species biologic activity in these species, and clinical trials have documented effective correction of anemia and improved well-being in veterinary patients. However, r-HuEPO administration has been associated with the development of anti-r-HuEPO antibody production and adverse effects (e.g., hypertension, seizures, iron deficiency) resulting from correction of the erythrocyte mass. The development of antibodies is variable but may approach 25% to 30% and is recognized by the development of refractory anemia and hypoplasia of the erythroid bone marrow. The severity of anemia is greater after treatment compared with pretreatment values, suggesting that anti-r-HuEPO antibodies interfere with endogenous erythropoietin in addition to recombinant erythropoietin.

Over several months (up to 1 year), antibodies dissipate after discontinuation of therapy and anemia resolves to pretreatment values. However, further use of r-HuEPO is prohibited. The patient will be transfusion-dependent during that time, with an increasing risk for transfusion reactions with each transfusion. This most problematic consequence of therapy must be discussed and carefully considered before initiation of therapy. Therapy should be considered only if anemia is severe (packed cell volume [PCV] <20%) and the patient is symptomatic. Signs of anemia include tachycardia, heart murmur, heart failure, exercise intolerance, and anorexia. Iron supplementation should be concurrently initiated because of increased demand on iron stores. Blood pressure (BP) should be evaluated before and during use. An initial dose of r-HuEPO (100 U/kg SC three times weekly) should be administered until the target hematocrit (i.e., 37% to 45% in dogs; 30% to 40% in cats) is achieved. As the target is reached, the dose interval should be decreased to twice weekly. Weekly or biweekly evaluations of hematocrit and clinical response are recommended for the first 2 to 3 months of therapy until the hematocrit stabilizes within the target range and the maintenance dose of r-HuEPO has been reached.

**All patients with renal disease should be evaluated for hypertension, which affects 19% to 61% of cats and 50% to 93% of dogs.**
HYPERTENSION

All patients with renal disease should be evaluated for hypertension, which is common in dogs and cats with CRF, affecting 19% to 61% of cats and 50% to 93% of dogs. Compensatory mechanisms serving to protect the glomerulus from hypertensive injury are lost in patients with CRF, resulting in elevated systemic BP transmitting directly to the glomerular capillary bed. The resultant glomerular hypertension may produce glomerular damage and a progressive fall in renal function, unless systemic hypertension is effectively treated.

A study of 45 dogs with spontaneous CRF that were followed for 24 months indicates that dogs with initial systolic BPs of 161 to 201 mm Hg had a three times greater relative risk for the development of uremic crisis and death than did dogs with CRF and initial systolic BPs of 107 to 160 mm Hg.

In our opinion, dogs and cats with repeatable systolic BPs greater than 180 mm Hg warrant treatment, with a goal of decreasing systolic BP to 120 to 160 mm Hg. An angiotensin-converting enzyme (ACE) inhibitor is the initial drug of choice in treating canine hypertension. A recent study revealed that the use of an ACE inhibitor (enalapril; 0.5 to 1 mg/kg PO bid) in dogs with induced CRF was effective in modulating progressive renal injury, which was associated with the reduction of glomerular and systemic BP and proteinuria. A calcium-channel blocker is the initial drug of choice in treating feline hypertension. Amlodipine should be prescribed at a dose of 0.625 mg PO sid for cats weighing less than 8.8 lb (4 kg) and 1.25 mg PO sid for cats weighing more than 8.8 lb (4 kg).

If proteinuria is present or amlodipine is ineffective, an ACE inhibitor should be added (e.g., benazepril [0.25 to 1 mg/kg PO sid], enalapril [0.25 to 0.5 mg/kg PO sid or bid]). Benazepril has been associated with a small but significant reduction in systemic hypertension and an increase in the whole kidney glomerular filtration rate and may prove to be effective in slowing the rate of CRF progression in cats with proteinuria.

With ACE inhibitors, the low end of the dose range should be initially selected and titrated based on serial BPs. A chemistry panel should be checked 1 week after dose escalations, and if azotemia has worsened, the dose should be decreased. If amlodipine and an ACE inhibitor are ineffective, a β-blocker can be added if tachycardia is present.

PROTEINURIA

Proteinuria has been identified as a risk factor that promotes progression of CRF. It also has emerged as an important marker for prognosis and therapeutic response. A urine protein:creatinine ratio should be evaluated in all patients with CRF. In dogs with CRF, having an initial urine protein:creatinine ratio of 1 or higher was associated with greater risk for the development of uremic crises and death. A recent abstract suggests that a urine protein:creatinine ratio greater than 0.43 in cats with CRF predicts shorter survival. Mean survival times in cats treated with benazepril were not significantly different than those in placebo-treated cats. However, in the small subset of cats with an initial urine protein:creatinine ratio greater than 1, survival rates at the end of the trial were significantly higher in the treated group. Whether the presence of microalbuminuria predicts survival is unknown, but the presence of microalbuminuria in the absence of an elevated urine protein:creatinine ratio does not warrant ACE inhibition. Monitoring is recommended to detect trends in patients with microalbuminuria, and increases in magnitude should prompt further investigation.

HEMODIALYSIS AND RENAL TRANSPLANTATION

Hemodialysis and renal transplantation are therapeutic considerations to improve quality and quantity of life in patients in which traditional conservative therapy has failed to provide satisfactory results. Patients with severe persistent azotemia (BUN level: >100 mg/dl; creatinine level: >8 mg/dl) and intractable clinical signs associated with uremia are candidates for long-term hemodialysis. Renal transplantation is another consideration in such patients and, with appropriate patient selection, can offer a markedly improved quality of life and potential long-term survival.

PATIENT MONITORING

Frequent patient monitoring provides multiple benefits to the patient, owner, and veterinarian. It allows the clinician to guide therapeutic modifications and detect signs of concurrent treatable disease and risk factors. Patient response should be discussed to improve owner compliance and provides a means of recognizing and correcting therapeutic errors. At each visit, a careful history, including diet, medications, and owner impression of clinical response, should be obtained. A physical examination, including a fundic examination, should be performed with particular attention to hydration, body weight and condition, and muscle mass. Systolic BP should be evaluated with the owner present, if possible.
Serial laboratory evaluation, including chemistry panel, complete blood count or PCV, urinalysis (including urine protein:creatinine ratio), and urine culture, should be considered at scheduled visits. The frequency of monitoring depends on the clinical condition of the patient. Using a staging system provides a clinically useful structure when considering patient reevaluations (Table 1). If the owner has questions about the patient’s stability or the patient’s status changes, a recheck examination should be performed. Dogs and cats with CRF should be reexamined within 2 to 4 weeks of initiating therapy or dose adjustments.

CONCLUSION

CRF is common, progressive, and irreversible. However, careful patient monitoring, identification and elimination of concurrent diseases and risk factors, and the use of multiagent therapy have improved the quality and quantity of life in patients with CRF. The efficacy of any therapy should be documented with serial rechecks, and many therapies require adjustments based on individual patient response. Treatment should be aimed at alleviating clinical signs and slowing progression. Current therapy allows many affected patients to live good-quality lives for years beyond the diagnosis of CRF.

REFERENCES


**ARTICLE #2 CE TEST**

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1. **Dietary intervention should be considered**
   a. when inappetence and other secondary GI complications become evident.
   b. only when phosphorus levels begin to rise.
   c. early in the course of the disease.
   d. when a patient’s urine protein:creatinine ratio exceeds 0.5.

2. **Hyperphosphatemia in patients with CRF**
   a. occurs as renal excretion declines.
   b. leads to increased PTH concentration.
   c. can be managed with diet and phosphate binders.
   d. all of the above

3. **Which statement regarding calcitriol is incorrect?**
   a. Calcitriol deficiency has been proposed to play a pivotal role in the development of hyperparathyroidism.
   b. Calcitriol therapy can promote hypercalcemia and renal injury.
   c. Calcitriol therapy should be discontinued if hypercalcemia develops.
   d. Patients should have their calcium levels evaluated 6 months after initiation of calcitriol therapy.

4. **GI manifestations of CRF**
   a. are rare and poorly documented.
   b. include inappetence, weight loss, vomiting, and hematemesis.
   c. should be treated with stanozolol.
   d. are caused exclusively by elevations in blood gastrin levels.

5. **Subcutaneous fluid therapy**
   a. is essential in all patients with CRF.
   b. can be associated with volume overload, hypokalemia, and hypotension.
   c. can help improve appetite and activity as well as alleviate constipation.
   d. can help more dogs than cats with CRF.

6. **The prevalence of hypokalemia in cats with CRF is**
   a. 20% to 30%.
   b. less than 10%.
   c. lower than that in affected dogs.
   d. approximately 50%.

7. **Which statement regarding r-HuEPO therapy is correct?**
   a. r-HuEPO should not be administered in patients receiving iron supplementation.
   b. r-HuEPO therapy should be discontinued if the development of anti–r-HuEPO antibodies is suspected but can be reinitiated when anemia resolves to pretreatment values.
   c. r-HuEPO has cross-species biologic activity in dogs and cats.
   d. The development of anti–r-HuEPO antibodies is rare, occurring in less than 10% of patients.

8. **Hypertension**
   a. improves glomerular filtration and renal blood flow, thereby improving renal function.
   b. is not associated with increased risk in patients with CRF.
   c. is uncommon in patients with CRF because of dehydration and hypovolemia.
   d. is a potential adverse effect of r-HuEPO therapy and should be controlled before its use.

9. **A urine protein:creatinine ratio of greater than ___ in cats with CRF predicts shorter survival.**
   a. 1  
   b. 0.43  
   c. 1.43  
   d. 2

10. **Which statement regarding patient monitoring is incorrect?**
    a. Frequent patient monitoring is stressful for patients with CRF and should be avoided, if possible.
    b. Frequent patient monitoring provides multiple benefits to the patient, owner, and veterinarian.
    c. A fundic examination should be performed at each visit.
    d. BP should be evaluated with the owner present, if possible.