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Chronic Renal Failure in Cats: Long Term Management

Chronic renal failure (CRF) is one of the most common illnesses of geriatric cats. In 1990, there were 45 cases of CRF for every 1000 cats admitted to veterinary teaching hospitals. In 2000, the number increased to 96 cases per 1000 cats. Clearly, the incidence of CRF is increasing.¹

Unless the underlying cause of the initial renal injury can be discovered and treated, CRF invariably progresses. In many cases, even after identifying the initial cause of the renal injury, a threshold or "trigger-point" has already been reached, and self-perpetuating mechanisms of kidney destruction are activated. Unfortunately, an underlying cause for the initial renal insult cannot be found in most cases of CRF.

In the past, most practitioners have qualitatively classified CRF as mild, moderate, or severe, based on laboratory findings and clinical signs. A less arbitrary classification system has been developed by the International Renal Interest Society (IRIS). (See Table 1). In this system, stages are based on degree of kidney function. In Stage I, the kidneys are experiencing some type of insult, however, azotemia and clinical signs have yet to develop. Renal disease is rarely detected in this stage. In Stage II, renal disease has progressed, glomerular filtration has decreased, and mild azotemia is detected. Clinical signs may or may not be detected. The earliest clinical signs attributable to renal dysfunction are polyuria and polydipsia, which occur when approximately 66% of nephron function is lost. This happens in late Stage II or early Stage III. Stages III and IV occur when at least 75% of nephron function has been lost. At this point, azotemia is present and most cats have overt clinical signs of renal dysfunction. Cats, it should be noted, are particularly adept at urine concentration, and some cats with primary glomerular disease may become azotemic while still retaining the ability to concentrate their urine above a specific gravity of 1.035.

The IRIS classification system should be used as a guideline and not necessarily as a strict prognostic indicator, as there is often a significant pre-renal component superimposed upon the azotemia. Correction of acute dehydration may reveal a different picture with regard to the true level of renal azotemia.

IRIS Classification of Stages of Kidney Disease²

Stage I	non azotemic	creatinine < 1.6 mg/dl
Stage II	mild renal azotemia	creatinine = 1.6 - 2.8 mg/dl
Stage III	moderate renal azotemia	creatinine = 2.9 - 5.0 mg/dl
Stage IV	severe renal azotemia	creatinine > 5.0 mg/dl

CRF is incurable. With the exception of a kidney transplant, it is difficult or impossible to improve kidney function in cats with chronic renal failure. Recent developments have made it possible, however, to delay the progression of renal failure, extend a cat's survival time, and improve the quality of life, through a variety of diet and drug interventions.

Therapy for cats presenting with CRF and clinical signs can run the gamut, from simple dietary changes to a hospital stay of several days duration, depending on disease severity and how early the disease has been detected. Fluid therapy remains the cornerstone of treatment for cats hospitalized with CRF. Fluid administration corrects dehydration and increases urine production, reducing azotemia. Fluid therapy also corrects acid/base imbalances, and helps to restore normal phosphorus and potassium levels. This is crucial, as increased levels of phosphorus and decreased levels of potassium can accelerate progression of the renal damage.^{3,4} Cats with CRF may have trouble conserving water-soluble vitamins (the B vitamins and vitamin C) due to excessive loss through urine^{5,6}, and some of these vitamins can be replaced through the fluid therapy as well.

Nutrition is an essential part of the therapy for CRF. Most cats hospitalized with CRF have decreased or absent appetite. During hospitalization, nutritional support can be achieved either through force feeding, tube (nasogastric or esophagostomy) feeding, or intravenous feeding, depending on the severity of the inappetence, the degree of malnutrition, and the cat's demeanor.

Nausea often accompanies anorexia, and is a common finding in cats with CRF. Because the kidneys are responsible for excreting the hormone gastrin, many cats with CRF will be hypergastrinemic and will produce excessive amounts of gastric acid.⁷ This may contribute to the anorexia and vomiting seen in many cats with CRF. Administration of H₂-receptor antagonists such as famotidine, either subcutaneously or orally, may be beneficial in this regard.

A major objective of acute therapy is to significantly decrease the level of azotemia. Reducing the blood urea nitrogen (BUN) and creatinine to normal levels is rarely possible, however, and should not necessarily be the practitioner's goal. During hospitalization, BUN and creatinine levels are measured every two or three days until a plateau is reached. After several days, many cats will have improved clinically – appetite has returned, vomiting has decreased or ceased, hydration is restored – and can be released from the hospital to the owner. A typical hospital stay lasts from three to six days.

It should be made clear to the owners of a cat with CRF that the treatment the cat received while hospitalized does not return the kidneys to normal, and that a conscientious home maintenance program will be necessary for the remainder of the cat's life.

Long term management and prevention of the progression of CRF

Dietary management

Protein, when metabolized, gives rise to uremic toxins that the failing kidneys cannot properly excrete. By reducing the amount of protein in the diet, azotemia is lessened, and this helps ameliorate clinical signs such as weight loss, poor appetite, vomiting, and lethargy. In the past, choices were very limited with regard to these

diets for cats. Fortunately, several companies now manufacture palatable feline "kidney failure diets" that are restricted in protein as well as phosphorus and sodium.

Much controversy has been generated as to whether dietary protein restriction can actually slow the progression of kidney disease in cats. Several studies in recent years, however, have confirmed that dietary modification can have a significant impact on mortality in cats. Cats with naturally occurring renal failure that were fed a veterinary renal diet lived considerably longer (median survival 633 days) than those cat that did not receive (or refused to eat) these diets (median survival 264 days).⁴ Another study compared 23 cats fed a maintenance food with 22 cats fed a prescription diet designed for renal failure. Cats fed the maintenance food had a significantly greater number of uremic episodes compared to cats fed the renal diet. Throughout the duration of the 2 year study, none of the cats fed the renal diet died from kidney-related causes, whereas five cats in the maintenance group died from renal causes.⁸ These data led the authors to recommend feeding a renal diet to cats with CRF early in the course of disease, i.e. when their serum creatinine level exceeds 2 mg/dL. More recently, a retrospective study compared 175 cats with kidney failure fed maintenance diets with 146 cats fed a special diet designed for renal failure. Survival time for cats on the conventional diet was 7 months, compared to 16 months for those fed the prescription diets.⁹ These studies confirm that cats that consume a prescription "kidney failure diet" have increased survival and good quality of life compared to cats that do not (or will not) eat this type of diet. Many manufacturers, for example, The Hill's Company (Topeka, Kansas), Iams Company (Dayton, Ohio), Royal Canin Company (St. Charles, Missouri), and Purina Company (St. Louis, Missouri), now offer these kinds of diets.

Compliance can be a problem when prescribing a prescription diet, given the finicky nature of the cat. If a client is sent home with a large (4 to 8 lb) bag of a dry renal diet and discovers their cat finds the food unpalatable, many clients mistakenly assume their cat will dislike all renal diets and become reluctant to purchase a second, different brand bag of a dry renal food, for fear of being "stuck" with another full bag of food. Rather than prescribing an entire bag of one type of dry food, or an entire case of canned renal diets, the author advocates creating a "sampler pack" (Veterinary Economics, "Samplers Boost Dietary Compliance", December 2006, pg 24) consisting of one can of each company's version of their renal failure diet, and several small Ziploc bags of the dry versions of these diets. Clients can then offer their cat a variety, maximizing the chances of finding a palatable choice. Whether or not one particular brand offers more benefit than another remains to be determined, however, the importance of diet in the management of CRF should not be underestimated.

Monitoring potassium

Hypokalemia is a common finding in feline CRF. Approximately 20 to 30% of cats with CRF are hypokalemic. Total body potassium depletion is likely to be even higher. It is unclear whether hypokalemia is a cause of CRF, a consequence of CRF, or both.¹ Most instances of hypokalemia are mild, with no apparent clinical signs. Marked hypokalemia, however, can lead to general muscle weakness. In more severe cases, cats can develop hypokalemic polymyopathy which, if misdiagnosed, can lead to paralysis of the respiratory muscles and death by respiratory arrest if aggressive potassium supplementation is not undertaken. Potassium depletion and

hypokalemia in cats with CRF may result from inadequate consumption of potassium, dietary issues, enhanced renal loss of potassium, or a combination of these factors.¹¹

Hypokalemia contributes to the progression of kidney failure.³ In many cats with CRF and hypokalemia, kidney function improves when low potassium levels are restored to normal using oral or parenteral potassium therapy, suggesting that hypokalemia may induce a reversible reduction in glomerular filtration rate.^{10,11} Potassium supplements (usually in the form of potassium gluconate) are currently available in a variety of palatable forms (tablets, liquids, granules or powder that can be added to food, and flavored ointments), increasing the likelihood of successful administration in cats who tend to be finicky or difficult to medicate. Potassium citrate can also be used to supplement potassium, and is an ideal choice for cats with metabolic acidosis, as the citrate serves as an effective alkalizing agent.¹² Serum potassium concentration should be monitored 7 to 14 days after supplementation is initiated, and the dose adjusted accordingly.

Vitamins and omega-3 fatty acids

Cats with CRF are often polyuric and may have difficulty conserving water soluble vitamins. As such, a daily multivitamin should be given to all cats with CRF.⁵

In human patients with CRF, increased free radical production and antioxidant depletion may play a role in progression of the disease¹³, and supplementation of the diet with antioxidants such as vitamins A, C, and E has been shown to reduce oxidative stress in humans with chronic kidney disease.¹⁴ A recent study in which cats with CRF were fed a prescription diet designed for renal failure that was supplemented with additional vitamin E (742 mg/kg), Vitamin C (84 mg/kg) and beta-carotene (2.1 mg/kg) showed a significant reduction of oxidative DNA damage.¹⁵

Prescription diets that are designed for cats with renal failure are restricted in protein, phosphorus and sodium. Recently, manufacturers have been adding a larger proportion of omega-3 fatty acids to these diets, based on studies showing evidence of beneficial effects these fatty acids have in dogs¹⁶, and presumably cats, with chronic renal failure. While it has been shown that cats fed prescription diets designed for renal failure live longer and have improved quality of life than cats fed a conventional diet^{4,8,9}, it is not possible to say which single nutrient alteration (or combination of alterations) is responsible for the benefit. In a retrospective study that evaluated the median survival time of cats fed a variety of "renal failure diets" vs. maintenance diets, not only did the cats fed the modified diets live longer (median survival: 7 months vs. 16 months), the diet associated with the longest survival time (23 months) had particularly high levels of eicosapentaenoic acid.⁹ The ideal ratio of omega-6: omega-3 fatty acids in diets designed for renal failure has yet to be determined. For cats unwilling to eat a prescription renal diet, it seems reasonable to consider daily administration of a supplement rich in omega-3 fatty acids.

Controlling excessive urinary protein loss

Proteinuria is a risk factor for the progression of chronic renal failure in humans, and controlling proteinuria has been shown to increase survival times in humans with CRF. A recent study has shown that the severity of proteinuria in cats with naturally occurring CRF has prognostic significance in regard to survival time.¹⁷

As the kidneys start to fail and nephrons are lost, hemodynamic adaptations occur in some of the remaining nephrons, causing increased single nephron GFR, glomerular plasma flow, and hydraulic pressure across the glomerulus.¹⁸ Angiotensin converting enzyme (ACE) catalyzes the generation of angiotensin-II from angiotensin-I within the kidney, causing vasoconstriction of glomerular arterioles. The efferent arteriole is preferentially constricted, leading to increased intraglomerular capillary pressure. Initially this is adaptive, allowing for maintenance of excretory function and total kidney GFR. Ongoing intraglomerular hypertension, however, is ultimately maladaptive, leading to increased trafficking of macromolecules into the mesangium, resulting in proliferation of mesangial cells and increased production of mesangial matrix. This is referred to as, glomerulosclerosis, and it results in further kidney damage.

Measuring the intraglomerular pressure is not possible in a clinical setting, however, proteinuria is a reasonable indicator of elevated glomerular pressure. Proteinuria can be detected and quantified through a simple urine test, the urine protein/creatinine ratio (UPC). In cats, a UPC ≥ 0.5 is indicative of persistent renal proteinuria.¹⁹ In a study that looked at the relationship between survival time and proteinuria in cats with CRF, the UPC was shown to be a significant predictor of survival time. Median survival time for cats with a UPC < 0.43 was 766 days compared to only 281 days for cats with UPC > 0.43 .¹⁷ Although cats with chronic renal failure typically have low concentrations of protein in their urine, the degree of proteinuria is of prognostic importance.

ACE inhibitors are ideally suited to treat elevated intraglomerular pressure because they selectively dilate the efferent arteriole of the glomerulus. The ACE inhibitor benazepril has been shown to prolong survival time and reduce proteinuria in a large clinical trial in humans²⁰ and to have beneficial hemodynamic effects (normalization of glomerular hypertension with maintained or increased glomerular filtration rate) in a model of CRF in cats.²¹ Benazepril has been studied in cats with naturally occurring CRF.^{22,23} In a double-blind, prospective, randomized clinical trial involving 192 cats with chronic renal failure, benazepril produced a significant reduction in proteinuria in all cats that received it, including those with minimal proteinuria (UPC < 0.2), although the effect was largest in cats with higher UPCs. There was no difference in survival time between cats receiving benazepril vs. those receiving placebo when all 192 cats were compared. However, there was a trend ($P = .27$) toward longer survival times in the 13 cats with more marked proteinuria (UPC > 1.0) (402 days) compared to those receiving placebo (149 days).²² A beneficial effect of benazepril on appetite was observed in cats with more pronounced proteinuria (UPC > 1.0). Benazepril was well tolerated in all cats. In another study of 61 cats with chronic renal failure, several nonsignificant trends were observed in cats that were given benazepril compared to those receiving placebo, including a lower plasma urea and creatinine concentration, improved quality of life, and a delay in the progression of CRF in cats with either IRIS Stage II or III to IRIS Stage IV.²³ In summary, benazepril appears to decrease proteinuria in all cats, and in doing so increases survival times in those with marked proteinuria and appears to slow progression of renal disease in cats diagnosed with CRF.

Phosphorus restriction, Renal Secondary Hyperparathyroidism, and Calcitriol

Renal secondary hyperparathyroidism occurs when the parathyroid glands secrete excessive parathyroid hormone (PTH) as a result of chronic renal failure. This is due to several factors, the primary factor being an impaired ability of cats with CRF to synthesize calcitriol, the natural, biologically active form of Vitamin D.

The kidneys are responsible for the final step in the synthesis of calcitriol from its precursor, 25-hydroxyvitamin D. As the kidneys fail, there are fewer healthy proximal tubule cells with the enzyme system necessary to catalyze this synthesis.

Phosphorus is filtered from the bloodstream by the kidneys. When the kidneys begin to fail, the phosphorus levels begin to rise. When serum phosphorus levels are high, phosphorus can combine with calcium in the bloodstream. This is known as the law of mass action. The formation and deposition of calcium phosphate in the soft tissues, including the kidneys, can cause further renal damage. Serum phosphorus levels in excess of 7 or 8 mg/dL will decrease the serum ionized calcium level approximately 0.1 mg/dL, which is enough to stimulate PTH secretion. Also, phosphorus inhibits the enzyme system involved in the synthesis of calcitriol. As phosphorus levels begin to rise in cats with CRF, calcitriol synthesis is further inhibited. This is yet another factor by which hyperphosphatemia promotes the development of renal secondary hyperparathyroidism.

Calcitriol plays a role in maintaining normal levels of calcium in the bloodstream, since calcitriol is necessary for the intestines to properly absorb dietary calcium. As the kidneys fail and become incapable of producing adequate amounts of calcitriol, the serum calcium level begins to fall. To maintain adequate levels of calcium in the bloodstream, the parathyroid glands release PTH, restoring and maintaining normal calcium levels.

In summary: the parathyroid glands will secrete excessive PTH as a result of elevated phosphorus levels, or because of inadequate calcitriol levels, or both. PTH levels can therefore be reduced in two ways: either through administration of calcitriol, or through control of dietary phosphorus.

Controlling PTH levels is beneficial in patients with CRF. Although production of PTH is physiologically appropriate, excessive amounts of PTH are toxic to the kidneys and other organs. Toxic effects of PTH on the brain likely contribute to the depression and stupor seen in cats with renal failure.²⁴ In experimental animals, excessive PTH also slows nerve conduction, contributes to the anemia often seen with CRF, and enhances the progression of kidney failure.²⁴ This likely occurs in cats as well.

When administered to animals with renal secondary hyperparathyroidism, calcitriol causes a reduction in PTH production by the parathyroid glands.²⁰ Calcitriol has been employed in the management of renal secondary hyperparathyroidism in humans with end-stage renal disease for its ability to decrease PTH secretion and inhibit parathyroid gland hypertrophy. Although calcitriol would be expected to normalize elevated PTH levels in cats with CRF, a recent study in which calcitriol was administered either daily (2.5 ng/kg orally q24h) or intermittently 8.75 ng/kg orally q84h) failed to reduce the PTH levels in the 10 cats in the study with CRF and high PTH levels.²⁵ A dose titration study, however, was not performed, and it is possible that the calcitriol dosage, which was based on clinical recommendations made for

dogs²⁴, could have been too low. Calcitriol has many direct beneficial effects in uremic animals independent of its PTH-lowering properties²⁴, and may still have a place in the treatment of renal secondary hyperparathyroidism in cats with CRF.

Prescription diets designed for cats with kidney failure contain reduced levels of phosphorus. Limiting phosphorus consumption appears to slow the progression of CRF in humans and dogs, and there is evidence that dietary phosphorus restriction also limits renal injury in cats with CRF.⁴

Orally administered phosphorus binders, such as aluminum salts (e.g. aluminum hydroxide) and calcium salts (e.g. calcium carbonate) are the most commonly used phosphate binders. Aluminum salts have been removed from the human market over concern for aluminum toxicity. Many clients (and some practitioners) mistakenly believe that the commonly used phosphorus binders work by directly lowering serum phosphate levels. Phosphate binders work by binding with phosphate in the food, which prevents it from then being absorbed. Administering a phosphate binder independent of feeding will have no effect on serum phosphate levels.

Sevelamer hydrochloride (Renalgel) is an organic polymer that is a non-calcium, non-aluminum containing compound that binds phosphorus in the intestinal tract. It has been used safely in cats, but has the potential to bind vitamins in the intestinal tract. Animals receiving this drug should receive a vitamin supplement as a precaution. Lanthanum carbonate (Fosrenol) is a new intestinal phosphate binder in human medicine that does not contain calcium or aluminum. Reports of its clinical use in dogs or cats are lacking. Epakitin (Vetoquinol USA, Buena NJ) is a phosphate binder consisting of calcium carbonate and chitosan. Most cats dislike the taste of liquid phosphorus binders, and the tablets are often difficult to administer due to their large size. Epakitin is a palatable powder that can be mixed into canned food. Because they are calcium-based, there is some concern that the use of calcium salts could raise the blood calcium level, especially if given in conjunction with calcitriol. Phosphorus binders are most effective when given at the time of feeding or shortly thereafter (within 2 hours).

The author uses intestinal phosphate binders based on a recently published roundtable discussion on the topic.²⁶ The degree of phosphate restriction depends on the IRIS stage of chronic renal failure. The target serum phosphate level (two months post-treatment) for cats in stage II should be 2.5 to 4.5 mg/dl. As the renal disease progresses to stage III, the high end of target range increases to 5.0 mg/dl, and increases further to 6.0 mg/dl as cats progress to stage IV. ²⁶Phosphorus restriction may be achieved initially through phosphorus restricted diets alone. However, if the serum phosphate concentration is greater than 6 mg/dl four weeks after dietary therapy, phosphate binders should be administered. ²⁶

Traditionally, phosphorus restriction was initiated when high phosphorus levels were detected on blood tests. However, phosphorus restriction may have benefit when initiated before the onset of overtly high levels of phosphorus, because renal secondary hyperparathyroidism occurs before serum phosphorus concentrations exceed the normal range, and because fasting serum phosphorus concentration may not accurately reflect overall phosphorus metabolism.^{11,26} More research is necessary before specific recommendations can be made, however, phosphorus should probably not be restricted in patients with serum phosphate levels less than 4.5 mg/dl unless the cat has elevated serum PTH levels. ²⁶ Return of serum

phosphorus to normal levels does not guarantee that PTH levels will return to normal, since phosphorus restriction is effective only in those animals that have an adequate number of healthy proximal tubule cells to synthesize calcitriol once the inhibitory effects of excessive phosphorus are controlled. For those patients whose PTH levels remain high despite a seemingly well-controlled phosphorus level, administration of calcitriol may be necessary to control PTH levels. Because the effective dose of calcitriol necessary to reduce PTH levels in cats with CRF and renal secondary hyperparathyroidism has yet to be determined^Y, and because reduction of PTH levels through control of dietary phosphorus intake has been shown to improve survival in cats^{4,27} with CRF, the initial approach to controlling elevated PTH levels in cats with CRF should be via dietary phosphorus restriction. If, after controlling hyperphosphatemia, PTH levels remain elevated, calcitriol should be considered. If using calcitriol, it should not be given to cats until hyperphosphatemia has been controlled. If the Ca x P product exceeds 70, or if the serum phosphorus remains higher than 6.0 mg/dl, calcitriol should not be administered, as soft tissue mineralization, including renal mineralization, is a risk.

Diets that are designed for the management of chronic renal failure are already restricted in phosphorus, and feeding this type of diet alone may be sufficient to prevent hyperphosphatemia. If a cat with CRF refuses to eat a prescription renal diet, the use of a phosphate binder becomes even more important. It has been shown that administration of a phosphate binder to cats eating a maintenance diet with standard phosphorus levels will decrease the serum phosphate level.²⁶

Fluid therapy

Fluid therapy is the cornerstone of treatment for cats acutely ill with CRF, and remains an important factor in the long-term management of cats with CRF. Cats with CRF are usually polyuric and have higher fluid requirements than those of other patients. If water losses exceed water consumption, dehydration and volume depletion may occur. Dehydration decreases renal perfusion and may lead to a rapid, severe decline in renal function. While there are ways to encourage additional water intake in the home setting (e.g., feeding canned food rather than dry food, adding water or broth to the food), the fluid intake for cats with CRF is often inadequate, and some cats require subcutaneous fluid administration. Most cats tolerate this well, and clients can easily be taught how to perform this procedure. Fluids should initially be administered every day, and may be tapered to every other day or even less frequently, depending on how the cat is feeling at home. There is apparently no consensus among veterinarians regarding whether or when subcutaneous fluid therapy should be initiated in any given feline patient. In the author's experience, cats presenting acutely ill with CRF that require hospitalization and intravenous fluid therapy usually require subcutaneous fluid therapy at home to maintain adequate diuresis. On the other hand, many cats that are incidentally discovered to be in IRIS Stage II (or even Stage III) on routine bloodwork are often managed well at home without the need for subcutaneous fluids. In general, cats seem to be clinically more sensitive to changes in hydration status compared to dogs and will sometimes show dramatic improvement in appetite and activity when given subcutaneous fluids, with no clear correlation to their level of azotemia. The decision to initiate subcutaneous fluid therapy at home should be made on a case-by-case basis.

High blood pressure

High blood pressure is seen in almost 20% of cats with CRF presenting to primary care facilities.²⁸ In referral practices, the incidence has been reported to be as high as 65%. In CRF, perfusion pressure in remnant glomeruli tends to be increased. Increased systemic blood pressure may be transmitted to the glomeruli, causing further damage. Hypertension can also cause damage to the brain, eyes, and heart if uncontrolled. Hypertension may be present at any stage of CRF, and the presence or absence of hypertension is unrelated to serum creatinine concentration.²⁹ High blood pressure is a major risk factor for the progression of chronic renal failure in humans and rats, and evidence has shown this to be true for dogs³⁰, and presumably for cats as well. Cats with CRF should have their blood pressure evaluated, preferably with the owner present. Hypertension in cats is defined as an indirect systolic pressure greater than 160 or 170 mm Hg, and a diastolic blood pressure greater than 100 mm Hg.^{31,32} Amlodipine besylate is currently the treatment of choice for the control of hypertension in cats. If amlodipine is ineffective, an ACE-inhibitor such as enalapril or benazepril may be added. Hypertensive cats need life-long therapy to keep their blood pressure under control.

Sodium restriction

The relationship between sodium and chronic renal failure remains nebulous. Many years ago, salt supplementation was recommended for cats and dogs with CRF, on the supposition that this would promote urinary excretion of nitrogenous wastes, thereby lessening the clinical signs of azotemia. As the relationship between CRF and hypertension later became apparent, it became standard practice to recommend sodium restriction for patients with CRF, out of a fear that salt would increase intraglomerular pressure, injure the kidney, and increase the risk of progression of CRF. Studies in dogs and cats with induced CRF, however, have failed to show a consistent relationship between increased sodium intake and elevations in systemic blood pressure.^{33,34} Cats with CRF are less flexible when it comes to handling changes in dietary sodium content, and many maintenance diets contain more sodium than needed (about 1%). Prescription diets for cats with renal failure provide about 0.2 - 0.3% sodium.

Cats with impaired renal function, when fed a diet high in sodium, show increased serum urea nitrogen, phosphorus, and creatinine concentrations, suggesting progressive deterioration of renal function.³⁵ Interestingly, hypertension was not a factor in this deterioration of renal function. Dietary treatment did not affect mean arterial, systolic, or diastolic blood pressure. Feeding a diet with too little sodium, however, may cause a reduction in glomerular filtration rate, resulting in excessive urinary loss of potassium, and activation of the renin-angiotensin-aldosterone system, with no beneficial effect on systemic blood pressure.³³ It is becoming clear that excessive amounts of dietary sodium may be harmful in cats with renal insufficiency, but there is insufficient data to confirm or refute any benefits or disadvantages of dietary sodium restriction. It should be noted that commonly used subcutaneous fluids (i.e. saline or lactated Ringer's solution) contain substantial amounts of sodium. It is unknown whether the sodium contained in subcutaneous fluids has any impact on hypertension and progression of CRF.

Urinary tract infections

The normally high osmolality of feline urine provides an inhospitable environment for bacterial colonization. As the ability to concentrate urine gradually wanes, cats with CRF become more susceptible to developing bacterial urinary tract infections. Urine culture should be performed if urinalysis suggests infection, or if clinical signs of bacterial urinary tract infection develops.

Metabolic acidosis

Cats with CRF have a decreased ability to excrete hydrogen ions. The resulting metabolic acidosis may contribute to the other signs commonly seen in CRF, including anorexia, nausea, vomiting, lethargy, and generalized muscle weakness. Fortunately, prescription renal diets are alkalinizing, and help control metabolic acidosis in most cats with CRF. However, if acidosis persists (serum bicarbonate consistently < 15 mmol/L) several weeks after dietary change, alkalinization therapy should be considered.¹² Although sodium bicarbonate is the most commonly used alkalinizing agent, potassium citrate may be a better choice in cats with low or borderline potassium levels, as it would address the acidosis and the hypokalemia simultaneously. Regardless of the alkalinizing agent chosen, serum bicarbonate levels should be monitored 10 to 14 days after therapy, and the dose adjusted accordingly.

Nausea, vomiting, poor appetite

Gastrin is a digestive hormone that causes the stomach to produce acid. The kidneys are responsible for excreting much of the gastrin produced in the body. As the kidneys fail, gastrin levels begin to rise, the degree of hypergastrinemia increasing with the severity of the renal insufficiency.⁷ This results in increased gastric acidity, nausea, vomiting, poor appetite, and possible gastric ulceration and justifies the use of appropriate treatments, such as

histamine-₂ receptor antagonists or proton pump inhibitors to suppress gastric acid secretion. Cimetidine, ranitidine, and famotidine are effective at decreasing gastric acidity in cats. Famotidine may offer an advantage in that it may be administered only once daily, compared to the others. Proton pump inhibitors, such as omeprazole, are also effective in controlling gastric acidity, and are effective in cats when given once daily. Cats that continue to vomit despite administration of histamine-₂ receptor antagonists or proton pump inhibitors may benefit from a centrally-acting antiemetic such as metoclopramide. For cats suspected of having gastric ulcers, sucralfate helps form a protective coating over the ulcer, reducing symptoms such as pain, nausea, and vomiting. The use of a compounding pharmacy may be necessary, as sucralfate tablets cannot be divided accurately to achieve the proper dose for most cats. Sucralfate is most effective in an acid environment, and should be given 30-60 minutes before histamine-₂ blockers or phosphate binders.

Although cats with severe azotemia are frequently anorectic, many cats with chronic renal failure experience poor appetite despite relatively mild degrees of azotemia. In some instances, appetite stimulation may be achieved using drugs that affect serotonin and dopamine receptors in the central nervous system. Cyproheptadine, an antihistamine with antiserotonin effects, is commonly used in practice for this purpose. Benzodiazepines such as diazepam and oxazepam have been used, however, they often cause an unacceptable degree of sedation. Mirtazapine, a tetracyclic antidepressant, is a newly recognized appetite stimulant in cats that, in small doses (3 – 4 mg/cat orally q72h), appears to act in a similar fashion to cyproheptadine in increasing appetite. Little data are available about the use of this drug in cats, so caution should be advised.

Anemia

As the kidneys fail, they produce inadequate amounts of erythropoietin, and many cats with CRF become progressively anemic. Anemia contributes to the lethargy and poor appetite seen in cats with CRF. Recombinant human erythropoietin (r-HuEPO), when given to cats dramatically reverses the anemia. Therapy should be considered only if the anemia is severe (PCV <20%) and the patient is symptomatic. Recombinant human erythropoietin is administered subcutaneously three times a week until the PCV exceeds 30%, and is then decreased to once or twice a week, to maintain an adequate PCV. Iron supplementation should be administered concurrently, and blood pressure should be evaluated before initiating and throughout treatment.

Recombinant human erythropoietin is not of feline origin, and approximately 25 to 30% of cats will develop antibodies against it. These antibodies not only bind the r-HuEPO being administered, but will also bind whatever remaining endogenous feline erythropoietin is present. Cats develop sudden, severe anemia as a result, and become transfusion dependent. It is usually at this point that owners elect euthanasia. For those clients who choose not to euthanize at this point, it may take several months before the anti-EPO antibodies dissipate. The anemia will eventually return to pre-treatment values and the cat will remain transfusion dependent. Further use of r-HuEPO is then no longer an option.

Intraintestinal Bacteriotherapy (“Enteric Dialysis”)

The concept of “enteric dialysis” is based on the premise that the intestinal wall functions as a semi-permeable membrane; solutes that are in high concentration in the bloodstream readily diffuse from plasma into the intestinal lumen. The use of live bacteria that catabolize uremic solutes in the gut when ingested would create a gradient favorable for the uremic toxins to diffuse from the plasma into the gut. Azodyl® (Vetoquinol USA, Buena, NJ) is a recently introduced nutritional supplement that contains the bacteria *Enterococcus thermophilus*, *Bifidobacterium longum*, and *Lactobacillus acidophilus*, in capsule form, for this purpose. However, there are no controlled clinical trials of the use of these probiotics for azotemia and chronic renal failure in cats. In the author’s experience, a favorable response – decreased azotemia and increased appetite – has been seen in the limited number of cases in which it has been prescribed.

Conclusion

Many advances have been achieved regarding the treatment of chronic renal failure. Although CRF is not curable, cats can live for many years after diagnosis if treated appropriately. Cats are remarkable animals and can often survive for long periods with a seemingly minute fraction of functional renal tissue.

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