Staging and Management of Chronic Kidney Disease

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Chronic kidney disease (CKD) is a common problem that affects an estimated 1–3% of all cats and up to 35% of geriatric cats in referral hospital populations. Nephron damage associated with CKD is usually irreversible and can be progressive. Renal failure, as defined by persistent renal azotemia superimposed on the inability to concentrate urine, results when three-quarters or more of the nephrons of both kidneys are not functioning. Whether the underlying CKD primarily affects glomeruli, tubules, interstitial tissue, or renal vasculature, irreversible damage to any portion of the nephron renders the entire nephron nonfunctional. Healing of irreversibly damaged nephrons occurs by replacement fibrosis and therefore a specific etiology is often not determined. Chronic kidney disease occurs over a period of months or years and is an important cause of death in cats. It is often not possible to improve renal function in CKD and therefore treatment is aimed at stabilizing renal function. Importantly, there is increasing evidence that dietary and antiproteinuric treatments can decrease the progressive nature of CKD.

Staging CKD

Many different terms have been used to describe renal disease and decreased renal function. Unfortunately, these terms can be confusing due to lack of standard definition and application. The International Renal Interest Society (IRIS) was created to advance the scientific understanding of kidney disease in small animals at the 8th Annual Congress of the European Society of Veterinary Internal Medicine in Vienna, Austria, in 1998. The following was developed by the IRIS Board as guide to staging stable feline CKD in order to 1) improve communications surrounding CKD and 2) link appropriate diagnostic and therapeutic efforts to patients with varying degrees of CKD. This staging system has been adopted (after input and modification) by both the American and European Societies of Veterinary Nephrology and Urology.

Serum creatinine concentration	Stage 1 (Non-azotemic CKD)	Stage 2	Stage 3 (Moderate azotemia)	Stage 4 (Severe azotemia)
mg/dl (Feline)	< 1.6	1.6–2.8	2.9–5.0	> 5.0
mg/dl (Canine)	< 1.4	1.4–2.0	2.1–5.0	> 5.0

It is important to note that although the staging system is based primarily serum creatinine concentrations, it cannot be applied to patients with pre- or post-renal azotemia or patients with acute or decompensated (sometimes termed "acute on chronic") renal failure. Serum creatinine concentrations must always be interpreted in light of the patient's urine specific gravity and physical examination findings in order to rule out pre- and post-renal causes of azotemia. The

patient history is important in ruling out acute and decompensated chronic renal failure. The above feline stages are further classified by the presence or absence of proteinuria and systemic hypertension as follows:

Urine protein/creatinine ratio	Classification
< 0.2	Nonproteinuric
0.2–0.4 (cats); 0.2–0.5 (dogs)	Borderline proteinuric
> 0.4 (cats); > 0.5 (dogs)	Proteinuric

Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	Risk level	Classification
< 150	< 95	Minimal	Arterial pressure 0
150–159	95–99	Low	AP 1
160–179	100–119	Moderate	AP 2
≥ 180	≥ 120	High	AP 3

Pathophysiology

The pathophysiology of CKD can be considered at both the organ and systemic level. At the level of the kidney, the fundamental pathology of CKD is loss of nephrons and decreased glomerular filtration. Reduced glomerular filtration results in increased plasma concentrations of substances that are normally eliminated from the body by renal excretion. In addition to excretion of metabolic wastes and maintenance of fluid and electrolyte balance, the kidneys also function as endocrine organs and catabolize several peptide hormones. Therefore, hormonal disturbances also play a role in the pathogenesis of CKD. For example, decreased production of erythropoietin contributes to the nonregenerative anemia of CKD and decreased metabolism and excretion of parathyroid hormone and gastrin contribute to mineral and bone disorders and gastritis, respectively. Finally, part of the pathophysiology of CKD is brought about by compensatory mechanisms. For example, the mineral and bone disorders of CKD occurs secondary to hyperparathyroidism, which develops in an attempt to maintain normal plasma calcium and phosphorus concentrations. Similarly, the individual glomerular filtration rate of intact nephrons increases in CKD in an attempt to maintain adequate renal function; however, proteinuria and glomerulosclerosis may be consequences or "trade-offs" of this hyperfiltration.

Clinical Signs and Diagnosis

Clinical signs of CKD may not be present in early stages and when present in later stages, are usually nonspecific (lethargy, depression, anorexia, gastroenteritis, and dehydration). Occasionally uremic breath and/or oral ulcers may be observed. Unique signs of CKD (vs. acute kidney injury) include a longstanding history of weight loss and polydipsia-polyuria, poor body condition, nonregenerative anemia, small and irregular kidneys, and renal secondary hyperparathyroidism. The classic diagnosis of renal failure based on renal azotemia (persistent

azotemia superimposed on the inability to concentrate urine) pertains to CKD Stages 2 through 4. Stage 1 CKD (nonazotemic CKD) could be diagnosed in cats with persistent proteinuria, urine concentrating deficits, increases in serum creatinine over time, even if the values remain in the normal range (e.g., serum creatinine that increases from 0.6 to 1.2 mg/dl could indicate a ≥ 50% reduction in GFR), or abnormal renal palpation or renal ultrasound findings.

In general, the diagnostic approach to patient once CKD has been identified and staged is focused on three areas: 1) characterization of the renal disease, 2) characterization of the stability of the renal disease and function, and 3) characterization of the patient's problems associated with the decreased renal function. Further definition of the renal disease (beyond a standard minimum data base) should include for example, quantitation of proteinuria, measurement of blood pressure, urine culture, and kidney imaging. The stability of the renal function would be assessed by serial monitoring of abnormalities identified during the initial characterization of the renal disease. This monitoring should always include serum biochemistry profiles, urinalyses, quantitation of proteinuria, and measurement of blood pressure but may also include follow-up urine cultures and ultrasound examinations. Characterization of the renal disease and its stability is most important in the earlier stages of CKD when appropriate treatment has the greatest potential to improve or stabilize renal function. Characterization of patient problems becomes more important in the later stages of CKD when clinical signs tend to be more severe. In the later stages of CKD, diagnostic (and subsequent therapeutic) efforts should directed at patient problems that may include anorexia, vomiting, acidosis, potassium depletion, hypertension, and anemia, etc.

Management

Similar to the diagnostic approach to CKD, the therapeutic approach should also be tailored to fit the patient's stage of disease. For example, disease-specific treatments for nephroliths and bacterial pyelonephritis as well as treatments designed to slow the progression of renal disease (so-called renoprotective treatments) will be of most value in the earlier stages of CKD. Examples of renoprotective treatments include dietary change designed to reduce serum phosphorus concentrations and angiotensin-converting enzyme inhibitors designed to normalize systemic and intraglomerular blood pressures and reduce proteinuria. In the later stages of CKD, treatment tends to be focused on decreasing the patient's clinical signs associated with the decreased renal function.

Hypertension

Systemic hypertension is relatively common in cats with CKD. Although the exact mechanism of the hypertension is not known, a combination of glomerular capillary and arteriolar scarring, decreased production of renal vasodilatory prostaglandins, increased responsiveness to normal pressor mechanisms, and activation of the renin-angiotensin system may be involved. Gradual reduction of dietary salt intake is often recommended as the first line of treatment; however, there are no studies that document the efficacy of dietary salt reduction in lowering blood pressure. In many cases vasodilators (angiotensin converting enzyme inhibitors [ACEI] and calcium channel antagonists [CCA]) may be necessary to control hypertension. Systemic hypertension may contribute to progressive nephron loss by causing irreversible glomerular damage via increased intraglomerular pressures and glomerulosclerosis. In cats, CCA (e.g., amlodipine) may be necessary in addition to control systemic hypertension.

Dietary Management

Reduction of dietary phosphorus and protein intake is the cornerstone of management of CKD. Dietary management may not only allow the animal to live more comfortably with decreased renal function but may also significantly prolong survival. Ideally, dietary protein reduction allows all essential amino acid requirements to be met without excesses. This is accomplished by feeding lowered quantities of high biological value protein and results in decreased need for renal clearance of urea and other nitrogenous metabolites. It is important to keep in mind when

feeding reduced protein diets that the energy requirements of the body have a higher priority than does protein anabolism and, therefore, if the available carbohydrates and fats are insufficient to meet caloric requirements, endogenous proteins will often be broken down as a source of energy. Catabolism of endogenous proteins for energy increases the nitrogenous waste the kidney must excrete and exacerbates the clinical signs of kidney disease.

Researchers postulate that protein requirements for patients with CKD are higher than those of normal animals. Ideally, cats with CKD should receive a minimum of 3.3–3.5 g protein/kg/day. Twenty percent of the 70 to 80 kcal/kg/day in cats should be high quality protein. A good recommendation for dietary protein reduction is to feed the maximum amount of high biological value, highly digestible protein that the animal can tolerate at his/her level of renal function. (Dietary protein reduction refers to decreased protein intake compared to normal protein intake. Most commercial pet foods contain relatively high levels of protein. Dietary protein should never be restricted, that is less than the patient's dietary requirements.) A favorable response to therapy is a stable body weight and serum creatinine and albumin concentrations and decreasing serum urea nitrogen and phosphorus concentrations. Moderate dietary protein reduction should be employed early in the course of renal failure and use of more markedly reduced protein diets should be reserved for patients that are refractory to moderate dietary protein reduction.

Management of the hyperphosphatemia that occurs in CKD is closely related to dietary protein reduction inasmuch as protein reduced diets are also phosphorus reduced. An increase in plasma phosphorus concentration occurs in CKD as a result of decreased renal excretion. Concurrently, decreased renal production of the active form of vitamin D_3 decreases intestinal absorption of calcium, which, in conjunction with impaired renal reabsorption of calcium, decreases plasma ionized calcium concentrations. Decreased vitamin D_3 and serum calcium concentrations stimulate parathyroid hormone (PTH) secretion, which facilitates renal excretion of phosphorus and increases serum calcium concentrations by increasing renal calcium reabsorption and calcium absorption from bones and the gastrointestinal tract. The "trade-offs" for this hyperparathyroidism, however, can be severe and include osteodystrophy, bone marrow suppression, and soft tissue mineralization. Soft tissue mineralization occurs predominately in damaged tissue, and if mineralization occurs in renal tissue, the result may be a progressive decline in renal function. If the product of the serum calcium and phosphorus concentrations is greater than 50–70 mg/dl, the patient is at risk for soft tissue mineralization. Studies in cats with remnant kidney CKD have shown that normal dietary phosphorus intake is associated with microscopic renal mineralization and fibrosis and these changes were prevented by reducing dietary phosphorus. Similarly, in cats with naturally occurring CKD, feeding a diet specifically formulated to meet the needs of cats with CKD, together with phosphate binding drugs if required, controls hyperphosphatemia and secondary renal hyperparathyroidism, and is associated with an increased survival time.

In addition to feeding a phosphorus-restricted diet, administration of enteric phosphate binders will help combat hyperphosphatemia. Enteric phosphate binders do not directly lower plasma phosphorus but bind phosphorus in the intestinal tract and prevent absorption. Enteric phosphate binders are generally more effective if dietary phosphorus intake is restricted. Although in canine CKD, low dosages of 1,25-dihdroxycholecalciferol (calcitriol) have been associated with decreased PTH concentrations and decreased renal mortality, preliminary studies in cats with CKD have not demonstrated benefit associated with calcitriol treatment.

Hypokalemia

Hypokalemia and potassium depletion may occur in cats with CKD. Anorexia, feeding high-protein, acidifying diets, PU-PD, and vomiting can all contribute to potassium depletion; however, only 20–30% of CKD cats have hypokalemia as an initial laboratory finding. Potassium is predominately an intracellular cation, and approximately 95% of total body

potassium is present in skeletal muscle, and therefore serum potassium concentrations may not accurately reflect total body potassium stores, especially in the early stages of potassium depletion. It has been documented that cats with CKD have lower muscle potassium concentrations and higher serum potassium concentrations than do normal cats. This data may suggest the need for oral potassium supplementation early in the course of CKD in cats. Generalized muscle weakness is the primary clinical sign associated with potassium depletion. Muscle weakness usually resolves within 1 to 5 days after initiation of oral potassium supplementation. Potassium depletion can also contribute to gut muscle weakness resulting in ileus and vomiting.

Calorie Malnutrition

Vomiting and anorexia are common in cats with CKD and can often result in decreased caloric intake. Causes of vomiting and anorexia include: 1) stimulation of chemoreceptor trigger zone by uremic toxins, 2) decreased excretion of gastrin and increased gastric acid secretion (plasma gastrin concentrations in cats with chronic renal failure may be as high as 20 times the normal concentrations), and 3) gastrointestinal irritation secondary to uremia. Vomiting may be treated with metoclopramide, which blocks the chemoreceptor trigger zone. Metoclopramide also increases gastric motility and emptying without causing gastric acid secretion and is the drug of choice for vomiting associated with renal failure. H_2 receptor blockers (e.g., famotidine) have been shown to effectively decrease gastric acid secretion, which may attenuate vomiting in cats with CKD. Oral ulcers, stomatitis, and glossitis may occur as a result of gastritis and vomiting or the effect of uremic toxins on mucosal membranes and will often also result in anorexia. If vomiting has been controlled but anorexia persists, placement of an esophagostomy or gastrostomy tube will often facilitate the maintenance of caloric intake and hydration status.

Pyelonephritis and Renoliths

Urinary tract infections (UTI) are rare in healthy cats but are more common in cats with CKD since the antibacterial properties of urine decline as urine concentration decreases. In studies of cats with naturally occurring CKD, as many as 29% had occult UTI. Bacterial infection of the renal pelvis and parenchyma can then result from an ascending urinary tract infection. Initially the renal cortex is not affected; however, with chronic pyelonephritis the entire kidney may become involved. Pyelonephritis can precipitate the development of renal calculi and conversely renal calculi can increase the risk of pyelonephritis. Calcium oxalate uroliths are the most common type of renoliths in older cats. Appropriate, long-term antibiotic therapy may halt the renal damage associated with pyelonephritis; however, if renoliths are present, antibiotic therapy alone is usually ineffective.

Anemia

The nonregenerative anemia observed in cats with CKD occurs as a result of a combination of decreased erythropoietin production, shortened red blood cell survival, gastrointestinal tract blood loss, and the effects of uremic toxins such as PTH on erythropoiesis. In addition, nutritional deficiencies (e.g., vitamins B_6 and B_{12}, niacin, and folic acid) and iron depletion can contribute to the anemia associated with CKD. Anabolic steroids are usually of little benefit; however, treatment with recombinant human erythropoietin treatment in cats and with CKD anemia has generally been successful. Although not approved for use in veterinary medicine, the dosage that has been recommended is 100 U/kg of recombinant erythropoietin given subcutaneously three times weekly. The dose interval is lengthened once a target packed-cell volume (PCV) is achieved (PCV of approximately 35% in cats). Usually a dosage of 75–100 U/kg, once or twice weekly, is sufficient for maintenance. This treatment, in addition to increasing the PCV, often results in increased appetite, weight gain, increased strength, and an improved sense of wellbeing. It should be noted, however, that there is a potential for antibodies to form in cats treated with human recombinant products. Studies show that anti-recombinant

erythropoietin-binding antibodies will develop in approximately 25–30% of cats, and that these antibodies may also react with endogenous erythropoietin, making the animal transfusion dependent. Development of anti-r-HuEPO antibodies should be suspected in patients with a sudden decrease in PCV. Iron deficiency, external blood loss, hemolytic disorders, and concurrent infectious, inflammatory, or neoplastic diseases should be ruled out in such patients. The absence of peripheral reticulocytes and severe erythroid hypoplasia (M:E ratio > 10) on bone marrow cytology is compatible with the presence of anti-r-HuEPO antibodies. Iron supplementation (iron dextran: 10 mg/kg IM every 3–4 weeks) should be employed during recombinant erythropoietin treatment because of the rapid initiation of erythropoiesis and marginal depletion of iron stores that occur in animals with CKD. Until feline recombinant erythropoietin becomes commercially available, treatment with human recombinant products should be reserved for those animals with weakness and lethargy attributable to their anemia.

Newer Treatments

Enteral dialysis may provide a significant extra-renal excretory route for accumulated "uremic toxins." Azodyl® contains *E. thermophilus*, *L. acidophilus*, *B. longum*, and psyllium and is designed to metabolize and adsorb uremic toxins that have diffused into the large bowel. In preliminary studies in cats with spontaneous CKD treated with Azodyl® for 60 days, serum urea nitrogen and creatinine concentrations were reduced by 16% and 27%, respectively. Similar probiotic microbes are common in many dairy products and are classified by the FDA as "generally regarded as safe." Currently there are several large-scale prospective clinical trials underway to better define the efficacy of this type of treatment.

Speaker Information

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