Renal Dysfunction in Small Animals

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Failure of the filtration function of the kidneys leads to the development of azotemia (an excess of nitrogenous compounds in the blood), which may be classified as prerenal, renal, postrenal, or of mixed origin. Prerenal azotemia develops whenever mean systemic arterial blood pressure declines to values <60 mmHg and/or when dehydration causes plasma protein concentration to increase. Conditions that may lead to development of prerenal azotemia include dehydration, congestive heart failure, and shock. Prerenal azotemia generally resolves with appropriate treatment, because kidney structure has not been altered, which allows normal function to resume once renal perfusion has been restored. Renal azotemia refers to a reduction in glomerular filtration rate (GFR) of ~75% during acute or chronic primary renal (or intrarenal) diseases. Postrenal azotemia develops when the integrity of the urinary tract is disrupted (eg, bladder rupture) or urine outflow is obstructed (eg, urethral or bilateral ureteral obstruction). Once adequate urine flow is restored, postrenal azotemia will resolve.

Chronic Kidney Disease

Chronic kidney disease (CKD) involves a loss of functional renal tissue due to a prolonged (≥2 mo), usually progressive, process. Dramatic changes in renal structure may be seen, although structural and functional changes in the kidney are only loosely correlated. CKD often smolders for many months or years before it becomes clinically apparent, and it is invariably irreversible and frequently progressive. Although congenital disease results in a transient increase in prevalence in animals <3 yr old, the prevalence increases with advancing age from 5–6 yr. In geriatric populations at referral institutions, CKD affects as many as 10% of dogs and 35% of cats. The prevalence in the general small animal population is likely to be lower, perhaps 1%–3%. Several breeds of dogs and cats are associated with heritable CKD (see Congenital and Inherited Anomalies of the Urinary System). There is no apparent breed or sex predisposition for nonheritable CKD in dogs or cats.

Chronic interstitial nephritis, pig

COURTESY OF DR. BRUCE LAWHORN.

CKD is generally classified into various stages (see Table: Classification of Stages of Kidney Disease) based on laboratory tests and clinical signs. In Stage 1, a process is damaging the kidneys but azotemia and clinical signs have not developed. Unfortunately, renal disease is uncommonly detected at this stage. In Stage 2, the disease has progressed, GFR has fallen to <25% of normal, and azotemia is present, but clinical signs are not yet seen. However, this stage may be associated with impaired urine-concentrating ability and increased urine volume. Stage 3 occurs when GFR has declined further, azotemia is present, and clinical signs are often seen. Stage 4 reflects further progression and severe azotemia, with clinical signs present. This staging system applies to CKD only.

TABLE

Classification of Stages of Kidney Disease

Substaging Based on Blood Pressure:

Systemic hypertension is present in ~20% of dogs and cats with CKD and is associated with target organ damage in the kidneys, eyes, CNS, and cardiovascular system. It is recommended that animals with CKD be substaged on the basis of blood pressure measurements (see Table: Substages of Chronic Kidney Disease Based on Arterial Blood Pressure (AP) Measurements and Risk of Target Organ Damage).

TABLE

Substages of Chronic Kidney Disease Based on Arterial Blood Pressure (AP) Measurements and Risk of Target Organ Damage

In general, animals in substage AP3 and those in substage AP2 with preexisting target organ damage (eg, retinal injury or CKD) should be considered candidates for antihypertensive therapy.

Substaging Based on Proteinuria:

The routine dipstick evaluation of urine for protein is not particularly specific, because many of the positive reactions (⅓ in dogs and ⅔ in cats) are false-positives. Although it is a useful screening test, a positive result should be followed with a more specific test, such as the sulfosalicylic acid test, the urine protein:creatinine ratio, or albumin-specific assays.

Species-specific antibodies for albumin have led to development of highly specific and sensitive assays for the detection and measurement of urine albumin concentrations. Microalbuminuria is defined as a urine protein content that leads to a negative reaction for the routine urine dipstick and a positive reaction with a species-specific antibody test. Animals with microalbuminuria frequently exhibit or subsequently develop kidney disease, systemic inflammatory or metabolic disease, neoplasia, or infectious diseases.

Proteinuria is an important finding and is associated with a poor prognosis in aged animals and in those with CKD. Changes in the magnitude of proteinuria represent a good marker for the efficacy of antihypertensive therapy. Animals with CKD should also be substaged on the basis of proteinuria (see Table: Substages of Chronic Kidney Disease Based on Proteinuria), using the protein:creatinine ratio.

TABLE

Substages of Chronic Kidney Disease Based on Proteinuria

Etiology:

Attempting to identify the primary process causing the kidney disease, especially in Stages 1 and 2, is important to form a prognosis and treatment plan. Known causes of CKD include diseases of the macrovascular compartment (eg, systemic hypertension, coagulopathies, chronic hypoperfusion), microvascular compartment (eg, systemic and glomerular hypertension, glomerulonephritis, developmental disorders, congenital collagen defects, amyloidosis), interstitial compartment (eg, pyelonephritis, neoplasia, obstructive uropathy, allergic and immune-mediated nephritis), and tubular compartment (eg, tubular reabsorptive defects, chronic low-grade nephrotoxicity, obstructive uropathy). Many causes of chronic, generalized renal disease are associated with progressive interstitial fibrosis. The severity of interstitial fibrosis is positively correlated with the magnitude of decline of GFR and negatively correlated with the prognosis. The glomerular, tubulointerstitial, and vascular lesions found in animals with generalized CKD are often similar, regardless of the initiating cause, particularly in Stage 4. At this point, renal histology may show only marked interstitial fibrosis, which may be called chronic interstitial nephritis or tubulointerstitial fibrosis. This term describes the morphologic appearance of kidneys with end-stage chronic disease of any cause. Because acute kidney injury may progress to a chronic condition, any cause of acute kidney injury is also a possible cause of CKD.

Clinical Findings:

Generally, no clinical signs are seen as a direct result of disease until ≥75% of nephron function has been impaired (Stages 3 and 4). Exceptions are chronic kidney diseases that develop as part of a systemic disease with clinical signs referable to involvement of other body tissues (eg, systemic lupus erythematosus, systemic hypertension), chronic kidney diseases accompanied by nephrotic syndrome, or those associated with marked renal inflammation and capsular swelling leading to flank pain and occasionally to vomiting. Usually, the earliest clinical signs commonly attributable to renal dysfunction are polydipsia and polyuria, which are not seen until the function of approximately two-thirds of the nephrons has been impaired (late Stage 2 or early Stage 3). Further destruction of renal tissue leads to azotemia without new clinical signs in Stage 2, and finally to the clinically apparent uremic syndrome in Stage 4. Initially, uremia is associated with occasional vomiting and lethargy. As the disease progresses within Stages 3 and 4 throughout months (dogs) to years (cats), anorexia, weight loss, dehydration, oral ulceration, vomiting, and diarrhea become fully manifest. Loose teeth, deformable maxilla and mandible, or pathologic fractures may be seen with renal secondary osteodystrophy (see Renal Secondary Hyperparathyroidism), but these are uncommon and generally seen only in young dogs with end-stage congenital renal disease. Physical examination and imaging studies of animals in Stages 3 and 4 usually reveal small, irregular kidneys, although normal to large kidneys can be seen in animals with neoplasms, hydronephrosis, or glomerulonephritis. Mucous membranes are pale in late Stage 3 and Stage 4, due to the presence of a nonregenerative, normocytic, normochromic anemia.

Diagnosis:

In Stages 1 and 2, diagnosis is often missed or made incidentally during imaging studies or urinalyses conducted for other purposes. In Stages 3 and 4, the BUN, serum creatinine, and inorganic phosphorus concentrations are increased. Potassium depletion, due to renal potassium wasting combined with inadequate intake and the kaliuretic effects of acidosis, is frequently seen in cats and occasionally in dogs. Hyperkalemia associated with oliguria and anuria may be noted in terminal Stage 4 or whenever marked prerenal azotemia is concurrent with CKD. Systemic hypertension and associated complications develop in ~20% of affected cats and dogs and can occur at any stage. Osteoporosis may be seen radiographically, although this late finding is generally not helpful for diagnosis.

The urine specific gravity may range from 1.001–1.060 in dogs and 1.005–1.080 in cats, depending on body needs for water homeostasis; the normal range overlaps the abnormal or inappropriate range. In animals with dehydration and normal renal function, urine specific gravity should be >1.030 in dogs and >1.035 in cats. The inability to produce concentrated urine when challenged by dehydration is an early sign of CKD; however, dogs with primary glomerular disease, and some cats, may become azotemic while retaining the ability to concentrate urine to a specific gravity >1.035. Even so, concentrated urine is rarely seen when the serum creatinine is >4 mg/dL in an animal with azotemia of renal origin.

The polydipsia and polyuria of CKD must be differentiated from diseases that cause primary polydipsia (eg, psychogenic polydipsia, hyperthyroidism) or interfere directly with the urine-concentrating mechanism. This includes conditions that lead to retention of solute in tubular fluid (eg, diuretic administration, diabetes mellitus), central diabetes insipidus, and nephrogenic diabetes insipidus (eg, hyperadrenocorticism, hypercalcemia, pyometra, diseases causing septicemia). Adrenal insufficiency leads to a urine-concentrating defect and may thus be confused with Stage 2 and 3 renal disease, because prerenal azotemia may be caused by the vomiting, diarrhea, and polydipsia associated with hypoadrenocorticism. Hyperkalemia, hyponatremia, and/or reduced plasma Na^+ to K^+ ratio helps establish a tentative diagnosis of adrenal insufficiency, which must be confirmed by hormonal assay(s). Also, animals with hypoadrenocorticism improve rapidly in response to proper therapy.
Combinations of survey radiography, abdominal ultrasonography, serial clinical pathology tests, including urinalyses and urine cultures, and blood pressure measurements should be performed to evaluate the severity of disease, establish a prognosis, monitor the response to therapy, and identify complicating factors. Specific renal function tests and renal biopsy may be helpful to identify the exact cause in Stages 1–3, but the presence of advanced pathologic changes in Stage 4 is nonspecific and often precludes identification of an underlying cause by histologic studies. This condition in late Stage 4 is often described as end-stage renal failure clinically and as chronic, generalized nephritis pathologically. CKD should be distinguished from the more readily reversible acute disease. Frequently, differentiation may be accomplished with an appropriate history, physical examination, and laboratory findings, although a renal biopsy may be required. However, therapy for CKD caused by a range of morphologic lesions is similar, so renal biopsies may not be warranted unless marked proteinuria is present or a treatable cause is suspected.

Treatment:

With appropriate therapy, animals can survive for long periods with only a small fraction of functional renal tissue, perhaps 5%–8% in dogs and cats. Recommended treatment varies with the stage of the disease. In **Stages 1 and 2**, animals usually have minimal clinical abnormalities. Efforts to identify and treat the primary cause of the disease should be thorough. The identification and supportive treatment of developing complications (eg, systemic hypertension, potassium homeostasis disorders, metabolic acidosis, bacterial urinary tract infection) should be aggressively pursued. The systemic hypertension seen in ~20% of animals with CKD may be seen at any stage and is not effectively controlled by feeding a low-salt diet. The usual antihypertensive medications for blood pressure substages AP2 and AP3 (see Table: Substages of Chronic Kidney Disease Based on Arterial Blood Pressure (AP) Measurements and Risk of Target Organ Damage) are a calcium-channel blocker such as amlodipine besylate (0.25–0.5 mg/kg/day, PO) or an angiotensin-converting enzyme (ACE) inhibitor such as enalapril or benazepril (0.5 mg/kg, once daily in cats and bid in dogs) or an angiotensin-receptor blocker (ARB) such as telmisartan (1 mg/kg, once daily in cats and bid in dogs). If an ACE inhibitor is used in conjunction with a renal diet, potassium should be carefully monitored. Hyperkalemia may develop, particularly in Stage 4, and dietary change or dosage adjustment should be considered if serum potassium exceeds 6.5 mEq/L. While ACE inhibitors (or ARBs) and calcium-channel blockers may be administered

together, a calcium-channel blocker is usually recommended as initial therapy in cats and an ACE inhibitor (or ARB) in dogs. In addition to providing a continuous supply of fresh drinking water and encouraging (and documenting) adequate dietary intake, body condition scoring should be used routinely to assess adequacy of intake. Animals in this stage should be fed standard, commercially available maintenance diets, unless they are markedly proteinuric (*see*below). All affected animals should be reevaluated every 6–12 mo, or sooner if problems develop.

In **Stages 2 and 3**, the principles for management of complications are the same, except that the animal should be evaluated every 3–6 mo. These evaluations should include hematology, serum biochemistries, and urinalysis. Because dogs and cats with CKD are prone to development of bacterial urinary tract infections, urine culture should be performed annually and any time urinalysis suggests infection. The progressive nature of this disease produces a vicious cycle of progressive renal destruction. Measures that may slow this progression include dietary phosphorus restriction, dietary fish oil supplementation, antihypertensive agents (for hypertensive dogs and cats), and administration of ACE inhibitors or ARBs (proteinuria substage P; see Table: Substages of Chronic Kidney Disease Based on Proteinuria). Dietary restriction of phosphate and acid load is essential in this stage, and specialized diets for management of kidney disease should be fed. Potassium citrate or sodium bicarbonate, given PO, may be indicated if the animal is severely acidotic (plasma bicarbonate <15 mEq/L) or remains acidotic 2–3 wk after diet change. If dietary restriction of phosphorus is unsuccessful in maintaining a normal level of serum phosphorus within 2–3 mo, phosphate-binding gels containing calcium acetate, calcium carbonate, calcium carbonate plus chitosan, lanthanum carbonate, or aluminum hydroxide should be administered with meals to achieve the desired effect. There is also a clear rationale for the inclusion of dietary n-3 polyunsaturated fatty acids in these stages.

In **late Stage 3 and Stage 4**, all of the principles of managing the preceding stages apply, except that the animal should be evaluated every 1–3 mo. Dietary restriction of protein may relieve some of the signs of uremia. High-quality protein (eg, egg protein) should be fed at a level of 2–2.8 g/kg/day for dogs and 2.8–3.8 g/kg/day for cats. Commercial diets formulated for cats and dogs with CKD generally meet this recommendation. Administration of a proton pump inhibitor such as omeprazole(0.5–1 mg/kg/day, PO) or an H_2-receptor antagonist such as famotidine (5 mg/kg, PO, tid-qid) decreases gastric acidity and vomiting. Anabolic steroids, such as oxymethalone or nandrolone, have been administered to stimulate RBC production in anemic animals, but this is not effective.

Recombinant erythropoietin and other erythropoiesis-stimulating agents (eg, darbopoietin, continuous erythropoietin receptor activator) may stimulate RBC production, but antierythropoietin antibodies develop in ~50% of animals treated with the human recombinant erythropoietin, epoetin alfa, and may result in refractory anemia. Darbopoietin may be less likely to produce this effect and may be preferred. Until species-specific products become generally available, erythropoietin administration is now recommended only for animals with clinically apparent signs of anemia (eg, weakness, marked lethargy not attributable to other factors), which generally occurs at a hematocrit <20%.

Fluid therapy with polyionic solutions, given IV or SC in the hospital or SC by owners at home, is often beneficial in animals with intermittent signs of uremia. Oral vitamin D administration may

reduce uremic signs and prolong survival, particularly in dogs. However, vitamin D administration requires prior resolution of hyperphosphatemia (goal is serum phosphorus <6 mg/dL), and it may induce hypercalcemia. Probiotic medications and certain dietary fibers may enhance gut catabolism of nitrogenous compounds and uremic toxins. Feeding tubes may help manage chronic anorexia. Euthanasia or renal replacement therapy (renal transplantation and/or dialysis) should be carefully considered if therapy does not improve renal function and alleviate signs of uremia.

Acute Kidney Injury

Because not all animals with acute kidney injury (AKI) will be identifed or exhibit azotemia, AKI has replaced the older term, acute renal failure. Animals with AKI are most often presented to the veterinarian when a sudden, major insult damages the kidneys. The principal causes are toxins (eg, ethylene glycol, aminoglycoside antibiotics, hypercalcemia, hemoglobinuria, melamine-cyanuric acid, grapes or raisins, NSAIDs), ischemia (eg, embolic showers from disseminated intravascular coagulation or severe prolonged hypoperfusion), and infection (eg, leptospirosis, borreliosis).

Clinical Findings:

Mild AKI often goes unrecognized; severe initial or repeated bouts may lead to CKD. Most often, AKI is recognized in advanced stages and is characterized clinically by anorexia, depression, dehydration, oral ulceration, vomiting and/or diarrhea, or oliguria. Physical examination findings often reveal dehydration but otherwise are usually not remarkable, although pain is occasionally elicited on palpation of the kidneys, which may be normal in size to slightly enlarged.

Diagnosis:

A history of hypotension, shock, or recent exposure to known nephrotoxins in an animal with sudden-onset uremia is the typical clinical picture of an animal with acute kidney disease. The presence of poorly concentrated urine (specific gravity 1.007–1.030) despite dehydration and/or azotemia suggests renal dysfunction. Differentiating between chronic and acute kidney disease (and establishing a specific cause in acute kidney disease) is important, because the prognosis and specific therapy may differ. Animals with AKI usually have a compatible history and other urinalysis abnormalities; marked cylindruria is a frequent and definitive finding. Other urinalysis findings may include the presence of a large number of renal epithelial cells and leukocytes in the urine sediment, glucosuria, crystalluria, enzymuria, and/or myoglobinuria/hemoglobinuria. Animals with AKI generally have increased serum urea nitrogen, creatinine, and inorganic phosphorus concentrations and metabolic acidosis. Oliguria or anuria after rehydration, which is often associated with hyperkalemia, is a poor prognostic sign; in contrast, polyuric animals have a better prognosis, although they may become hypokalemic. The kidneys are typically normal in size and shape and an anemia is often, but not always, absent—findings that may help differentiate acute from chronic kidney disease.

After injury, the kidney has considerable potential for functional regeneration through the process of compensatory hypertrophy and adaptive hyperfunction. In animals with CKD, it is likely that most of this regenerative process has occurred before the initial diagnosis. In contrast, animals with AKI have considerably more potential for improvement of renal function, if they can be sustained through a uremic episode. The duration of the uremic episode may be substantial with some nephrotoxins (eg, 1–3 wk with aminoglycoside antibiotics and 4–8 wk with ethylene glycol). A renal biopsy may be of value in assessment of the severity, extent, cause, and potential reversibility of the disease.

As a disease process, AKI is a spectrum, and the International Renal Interest Society recommends that patients with AKI be categorized primarily on the basis of serum creatinine. Animals with Grade I AKI have nonazotemic AKI (serum creatinine ≤1.6 mg/dL). Animals with Grades II–V AKI exhibit varying degrees of azotemia, with serum creatinine levels of 1.7–2.5 mg/dL in Grade II, 2.6–5 mg/dL in Grade III, 5.1–10 mg/dL in Grade IV, and >10 mg/dL in Grade V.

Treatment:

Severe AKI that necessitates medical intervention is a serious condition, with a survival rate of ~50%. If the cause is known, specific therapy should be instituted, eg, 4-methylpyrazole or ethanol for ethylene glycol toxicity in dogs (see Ethylene Glycol Toxicity). Fluid therapy is indicated for all dehydrated and inappetant animals. A polyionic fluid such as lactated Ringer's solution is satisfactory unless hyperkalemia is present, in which case normal saline is recommended. Sodium bicarbonatemay be cautiously added to the fluids to correct acidosis.
In oliguric or anuric animals, therapy to promote increased urine volume is often recommended if the animal is well hydrated and urine production is <0.5 mL/kg/hr. This approach has been questioned because urine flow may increase without corresponding increases in renal blood flow and GFR. Administration of excess fluid to an animal in the maintenance phase of oliguric renal failure may result in life-threatening pulmonary and cerebral edema. Nonetheless, efforts to increase renal blood flow and GFR may enhance urine production and do have a role in the management of these animals. For this therapy, urine production must be quantitatively monitored closely via an indwelling urethral catheter. Monitoring central venous pressure is advised to prevent overhydration. A sequential approach generally includes an initial slight overhydration by administration of a test dosage of polyionic solution IV at 50 mL/kg. If this fails to yield adequate urine flow within 3 hr, further measures include osmotic diuresis (10% or 20% mannitol or dextrose, 0.5–1 g/kg, IV, as a slow bolus throughout 15– 30 min, alternated with infusion of lactated Ringer's solution, 30 mL/kg, IV, throughout 30 min). Subsequent measures generally include furosemide (2 mg/kg, IV, which can be doubled and then tripled at 2-hr intervals if urine production does not increase above the target of 0.5 mL/kg/hr).
However, furosemide may worsen the severity of AKI caused by aminoglycosides. Finally, renal vasodilators (dopamine diluted in 5% dextrose, IV, to provide 1–5 mcg/kg/min)
plus furosemide(2 mg/kg, IV) may be tried for 2 hr. Dopamine may lead to ventricular arrhythmias, and high doses of dopamine may cause renal vasoconstriction. Dopamine produces minimal renal vasodilation in cats and calcium channel blockade (eg, amlodipinebesylate, 0.25–0.5

mg/kg, or diltiazem, 1–3 mg/kg) may be preferred. If attempts to restore urine flow fail, aggressive measures should be discontinued to avoid overhydration. Daily fluid therapy based on maintenance and rehydration needs is continued until renal function and clinical condition improve. Feeding tube placement greatly facilitates patient management at this stage and should be implemented for any animal with marked renal azotemia (serum creatinine >10 mg/dL after rehydration).

A second therapeutic option, rather than the aggressive measures discussed above, is to proceed directly to fluid therapy with polyionic solutions while waiting for renal regeneration. Again, feeding tube placement for parenteral nutrition should be implemented in anorectic animals with marked azotemia. Peritoneal dialysis or hemodialysis may be necessary if none of the above measures restores urine production.