Chronic Kidney Disease

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Contributors:

Revised by Kari Rothrock DVM
Original author was Linda Shell DVM, DACVIM (Neurology), 1/13/2010

Synonyms:

Chronic kidney failure
Chronic kidney insufficiency
Chronic renal insufficiency
Chronic renal disease

Disease description:

Chronic kidney disease (CKD) is an irreversible, progressive loss of kidney function and/or structure. In order to be defined as chronic (as opposed to acute kidney injury), kidney damage must exist for at least 3 months.[1]

Prevalence

CKD is the most common form of kidney disease of dogs and cats. CKD is estimated to affected 1-3% of the general feline population and 0.5-1.5% of the canine population.[1-3] Though CKD can affect any age, it is more common in older patients. Studies have reported that 10% of dogs and 30% of cats >15 years old have CKD.[4]

Etiology

Numerous causes of CKD exist, including various congenital and acquired diseases. Possible causes include renal dysplasia, amyloidosis, Fanconi syndrome, glomerulopathies, polycystic kidney disease, renal neoplasia, pyelonephritis, infection with feline leukemia virus, feline immunodeficiency virus or feline infectious peritonitis virus, hypercalcemia, hypokalemia, ureteroliths, nephroliths, nephrotoxin exposure, obstructive renal diseases, fungal infections, leptospirosis, tubulointerstitial disorders, renal ischemia, immune-mediated diseases, nephrotoxic drugs (e.g. nonsteroidal anti-inflammatory drugs, aminoglycosides, amphotericin), and various metabolic and endocrine disorders. CKD can also be idiopathic or a sequela of acute kidney injury.[1,5]

Pathophysiology

During the initial phase of kidney injury, the kidneys adapt to nephron injury or loss by increasing the single glomerular filtration rate (GFR) of surviving nephrons. Single GFR improves with afferent arteriole dilation and reduction in glomerular arteriolar resistance. As renal mass decreases, surviving nephrons lose autoregulation and systemic arterial pressure is transmitted to the glomerulus, which leads to glomerular hypertension, hypertrophy, and hyperfiltration.[1,5] Over time, these changes lead to loss of filtration barrier integrity through podocyte damage, proteinuria, glomerulosclerosis, and eventual reduction in GFR.[5] Further nephron loss then occurs.

Tubulointerstitial fibrosis is the most common pathologic change noted in CKD.[6] Patients with CKD have excessive fibrogenic responses, with upregulation of various pro-fibrotic mediators such as TGF-β. Excessive extracellular matrix accumulation; loss of renal microvasculature; mononuclear cell infiltration; and tubular atrophy are all common in cases of renal fibrosis.[6]

Proteinuria potentially facilitates progression of CKD through further glomerular and tubulointerstitial damage. Various cytokines, vasoactive peptides, and growth factors are produced in response to proteinuria, leading to tubulointerstitial inflammation and fibrosis.[7] Excess protein within the glomerular filtrate has been associated with proximal tubular apoptosis and upregulation of pro-inflammatory and pro-fibrotic mediator genes.[6]

Tubular ischemia and chronic hypoxia also develop subsequent to glomerular disease.[1] Decreased blood flow through the efferent arteriole of damaged glomeruli leads to atrophy and fibrosis of the renal tubules. Oxygen consumption of remaining functional nephrons in a diseased kidney is up to three times the oxygen requirement of nephrons in a normal functioning kidney.[6] Chronic hypoxia occurs from compromised blood

flow through the interstitial capillary network. Tubulointerstitial hypoxia leads to fibrosis of renal tubules by upregulation of a variety of growth factors, vasoactive substances, and fibroblasts.[1]

Upregulation of the renin-angiotensin-aldosterone system (RAAS) occurs early in CKD. RAAS upregulation leads to progressive renal injury due to increased glomerular pressure and upregulation of pro-inflammatory and pro-fibrotic gene transcription.[6]

Consequences of CKD

As more nephrons are damaged and numbers of healthy nephrons are insufficient to maintain GFR and renal function, several derangements occur. Retention of toxic metabolites; reduced excretion of organic solutes; abnormal excretion of electrolytes and water; and impaired renal hormone synthesis all occur.[1] CKD causes a variety of clinical consequences that effect numerous organ systems.

Abnormal Excretion or Retention of Water, Electrolytes, and Organic Solutes

Abnormal excretion of electrolytes and water leads to various clinical abnormalities. As renal function declines, the kidneys are unable to adequately concentrate urine because of increased solute load per functioning nephron. Loss of urine concentration leads to solute diuresis; renal medullary architecture disruption; and loss of renal responsiveness to antidiuretic hormone (ADH).[1] Polydipsia occurs to compensate for polyuria but dehydration can develop with inadequate fluid intake.

As GFR falls, excretion of various waste products of protein catabolism (e.g. urea, creatinine) also declines. The excretion of other substances (e.g. various cytokines, growth factors) is also reduced in CKD. Finally, levels of certain hormones (e.g. insulin, glucagon, parathyroid hormone, prolactin) occur secondary to decreased renal catabolism or increased glandular secretion.[1]

Hyperphosphatemia occurs with CKD since the kidneys are the primary route of phosphorus excretion. Hyperphosphatemia contributes to further progression of CKD disease; may lead to tissue mineralization; and stimulates increased production of parathyroid hormone (PTH).[5,8] Hyperphosphatemia may directly damage the renal microvascular endothelium and may also lead to increased extracellular matrix, and increased production of pro-fibrotic substances.[6] Serum phosphate levels are directly linked to mortality in patients with CKD.[3,9] In one study of 211 cats with CKD, an 11.8% increase in the risk of death occurred for each 1U increase in serum phosphorus.[3]

Hypokalemia can occur and is more frequently found in cats than dogs with CKD. Hypokalemia can occur from activation of RAAS, which causes kaliuresis; decreased food intake; and persistent dehydration. Hypokalemia may promote progression of CKD in cats.[5] Hypokalemia can result in polyuria from decreased renal responsiveness to ADH and can lead to muscle weakness. Hypokalemia may also cause reduced renal blood flow from angiotensin II-related vasoconstriction. Hypokalemia hyperpolarizes the cell membrane, making cells less responsive to stimuli, with subsequent neuromuscular dysfunction (e.g. muscle weakness).[1]

Metabolic acidosis occurs late in the course of CKD from impaired ability of the kidney to excrete hydrogen ions; decreased filtration of phosphate and sulfate compounds; impaired renal tubular proton secretion; and impaired renal tubular bicarbonate resorption.[1,5] Chronic metabolic acidosis can cause many adverse clinical effects, such as vomiting, anorexia, weight loss, muscle wasting, malnutrition, and weakness.[1]

Impaired Renal Hormone Synthesis

Patients with CKD have impaired ability to synthesis erythropoietin (EPO), the principle hormone controlling erythropoiesis. The renal inner cortex and outer medulla are the main sites of EPO synthesis. EPO synthesis declines with insufficient functioning renal tissue and a nonregenerative anemia can develop.[10] Anemia can also occur from gastrointestinal blood loss, decreased red blood cell lifespan, and malnutrition.[5]

CKD causes derangement in calcitriol synthesis and subsequent renal secondary hyperparathyroidism. One of the most important factors contributing to elevated PTH synthesis and secretion in patients with renal disease is a deficiency in calcitriol. Calcitriol is formed by 1α-hydroxylation of 25-hydroxycholecalciferol in renal tubular cells through action of the enzyme, 1α-hydroxylase.[11] Calcitriol limits PTH synthesis through negative feedback inhibition. Calcitriol promotes intestinal absorption of calcium and phosphorus, thereby increasing serum calcium and phosphorus levels. As GFR declines in CKD, serum phosphorus levels rise and stimulate PTH production. Phosphorus retention also inhibits 1α-hydroxylase activity, thereby decreasing calcitriol synthesis and promoting PTH synthesis. Initially, increased PTH synthesis can restore calcitriol levels back to

normal. However, as CKD progresses more renal tubular cells are lost and adequate calcitriol synthesis is not possible. Feedback inhibition of PTH by calcitriol is no longer present.[1,11]

Systemic Hypertension

Systemic hypertension is one of the most common complications of CKD.[2] CKD is the most commonly recognized cause of systemic hypertension in dogs and cats.[1] Hypertension has been reported in 20-65% of cats and in 20-30% of dogs with CKD.[1,5] Hypertension develops for several reasons, including RAAS activation, increased sympathetic nervous system activity, fluid retention, and altered sodium excretion. Untreated hypertension can exacerbate CKD owing to end-organ injury. Hypertension is also a negative prognostic indicator in CKD.[1]

Gastrointestinal Abnormalities

Vomiting can develop due to effects of uremic toxins on the chemoreceptor trigger zone. Periodontal disease, oral ulcerations, dysphagia, and halitosis can also occur.[1,2]

Patients with CKD have increased levels of gastrin due to reduced renal clearance of the hormone.[1,4] Gastrin induces gastric acid secretion and increases histamine release from gastric mucosal mast cells. Increased levels of gastrin may lead to gastrointestinal (GI) ulceration and ischemic mucosal necrosis. However, GI mucosal necrosis and ulceration appear to be uncommon findings with CKD, and gastric hyperacidity has not been documented in dogs and cats.[1] In one study of 37 cats with CKD, the most common gastric lesions noted on histopathology were gastric fibrosis and mineralization; gastric ulceration was not found.[12]

Staging of CKD

The International Renal Interest Society (IRIS) has created a staging system for CKD based on patient assessment on at least 2 separate occasions. Staging CKD in the IRIS classification system is helpful for monitoring patients; making therapeutic recommendations; and estimating prognosis. IRIS staging is based on serum creatinine levels, with substaging based on the presence of proteinuria (as determined by the urine protein:creatinine ratio [UPC]) and systemic hypertension.[1]

IRIS Staging of CKD in Dogs and Cats Based on Serum Creatinine (mg/dL)

Stage	***Dogs***	***Cats***
Stage 1	<1.4	<1.6
Stage 2	1.4-2.0	1.6-2.8
Stage 3	2.1-5.0	2.9-5.0
Stage 4	>5.0	>5.0

IRIS Substaging of CKD Based on Presence of Proteinuria by UPC

Classification	***Dogs***	***Cats***
Nonproteinuric (NP)	<0.2	<0.2
Borderline proteinuric (BP)	0.2-0.5	0.2-0.4
Proteinuric (P)	>0.5	>0.4

IRIS Blood Pressure Stages for CKD and Risk for Systemic Hypertension Complications

Substage	***Systolic BP (mmHg)***	***Diastolic BP (mmHg)***
Stage 0 (Minimal Risk)	<150	<95
Stage 1 (Low Risk)	150-159	95-99
Stage 2 (Moderate Risk)	160-179	100-119
Stage 3 (High Risk)	>180	>120

Diagnosis

History/Physical Examination Findings: Examination findings and clinical signs can vary in patients depending on what stage is present. Patients with stage 1 are typically asymptomatic. Polyuria (PU), polydipsia (PD), weight loss, and decreased appetite may be present in stage 2 CKD. PU/PD are the most common and some of the earliest clinical signs of CKD.[1] Other clinical signs seen may include vomiting, weight loss, anorexia, lethargy, diarrhea, urinary incontinence, weakness, halitosis, and dysphagia.[1,2,5]

Abnormalities on physical exam can include dehydration, oral ulcerations, gingivitis, poor body condition, pale mucous membranes, tachycardia, tachypnea, halitosis, and cardiac arrhythmias.[1,5] Kidneys are usually palpably small, firm, and irregular.[5] Patients with hypokalemia may exhibit cervical ventroflexion, muscle weakness, and a stiff gait. Neurologic signs have been reported in as many as 65% of dogs and cats with renal disease.[1] Seizures and altered mentation are the most common abnormalities noted.[1] Patients with systemic hypertension may have signs of blindness, hyphema, and neurologic abnormalities.[1,5]

Complete Blood Count: A normocytic, normochromic, nonregenerative anemia can occur in the later stages of CKD (stage 3-4). Approximately 30-65% of cats with CKD are anemic.[10]

Biochemistry Panel: Azotemia is the hallmark abnormality of CKD. Azotemia implies at least a 75% reduction in GFR is present.[1] Other abnormalities include hyperphosphatemia, hypokalemia, hypermagnesemia, hypercalcemia, and hypocalcemia. In one study of 54 dogs with CKD, hyperphosphatemia was present in 18% of dogs in stage 1 and 100% of dogs in stage 4 CKD.[8] Hyperphosphatemia has been reported in 60% of cats with CKD.[5] Both hypokalemia and hyperphosphatemia are more common in stages 3 and 4 of CKD.[1]

Patients with CKD may be hypocalcemic, hypercalcemic, or normocalcemic. Ionized calcium should be evaluated in patients with CKD because total serum calcium does not accurately reflect ionized serum calcium concentrations. Patients with CKD can have an increase in the complexed calcium fraction, leading to elevated total serum calcium but normal to reduced ionized calcium levels. Ionized calcium is the biologically active form of calcium. Deleterious effects of hypercalcemia only occur in patients with increased serum ionized calcium levels.[11] In one study of 80 cats with CKD, ionized hypercalcemia was found in 6% and ionized hypocalcemia was found in 26%.[1] In a study of 490 dogs with CKD, 9% were ionized hypercalcemic and 36% were ionized hypocalcemic.[11]

Metabolic acidosis is a common abnormality and usually occurs in stages 3 and 4.[4]

Urinalysis: Inappropriately dilute urine (as detected by decreased urine specific gravity) is found in patients with CKD. Many patients are isosthenuric while others are able to maintain some urine concentrating ability.[1,5] Proteinuria, hematuria, pyuria, and/or bacteriuria may also be present. Urine sediment is always evaluated as part of the urinalysis.

Urine Culture: Urine culture is recommended even if urine sediment appears inactive. Urinary tract infections (UTI) are a common comorbid condition.[1] One study reported that 18/25 cats with CKD had an occult UTI (i.e. positive urine culture not associated with clinical signs of lower urinary tract disease or pyelonephritis).[13]

Urine Protein:Creatinine Ratio: Measurement of UPC assesses the quantity of protein excreted in urine over a 24-hour period. Urine sediment must be evaluated at the same time since the presence of blood cells, sperm, bacteria, or casts can artificially increase UPC. UPC can vary daily, so it is recommended that pooled samples be collected over 3 days, stored at 40°F, and submitted for analysis. Alternatively, UPC can be performed on at least 2 separate samples taken from different times. Normal dogs have a UPC <0.5. Normal cats have a UPC <0.4.[14]

Symmetric Dimethylarginine (SDMA): SDMA is a byproduct of protein methylation and is excreted primarily by the kidneys. Serum concentrations are affected by changes in GFR. SDMA has been shown to be a more sensitive biomarker than serum creatinine for assessing renal dysfunction in people. A serum test for dogs and cats has been developed. In one study serum SDMA concentrations were increased above the normal reference interval before serum creatinine became elevated, by a mean interval of 17 months in cats and 11 months in dogs.[15] SDMA increases after 40% of kidney function is lost, in comparison with 75% for an increase in serum creatinine.[20]

Blood Pressure (BP) Monitoring: Since systemic hypertension is a common consequence of CKD and can lead to further progression of CKD, BP monitoring is recommended.[1] Although measurement of BP by the Doppler technique has been recommended for indirect BP measurement, only systolic BP is detected by this method.[5]

Diagnostic Imaging: Abdominal radiographs and ultrasound may be done to search for underlying causes and complicating factors of CKD. Nephrolithiasis, renal masses, or evidence of pyelonephritis may be detected.[5]

Renal Cytology or Biopsy: Renal aspirates for cytology or biopsy for histopathology may be done to evaluate for renal neoplasia, amyloidosis, glomerulonephritis, or various infectious diseases.[5]

Disease description in this species:

Chronic kidney disease (CKD) is the most common kidney disease in dogs, affecting approximately 0.5-1.5% of the general canine population.[1] CKD occurs less often in dogs compared to cats, however. The incidence of CKD increases with age. In one study, >63% of dogs diagnosed with CKD were >12 years old.[2] No gender predilection has been identified. Any breed of dog can have CKD. Many dogs with CKD have non-specific renal lesions, and the predominant histological diagnosis is chronic tubulointerstitial inflammation and fibrosis.[1]

Clinical Signs

Clinical signs and physical abnormalities vary according to the severity of CKD. Patients with IRIS stage 1 or 2 CKD may have no clinical signs. PU/PD are the most common and some of the first clinical signs to appear.[1] Other possible abnormalities include weight loss, poor body condition, anorexia, dehydration, vomiting, diarrhea, halitosis, pale mucous membranes, oral ulcerations, dysphagia, gingivitis, lethargy, muscle weakness, constipation, palpably small kidneys, tachycardia, tachypnea, retinal hemorrhages, hyphema, retinal detachment, sudden blindness, dysuria, hematuria, seizures, neurologic signs, hypothermia, and hematemesis.[1,2,5]

Laboratory Profile:

Sodikoff's Laboratory Profiles of Small Animal Diseases: Renal Failure, Chronic

Etiology:

Aminoglycosides
Amphotericin B
Amyloidosis
Bacterial infection
Blastomyces dermatitidis
Congenital anomalies
Drugs
Ethylene glycol
Glomerulonephritis
Glomerulosclerosis
Grape, raisin ingestion
Hypercalcemia
Idiopathic, unknown
Immune-mediated disease
Ischemia
Lymphosarcoma
Metabolic disorders
Neoplasia
Nephroblastoma, embryonal nephroma
Nonsteroidal antiinflammatory drug
Pyelonephritis
Renal infarction
Renal neoplasia
Renal tubular disease
Urinary tract obstruction
Urolithiasis
Vitamin D rodenticide

Breed predilection:
None, no breed signalment

Sex predilection:
None

Age predilection:
Mature, middle-aged
Old

Diagnostic procedures:	Diagnostic results:
Calcitriol assay in serum	Calcitriol assay decreased
Symmetric Dimethylarginine (SDMA) on serum	SDMA >14 mcg/dL
Hemogram (complete blood count)	ANEMIA
Serum chemistry	Azotemia/uremia Blood urea nitrogen (BUN) increased Creatinine increased Hypercalcemia Hyperphosphatemia Hypocalcemia Hypokalemia
Urinalysis	Proteinuria, albuminuria Pyuria, increased white blood cells URINE CASTS Urine specific gravity isosthenuric (1.008 - 1.012)
Radiography of abdomen	Kidney small, irregular Renal or bladder lithiasis Renomegaly
Blood pressure measurement	Hypertension (>160/100 mmHg)
Electrocardiography (ECG)	ARRHYTHMIA, CARDIAC IRREGULARITY
Ocular examination	Hyphema, blood anterior chamber eye Retinal detachment Retinal hemorrhages
Ultrasonography of abdomen	Nephrocalcinosis Renal cyst Renal opacity observed
Urine protein:creatinine ratio	Urine protein loss increased, > 0.5 g/day
Culture of urine by cystocentesis	Aerobic culture may be positive for pathogen
Biopsy and histopathology of kidney	Glomerulosclerosis Renal fibrinoid degeneration Renal interstitial fibrosis Renal necrosis
Parathormone assay of serum	Parathormone increased

Images:

Click on each image to see a larger view

Figure 1. Gastritis secondary to renal failure

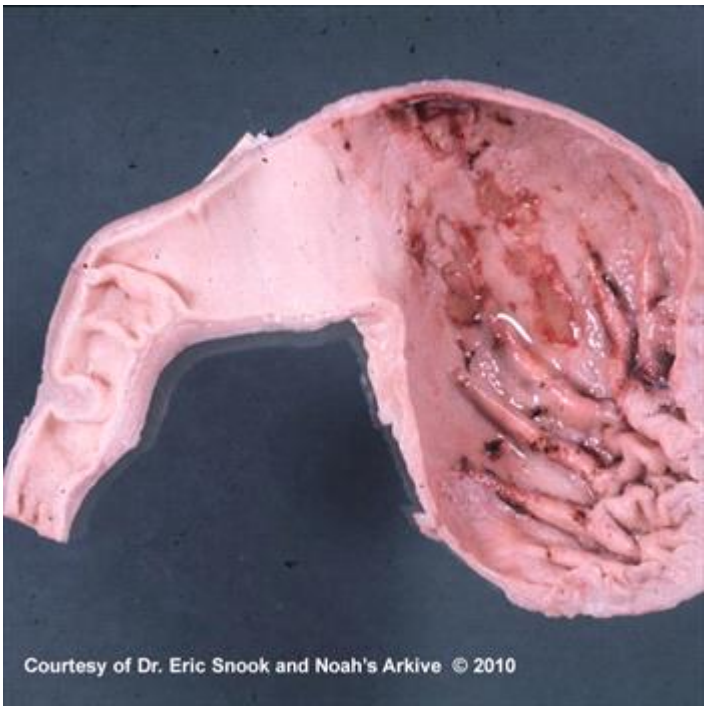

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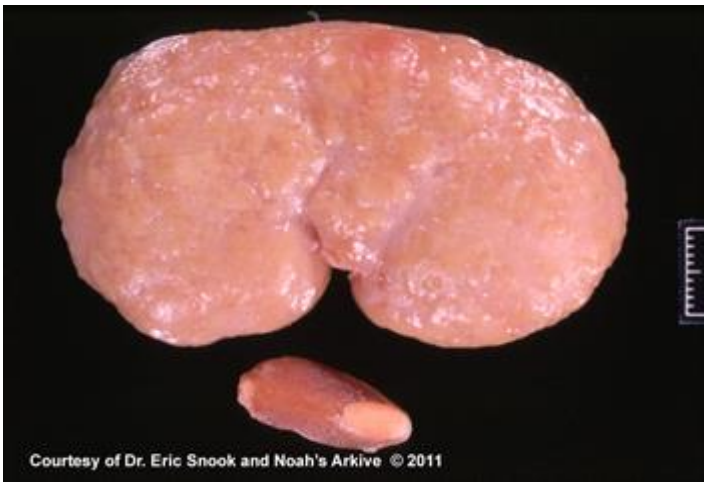
Figure 2. Chronic interstitial nephritis - dog



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Treatment/Management/Prevention:

SPECIFIC THERAPY

Therapy for CKD is aimed at identifying and treating the underlying causes; preventing and treating complications of decreased renal function; managing comorbid conditions; and slowing the progression of functional kidney loss.[1] In many instances, specific therapy for CKD is not available and supportive therapy is the mainstay of treatment.

SUPPORTIVE THERAPY

Dietary Therapy

Dietary therapy has been one of the most common recommended steps for patients with CKD. Prescription diets designed to treat CKD typically differ from maintenance diets. They often contain less protein, phosphorus, and sodium, and have increased soluble fiber. They have a higher caloric density and are

supplemented with omega 3 fatty acids and antioxidants.[1] Kidney diets have a neutral effect on acid-base balance.[1]

Renal diets have been shown to minimize uremic episodes and mortality in dogs and cats with CKD stage 2 and 3.[4,16] In one canine study, the risk of developing a uremic crisis was reduced by about 75% in dogs fed a renal diet compared to dogs fed a maintenance diet. The median symptom-free interval for dogs fed a renal diet was 615 days compared to 252 days for dogs fed a maintenance diet.[16]

The exact beneficial mechanism for renal diets is not completely understood. Dietary protein restriction alone does not appear to slow progression of renal disease.[1,4] Dietary phosphorus restriction has been shown to slow progression of disease and enhance survival in dogs with CKD, and reduced dietary phosphorus intake has limited renal mineralization in affected cats.[1] Omega 3 polyunsaturated fatty acids (PUFA) may be beneficial because they decrease inflammation; lower BP; provide antioxidant effects; and limit renal calcification. In one study comparing dogs fed a diet high in omega 6 PUFAs compared to a diet high in omega 3 PUFAs, dogs fed omega 3 PUFAs had lower mortality levels, less renal tubulointerstitial fibrosis and glomerulosclerosis, and less proteinuria.

It is generally recommended to feed a renal diet to dogs in stages 3-4 of CKD, and possibly also in stage 2.[1] Dogs with CKD should be fed 14-20% protein on dry matter basis (DMB). Less total dietary protein may be fed if the protein has high biologic value.[16] A low ratio of omega 6: omega 3 PUFAs is also encouraged.[4]

It is important that patients with CKD maintain adequate caloric intake to prevent protein-calorie malnutrition. Renal diets are gradually introduced over 2-4 weeks. Patients with CKD stage 4 are often anorexic no matter what diet is offered. Heating the diet to room temperature or adding water/tuna juice may enhance palatability.[17]

Subcutaneous Fluid Therapy
Daily or alternate-day subcutaneous fluid therapy of an alkalinizing, balanced electrolyte solution may be beneficial in patients with stage 3-4 CKD. Subcutaneous fluid therapy does not increase GFR or renal function. Instead, it helps keep patients hydrated; increases elimination of BUN by increasing tubular flow rates; and can help prevent additional elevations of BUN and creatinine from pre-renal causes.[4] Subcutaneous fluid therapy may improve appetite and activity level in some patients. However, no controlled clinical studies have been performed that show subcutaneous fluid therapy prolongs survival or improves quality of life.[4,17]

Therapy for Hyperphosphatemia
Hyperphosphatemia occurs in many patients with CKD and the incidence increases as the disease worsens.[1,8] Ideally serum phosphorus levels are maintained <4.5 mg/dL in stage 2 CKD, <5.0 mg/dL in stage 3, and <6.0 mg/dL in stage 4.

Restriction of dietary phosphorus by feeding a renal diet is one method of treating hyperphosphatemia. Renal diets for dogs typically contain as little as 0.13-0.28% phosphorus on a DMB compared to 1-2% phosphorus in typical maintenance diets.[1]

Intestinal phosphate-binding agents may be beneficial in patients that require additional therapy for hyperphosphatemia. Options include aluminum containing agents, such as aluminum hydroxide or aluminum carbonate (30-100 mg/kg/day PO).[1] Calcium-containing agents (e.g. calcium acetate 60-90 mg/kg/day PO, calcium carbonate 90-150 mg/kg/day PO) may also be used. Avoid calcium-containing agents in hypercalcemic patients, and monitor serum calcium levels when they are use since clinically significant hypercalcemia may occur.[1]

Therapy for Metabolic Acidosis
Reversing metabolic acidosis will decrease signs of uremic acidosis (e.g. anorexia, vomiting); minimize catabolic effects on protein metabolism; limit skeletal damage; and minimize adverse effects of acidosis on the cardiovascular system.[1]

Renal diets are neutral to slightly alkalinizing and are an appropriate first line of therapy. Oral sodium bicarbonate at 8-12 mg/kg PO q 8-12 hrs or potassium citrate at 40-60 mg/kg PO q 8-12 hrs may be considered for patients with metabolic acidosis unresponsive to dietary therapy.[1] Blood gas monitoring can be

performed in patients on oral alkalization therapy to determine success of therapy and to identify the need for dosage changes.

Therapy for Renal Secondary Hyperparathyroidism
Therapy for renal secondary hyperparathyroidism is described in the canine Associate chapter Renal Secondary Hyperparathyroidism.

Therapy for Anemia
Anemia is a common complication of CKD, affecting 30-65% of cats with CKD.[10] Hormone replacement therapy with either recombinant human erythropoietin (r-HuEPO) alfa (Procrit®, Epogen®) or darbepoetin alfa (DPO, Aranesp®) is the most effective therapy for anemia secondary to CKD long term.[17]

rHU-EPO is administered at 50-150 units/kg SC 3 times weekly. Hematocrit is monitored 1-2 times weekly until a target hematocrit of 37-42% is achieved. At that time, dosing is decreased to twice weekly. It typically takes 2-8 weeks to achieve the target range. It is important to continue monitoring hematocrit to ensure that iatrogenic polycythemia does not develop. Iron supplementation is also usually required.[1]

Approximately 30% of patients develop anti-EPO antibodies that can lead to severe anemia. For this reason, r-HuEPO therapy should not be started until a patient has a sustained hematocrit of ≤20%. Other side effects of r-HuEPO therapy include allergic reactions, hypertension, and seizures.[1]

Darbepoetin is less antigenic than r-HuEPO. Initially darbepoetin is given at 0.45-1.0 µg/kg SC once weekly until the hematocrit reaches the low end of the reference range, then it is reduced to q 2 weeks. If the hematocrit reaches the upper end of the reference range, the dose is reduced to 0.25 µg/kg SC q 2-3 weeks. Iron therapy may also be needed.[4]

Erythropoietic drugs are expensive. Current cost (April 2016 using GoodRx or Costco Pharmacy) for a 10,000 unit vial (about 5 doses for 20 kg dog) of r-HU-EPO is $224 for Procrit® and $162 for Epogen®. Aranesp® costs $310 for a 40 µg vial (2-4.4 doses for 20 kg dog). Since both drugs are sold in cartons of 4 vials, initial outlay can range from $650-$1240 unless a single vial can be purchased from the source, or a carton can be shared with colleagues. Be careful when prescribing Aranesp as it also is available in pre-loaded syringes, which makes dosing difficult.

Anti-Hypertension Therapy
Therapy should be instituted if systemic hypertension is confirmed. See the canine Associate chapter on Systemic Hypertension for details.

Therapy for Proteinuria
Dogs with proteinuria have increased risk of progression of CKD, shortened survival times, and increased mortality.[7,18] Angiotensin converting enzyme inhibitor (ACEI) therapy lowers intraglomerular pressure and can lessen proteinuria. A renal diet and ACEI (e.g. enalapril, benazepril) are indicated for dogs with UPC ratio ≥0.5.[17]

Therapy for Gastrointestinal Complications
Therapy for vomiting, nausea, and anorexia associated with CKD are instituted as needed. H2 receptor antagonists, ondansetron, omeprazole, and maropitant may be used for vomiting or nausea.[4] Mirtazapine or cyproheptadine can help stimulate appetite. The dose of mirtazapine should be reduced in stage 4 CKD patients since renal disease affects the drug's elimination.[4]

Dialysis and Renal Transplantation
Hemodialysis and continuous renal replacement therapy are not commonly performed in the dog and are available only at select institutions. Peritoneal dialysis is more widely available but is most commonly applied to cases of reversible, acute kidney injury because complications are common with chronic dialysis for dogs with CKD. Renal transplantation in the dog has been plagued with high rejection rates of the transplanted kidney in dogs and is not offered by most institutions that do transplantation surgery in cats.

MONITORING
Repeated physical exams and laboratory testing are required to monitor progression of disease; to identify and treat secondary complications; and to determine success of therapy. Serum biochemistry panel, urinalysis with urine culture, UPC measurement, and peripheral BP monitoring are all worthwhile. The frequency of monitoring varies depending on the stability of the patient and if any new therapies are

instituted. Once initial response to therapy is determined and the patient is stable, it is reasonable to monitor patients with stage 1 CKD q 6-12 months, stage 2 q 3-6 months, and stage 3 and 4 q 2-4 months.[1]

PROGNOSIS

Many variables contribute to the prognosis of CKD in the individual patient. These can include the nature of the primary renal disease; severity and duration of clinical signs; severity of renal dysfunction; and rate of progression of CKD.[1] Less information has been reported on prognosis for dogs with CKD compared to cats but dogs typically do not survive as long. Median survival for dogs with serum creatinine of 3.3 mg/dL was 615 days in one study.[1] Another study reported a median survival time of 226 days. Dogs with stage 3 and 4 CKD were reported to have a higher risk of death than dogs with stage 1 or 2 CKD.[2] Hyperphosphatemia and proteinuria reflect the presence of more progressive CKD and have a negative impact on survival.[1,9]

Special considerations:

Other Resources:

Recent VIN Message Board discussions on diagnosis of CKD
Recent VIN Message Board discussions on CKD treatment
Recent VIN Message Board discussions on IRIS staging of CKD
Recent VIN Message Board discussions on renal diets for CKD
Informational links for owners of cats with CKD by Dr. Brooks
Client Handout on subcutaneous fluid administration
Client Handout on chronic renal failure
Client Handout on kidney dialysis
Client Handout on kidney transplantation for dogs and cats
Client Handout on erythropoietin
Medical FAQ on use of calcitriol for CRF in dogs & cats
Medical FAQ on Calcium, Calcitriol & Renal Hyperparathyroidism
Medical FAQ on azodyl
Proceedings articles that discuss CKD
Path Case 78

Differential Diagnosis:

Acute kidney injury
Diabetes insipidus
Diabetes mellitus
Glomerulonephritis
Lower urinary tract disease
Other causes of PU/PD
Renal neoplasia
Certain toxins, e.g. ethylene glycol, grapes and raisins
Urolithiasis

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800.700.4636 | VINGRAM@vin.com | 530.756.4881 | Fax: 530.756.6035
777 West Covell Blvd, Davis, CA 95616