Acute Kidney Injury

The focus of this discussion will be intrinsic renal failure (pathophysiology, causes, and treatment).

- Both pre-renal and post-renal insults can also lead to acute kidney injury (AKI)
- Pre-renal—decreased renal blood flow (RBF) or excessive vasoconstriction
  o RBF is compromised when mean arterial pressure (MAP) drops below 70–80 mmHg (autoregulation maintains consistent flow ~60–160 mmHg)
- Post-renal—obstruction or diversion of urine flow
  o Prolonged obstruction may be more likely to lead to intrinsic parenchymal renal failure

There are many potential causes of AKI (see table below); however, there are really only a limited number of mechanisms that contribute to failure and its progression.

- Intrarenal vasoconstriction—occurs early in the disease process both as a function of reduced circulating volume and as a result of the disease/toxic process
- Reduced ultrafiltration—insult can cause disruption of podocyte architecture
- Tubular backleak—leakage of filtrate across damaged tubular epithelial cells, which can lead to worsening interstitial edema
- Tubular obstruction—sloughed tubular epithelial cells and debris combine with protein to occlude (or reduce) filtrate flow

The course of AKI and acute renal failure (ARF) has been divided into four phases:

- Initiation—exposure to a renal insult leading to sublethal renal tubular epithelial injury
  o Phase is short (usually lasts only hours, but can be up to days)
  o This is the period when early intervention can prevent progression to ARF
- Extension—now defined as a distinct phase following initiation
  o Cellular damage can progress to being lethal at this point
  o Point at which glomerular filtration rate (GFR) declines, concentrating ability is lost, and oliguria/anuria may develop
- Maintenance—critical level of tubular damage has occurred and clinical signs of acute uremia become evident
  o Removing the inciting cause now will not restore function as tubular lesions are established
  o Lasts for days to weeks—longer maintenance phases correlate with longer recovery phases
- Recovery—period of tubular epithelial repair and regeneration
  o Intratubular debris is removed and functions can gradually return
  o Lasts for weeks to months, but not all ARF is reversible and fibrosis may also develop

Many potential causes of AKI exist. They include commonly used medications and many toxins—in addition, while not necessarily causing AKI directly, infections and other systemic disorders can result in AKI.

- Nonsteroidal anti-inflammatory drugs (NSAIDs)—including selective cyclooxygenase (COX)-2 inhibitors
  o Essentially, NSAIDs cause an ischemic nephropathy
- Ethylene glycol (EG)—toxicant contained in antifreeze and industrial solvents
  o Blood concentrations peak 1–4 hours after ingestion, metabolized within 18–24 hours
- Vitamin D—most commonly ingested as a cholecalciferol (vitamin D₃)-containing rodenticide
  o Hypercalcemia and hyperphosphatemia are seen within 18–72 hours
- Raisins/grapes—first recognized as nephrotoxic in 2001
- Lilies—toxic genera include Lilium (Easter, tiger, stargazer, Asiatic hybrid) and Hemerocallis (common and early daylily)
- Leptospira spp. infection—dogs serve as the reservoir host for L. canicola but can also serve as secondary hosts for other serovars which cause illness
• Pyelonephritis—most often occurs secondary to a lower urinary tract infection (UTI, generally bacterial cystitis), which ascends, leading to renal colonization
• Numerous other potential causes!!!

General principles to consider in the treatment of AKI (most are centered on prevention of ongoing damage and correction of metabolic abnormalities):

• Minimize renal injury—includes discontinuing any potentially nephrotoxic drugs
  o Rapidly replenish fluid deficits
  o Maintain blood pressure in the normal range
• Correct hyperkalemia (if present) and improve acid-base status
• Frequent assessment of fluid plan, urine production, body weight—early identification of conversion to polyuria or oliguria
  o Urine output should increase to 2–5 ml/kg/hr → if not, the patient is oliguric
  o Do not consider pharmacologic intervention until the patient is rehydrated
• Oliguria—various definitions starting as low as 0.25 ml/kg/hr
  o Absolute oliguria → <1 ml/kg/hr in a hydrated, well-perfused patient
  o Relative oliguria → 1–2 ml/kg/hr in a patient receiving fluid therapy
• CVP values—monitoring can show trends toward euvoelema and overhydration
  o CVP < 0 cm H₂O indicates hypovolemia
  o CVP > 10–12 cm H₂O is a contraindication to further fluid therapy
  o Aim to keep CVP in range of 4–8 cm H₂O
• Fluid rate recommendations—first estimate/calculate dehydration deficits and make efforts to achieve euvoelema using replacement fluids

Various drugs may be considered to help convert oliguria to polyuria:

• Mannitol—osmotic diuretic that causes extracellular volume expansion
  o Dose → 0.25–1.0 g/kg slow IV bolus (15–30 mins) and 1–2 mg/kg/min CRI if bolus helps increase urine production
    ▪ Doses > 2–4 g/kg/day may induce or worsen AKI
• Loop diuretics (furosemide)—inhibit Na⁺-2Cl⁻-K⁺ pump in the luminal membrane of Henle’s loop
  o Dose → 2–6 mg/kg IV bolus, can be readministered every 6–8 hours if increased urine production is noted
    ▪ Response should be seen within 20–60 minutes
    ▪ 0.25–1.0 mg/kg/hr CRI may be more effective at inducing diuresis than boluses

The following are general approaches toward diagnostics or therapeutics for a patient with AKI:

• Obtain a full minimum database (CBC/chem/UA → preferably via cystocentesis)
  o In addition, submit the urine for aerobic culture and Leptospira PCR
  o If already on antibiotics or unable to submit urine PCR, submit serum for Leptospira serology
• Discontinue all potentially nephrotoxic drugs
• Obtain a baseline blood pressure (note that blood pressure is often normal but can increase with rehydration, so continued monitoring is recommended)
  o Check blood pressure 2–3 times daily
• Especially for cats, consider abdominal radiographs searching for ureteroliths
• Ideally, place a jugular catheter (multiple blood draws, CVP measurement)
• Treat secondary side effects of azotemia

Chronic Kidney Injury
Chronic kidney disease (CKD) is the most common kidney disease in dogs and cats. Prevalence is estimated between 0.5% and 7% in dogs and between 1.6% and 20% in cats. CKD is an irreversible and progressive disease. Diagnosis of CKD requires a complete history, thorough physical examination, and a number of tests that help to determine: (1) whether kidney disease is present, (2) whether kidney disease is acute or chronic, and (3) the extent of disease.
In addition to elevated BUN and creatinine, a serum chemistry profile may also show other markers of kidney disease, including hypokalemia (especially in cats), hyper- or hypocalcemia, and hyperphosphatemia. Urinalysis is a mandatory part of the minimum database for evaluation of CKD. Evidence of decreased urine concentrating ability (< 1.035 for cats; < 1.030 for dogs) in the face of azotemia supports the diagnosis of renal dysfunction, provided that concurrent illnesses that might interfere with urine concentrating ability have been ruled out. A full urinalysis also helps to evaluate for the presence of proteinuria, as well as evidence for inflammation or infection in the urinary tract (pyuria, bacteriuria). A urine culture is recommended in all patients undergoing evaluation for CKD. Cats are normally resistant to urinary tract infections due to their well-concentrated urine. However, cats with kidney disease have dilute urine and are more susceptible to infections, and a long-standing infection (pyelonephritis) may lead to or exacerbate CKD. A urine culture should also be performed in any patient with acute worsening of azotemia, as pyelonephritis is one of the more common causes of acute-on-chronic kidney disease.

Once a patient is diagnosed with CKD, it is important to evaluate objective criteria to determine the severity of CKD; staging helps to determine what therapy is necessary, what type of monitoring is indicated, and the prognosis for the patient. Guidelines for staging of veterinary patients with CKD have been provided by the International Renal Interest Society (IRIS). Typically, staging should only be undertaken in a stable patient, and creatinine should be assessed on at least two separate occasions. Further substaging is based on proteinuria and blood pressure.

Proteinuria is one of the few factors associated with worse prognosis in patients with CKD; early detection of proteinuria allows early therapeutic intervention, and monitoring of proteinuria provides prognostic information for owners. Proteinuria may be detected initially on a urine dipstick from routine urinalysis, but more specific tests, including the sulfosalicylic acid turbidometric test (SSA) or Early Renal Detection (E.R.D.) microalbuminuria test, may be used to verify proteinuria. Patients with CKD that have even trace amounts of proteinuria on urinalysis should have a urine protein/creatinine (UPC) ratio performed to quantify proteinuria. Standard therapy includes a renal diet and administration of an angiotensin-converting enzyme inhibitor (ACEI), with a goal of normalization, or at least 50% reduction, of the UPC ratio. Initial dosing with enalapril or benazepril is 0.25–0.5 mg/kg orally every 12–24 hours. Benazepril may be preferred over enalapril because it is cleared mainly through hepatic metabolism. Monitoring includes potassium and creatinine levels within 1–2 weeks of starting therapy, as both may increase with this medication. UPC should be measured approximately 4 weeks after starting ACEI therapy to determine efficacy of therapy.

Blood pressure is the second component of IRIS substaging for CKD. Although blood pressure has not been shown to directly decrease survival time, systemic hypertension contributes to glomerular hypertension, and ultimately proteinuria, which does have prognostic significance in patients with CKD. Therefore, monitoring and managing blood pressure is an important part of therapy for CKD. Blood pressure should ideally be measured in a patient who has been acclimated to the environment. For one blood pressure measurement, several readings should be taken using an appropriately sized blood pressure cuff. Multiple readings are then averaged to determine the blood pressure. Therapy should only be initiated in patients with persistently documented hypertension. The goal of therapy is to reduce blood pressure to at least < 160/100 mmHg. ACEIs and calcium channel blockers, such as amlodipine, are the medications of choice in dogs and cats with CKD. ACEI dosing is the same as for proteinuria. Dosing for amlodipine is 0.625 mg/cat in cats < 5 kg, and 1.25 mg for cats > 5 kg. Amlodipine dosage in dogs is 0.1–0.5 mg/kg orally every 24 hours and should be combined with an ACEI.

Diet plays one of the most important roles in management of CKD, and studies have shown that it delays onset of uremia and premature death due to complications of CKD. Renal diets have high caloric content to maintain body weight, moderate protein and phosphorus restriction to slow renal damage, sodium restriction, potassium supplementation (feline diets), an increased omega 3:omega 6 fatty acid ratio for anti-inflammatory effects, and B vitamin supplementation. The standard of care is to recommend feeding a renal diet to dogs with CKD stages 3 and 4 and cats with CKD stages 2 to 4.

Potassium depletion is especially common in cats with CKD stages 2 and 3 (~20–30%). Feline renal diets are supplemented with potassium; however, cats with persistent hypokalemia should also receive potassium supplementation. Oral replacement is the safest and preferred route. Good choices include potassium gluconate (Tumil-K) or citrate (Polycitra-K Syrup). The dosage for potassium gluconate ranges from 2 to 6 mEq/cat/d. Potassium citrate is also alkalinizing, which is beneficial, and is initially dosed at 40–60 mg/kg/d divided into 2 or 3 doses. Dosing should then be based on serial evaluations of serum potassium concentration.
Anemia is common in dogs and cats with CKD stages 3 and 4 and results primarily from impaired production of erythropoietin, but also results from GI bleeding and chronic disease. Options for treatment include correcting factors resulting in blood loss, blood transfusions, and hormone replacement therapy. The most common erythropoietin products used in veterinary patients include recombinant human products, Epogen and darbepoetin (Aranesp). Darbepoetin is initially administered at 1.5 µg/kg subcutaneously once weekly until the hematocrit reaches the lower end of the normal range. The dose is then reduced to every other week, and possibly every third week as needed, to maintain the hematocrit in the low end of the normal range. The hematocrit should then be monitored at least every 3 months. Iron supplementation is also recommended for all patients receiving erythropoietin therapy; a minimum of 50–300 mg IM injection of iron dextran should be provided at initiation of therapy. The most common complication is development of antibodies directed toward the recombinant product, and if the hematocrit does not increase or declines, the drug should be discontinued immediately.

Patients with stage 1–2 CKD should be monitored every 4 to 6 months. Patients with stage 3–4 CKD should be monitored every 3 to 4 months. Those patients with proteinuria and hypertension or evidence of progression should be monitored more frequently. Prognosis is variable—dogs with stage 3–4 CKD tend to have progressive disease, with survival times of 2 months to a year reported. Cats with CKD have a more variable prognosis, with some patients showing minimal progression and surviving several years. The best tool to assess progression and prognosis is appropriate monitoring, which should include a good history and physical examination, PCV/TP, BUN, creatinine, calcium (ionized is preferable), phosphorus, electrolytes, urine specific gravity, UPC, and blood pressure.

References