Acute Kidney Injury in Dogs and Cats

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KEYWORDS

• Acute kidney injury • Oliguria • Glomerular filtration rate

Acute kidney injury (AKI) has 4 stages. The first, or initiation phase, occurs during and immediately after the insult to the kidneys when pathologic damage to the kidney is initiated. The second stage is the extension phase, during which ischemia, hypoxia, inflammation, and cellular injury continue, leading to cellular apoptosis, necrosis, or both. Clinical and laboratory abnormalities may not be evident during the first 2 stages. The third stage, or maintenance phase, is characterized by azotemia, uremia, or both and may last for days to weeks. Oliguria (<0.5 mL urine per kg body weight per hour) or anuria (no urine production) may occur during this stage, although urine production is highly variable. The fourth stage is recovery, during which time azotemia improves and renal tubules undergo repair. Marked polyuria may occur during this stage as a result of partial restoration of renal tubular function and of osmotic diuresis of accumulated solutes. Renal function may return to normal, or the animal may be left with residual renal dysfunction. Nonazotemic renal failure can occur and is characterized by abnormalities similar to those seen during the polyuric recovery phase of AKI.[1,2]

There are many potential causes of AKI in dogs and cats (**Box 1**). Because the prognosis and outcome have been shown to be heavily dependent on the cause, every attempt should be made to identify the cause as early as possible in the management of the case.[3,4]

PATHOPHYSIOLOGY

The decrease in renal function that occurs with AKI is multifactorial and includes decreased intrarenal blood flow (RBF) and cellular damage. Ischemia causes a rapid degradation of intracellular adenosine triphosphate (ATP) to adenosine diphosphate and adenosine monophosphate (AMP). AMP may be further degraded to other adenine nucleotides that diffuse out of cells, preventing ATP resynthesis. Decreased intracellular ATP leads to several metabolic and structural changes within renal tubular cells. It causes an increase in intracellular calcium, which may activate proteases and phospholipases, with subsequent cellular damage. It also results in decreased activity of Na^+K^+-ATPase, which can alter the intracellular concentration gradient. This can

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Box 1
Common causes of AKI in the dog and cat

- Ischemia
- Infarction
- Toxins
  - Ethylene glycol
  - Heavy metals
  - Organic compounds
  - Grapes or raisins[a]
  - Hemoglobinuria/myoglobinuria
  - Lily plant[b]
  - Envenomation (eg, snake, bee, wasp, bull ants)
  - Melamine/cyanuric acid
- Infectious diseases
  - Pyelonephritis
  - Leptospirosis[a]
- Drugs
  - Aminoglycoside antibiotics
  - Amphotericin B
  - Cisplatin
  - Nonsteroidal anti-inflammatory drugs
  - Radiographic contrast agents
- Hypercalcemia
  - Calciferol-containing rodenticides
  - Human dermatologic preparations containing vitamin D analogues
- Hyperviscosity
  - Hyperglobulinemia
  - Polycythemia
- Multiple organ dysfunction syndrome
- Sepsis
- Acute pancreatitis

[a] Reported only in dogs.
[b] Reported only in cats.

result in movement of water into the cell and cell swelling, which may contribute to tubular obstruction.[2,5] The breakdown of other substances may result in the generation of hydrogen peroxide and superoxide. Ischemia induces nitric oxide synthase in renal tubular cells. Nitric oxide can react with superoxide to form peroxynitrite, which in turn can directly oxidize molecules, such as lipids and sulfhydryls. Also, peroxynitrite can inhibit renal tubular cell-matrix attachment, delaying recovery of tubular epithelial regeneration.[6,7]

The renal tubular cellular cytoskeleton undergoes significant changes with ischemia. Microvillar actin cores disassemble, resulting in loss of apical microvilli. Cells lose their polarity, resulting in altered solute trafficking. Na^+K^+-ATPase dissociates from its normal location on the basolateral plasma membrane (where it is anchored by the actin cytoskeleton) and is redistributed to the apical cell membrane. This alters proximal tubular sodium handling and results in an increased fraction of filtered sodium reaching the macula densa. The resulting afferent arteriolar constriction as the result of tubuloglomerular feedback leads to decreased glomerular filtration rate (GFR). Tight junction integrity is lost, affecting the "gate" and "fence" functions of this structure; this may contribute to the "backleak" phenomenon in AKI. Integrins are heterodimeric glycoproteins that mediate cell-cell adhesion. With ischemia, they redistribute from the basal to the apical tubular cell membrane. This results in loss of anchorage of tubular cells to the basement membrane and cell desquamation. Expression of integrin receptors may result in clumping of desquamated cells and adherence to the apical cell membrane of intact tubular cells, contributing to tubular obstruction.[2,6,8]

The inflammatory response is now believed to play a major role in AKI. Neutrophil activation, resulting in the release of inflammatory mediators, plays an important role in renal ischemia/reperfusion injury. Neutrophils adhere to endothelial cells, mediated, at least in part, by adhesion molecules P-selectin and intracellular adhesion molecule I. They migrate into the interstitium, resulting in changes in vascular permeability and endothelial and renal tubular cell integrity. Capillary plugging may be caused by neutrophil accumulation along with platelets and red blood cells. Neutrophils also release proteases and cytokines, exaggerating the inflammatory response.[6,9–11]

In humans, the mortality rate from AKI remains high (50%–60%), despite the availability of dialysis.[8] Death in these patients is frequently the result of distant organ damage secondary to AKI and/or uremia. Acute lung injury (ALI) in patients with AKI is common, and mortality of people with both AKI and ALI increases to 80%.[8] The mechanism of ALI is not well understood and is an area of current research. Studies have shown an increase in circulating cytokines in animals with AKI, including the proinflammatory cytokines interleukin-6 and interleukin-1β.[12,13] Others have demonstrated upregulation of certain lung genes that involve proinflammatory and proapoptotic pathways in rodents with AKI.[14,15] Neurologic dysfunction, including abnormal mentation, obtundation, and seizures are seen in people with AKI. Experimental studies in rodents have found increased neuronal pyknosis and microgliosis and elevated levels of proinflammatory cytokines (keratinocyte-derived chemoattractant and granulocyte colony-stimulating factor (G-CSF) in the brain.[16] Other possible mechanisms of neurologic dysfunction include AKI-induced changes in the blood-brain barrier, allowing passage of cytokines and uremic toxins, such as guanidine compounds and indoxyl sulfate.[17,18]

Necrosis is the process by which cells die acutely and is characterized by rapid metabolic collapse, cell swelling, and loss of plasma membrane integrity. Cell rupture results in release of proteolytic enzymes, which then incite inflammation. Apoptosis, or programmed cell death, is an active, energy-dependent process in which affected cells detach and nuclear chromatin becomes condensed while the plasma membrane remains intact. Eventually, the cell disintegrates into membrane-bound vesicles containing cell debris, including condensed chromatin, called apoptotic bodies. Phagocytic cells can recognize and ingest apoptotic bodies or even entire apoptotic cells Apoptosis usually occurs without inciting tissue injury or inflammation. In AKI, tubular necrosis is known to occur as a result of ischemia and toxic injury. However, apoptosis

of renal tubular cells also occurs. It seems that less severe insults may result in apoptosis, whereas those that are more severe cause necrosis. Different types of renal insults may produce necrosis or apoptosis or may cause either to occur in different portions of the renal tubule. For example, apoptosis can occur as the result of some endotoxins, gentamicin, and cyclosporine. Lower doses of cisplatin cause apoptosis, whereas higher doses result in necrosis. A *second wave* of tubular cell apoptosis seems to occur during the recovery phase of acute renal failure, which may play a part in the tubule remodeling process by limiting proliferation of regenerating cells.[8,19]

DIAGNOSIS

Although AKI is defined as the rapid loss of nephron function, exact criteria defining the decrease in renal function and the duration of loss have not been well defined in animals. In humans, a recent classification scheme has been proposed to address this issue (RIFLE: risk, injury, failure, loss, end-stage renal disease; **Table 1**).[20] Unfortunately, it is difficult to apply to veterinary patients, because pre-AKI information about serum creatinine concentration and urine output are rarely available. A scoring system using various laboratory and clinical parameters for outcome prediction in dogs with AKI that underwent hemodialysis has recently been described.[4] Further studies are needed to validate this system in other settings.

Examination of the animal with AKI should include a clinical estimate of hydration, assessment of cardiovascular status, evaluation of renal or abdominal pain, and measurement of arterial blood pressure. Diagnostic imaging is indicated for the assessment of renal size and shape and the presence of uroliths. Abdominal radiographs allow evaluation of renal size (normal length as measured on the ventrodorsal view is 2.5 to 3.5 times the length of the second lumber vertebra in dogs and 2 to 3 times, in cats); identification of radio-opaque uroliths (especially feline ureteroliths); and assessment of the amount of urine in the bladder. Ultrasonography may be performed in addition to or instead of radiography, yielding more precise measurements of renal size, determination of the echogenicity of the renal parenchyma, and identification of cysts or masses in the kidneys. Pyelectasia (dilation of the renal pelvis) may

Table 1
RIFLE classification scheme for AKI

	GFR Criteria	Urine Output Criteria
Risk	Increased SCreat × 1.5 or GFR decrease >25%	<0.5 mL/kg/h × 6 h
Injury	Increased SCreat × 2 or GFR decrease >50%	<0.5 mL/kg/h × 12 h
Failure	Increased SCreat × 3 or GFR decrease >75% or SCreat ≥4 mg/dL or Acute increase in SCreat ≥0.5 mg/dL	<0.3 mL/kg/h × 24 h or anuria × 12 h
Loss	Persistent acute renal failure; complete loss of kidney function >4 wk	
End-Stage Renal Disease	End-stage renal disease >3 mo	

Abbreviation: SCreat, serum creatinine concentration.

be seen with pyelonephritis and diffuse thickening of the cortex, with lymphosarcoma; an echogenic "rim" at the corticomedullary junction may be seen with ethylene glycol toxicity; abnormal subcapsular fluid accumulation can be seen with inflammation, infection, toxicity (ethylene glycol, lily), or neoplasia (feline lymphoma). Intravenous urography (IVU) is usually not beneficial in identifying causes of AKI, with the exception of ureteral obstruction by uroliths in cats. Animals with a serum creatinine concentration greater than 4 mg/dL should not have a diagnostic IVU, because they lack sufficient renal function to excrete and concentrate the contrast medium; also, iodinated contrast media are potentially nephrotoxic. Computerized tomography and magnetic resonance imaging do not usually provide more information than ultrasonography and have the disadvantage of requiring general anesthesia.

Initial laboratory evaluation should include a complete blood count, serum biochemistry profile, assessment of acid-base status, urinalysis, and urine culture. Additional serum and urine should be saved in case further tests are necessary. Leukocytosis may indicate an infectious cause of AKI. Blood urea nitrogen (BUN) and creatinine may be elevated, but AKI should not be ruled out if azotemia is not present. Sodium concentration may be low, normal, or high depending on the disease process, degree of vomiting and/or diarrhea, and any prior therapy. Hyperkalemia occurs primarily in animals that are in the oliguric or anuric phase of AKI. Other causes of azotemia and hyperkalemia, such as hypoadrenocorticism (Addison's disease) and postrenal azotemia, must be differentiated from AKI. Serum calcium levels are usually normal in the absence of hypercalcemia-induced AKI; hypocalcemia may occur in animals with ethylene glycol toxicity. Serum phosphorus levels are often elevated; however, the degree of elevation may reflect the degree of reduced GFR rather than the duration of disease. Metabolic acidosis is often present. Urinalysis shows isosthenuria with AKI, whereas a prerenal cause of the azotemia may be suspected with an increased urine specific gravity. Measurement of urinary electrolytes and/or creatinine can help distinguish prerenal from primary renal azotemia. Animals with prerenal azotemia but normal renal function retain sodium and chloride while excreting creatinine; those with AKI have increased urinary levels of sodium and chloride while retaining creatinine (**Table 2**).[21] Mild-to-moderate glucosuria may be seen with acute tubular damage, and microscopic hematuria can occur with glomerular or tubular damage. Urine pH level is usually acidic, although it may be alkaline in the presence of some bacterial urinary tract infections. The urine sediment should be carefully examined for the presence of casts, white blood cells, bacteria, and crystals.[1]

Tests to identify specific causes of AKI should be performed as appropriate to the animal. Serum ethylene glycol levels can be measured with a rapid in-house test (EGT Test Kit, PRN Pharmacal, Pensacola, FL, USA). This kit detects intact ethylene glycol molecules, and negative results may occur with low blood levels or if sufficient time has passed since ingestion such that all of the intact ethylene glycol has been metabolized. False-positive results can occur if the animal has received drugs containing

Table 2
Selected urinary parameters in prerenal azotemia and AKI

Test	Prerenal	AKI
Urine sodium	<20 mEq/L	>40 mEq/L
Urine chloride	<20 mEq/L	>40 mEq/L
Urine creatinine/plasma creatinine	>40	<20
Fractional excretion of sodium	<1%	>2%

propylene glycol, such as some activated charcoal products, injectable diazepam, and etomidate, or ingested nontoxic antifreeze containing propylene glycol instead of ethylene glycol.[2,22] Serum levels of intact ethylene glycol or its metabolites can be measured by some medical laboratories. In the absence of blood levels, metabolic acidosis with an elevated anion gap supports a diagnosis of ethylene glycol toxicity. Animals with hypercalcemia suspected to be due to ingestion of rodenticides or vitamin D supplements should have serum cholecalciferol levels measured. All dogs with AKI living in endemic areas should initially be suspected of having leptospirosis.[1,23] Microscopic agglutination titers for the most common infecting serovars should be submitted. Vaccination can produce a low titer, and there is some cross-reactivity between serovars; however, a single titer of 1:800 or greater in conjunction with appropriate clinical signs has been considered diagnostic.[24] Titer results may be negative early in the course of disease, and in the absence of other causes, leptospirosis should not be ruled out until convalescent titers performed 2 to 4 weeks later also have negative results. A recent study found that dogs most often had positive titer results, defined as 1:1600 or greater, to serovars Autumnalis, Grippotyphosa, Pomona, and Brastislava; although titers to Autumnalis may indicate cross-reactivity with other serovars rather than actual infection.[23] Fluorescent antibody testing for leptospires can be performed on blood, urine, or tissue. More recently, polymerase chain reaction (PCR) testing has become available for early diagnosis. However, the sensitivity and specificity of PCR testing is not yet known, and false negatives can occur if the dog has received antibiotics before testing.[25] Serologic screening can be performed if other infectious diseases are suspected.

Histopathologic examination of renal tissue yields the most definitive information about the chronicity of the disease process but does not necessarily identify a specific cause. Because much of the therapy for AKI is the same regardless of cause, renal biopsy is indicated only when the results would change therapy or prognosis. The benefit should also be weighed against the risks of biopsy. An ultrasound-guided biopsy performed under injectable anesthesia may be the safest for the animal, although biopsies obtained via laparoscopy or laparotomy are also options. A renal aspirate is useful only when lymphosarcoma is suspected, although false-negative results may occur even in the presence of malignancy.[1]

TREATMENT

Treatment of AKI consists of specific therapy for the cause, as well as supportive therapy based on the stage of acute renal failure and the animal's fluid, electrolyte, and acid-base status.

Specific Therapy

Specific therapy to correct or eliminate the cause of AKI should be instituted if the cause is known or suspected. Vomiting should be induced in animals with known recent toxin ingestion, such as ethylene glycol, or lilies in cats. Animals that have been exposed to toxins should receive an antidote if available. Those that have ingested ethylene glycol should receive 4-methylpyrazole or ethanol to prevent the metabolism of ethylene glycol to its toxic components. The renal excretion of intact ethylene glycol can be enhanced by intravenous fluid diuresis. Intact ethylene glycol and its metabolite glycolic acid can be removed by hemodialysis.[26] In geographic areas where leptospirosis occurs, all dogs with presumed AKI should receive antibiotics effective against leptospires (penicillin, amoxicillin, or doxycycline). Empiric

therapy with an antibiotic that is primarily excreted by the kidneys is indicated until pyelonephritis is ruled out.

Supportive Therapy

Fluid therapy

Correction and maintenance of the animal's hydration, acid-base, and electrolyte status are the mainstays of treatment of AKI. Intravenous (IV) fluid therapy is almost always required. Placement of a catheter in the jugular vein allows monitoring of central venous pressure and more precise assessment of intravascular volume status. However, if hemodialysis is a treatment option, the jugular veins should not be used for IV catheters or even venipuncture for blood samples; rather, they should be preserved for placement of the hemodialysis catheter. Frequent monitoring is essential for making appropriate adjustments in therapy, including clinical assessment of hydration, mucous membrane capillary refill time, heart and respiratory rate, arterial blood pressure, packed cell volume and plasma total solids, and serum chemistry parameters, including BUN, creatinine, sodium, potassium, chloride, and phosphorus.

The initial volume of fluid to be administered should be calculated based on the animal's body weight and degree of hydration. Water deficits should be replaced within 4 to 6 hours to restore RBF to normal as soon as possible. Maintenance fluid requirements must be met (44–66 mL/kg/d), as well as estimated fluid losses from causes such as vomiting and diarrhea. An isotonic, polyionic fluid, such as lactated Ringer's solution (LRS) or Plasma-Lyte A (Baxter, Deerfield, IL, USA) may be administered initially. If hyperkalemia is present or suspected because of oliguria or anuria, a potassium-free fluid, such as 0.9% sodium chloride, may be indicated. Following rehydration, the type of fluid should be adjusted based on the animal's fluid and electrolyte status.[1,2,27,28] Continued administration of fluids high in sodium relative to maintenance needs may lead to hypernatremia, especially in cats. Fluids containing less sodium, such as half-strength LRS or 0.45% sodium in 2.5% dextrose, may be used in these animals for longer maintenance therapy.[28] Traditionally, IV fluids have been administered at as high a rate as the animal can tolerate without adverse signs, with the goal of maximizing GFR and RBF and increasing elimination of metabolic waste products. However, increasing fluid administration does not necessarily equate to increased urinary excretion of such substances. In humans, recent studies have concluded that fluid overload is associated with adverse consequences and decreased survival; mortality decreased when fluid overload was corrected by dialysis.[29,30] Although similar studies in clinical veterinary patients have not been published, it would seem reasonable that avoiding fluid overload would similarly be beneficial, especially because dialysis is not readily available to many practices. The primary reason for fluid overload is failure to adjust the fluid administration rate in the face of decreased urine production.

Assessing urine output is one of the most important and probably the most neglected aspects of monitoring animals with AKI. Placement of an indwelling urinary catheter is the most accurate method for monitoring urine volume. However, the benefits of an indwelling catheter must be weighed against the risks of ascending infection, and in cats, sedation or anesthesia to place the catheter.[31] The risk of infection can be reduced by scrupulous attention to sterile placement of the catheter, maintenance of a closed collection system, and daily cleaning of the visible portions of the catheter with disinfectant. Because the incidence of catheter-induced infections increases rapidly after 3 days, changing the urinary catheter every 2 to 3 days may be beneficial.[31]

Management of oliguria or anuria

Once the animal has been hydrated, urine flow should rapidly increase to 2 to 5 mL/kg/h, depending on the rate of IV fluid administration. If urine production is not sufficient, the following steps should be taken. First, the clinician should reassess the animal's hydration status, including arterial blood pressure and central venous pressure (jugular catheters should be avoided if hemodialysis is a possibility). Decreased circulating blood volume can result in decreased GFR and an appropriate decrease in urine volume. If the animal is normally hydrated or volume overloaded, the rate of fluid administration should be slowed to prevent further fluid overload and associated adverse effects. An indwelling urinary catheter should be placed if not already present. Calculation of the "ins and outs" can then be used to provide appropriate quantities of IV fluids to match urine output. The maintenance fluid requirement (estimated at 22 mL/kg/d for insensible losses) is calculated for a short interval of time, typically 4 hours. An estimate of the amount of fluid lost due to vomiting, diarrhea, or other loss is added. The volume of urine produced during the previous time interval is added to the maintenance amount, giving the volume of IV fluids to be administered over the subsequent 4-hour period. This regimen helps maintain hydration while minimizing the risk of fluid overload.[1,2]

Specific therapy to increase urine flow is the next step (**Table 1**). Furosemide, a loop diuretic, is the first drug to be administered. Although furosemide may increase urine output by acting on renal tubules, it does not increase GFR or improve outcome. Its value lies in increasing urine output so that IV fluid therapy to correct acid-base and electrolyte imbalances can continue. Traditionally, furosemide has been administered as a bolus at an initial dose of 2 mg/kg IV, with escalating doses to 4–6 mg/kg at hourly intervals if the initial dose fails to increase urine production. However, a loading dose of 0.66 mg/kg followed by continuous rate infusion (CRI) at 0.66 mg/kg/h has been shown to be more effective in producing diuresis in normal dogs.[32] A CRI of 0.5 to 1.0 mg/kg/h is the currently recommended protocol.[1,2]

If furosemide administration fails to increase urine production, osmotic diuresis can be attempted. A 20% mannitol solution can be given as a bolus dose of 0.5 to 1.0 g/kg body weight over 15 to 20 minutes. If effective, urine flow increases within one hour. Repeat bolus doses can then be administered every 4 to 6 hours, or it can be administered as a CRI at a dosage of 1–2 mg/kg/min. Dosages greater than 2 to 4 gm/kg/d can actually cause AKI and should be avoided. Mannitol may have additional beneficial effects in addition to its action as a diuretic. It inhibits renin release because of its hyperosmolar effect on tubular luminal filtrate. Also, it acts as a free radical scavenger, blunts damaging increases in intramitochondrial calcium, and may result in a beneficial release of atrial natriuretic peptide.[1,2,28,33,34] Because mannitol is not metabolized, its effects remain in the intravascular space longer than those of dextrose. Administration of hypertonic solutions are contraindicated in oliguric animals that are volume overloaded because they result in increased serum osmolality, circulating blood volume, and blood pressure. Alternatively, a 20% dextrose solution can be given at 2 to 10 mL/min for the first 10 to 15 minutes, followed by a rate of 1 to 5 mL/min for a total daily dose of 22 to 66 mL/kg. Administration of hypertonic dextrose should be alternated with a polyionic solution to prevent dehydration from osmotic diuresis. Urine should be monitored for glucose to determine the effectiveness of this therapy.[1]

Administration of dopamine has traditionally been recommended for oliguric or anuric animals. Dopamine stimulates 2 types of dopamine receptors (DA-1 and DA-2) as well as α- and β-adrenergic receptors. In normal dogs, it causes an increase in RBF and urine volume; GFR increases or is unchanged. Studies in experimental models of canine AKI have shown conflicting results regarding improvement in RBF and/or

sodium excretion.[35] In normal cats, increased urine production can occur in the absence of increases in RBF or GFR, possibly due to α-adrenergic stimulation that increases cardiac output and blood pressure and induces natriuresis.[28] Although it was thought for some time that cats lacked renal dopamine receptors, one study detected a putative DA-1 receptor in the feline renal cortex.[36] Dopamine is no longer considered to have a role in the prevention or treatment of AKI in humans based on several meta-analyses that failed to show a clinical benefit in survival or need for dialysis.[37,38] There is little or no documentation on the efficacy of dopamine in dogs and cats with AKI, and its routine use to increase urine production in oliguric or anuric AKI cannot be justified.

In contrast, fenoldopam, a selective DA-1 agonist, has been found to be renoprotective in humans. A meta-analysis of humans undergoing cardiovascular surgery found that fenoldopam consistently and significantly reduced the need for renal replacement therapy and in-hospital death.[39] Another study found that humans who received fenoldopam while undergoing complex cardiac surgical procedures had a significantly lower rate of postsurgery AKI than those who received a placebo.[40] In animals, one experimental study in healthy cats found that an infusion of 0.5 mcg/kg/min produced more diuresis than dopamine.[41] However, a study in experimental dogs undergoing nephrotomy showed no difference in GFR or urine volume between dogs receiving fenoldopam or saline.[42] No clinical studies have been reported in dogs or cats with AKI, and its role in the management of oliguric AKI is not yet known.

One study reported that administration of diltiazem for therapy of dogs with AKI from leptospirosis resulted in increased urine output and more rapid reduction of serum creatinine, although the differences were not statistically significant.[43] The rationale for using diltiazem is that it is thought to reverse renal vasoconstriction via preglomerular vasodilation, inhibit tubuloglomerular-feedback-induced preglomerular vasoconstriction, and cause natriuresis independent of GFR. In humans, diltiazem has been used to treat or prevent AKI associated with cardiovascular surgery and renal transplantation.

If pharmacologic measures fail to increase urine output or improve azotemia and uremia, renal replacement therapy is indicated.

Management of polyuria

Animals that recover from the oliguric or anuric phase of AKI or those that have milder renal injury and do not become azotemic often have profound polyuria for days to weeks. These animals can develop electrolyte abnormalities, especially hyponatremia and hypokalemia, that need to be corrected with IV or, sometimes, oral therapy. Frequent monitoring of serum electrolytes and adjustment of therapy should be performed until urine output decreases and renal function and serum electrolyte concentrations stabilize.

Correction of acid-base and electrolyte abnormalities

Metabolic acidosis may occur in animals with AKI. Alkalinizing therapy is not recommended unless the blood pH level is less than 7.2 or the serum bicarbonate level is less than 14 mEq/L after correcting fluid deficits. Such therapy can result in significant complications, including paradoxical CSF acidosis, decreased ionized serum calcium level, and hypernatremia. If necessary, the bicarbonate deficit is calculated as follows:

Body weight (kg) x 0.3 x (24: measured bicarbonate) = mEq bicarbonate deficit. One-quarter of the deficit is administered over 12 hours and acid-base status reassessed before further administration.

Moderate to severe, life-threatening hyperkalemia may occur if the animal is oliguric or anuric. The first and most important step in therapy for hyperkalemia is to ensure urine production and excretion. Animals with severe hyperkalemia or those with persisting oliguria may benefit from additional specific therapy, such as with sodium bicarbonate, regular insulin and glucose, or, in life-threatening situations, calcium gluconate.

Treatment of other uremic complications

Vomiting Vomiting is one of the most common signs of uremia in animals with AKI. The cause of vomiting is multifactorial; it is centrally mediated by uremic toxins that act on the chemoreceptor trigger zone and locally mediated by uremic gastritis. Hypergastrinemia occurs in animals with decreased renal function and may contribute to increased gastric acidity and associated inflammation.[44] Drugs that inhibit gastric acid production may be beneficial, including histamine receptor antagonists, such as famotidine (0.5–1.0 mg/kg every 24 hours [q24h] by mouth [PO]), and proton pump inhibitors, such as omeprazole (Prilosec; 0.7 mg/kg q24h PO), or lansoprazole (Prevacid; 0.6–1.0 mg/kg q24h IV). Centrally acting antiemetics may also be necessary in some animals. Maropitant (Cerenia) is a neurokinin-1 (NK-1) receptor antagonist that has efficacy against peripheral and centrally mediated vomiting. The dose is 1 mg/kg subcutaneous (SQ) or 2 mg/kg PO once daily for up to 5 days. Metoclopramide, a dopamine antagonist, may be given as intermittent therapy at a dose of 0.2 to 0.5 mg/kg every 8 hours [q8h] IV or as a CRI at 1-2 mg/kg/d IV. Other centrally acting drugs include dolasetron (Anzemet; 0.6 mg/kg q24h PO or SQ or diluted in compatible IV fluid and administered over 15 minutes IV) and ondansetron (Zofran; 0.1–0.2 mg/kg q8h SQ or 0.5 mg/kg IV loading dose, then 0.5 mg/kg/h CRI). Phenothiazine-derivative antiemetics, such as chlorpromazine (0.2–0.5 mg/kg every 6–8 hours SQ, intramuscular, or IV) can be tried if vomiting persists despite other therapy. Side effects of phenothiazines include sedation and decreased blood pressure.

Hypertension Arterial hypertension is common in animals with AKI and may be exacerbated by overhydration.[26] Treatment includes reducing the rate of IV fluid administration, administration of diuretics, and dialysis to remove excess fluid if the animal is oliguric or anuric. Pharmacologic treatment is limited because most antihypertensive drugs are only available in oral formulations, and the vomiting associated with AKI often precludes oral medication. If hypertension is severe, parenteral antihypertensives may be necessary; however, these require very close monitoring of blood pressure. Such drugs include nitroprusside (initial dose 1–2 mcg/kg/min CRI IV; titrating the dose up every 5 minutes to achieve desired blood pressure) or hydralazine (0.5–3 mg/kg every 12 hours IV or 0.1 mg/kg loading dose IV, then 1.5–5 mcg/kg/min CRI IV). In the blood, nitroprusside releases cyanide through a nonenzymatic breakdown process. Cyanide is metabolized by the liver to form additional toxic metabolites (eg, thiocyanate) that must be cleared by the kidney. Seizures, coma, permanent neurologic dysfunction, and death have been documented in human AKI patients treated with nitroprusside. Oral antihypertensives include amlodipine (Norvasc; 0.1–0.25 mg/kg every 12–24 hours [q12–24h] PO in dogs, 0.625–1.25 mg/kg q24h PO in cats) and angiotensin-converting enzyme (ACE) inhibitors, such as enalapril (0.25–0.5 mg/kg q12–24h PO) or benazepril (Lotensin; 0.25–0.5 mg/kg q24h, PO). ACE inhibitors have been associated with worsening of renal function in humans.[1]

Nutritional management Animals with AKI that are anorexic are at risk of becoming malnourished if the lack of food intake persists beyond several days. Adverse consequences associated with malnutrition include immunosuppression, decreased tissue

synthesis and repair (including renal tubular cells), and altered drug metabolism.[45] Enteral nutrition, using a nasogastric esophagostomy or gastrostomy tube can be used if the animal is not vomiting; otherwise, parenteral nutrition is indicated. Detailed information on enteral and parenteral nutrition can be found elsewhere.[45–47] A recent review and meta-analysis concluded that there was insufficient evidence to support the effectiveness of nutritional support in humans with AKI.[48] However, the number of people included in this review was small (257), making it difficult to draw conclusions.

Prognosis and duration of treatment The prognosis for dogs and cats with AKI has been reported to be highly correlated with the cause.[1,2] Overall, the reported mortality rate in dogs with AKI is approximately 53% to 60%[3,4,49] and in cats, 50%.[50] Dogs with leptospirosis have a good prognosis, with reported survival of 85%. Conversely, dogs with ethylene glycol toxicity that are already azotemic when diagnosed have been shown to have a poor-to-grave prognosis, even with therapy[3,4] Other criteria that have been shown to confer a poor prognosis for dogs with AKI include severe azotemia (serum creatinine >10 mg/dL), hypocalcemia, anemia, decreased urine production, hyperphosphatemia, lack of improvement or worsening of azotemia with appropriate fluid and supportive therapy, and comorbid disorders, such as pancreatitis or sepsis.[3,4,49] For cats with AKI, hyperkalemia, hypoalbuminemia, and decreased serum bicarbonate levels at presentation were associated with decreased survival. In contrast to dogs, the degree of azotemia and serum phosphate and calcium concentrations did not predict survival.[50]

Supportive and specific treatment should be continued until one of the following occurs: (1) renal function returns to normal; (2) renal function improves and stabilizes, although not to normal levels and the animal is doing well clinically; (3) renal function worsens, fails to improve, or does not improve sufficiently for the animal to be managed medically at home for the resulting renal insufficiency. In the first 2 scenarios, fluid therapy can be tapered off and other supportive medications adjusted in response to the animal's clinical signs. In the third scenario, dialysis may be considered to support the animal for a period of time to see if renal function improves. If dialysis is not an option, euthanasia may be indicated at this point.

SUMMARY

AKI is characterized by the rapid loss of nephron function, resulting in azotemia and/or fluid, electrolyte, and acid-base abnormalities. The decrease in renal function that occurs with AKI is multifactorial and includes decreased intrarenal blood flow and cellular damage. There are many potential causes of AKI in dogs and cats.

The prognosis for dogs and cats with AKI has been correlated with the cause. Overall, the reported mortality rate in dogs with AKI is approximately 53% to 60% and in cats, 50% . If medical management fails to increase urine output or improve azotemia, renal replacement therapy is indicated.

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