Acute Kidney Disease in Cats: Diagnosis, Management, and Prevention

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Acute kidney injury (AKI) is the term used to describe a spectrum of acute alterations in kidney function and structure that range from mild (clinically inapparent) to overt acute renal failure (varying degrees of azotemia). Portions of the nephron may be temporarily injured or they may sustain lethal injury resulting in permanent loss of nephron mass depending on the severity of the insult. Recovery of full renal function and histopathological structure is possible in some cases. Partial recovery with substantial nephron loss will result in recovery as a CKD patient in some. In other patients, severe injury results in substantial loss of nephron mass and renal function that will not allow a reasonable quality of life without dialysis. Severely azotemic AKI patients often require dialysis to be managed adequately.

The details of a new grading system for categorization of acute kidney injury (AKI) developed by IRIS (International Renal Interest Society) are available for further review at http://www.iris-kidney.com/guidelines/grading.shtml. Much like the IRIS staging system for CKD, this grading system is designed to detect AKI at early stages when it is more likely that therapeutic interventions can avert further injury and allow recovery of renal function and tissue repair. The clinical prognosis is likely to align with the AKI grade that develops. Historically, attention was mostly directed to patients with serum creatinine that exceeded the reference range. In the IRIS AKI scheme, even a small increase in serum creatinine within the reference range is considered an important marker for potential acute renal injury. The IRIS AKI grading system involves evaluation of fasting serum creatinine concentration as the first step and then the staging is refined based on urine output if it is known (see Table 1). The same cutoffs for creatinine and urine output have been chosen for use in the dog and the cat. Oliguria, normal urine production, or polyuria can all occur depending on the specific cause and severity of renal injury sustained during AKI. History and physical examination parameters also enter into assignment of the grade. AKI typically focuses on those with acute injury to kidneys that were intrinsically normal prior to the acute injury. Pre-renal and post-renal disorders can occur in the absence of primary renal injury but they can also occur on top of a primary renal injury. Patients with CKD often have an "acute-on-chronic" presentation with changes in level of azotemia that falls into the AKI grading scheme. An inability to regulate solute and water balance is often present and renal synthetic and degratory functions are impaired to varying degrees during AKI. It should be noted that this AKI staging scheme is dynamic in that the grade may increase or decrease in severity over time and treatment. Extensive diagnostic evaluation may be needed to determine the specific cause(s)/diagnosis underlying the AKI; specific diagnosis is not specified by the AKI grading status.

Differential diagnosis and frequency of AKI – See Table 2. Causes of AKI in cats

The frequency of underlying conditions associated with AKI varies with the nature of the veterinary practice. Nephrotoxicity is the leading cause for AKI at The Ohio State University Veterinary Hospital, followed by ischemia. The aggressive use of potentially nephrotoxic antibiotics, particularly the aminoglycosides, can contribute to nephrotoxic AKI. The exposure to cholecalciferol rodenticides, use of non-steroidal anti-inflammatory drugs (NSAID), and exposure of veterinary patients to extensive surgical procedures and aggressive post-traumatic resuscitative maneuvers as emergency patients can result in AKI. Ischemic and nephrotoxic AKI occur more readily in patients that have underlying chronic renal disease or renal failure.

Diagnosis of AKI

Rapid increases of BUN, serum creatinine, and serum phosphorus may be observed during severe AKI. This is particularly helpful to document AKI in the absence of recent serum biochemistry values for comparison. For example, a patient's serum creatinine of 4.3 mg/dl, 6.0 mg/dl, and 7.5 mg/dl sequentially over three consecutive days supports a diagnosis of azotemic AKI. Serum creatinine and BUN do not increase over this short a time period in hydrated patients with CKD. Hyperphosphatemia may be out of proportion to the degree of increase in BUN or serum creatinine in those with AKI compared to CKD. The magnitude of elevation in BUN or serum creatinine concentrations is not helpful in the diagnosis of azotemic AKI vs CKD or in the differentiation of pre-renal, intrinsic renal, or post-renal azotemia. See Table 1 AKI grading for how to detect AKI at earlier levels of increasing serum creatinine. Urinalysis reveals a low specific gravity (USG) during the maintenance phase of azotemic AKI (SG less than 1.030, but most-often in the 1.007 to 1.015 range). Decreased maximal USG may be detected before an increase in serum creatinine is detected. Dipstrips may show proteinuria, hematuria or glucosuria on occasion. UPC can be increased due to increase in protein excretion normally handled by renal tubules. Urinary sediment is typically "active" at early stages of the maintenance phase of severe AKI exhibiting increased numbers of casts (particularly cellular casts) and small epithelial cells compatible with renal tubular epithelium. Animals with AKI as the sole problem should have smooth kidneys with normal or increased kidney size whereas those with chronic renal failure may show small and or irregular kidneys both on palpation and abdominal radiographs. Renal ultrasonography can provide additional anatomic

information to confirm intrarenal lesions, but cannot be relied on to distinguish acute from chronic renal failure or to suggest a specific microscopic lesion. Failure to document ultrasonographic renal changes does not exclude a diagnosis of AKI. Kidneys may enlarge during AKI but this may not be detected if they are still within the normal range for kidney size; kidneys tend to become "plump" before they measure elongated. Peri-renal effusion was described in 6 cats with azotemic AKI.[1] Renal biopsy may be helpful to determine that an azotemia is due to primary renal lesions and to characterize the changes as acute or chronic. A positive urine culture in the face of AKI is of concern for upper urinary tract infection, but this finding alone is not definitive to establish a diagnosis of pyelonepohritis.

It is imperative to exclude acute post-renal azotemia due to ureteral stones or stricture in cats presenting with azotemia that appears to have developed suddenly. In some cats ureteral stones cause complete obstruction of one or both ureters resulting in varying degree of oliguria or anuria and rapidly escalating magnitude of azotemia. Due to the frequency of this syndrome associated with calcium oxalate urolithiasis, survey radiographs need to be evaluated in all cats suspected to have AKI. If renal or ureteral stones are noted, ultrasonography to determine the degree of any hydronephrosis and or hydroureter is the next step. Many of these cats have pre-existing chronic kidney disease that makes it relatively easy for azotemia to develop even when only one ureter is obstructed. In many instances, there is the presence of "big-kidney little-kidney" syndrome likely reflecting previous chronic kidney injury reducing the size of one kidney and hydronephrosis increasing the size of the second kidney.[2] Though the azotemia can be quite striking and rapid in development, these cases represent acute post-renal azotemia on top of chronic primary kidney disease. Medical therapy is not often successful in management of these cats and relief of the ureteral obstruction by minimally invasive stenting or traditional surgery will be needed in order to sustain life without dialysis. The prognosis following relief of the obstruction is often guarded due to the underlying chronic kidney disease.

Prognosis of AKI

The attending veterinarian and client often have greater expectations for immediate improvement following treatment than is realistic, remembering that the maintenance phase of azotemic AKI can last weeks in some cases before adequate renal repair and function can occur. The most likely causes for death during the initial management of the azotemic AKI patient in the maintenance phase are from the effects of hyperkalemia, metabolic acidosis, and severe azotemia. Overhydration and resulting pulmonary edema are the next major causes of death during vigorous fluid therapy.

There is no magnitude of increased serum creatinine concentration measured at one time point that determines prognosis. Serial serum creatinine measurements over time are much more informative. Acute changes in the concentration of serum creatinine were associated with prognosis in one study of 209 cats with an initial serum creatinine of < 1.6 mg/dl and at least 2 serum creatinine measurements within 7 days. A poorer prognosis was found in cats that increased their highest serum creatinine to > 1.6 mg/dl with at least an increase of 0.3 mg/dl. If this increase in serum creatinine were achieved within 3 or 7 days, cats were about 3 times more likely to die at 30 days and 4 times more likely to die within 7 days. When this increase in serum creatinine occurred within 2 or 3 days, death within 90 days was 3 times more likely.[3] Azotemic AKI was diagnosed in 32 cats of an earlier study (serum creatinine >2.5 mg/dl); 18 cats were oliguric at the time of diagnosis. About half of these AKI cats survived (53%) with complete resolution of azotemia in 25% and persistent azotemia (CKD recovery) in 28%. The initial BUN or serum creatinine concentration did not predict survival nor did oliguria. Serum potassium increases seemed to be the most important predictor of survival; a 57% decreased chance in survival occurred for each mEq/L increase over the initial serum potassium concentration. Low initial serum albumin and bicarbonate were also associated with less survival.[4]

A grave prognosis is warranted for cats that develop anuric AKI after IV fluid treatment, a situation most-likely to develop in ethylene glycol intoxication but may also be encountered in cats following ingestion of Easter or day lilies. It should be noted that dogs and cats with severe oliguric AKI have recently been shown to survive with return of renal function and urine production following several months of hemodialysis. The presence of non-oliguria does not guarantee survival either. Due to the poor to grave prognosis for many cases with severely azotemic AKI, prevention is far preferred to treatment.

General goals for treatment of azotemic AKI during the maintenance phase

Placement of an indwelling intravenous catheter is necessary to adequately administer fluids and drugs in the management of azotemic AKI. Rapid correction of dehydration is indicated and can be individually calculated (estimated % dehydration x body weight in kg = Liters of dehydration) or given as 2 to 3 times maintenance fluid needs (60 to 90 ml / pound per day). Further fluids are given to match sensible (urinary volume), insensible (respiratory losses at about 10 ml/lb/day),and contemporary (an estimated volume from vomiting and diarrhea) fluid losses. Since urine output is widely variable in AKI, it is advisable to place an indwelling urinary catheter to monitor urine output to facilitate fluid therapy decisions for the initial 24 to 48 hours. The recognition of oliguria is important initially as it dictates the volume of IV fluid therapy that can be safely given. Urine production less than 1.0 ml/kg/hour (24 ml/kg/day) qualifies for oliguria in our hospital prior to rehydration and volume expansion. Relative oliguria exists if urine production is form 1.0 to 2.0 ml/kg/hour while on IV fluids. Urine output should be from 2.0 to 5.0 ml/kg/hour during vigorous administration of

IV fluids if the kidneys are healthy. It is essential to curtail the fluid prescription for volume to be further infused once hydration has been established especially when urine output does not increase. It is the author's impression that it is easier for cats with AKI to develop overhydration compared to dogs with AKI even with careful monitoring.

Newer thinking about the dangers of IV fluid therapy in the critically ill

If insufficient fluids are given to the AKI patient, the kidneys are not optimally perfused and sustain further ischemic injury. If too much fluid is given, then overt overhydration with pulmonary edema, congestive heart failure, and death follow. A new paradigm suggests that too many fluids and subclinical development of overhydration also result in further renal injury from visceral overhydration and reductions in renal blood flow and GFR as renal interstitial edema develops.[5-9] Renal edema can be an early development following some forms of renal injury. It appears that renal edema can also develop as a consequence of too aggressive fluid therapy. Conventional wisdom has been that it is better to have a little over-hydration than to have the damaged kidneys endure any chance for underperfusion and ischemic injury. It now appears that contrary to popular opinion, it is better to be a little on the "dry" side following rehydration and moderate resuscitation rather than to risk the development of over-hydration. It is possible that declining renal functions in the face of aggressive fluid therapy (reflected by rising BUN, creatinine, and phosphorus) may actually be caused by this treatment and resulting renal edema. Interstitial edema decreases renal blood flow by compression of renal vessels, and opposes GFR by compression of Bowman's capsule and compression of renal tubules. This concept needs to be further evaluated in both human and veterinary medicine. For now, caution is advised so that minimal fluids following correction of hypotension and rehydration are administered. The concept that "less is more" has been advocated in a veterinary review of AKI in cats.[10]

Conversion from oliguria to non-oliguria

Mannitol, furosemide, dopamine, or combinations of these are the diuretics most often employed in attempts to convert oliguria to non-oliguria or to increase renal function (RBF, GFR) Rehydration prior to use of diuretics should occur first to allow greater delivery of the diuretic to its site of action. There are no reports that detail the response of cats or dogs with clinical AKI to these treatments. The so-called "renal-dose" of dopamine (below the vasopressor dose, often from 2 to 5 micrograms/kg/minute) has surprisingly little clinical documentation to support its use in either human or veterinary medicine.[11,12] A combined infusion of dopamine and furosemide to awake normal cats increased urine output but did not increase GFR.[13] Fenoldopam as a selective DA-1 receptor agonist has the potential to cause renal vasodilatation with increased RBF, GFR, and natriuresis without activation of alpha and beta adrenergic receptor effects that occur with dopamine at higher doses.[14]

Ethylene glycol nephrotoxicity

The gold standard to prove the presence of ethylene glycol or its toxic metabolites following bioconversion remains testing with HPLC on serum or plasma samples. This type of testing is not commonly available, though it can be performed at local human hospital laboratories. The EG Test Kit (Allelic Biosystems, Kearnesville WV) is supposed to be able to detect 50 mg/dl of ethylene glycol in a serum/plasma sample but this has not been studied in cats. Test strips designed to detect ethylene glycol (Kacey ethylene glycol test, Kacey Inc, Asheville, NC.) were found to have too many false positives and false negatives to be useful for clinical work in cats.[15] The Catachem test kit (Catachem Inc., Oxford, Connecticut) detected the presence of EG when added to serum or plasma of dogs and cats but did have a positive bias in slightly overestimating actual EG concentrations.[16] This company provides both a quantitative and qualitative test to detect EG. The utility of the osmole gap has been ignored by many in the critical care community. A large osmole gap is proportional to the amount of unmetabolized ethylene glycol in many cases. A large osmole gap is most commonly created by ethylene glycol ingestion in small animals, but a large osmole gap could also result in animals that have consumed propylene glycol as an alternate and less toxic formulation of antifreeze. The presence of calcium oxalate crystalluria is supportive for the diagnosis of ethylene glycol intoxication in the appropriate setting – cat that is sick, possible history or observation of ingestion, and sub-maximally concentrated urine. Calcium oxalate crystalluria is observed in fewer cats than in dogs with ethylene glycol intoxication.[17,18] Calcium oxalate monohydrate crystalluria is more commonly detected than calcium oxalate dihydrate crystal following EG ingestion. Calcium oxalate monohydrate has several different morphologic appearances that can be difficult to identify whereas calcium oxalate dehydrate is more easily recognized.[19] An extremely hyperechogenic renal cortex and medulla may be observed soon after ingestion of lethal quantities of EG in the cat as in the dog.[20,21]

Fomepizole at high doses is the antidote of choice to treat cats following EG ingestion. Fomepizole is administered in higher doses than needed in dogs in order to effectively inhibit alcohol dehydrogenase[22], which otherwise is the first step in the bioactivation of EG to its toxic intermediary metabolites. Fomepizole is given to cats with an initial dose of 125 mg/kg IV followed by 31.25 mg/kg at 12, 24, and 36 hours. Use of this treatment protocol was effective in prevention of azotemic AKI in experimental cats treated within 3 hours of exposure to an otherwise lethal dose of EG. Fomepizole was a more effective treatment than ethyl alcohol and provided less CNS depression (some sedation was observed).[23] This fomepizole protocol was successfully used to treat 3 cats with naturally occurring EG poisoning that were not azotemic at presentation.[24] If fomepazole is not available and it is within 3 hours of EG ingestion, 20% ethanol at 5mL/kg IV initially, followed by the same dose every 6 hours for 5 treatments and then every 8 hours for 4

treatments could be a life-saving alternative antidote. Ethyl alcohol should ALWAYS BE DILUTED prior to administration, otherwise IV administration can cause cardiac arrest.

Lily nephrotoxicty [25-32]

The cat is exquisitely and perhaps uniquely sensitive to the nephrotoxic effects following lily ingestion. The specific toxic principle is unknown but all parts of the lily are toxic to cats. Nephrotoxicity has been observed in cats that have chewed only a small portion of a single lily leaf. The Lilium genus contains nearly 100 species and hundreds of hybrids that are thought to be toxic too. Aqueous extracts of the flower and leaf from the Easter lily contain the toxic principle, with the flower being more potent. Calla lily and peace lily are not real lilies and are not associated with AKI in cats. Lily of the valley does not contain a nephrotoxin, but does contain a digitalis-like toxin. Pancreatic histopathology is observed in some cats.

A history that the cat was observed chewing on lily plants or the finding of fragments of the plant observed in the cat's vomitus provides pivotal clues to the diagnosis. Hypersalivation and vomiting may occur soon after ingestion of lilies due to local irritant effects on the GI tract. Vomiting and lethargy are commonly described 1 to 5 days after plant ingestion in those suffering AKI. Renomegaly and abdominal pain may be detected on physical examination. Varying degrees of azotemia may be documented in cats presenting days after lily ingestion. On urinalysis, isosthenuria, proteinuria, glucosuria, cylindruria, and occasionally ketonuria are present in those with severe AKI but crystalluria is notably absent. Oliguria or anuria may persist despite intravenous fluid therapy in those with severe AKI.

Decontamination combined with fluid diuresis for 48 hours prevents development of azotemic AKI for up to 6 hours after ingestion of lilies. Decontamination 18 hours or more after lily ingestion does not prevent development of azotemic AKI. Induction of vomiting followed by administration of activated charcoal and a cathartic is recommended by the Animal Poison Control Center. Vomiting should not be induced in cats that already are vomiting as a consequence of lily ingestion. No antidote is available to counteract effects of the absorbed nephrotoxin. Nearly all cats presented early with GI signs alone survive after decontamination and induction of diuresis.

As many as 33% to 50% of cats that ingest lilies will develop azotemic AKI if not treated within a few hours following lily ingestion. Anuric AKI can occur 18 to 24 hours after ingestion. Prognosis for recovery is poor after lily-induced development of severely azotemic AKI. The magnitude of azotemia that develops during AKI does not predict survival, but urine output does. Cats with aoztemic AKI that are polyuric are more likely to survive. Cats with azotemic AKI and persistent oliguria or anuria are unlikely to survive. Cats that survive severe azotemic AKI after lily ingestion tend to have substantial permanent loss of renal mass and go on to develop various stages of CKD.

In a recent abstract, 30 cats were treated for lily ingestion associated AKI and 22 cats survived. Eighteen of the 30 cats were managed with aggressive medical treatment in which 89% survived. Twelve of the 30 cats were treated with intermittent hemodialysis with a 50% survival rate. Urine output and hydration status at time of diagnosis were not related to survival. Cats with a serum creatinine > 2.0 mg/dl at the time of diagnosis were more likely to die.[33]

NSAID AKI

NSAIDs are not directly nephrotoxic, but rather work as nephrotoxicants that cause their damaging effect through intense vasoconstriction that develops under special circumstances. NSAID cause AKI only if systemic vasoconstrictor signals have been activated following hemodynamic insult (sodium depletion, volume contraction, hypotension, shock, anesthesia). Normal renal vascular resistance and renal blood flow are relatively well maintained during times of vasoconstriction if synthesis of renal vasodilator substances is normal. Renal vasoconstriction however proceeds unopposed if the synthesis of renal vasodilatory prostaglandins has been blocked by NSAID administration. In these instances, progression to acute azotemic AKI and papillary necrosis may occur. An increased frequency of azotemic AKI was reported in 16 young cats given NSAID at the time of routine desexing without IV fluid administration. Four of these cats were euthanized due to failure of severe azotemia to resolve, 4 cats survived with azotemic CKD, and 8 cats recovered with complete resolution of azotemia[34] In 21 cats with NSAID AKI of another study, the mortality rate was 25% mostly in cats associated with papillary necrosis. Supportive therapy for up to 4 weeks was required for some survivors.[35] The FDA recently required the following statement to be added to the label for meloxicam use in cats, "Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats…" Robenacoxib, a long acting NSAID, recently has become available for use in cats in North America. Whether the incidence of NSAID-associated AKI is less during treatment with newer generation NSAIDs touted to have less GI side effects remains to be determined.

Table 1. IRIS AKI grading criteria – 2013 guidelines

Each grade is sub-graded as non-oliguric (NO) or oligoanuric(O) and if needing renal replacement therapy (RRT)

AKI Grade	Serum Creatinine	Clinical Description
Grade 1	< 1.6 mg/dL < 140 μmol/L	Non Azotemic AKI: a. Documented AKI: Historical, clinical, laboratory, or imaging evidence of acute kidney injury, clinical oliguria/anuria, volume responsiveness**, and/or b. Progressive non azotemic increase in blood creatinine; ≥ 0.3 mg/dl (≥ 26.4 μmol/L) within 48 hours c. Measured oliguria (< 1 ml/kg/hr) or anuria over 6 hours
Grade 2	1.7 – 2.5 mg/dl 141 – 220 μmol/L	Mild AKI: a. Documented AKI and static or progressive azotemia b. Progressive azotemic increase in blood creatinine; ≥ 0.3 mg/dl (≥ 26.4 μmol/L) within 48 hours, or volume responsiveness** c. Measured oliguria (< 1 ml/kg/hr) or anuria over 6 hours
Grade 3	2.6 – 5.0 mg/dl 221 – 439 μmol/L	Moderate to Severe AKI: a. Documented AKI and increasing severities of azotemia and functional renal failure
Grade 4	5.1 – 10.0 mg/dl 440-880 μmol/L	
Grade 5	> 10.0 mg/dl > 880 μmol/L	

** Volume responsive is an increase in urine production to > 1 ml/kg/hr over 6 hours; and/or decrease in serum creatinine to baseline over 48 hours

Table 2. Causes for AKI in cats

Renal ischemia (hypoperfusion)

Dehydration	Shock
Trauma	Hemorrhage
Anesthesia	Surgery
Sepsis	Burns
Hyperthermia	Hypothermia
Hemolysis	Myoglobinuria
ACE Inhibitors	Non-Steroidal Anti-Inflammatory Drugs (NSAID)

**Note that renal ischemia can occur in the absence of systemic arterial hypotension.

Nephrotoxins

More common

- Glycols (Ethylene Glycol)
- Antimicrobials
  - Aminoglycosides
  - Amphotericin-B
  - Sulfonamides - dehydration
  - Tetracyclines – IV
  - Fosfomycin – not dogs[36]
- Easter Lilly – Cats

Less common

- Hypercalcemia
  - Cholecalciferol Rodenticide
  - Cholecalciferol – Diet
  - Calcipotriene – antipsoriasis cream
- Cancer Chemotherapeutics
  - Platinum compounds alone and more so when combined with piroxicam
  - Radiocontrast Agents - IV

- Heavy Metals

Miscellaneous causes of AKI

- Renal thromboembolism – renal infarction
- Acute-on-chronic renal failure
- Renal amyloidosis with acute papillary necrosis

Acute hyperphosphatemia

- Tumor lysis syndrome
  - Phosphate enema
  - Phosphate acidifier
  - Massive soft tissue trauma
- Pancreatitis
- Food-associated renal failure – FARF
- (melamine with cyanuric acid tainting)

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