Tips for minimizing Acute Kidney Injury in the Older Pet

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The incidence of acute kidney injury (AKI) is quite high in veterinary medicine and is particularly prevalent among geriatric patients. Anatomic and physiologic changes related to aging, in addition to comorbid conditions that may include pre-existing kidney damage, increase the risk of developing AKI in older patients. There are several strategies that we can use to minimize the occurrence of AKI in older pets.

Introduction

Acute renal failure may be defined as an abrupt reduction in renal function resulting in accumulation of nitrogenous waste products and dysregulation of water, electrolyte, and acid base balance. The accumulation of waste products in the blood is termed "azotemia", while the polysystemic clinical manifestation of renal disease is called "uremia". Differentiating acute from chronic kidney disease is important for both therapeutic and prognostic reasons. Inherent in the diagnosis of acute kidney injury is the potential for complete functional recovery. Similarly, expedient treatment of factors causing acute decompensation of CKD (e.g., pyelonephritis, hypovolemia) may permit reversion to pre-crisis levels of function. In contrast, patients with end-stage CKD lack substantial recovery potential. Careful examination of medical history, physical exam, past and current laboratory data and imaging studies will usually enable differentiation.

Structural and Functional changes in older kidneys

Even in the absence of specific disease, the kidney undergoes age-dependent structural and functional alterations leading to a significant decline in functioning nephron numbers and thus baseline kidney function. Under normal conditions, the kidney adaptations in renal hemodynamics are able to compensate for the decline in function and maintain an adequate GFR. However, when faced with a pathophysiologic challenge, the older kidney lacks sufficient functional reserve and is more likely to develop clinically relevant damage. Perhaps more important than the decline in renal mass, are the cellular and molecular alterations that occur with aging. For example, a rat model of gentamycin induced AKI shows that nitric oxide production is protective due to its vasodilatory effects. When both young and old rats are treated with gentamicin, the older rats developed more severe AKI which was related to their blunted nitric oxide production. In addition to altered autoregulation, aging tubular cells may be more vulnerable to ischemic damage due to declining antioxidant defenses.

Table 1 : Changes in the Aging Kidney

- Decrease in total renal mass
- Glomerulosclerosis
- Thickening of the glomerular basement membrane

- Mesangial expansion
- Decrease in the number and length of tubules
- Thickening of the large vessel walls
- Decrease in renal blood flow (in humans 10%/decade past age 40yr)
- Decrease in GFR (in humans 1ml/min/y at age 45yr)

Causes of AKI in the Senior Pet

Older pets show the same spectrum for the causes of AKI as the general population, but iatrogenic and multifactorial causes seem to be overrepresented. For example, older pets are likely to have received multiple concurrent renal insults that could result in AKI. Acute kidney injury may be classified as pre-renal, intrinsic renal, and/or post-renal in origin. A thorough clinical exam of patients presenting with signs of an acute uremic crisis usually provides adequate information to identify pre-renal, renal and post-renal components of uremia. Although these categories help establish cause and predict prognosis, they share many features and may overlap.

Pre-renal azotemia develops as an adaptive response to any cause of reduced renal perfusion (e.g., hypovolemia, inadequate cardiac output, marked vasodilatation). Initially, nephrons remain intact allowing a rapid return to function once perfusion has been restored. However, some cases may progress to acute tubular necrosis. Older patients with heart disease may have episodes of decreased renal perfusion due to poor cardiac output. One of the major contributory factors to AKI in the older patient is dehydration. Patients with kidney disease or diabetes are often not able to compensate for free water loss with oral intake. Many older patients also receive medications that can also increase water loss from the body (eg diuretics, prednisone, etc.) An often overlooked cause of chronic dehydration is poor mobility due to osteoarthritic or weakness resulting in limited access to a water bowl.

Assessing dehydration in the geriatric patients may be difficult. Typical clinical signs such as skin tenting and tachycardia are often unreliable. It is important to thoroughly evaluated the hydration status of each patient to minimize the possibility of dehydration. If correcting renal perfusion does not ameliorate the azotemia, the patient should be carefully evaluated for intrinsic renal and/or post-renal causes of azotemia. (**Table 2**)

Table 2: Common causes of Acute Uremia in Cats and Dogs

Pre-renal
Intravascular volume depletion
Gastrointestinal losses
Hemorrhage
Renal losses
Third space sequestration of fluid
Hypotension
Shock (hypovolemic, septic (distributive), cardiogenic)
Antihypertensive drugs
Prolonged or deep anesthesia
Cardiogenic (congestive failure, arrhythmias, tamponade)
Hemodynamic (intrarenal vasoconstriction)
NSAIDs
ACE inhibitors
Radiographic contrast agents

Cyclosporine and tacrolimus
Non-renal systemic disease

Intrinsic renal
Vascular
Bilateral renal artery obstruction (thromboembolism)
Vascular lesions in a single functioning kidney
Glomerular
Acute severe protein losing nephropathy
Amyloidosis
Tubular
Ischemic (persistent prerenal causes)
Nephrotoxic (eg. lily, ethylene glycol, aminoglycosides, sulfonamides, adriamycin)
Interstitial
Pyelonephritis
Adverse drug reactions (NSAIDs, penicillins, etc.)
Hypercalcemia
Neoplastic infiltration (lymphosarcoma)

Post-renal
Ureteral obstruction (bilateral or unilateral with compromised contralateral kidney)
Bladder outflow obstruction
Urinary tract rent

Acute intrinsic kidney injury occurs when damage occurs to the nephron itself. Acute intrinsic kidney injury is commonly caused by nephrotoxins or an ischemic event; other etiologies include infection, prolonged urine outflow obstruction, and severe non-renal systemic disease (e.g., pancreatitis, neoplasia).

The two most common forms of acute intrinsic kidney injury in the geriatric patient are hemodynamically mediated injury and acute tubular necrosis. Many drugs commonly prescribed to geriatric patients impair autoregulation or interfere with the vasodilatory capacity of the kidney. Such drugs include non-steroidal anti-inflammatory agents (NSAIDs), angiotensin converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs). It is very important that patients receiving these medications remain well hydrated and have intermittent exams and laboratory assessments to ensure adequate renal function.

Acute tubular necrosis (ATN) is common in older pets as they are more likely to have severe predisposing comorbid conditions such as surgery, hypertension, poor cardiac function, be on multiple medications, and /or develop sepsis or multisystem organ failure. Prevention of ATN requires careful attention to the patient's baseline renal function. Although it would be ideal to monitor the patient's GFR, this is hardly practical in a clinical setting. Therefore serum creatinine concentration must be used as a surrogate marker of GFR. It is very important to recognize that small increases in serum creatinine concentration could indicate a large decline in GFR.

There are generally considered to be 4 stages of acute intrinsic renal failure; 1) initiation, 2) extension, 3) maintenance, and 4) recovery. Clinically, transition from one stage to the next may not be clearly evident and not all stages need be present in an individual

patient. Initiation is the period during which the kidneys are exposed to the damaging agent or event. Initiation may last hours to days and is often clinically silent; however, therapeutic intervention at this phase may reduce severity of renal damage and enhance the likelihood of recovery. During the extension phase, damage occurs to the tubular epithelium leading to a decline in glomerular filtration rate (GFR), the loss of urine concentrating ability and potentially oliguria.

During the maintenance phase, polysystemic signs of kidney damage may become apparent and the animal may be presented for veterinary care. Unfortunately, significant renal damage may have already occurred thus limiting management to supportive and symptomatic therapies. The forth stage, recovery, represents tubular epithelial regeneration, and, if it occurs, may last for days to months. Recovery is characterized by increasing GFR, improved urine quality, and amelioration of the polysystemic consequences of renal dysfunction.

Post-renal azotemia results from obstruction of urine flow after it has left the nephron, or leakage of urine from the urinary tract within the body. Fairly classic clinical signs and physical exam findings of urethral obstruction facilitate rapid diagnosis and relief of the obstruction. Likewise, urinary tract leakage from the urinary tract is usually readily identified from physical exam and imaging. Feline ureteral obstruction has recently emerged as the leading cause of severe acute uremia in cats. Since 1996, approximately half of the cats dialyzed at UC Davis and at the UCVMC-San Diego were diagnosed with acute ureteral obstruction. The most common cause of the ureteral obstruction is calcium oxalate uroliths, although concretions of blood and plugs of cellular material or inflammatory debris have also been reported.

Unilateral ureteral obstruction rarely produces clinically apparent disease if the contralateral kidney is functioning. Perceptive owners may notice flank licking or anti-social behavior that presumably is a manifestation of pain, but cats are rarely presented at this stage. If the obstruction is sustained, the kidney undergoes fibrosis and atrophies while the contralateral kidney undergoes compensatory hypertrophy. The disease remains clinically silent until the ureter of the remaining functional kidney becomes obstructed. This clinical scenario explains the classic “big kidney- little kidney” presentation seen most commonly with this syndrome. Alternatively, some cats may present with bilaterally small kidneys suggesting underlying chronic kidney disease that has acutely decompensated following ureteral obstruction.

Cats with acute ureteral obstruction present with the same manifestations and complications as cats with acute intrinsic renal failure as thus require similar therapeutic interventions. It is important that all cats presenting with severe acute uremia be evaluated for the possibility of ureteral obstruction as return of renal function is inversely related to the duration of the obstruction. In dogs, complete return of function is possible if the obstruction is relieved within 4 days while only 46% of function returns if the obstruction persists for 2 weeks.

Diagnosis of AKI in The Geriatric Pet

The clinical and laboratory evaluation of the geriatric patient with AKI is no different than for other patients. Careful attention to the history, including all medications, and physical exam are important in helping to identify the etiology of the AKI. Given the high prevalence of obstructive causes for AKI among older felines, abdominal ultrasound is strongly encouraged.

Treatment of AKI In the Geriatric Pet

As with diagnostics, treatment of AKI in the geriatric pet follows the same principles as for the general pet population. The first step in the management of acute uremia is to identify and correct any life-threatening fluid electrolyte and acid-base abnormalities. Once the patient has bee stabilized initially, pre or post-renal problems should be identified and reversed. If an underlying cause of the azotemia is identified, specific therapy should be initiated immediately. Aggressive supportive and symptomatic care will optimize the chance for recovery of renal function. The scope of this lecture preclused setailed discusseion of management, but **Table 3** provides a summary of the general clinical approach to managing patients with acute uremia.

Table 3: Clinical approach to the management of acute uremia

- Obtain baseline blood and urine samples prior to initiating treatment
- Identify and correct pre-renal and post-renal causes of azotemia if possible
- Discontinue nephrotoxic drugs and adjust dosages of others as required
- Place intravenous catheter aseptically and rapidly rehydrate with appropriate crystalloids
    - Fluid deficit (ml) = % dehydration x body weight (kg) x 1000
    - Replace deficit in 4-6 hours, monitor cardiovascular status
    - Avoid overhydration: monitor weight, blood pressure, central venous pressure, respiratory rate and effort, and clinical condition
- Correct life threatening electrolyte and acid-base disturbances
    - Hyperkalemia (see table 3)
    - Metabolic acidosis
        - mEq bicarbonate required = body wt (kg) x 0.3 x base deficit or (20-$TCO_{2)}$
        - administer ½ of the calculated dose over 15-30 minutes
        - reassess acid base status
        - ensure adequate respiratory function *prior* to administration
- Following correction of dehydration and hypotension determine if patient is oliguric or nonoliguric
- Attempt to convert oliguria, if present, to non-oliguria. Administer diuretics (benefit unproven)
    - Initially, Mannitol: 0.5 gm/kg IV over 10 to 20 minutes
    - If effective, repeat bolus of 0.5gm/Kg every 8 hours (monitor hydration and cardiovascular status very carefully).
    - Furosemide: 2-6mg/kg IV once. If effective, repeat dosage q8h OR administer 2mg/kg IV followed by CRI of 0.5mg/kg/h.
- Ensure adequate fluid balance
    - Compensate for maintenance fluid requirements: 60ml/kg/day
    - Consider ongoing fluid losses: estimate fluid loss from vomit, feces, etc.
- Identify and correct hypertension
    - Amlodipine: 0.625mg/cat q 24h, adjust to maintain systolic blood pressure 120-170mmHg
    - Monitor blood pressure frequently (bid-qid)
- Optimize nutritional support
    - Supply adequate calories: ≈ 80kcal/kg/day, adjust to maintain lean body mass
    - Minimize nitrogenous wastes, feed “renal diet” if possible
    - Strongly consider early intervention with eneteral feeding tubes (e.g. E-tube)
- Control hyperphosphatemia

  - Diertary phosphorous restriction
  - Enteric phosphorous binders
- Manage gastrointestinal complications
  - Hypergastrinemia, consider either
    - Famotidine 0.5mg/kg PO, IV q24h
    - Omeprazole 0.7mg/kg PO q24h
  - Nausea,vomiting consider one of the following:
    - Metoclopramide 0.2-0.5mg/kg IV, SQ, PO q8h *or* CRI 1-2mg/kg/d
    - Prochlorperazine 0.1-0.5mg/kg SC, IM q6-8h
    - Dolasetron 0.4mg/kg IV q24h
    - Ondansatron 0.22mg/kg IV q8-12h
- Manage anemia
  - If significant clinical signs, transfusion from compatible donor
  - Minimize sampling frequency and volume
  - Erythropoietin 100U/kg SQ 3xweek or Darbopoietin 6.25mcg/cat SQ q7d
- Manage pain, initially consider either
  - Buprenorphine 0.005-0.03 mg/kg IM, IV, SC, sublingual q6-8h
  - Butorphanol 0.2-0.4 mg/kg SQ, IM q6-8h, 0.2mg/kg IV q6-8h
- If inadequate response to medical management consider peritoneal or hemodialysis

Prevention of AKI in the Geriatric Pet

Although most veterinary cases of AKI are community acquired in contrast to the high prevalence of hospital acquired AKI in human medicine., There are still several measure that may be take with geriatric patients to minimize the risk of developing AKI. Recognizing that the older pet is at an increase risk for developing kidney injury and taking steps to ensure adequate renal perfusion while minimizing ischemic ad toxic renal insults will help to preserve renal function in this group of patients. Table 3 lists some approaches to minimize AKI in patients.

Table 4 : General approaches for the prevention of AKI

Avoid nephrotoxic agents - Recognize potential nephrotoxicity - Recognize high risk patients and settings - Avoid combined use of multiple nephrotoxic substances - Adjust drug dosage if needed - Monitor drug levels if appropriate - Frequent monitoring of renal function
Minimize nosocomial infections
Maintain adequate hydration
Avoid agents that impair renal blood flow autoregulation - NSAIDs, ACE inhibitors, ARBs

Prognosis and Outcome

The prognosis for geriatric patients with AKI has not been established in veterinary medicine. In human medicine, recovery of renal function after an episode of AKI is 28% less likely to occur when the patient is older than 65 years. In general, the prognosis for veterinary patients with acute kidney injury depends on the extent of renal damage, concomitant diseases, age, and response to therapy. A retrospective study from 1997 reported that 56% of dogs diagnosed with AKI and receiving non-dialytic management at a university hospital, were euthanatized or died before discharge. An overall mortality

rate of 47% was recently reported for a group of 32 cats with acute, intrinsic renal failure. Overall, the long-term prognosis for patients surviving episodes of acute uremia is fair to good depending on the underlying etiology. Early diagnosis and appropriate intervention improve survival and minimize the potential of persistent renal injury.

Addendum:

Staging System for Acute Kidney Injury

Recently, the International Renal Interest Society (IRIS) has adopted a staging system for the classification of Acute Kidney Injury in dogs and cats. Unlike the IRIS staging for chronic kidney disease, the staging of AKI would not imply the kidney disease is stable or at steady-state. On the contrary, the "stage" represents a moment in the course of the disease and is predicted to change as the condition worsens or improves or transitions to CKD. **Table 5** outlines the proposed IRIS AKI staging scheme for dogs and cats based on serum creatinine, urine formation, and the requirement for renal replacement therapy which is intended to facilitate classification, functional stratification, and therapeutic decision making.

IRIS AKI Stage I defines animals with historical, clinical, laboratory (biomarker, glucosuria, cylinduria, inflammatory sediment, microalbuminuria, etc.), or imaging evidence of acute kidney injury that are non azotemic and/or whose clinical presentation is readily fluid volume-responsive. IRIS AKI Stage I also would include animals with progressive (hourly or daily) increases in serum creatinine of 0.3 mg/dl within the non azotemic range during a 48 hour interval.

IRIS AKI Stage II defines animals with documented acute kidney injury characterized by mild azotemia in addition to other historical, biochemical, or anatomic characteristics of AKI. This would include animals that have an increase from their baseline serum creatinine associated with pre-existing CKD.

IRIS AKI Stages III, IV, and V define animals with documented AKI and progressively greater degrees of parenchymal damage and functional failure (uremia). Each stage of AKI is further substaged on the basis of current urine production as oligoanuric (O) or non oliguric (NO) and on the requirement for renal replacement therapy (RRT). The inclusion of substaging by urine production is based on the importance of the interrelationship of urine production to the pathological or functional contributions to the renal injury and its influence on the clinical presentation, therapeutic options, and outcome of AKI. Substaging on the requirement for renal replacement therapy is established on the need to correct life-threatening iatrogenic or clinical consequences of AKI including severe azotemia, hyperkalemia, acid-base disorders, overhydration, oliguria or anuria, or the need to eliminate nephrotoxins. The requirement for renal replacement therapy could occur at any AKI stage. Substaging on the requirement for renal replacement therapy has similar clinical, therapeutic, and prognostic implications as for urine production to categorize the severity of the renal injury as well as its influence on outcome.

Animals recognized and managed with IRIS AKI Stages I and II may regain adequate renal function within 2 to 5 days, forestalling life-threatening azotemia and electrolyte disorders and usually need only short-term support. Those with higher IRIS Stages of AKI at presentation or whose IRIS AKI stage progresses during hospitalization may require weeks of supportive care before the onset of renal repair. Animals with severe kidney failure, IRIS AKI Stage IV or V, may die within 5 to 10 days despite appropriate

conventional management unless supported with renal replacement therapy for an indefinite time. This disparity between the window of survival with conventional supportive therapy and the extended time required to repair severe acute renal injury underlies, in part, the poor prognosis and outcomes associated with severe stages of AKI.

Table 5: IRIS Staging System for Acute Kidney Injury in Dogs and Cats

AKI Stage	**Creatinine (Cr) mg/dl**	**Clinical Description**
Stage 1	<1.6	Non-azotemic AKI or volume-responsive AKI Historical, clinical, laboratory or imaging evidence of renal injury Increase in Cr ≥ 0.3 mg/dL within 48 hours
Stage II	1.6-2.5	Mild AKI: historical, clinical, laboratory, or imaging evidence of acute kidney injury and mild static or progressive azotemia
Stage III	2.6-5	Moderate to severe AKI: documented AKI and increasing severities of azotemia and functional renal failure
Stage IV	5.1-10	
Stage V	>10	
Each stage of acute kidney injury is further sub-staged on the basis of current urine production as oliguric (O) or non-oliguric (NO) and on the requirement for renal replacement therapy (RRT)		