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International Renal Interest Society best practice consensus guidelines for the diagnosis and management of acute kidney injury in cats and dogs

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ABSTRACT

Acute kidney injury (AKI) is defined as an injury to the renal parenchyma, with or without a decrease in kidney function, as reflected by accumulation of uremic toxins or altered urine production (i.e., increased or decreased). AKI might result from any of several factors, including ischemia, inflammation, nephrotoxins, and infectious diseases. AKI can be community- or hospital-acquired. The latter was not previously considered a common cause for AKI in animals; however, recent evidence suggests that the prevalence of hospital-acquired AKI is increasing in veterinary medicine. This is likely due to a combination of increased recognition and awareness of AKI, as well as increased treatment intensity (e.g., ventilation and prolonged hospitalization) in some veterinary patients and increased management of geriatric veterinary patients with multiple comorbidities.

Advancements in the management of AKI, including the increased availability of renal replacement therapies, have been made; however, the overall mortality of animals with AKI remains high. Despite the high prevalence of AKI and the high mortality rate, the body of evidence regarding the diagnosis and the management of AKI in veterinary medicine is very limited. Consequently, the International Renal Interest Society (IRIS) constructed a working group to provide guidelines for animals with AKI. Recommendations are based on the available literature and the clinical experience of the members of the working group and reflect consensus of opinion. Fifty statements were generated and were voted on in all aspects of AKI and explanatory text can be found either before or after each statement

Introduction

Acute kidney injury (AKI) is increasingly recognized in small animal veterinary practice (Cowgill and Langston, 2012, Bar-Nathan et al., 2022). In recent years, there has been a focus on the identification of not only community- but also hospital-acquired AKI, with the latter recognized through increased awareness of risk factors that may drive development of AKI, enhanced ability to monitor and detect early change in kidney function, and the provision of advanced veterinary care for veterinary patients with AKI such as renal replacement therapies (Cowgill and Langston, 2012). Whilst severe community-acquired AKI may be easily recognized, the ability to recognize those veterinary patients at risk of AKI or those with more subtle early AKI is of paramount importance to ensure that management and treatment can be instituted promptly (Yerramilli et al., 2016). Failure to adjust medical and supportive care during the hospitalization of veterinary patients with AKI can result in clinical deterioration that may be avoidable in some situations.

The aims of these guidelines were to generate expert consensus, supported by current veterinary evidence base where available, to provide a resource to the practitioner in the form of a standardized approach to the diagnosis and management of cats and dogs with AKI.

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Methodology

These clinical guidelines were developed by an International Renal Interest Society (2016) (IRIS) working group including six board certified internists and two board certified criticalists with formal training and expertise in veterinary nephrology. The working group generated recommendations in all aspects of AKI medical management, based on the available literature and discussions within the group. Statements were generated and a formal Delphi method was used to validate the statements. IRIS board members who were not part of the working group (11 IRIS board members) were asked to review the statements and vote anonymously using the following scale: "strongly agree", "agree", "neutral", "disagree", or "strongly disagree". Anonymity was maintained by performing the ballots via a third party who forwarded the results once the voting process had been completed. To achieve a consensus, a minimum of 75% of the voting participants had to choose either "strongly agree" or "agree." Statements are in bold font and the percentage agreement is reported at the end of each statement. Rationale and references are included either before or after the statements.

Results

Definitions

Statement: AKI can range from a mild renal insult to overt renal failure and can be either community- or hospital-acquired. The development of an AKI implies that there has been sudden renal injury, decline in renal function, or both (91% agreement).

Statement: In community-acquired AKI the initial renal insult occurs whilst the veterinary patient is outside of the hospital setting. Typically, there is a delay of a few days between insult and presentation, depending on the etiology, severity, and progression of injury (100% agreement).

Statement: AKI identified during a period of hospitalization (hospital-acquired AKI), is being recognized with increasing frequency as a consequence of increased monitoring, advancement in management of critical veterinary patients, and increased use and awareness of available guidelines (91% agreement).

Statement: Hospitalized veterinary patients with recognized risk factors for the development of AKI should be actively monitored at least once daily as early detection has important therapeutic and prognostic implications (100% agreement).

The event that causes kidney injury and starts the cellular consequences of AKI is referred to as the 'initiation phase' and may or may not be identified. In human medicine AKI is defined as an abrupt decrease in kidney function < 7 days, whilst acute kidney disease (AKD) develops over 7–90 days and chronic kidney disease (CKD) over > 90 days (Chawla et al., 2017). Historical knowledge of exposure to nephrotoxins or infectious agents increases clinical suspicion of AKI (Rimer et al., 2022). It is possible for AKI to affect veterinary patients with pre-existing CKD, i.e. acute on chronic disease. However, the clinical definitions applied to the acute deterioration associated with the AKI element will remain the same.

In community-acquired AKI, historical information is key to establishing a timeframe to differentiate AKI from CKD. In contrast, identification of hospital-acquired AKI requires proactive and serial monitoring of kidney function or injury. Established veterinary patient factors or comorbid disease (e.g. pre-existing kidney disease, heart disease, sepsis, administration of known nephrotoxic drugs, anesthesia) impacting on kidney perfusion or function increase the risk for the development of hospital-acquired AKI. Clinical signs, at least initially, may primarily relate to the clinical reason for hospitalization and may not be renal in origin.

Diagnosis

Statement: AKI should be diagnosed using a combination of compatible historical data, clinical examination findings, and laboratory diagnostics that document acute (within 48 h) decline in kidney function and/or kidney injury (e.g. tubular, glomerular). For community-acquired AKI, no prior baseline may be available to document acute decrease in kidney function and veterinary patients are commonly azotemic at presentation (100% agreement).

Statement: AKI can be diagnosed by either documentation of acute (within 48 h) decrease in kidney function or increase in kidney injury biomarkers (81% agreement; inclusive of bullet points below).

- **Decreased kidney function can be documented by serial assessment of serum creatinine concentrations (sCr), using the same analyzer, documenting an increase of 0.3 mg/dL (26.5 µmol/L), even within the reference interval, from a known baseline.**
- **Animals presenting with acute onset of clinical signs and increased sCr above a presumed baseline are suspected to have AKI. Serial sCr measurements are indicated and can be used to document AKI.**
- **Change in urine production ranging from polyuria (>2 mL/kg/h) to anuria (no urine production) can indicate alteration in kidney function. Sustained decrease in urine production (<1 mL/kg/h over 6 h) in euhydrated and euvolemic veterinary patients receiving intravenous fluid therapy should raise suspicion for reduced urine production and onset of AKI, whilst urine production < 0.3 mL/kg/h over 6 h indicates an oligoanuric state of AKI.**
- **Presence of kidney injury biomarkers, even without any indication of reduced kidney function, implies AKI.**

Physical examination attributes that may indicate AKI include good body and muscle condition, normal to enlarged and often painful kidneys, and an absence of signs of chronicity (e.g. polyuria and polydipsia, weight loss, pale mucous membranes) (Rimer et al., 2022). For veterinary patients that develop acute on chronic disease, clinical indicators of chronicity may be present, and an acute deterioration is more likely demonstrated through comparative evaluation of laboratory diagnostic results to differentiate AKI from progression of CKD (Dunaevich et al., 2020).

The diagnosis of AKI is hampered by the low sensitivity (15–30%) of currently available injury markers (e.g. glucosuria, cylindruria) (Rimer et al., 2022), which might reflect AKI not necessarily associated with a decrease in kidney function. Sensitivity is also hampered by the nonlinear relationship between the functional markers and glomerular filtration rate (GFR), namely, a marked reduction in GFR initially is associated with only a modest increase in these functional markers (Braun et al., 2008).

Azotemia is often evident in veterinary patients with community-acquired AKI, whilst hospital-acquired AKI is typically determined by serial monitoring of functional markers (Cowgill and Langston, 2012, Dunaevich et al., 2020). Increases in sCr might be initially within reference interval. Having identified azotemia or increasing sCr it is important to determine whether either is volume responsive, renal in origin, post-renal, or a combination thereof. A volume-responsive component may be due to reduced renal perfusion, intrarenal vasoconstriction (hemodynamically mediated), systemic vasodilation (e.g. sepsis or shock), or volume depletion. Evaluation of urine production is important to establish concern for oligoanuria and is ideally performed in an euhydrated and euvolemic state.

Where serial monitoring of kidney function is required, repeated use of the same high-quality analyzer is preferable to decrease analytical

variability (Ulleberg et al., 2011). Other markers of GFR, e.g. symmetric dimethylarginine (SDMA), can also indicate the onset of an AKI (Harjen et al., 2021; Nivy et al., 2021; Loane et al., 2022). Direct GFR evaluation offers little advantage over sCr once the veterinary patient is azotemic (Finch et al., 2018, McKenna et al., 2020). For non-azotemic veterinary patients, where improved diagnostic sensitivity might be beneficial, exogenous or endogenous clearance can be used, however the turn-around time of some of these tests might limit clinical impact in the AKI setting.

Having identified clinical concern for an AKI, AKI-specific grading systems should be used to categorize the severity of kidney injury. Unlike CKD, where injury is considered irreversible, AKI affords the potential for kidney recovery, therefore separate systems are required. Veterinary studies have historically adapted categorizing systems used in human medicine, but in recent years IRIS grading has been advocated for the standardization of dogs and cats with AKI (IRIS website http://www.iris-kidney.com/guidelines/grading.html). It should be recognized that whilst a veterinary patient may start their AKI journey in a particular grade, bidirectional movement is possible i.e. increasing grade with clinical deterioration or decreasing grade with kidney recovery. Veterinary patients can also be subclassified in terms of the development of oligoanuria and ultimately their requirement for renal replacement therapy initiation.

There is active investigation of AKI biomarkers with the potential to identify kidney injury prior to decrease in kidney function (i.e. Grade 1 AKI). These include neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin-B, clusterin, inosine, cytokines (IL6), and other proteins (e.g. retinol binding protein) but other than cystatin-B, these markers are currently the preserve of clinical research (De Loor et al., 2013; Yerramilli et al., 2016; Nivy et al., 2021; Chen et al., 2022).

Statement: Diagnostic tests that inform on etiology of AKI specific to the geographical area should be performed, as knowledge of the underlying cause may guide treatment. Urinalysis should be performed in all veterinary patients with AKI. When the etiology is unknown, urine culture is also indicated. Diagnostic imaging studies (e.g. ultrasound) should be performed to inform on potential etiology of AKI (e.g. ureteral obstruction or changes suggestive of ethylene glycol toxicity), comorbid conditions, and may provide important prognostic information if kidney morphology indicates chronic disease (100% agreement).

Complete urinalysis inclusive of specific gravity, dipstick, and sediment examination should be performed as part of the diagnostic workup of AKI. Evidence of AKI can include cast formation indicative of direct tubular injury, crystalluria (e.g. calcium oxalate monohydrate or dihydrate in ethylene glycol toxicity), or bacteriuria (e.g. pyelonephritis). Urine culture is recommended where there is concern for infection or where pyelonephritis cannot be excluded. Acquired renal glycosuria indicates proximal tubular injury whilst renal proteinuria, dependent on magnitude, may indicate glomerular and/or tubular insult.

Ultrasound is the most common diagnostic imaging modality used to evaluate the urinary tract including kidney morphology and can assist in the differentiation of acute from chronic disease (Cole et al., 2019; Forrest et al., 1998). Ultrasound evaluation is also useful for the identification of ureteral obstruction where pyelectasia and ureteral dilation proximal to an obstruction may be observed. Careful evaluation of the ureter may reveal the cause of the obstruction (e.g. ureterolith) (Quimby et al., 2017, Wormser et al., 2019); however, failure to identify a ureterolith (e.g. stricture formation) and lack of or only minimal pyelectasia does not preclude an obstructive disease process (Wormser et al., 2019, Lemieux et al., 2021). Antegrade pyelography may be considered in cases where obstruction is uncertain (Etedali et al., 2019). Ultrasound evaluation has also been documented to support the identification of ethylene glycol toxicity in both naturally occurring and experimentally induced intoxication (Adams et al., 1989, Adams et al., 1991). Radiography and computed tomography (CT) are supportive modalities, depending on the individual case and requirement for imaging of other body systems. The risks relating to use of contrast agents (e.g. iohexol) and contrast-induced nephropathy in veterinary patients with AKI are unquantified and limited in veterinary patients in general. However, individual case reports of contrast-induced nephropathy in veterinary patients with apparently normal baseline kidney function have been documented (Griffin et al., 2021) and a retrospective study suggests that approximately 2% of dogs may demonstrate clinically relevant kidney injury after contrast administration, although the degree to which underlying disease conditions or anesthesia protocols may have contributed to the increase in sCr cannot be determined (Goic et al., 2016). The relative risk of performing a contrast-enhanced CT must, therefore, be balanced against potential benefits of advanced imaging in the individual case.

Statement: Kidney aspirate or biopsy evaluation are not commonly performed for the diagnosis of AKI but might be used to characterize the pattern of injury within the kidney (e.g. acute glomerulonephritis, neoplasia) (100% agreement).

Cytological analysis of ultrasound-guided fine needle aspirates can be considered where there is concern for neoplasia e.g. lymphoma, but rarely confirms other etiologies. Coagulation status should be considered when sampling any veterinary patient with AKI.

Additional diagnostics will be case-specific. Travel history specific testing for infectious disease may be required, e.g. leptospirosis (Schuller et al., 2015a, 2015b), leishmaniosis (Baneth et al., 2018), Lyme disease (*Borrelia burgdorferi*; Littman, 2013), and Rocky Mountain spotted fever (*Rickettsia rickettsii*; Kidd, 2022). Point-of-care ethylene glycol serological assays can be useful and have reported high sensitivity and specificity; however, serum concentrations below the limit of detection can still result in kidney pathology (Creighton et al., 2014).

Treatment

Statement: Animals diagnosed with non-azotemic AKI (IRIS Grade I) do not necessarily need to be hospitalized, but a diagnostic workup is recommended to identify the underlying etiology. Any nephrotoxic medications should be discontinued, and animals should be closely monitored (daily at first). Animals progressing to higher grades (IRIS Grade II-V) should be hospitalized (100% agreement).

In both non-azotemic and azotemic AKI, drugs with nephrotoxic potential should be discontinued. Animals with Grade 1 AKI might not have excretory failure and thus do not necessarily need to be hospitalized; yet, these animals are prone to progressing to higher AKI grades, thus close monitoring is warranted until recovery is documented. As progression from one grade to another might occur within hours to days, initially animals should be monitored daily, with increasing intervals once stabilization is documented.

Fluids

Statement: Hypovolemia should be corrected within 1–2 h of detection. Dehydration should be corrected within 6 h of detection, in the absence of contraindication for rapid fluid administration (e.g. cardiac disease). If there is a concern for cardiac disease, consider slower fluids administration (correction over 12–24 h). All veterinary patients need to be monitored and serially reassessed during fluid administration (i.e. avoiding volume overload, hypertension, pulmonary edema, and pleural effusion) (100% agreement).

As shock can lead to organ dysfunction, including perpetuation and aggravation of AKI, acute tubular necrosis, and death, treatment of AKI begins with rapid restoration of adequate tissue perfusion. Hypovolemia

should be treated with balanced isotonic crystalloid solutions administered in boluses of 10–20 mL/kg in the dog and 5–10 mL/kg in the cat. Resuscitation therapy should be targeted to normalize perfusion parameters, which should be re-evaluated following each bolus. The use of central venous pressure measurement has fallen out of favor in assessment of volume status, whilst point-of-care ultrasound techniques, including the caudal vena cava collapsibility index, velocity-time integral of the subaortic blood flow, and lung ultrasonography, might prove beneficial in the future for assessment of volume-responsiveness (Donati et al., 2020).

Sodium chloride 0.9% solution should be avoided due to renal vasoconstriction and decreased GFR associated with tubuloglomerular feedback-induced mesangial contraction triggered by the excessive chloride tubular load (Wilcox, 1983). Chloride-rich fluids have also been associated with persistent acidosis and lower base-excess in critically ill human patients and risk of AKI in selected populations (Chowdhury et al., 2012; Mao et al., 2019; Fernández-Sarmiento et al., 2022).

It is controversial whether there is superiority of the use of colloids compared to crystalloids in fluid resuscitation. This combined with potential nephrotoxicity (Sigrist et al., 2017; Boyd et al., 2019; Schmid et al., 2019; Adamik et al., 2022) associated with the administration of synthetic colloids in dogs and people suggests that their use should be avoided (Evans et al., 2021). In animals with refractory hypotension (e.g. due to sepsis) early initiation of vasopressors reduces intravascular volume loading (Rachoin and Dellinger, 2015). Once perfusion has been optimized, dehydration should be corrected. Assessment of dehydration and volume status should be based on physical examination and interpretation of laboratory data including hematocrit, total solids, and sodium concentrations.

Statement: Fluid balance needs to be monitored at least twice a day by physical examination, body weight monitoring, and assessment of urine production. When animals are euhydrated, the rate of fluid administration should be equal to ongoing losses (urine production, gastrointestinal losses, and insensible losses) including fluid discontinuation in anuric patients. Animals with AKI are prone to electrolyte disorders (e.g. hypernatremia) due to compromised tubular function. Fluid type needs to be adjusted based on changes in the electrolyte and acid-base status of the animal. Hypotonic solutions are often indicated in veterinary patients with AKI to prevent hypernatremia (100% agreement).

Fluid therapy should be titrated and individualized for each veterinary patient considering both sensible and insensible losses. Once euhydrated, a zero-fluid balance (no water gain or losses) is essential, as animals with AKI might not be able to excrete excessive fluid leading to development and clinical consequences of volume overload (e.g. pulmonary edema). As a result, intravenous fluid therapy should be discontinued in euhydrated anuric animals with no additional losses.

Monitoring of fluid balance should include regular body weight assessment (at least twice daily), urine production, and cardiovascular parameters. Humans with AKI show protein energy wasting and catabolism (Kohr et al., 2020). The same is recognized clinically in dogs and cats with AKI (Rimer et al., 2022), therefore, any decreases in lean body mass should be considered when determining the target body weight use for fluid balance evaluation in veterinary patients hospitalized for relatively long periods of time. Point-of-care ultrasound techniques can facilitate urine production estimation with bladder volume estimation (Vazquez et al., 2021).

Forced diuresis with high fluid rates beyond optimization of kidney perfusion does not improve outcomes but rather increases the risk of volume overload and is associated with severe clinical consequences such as hypertension and interstitial edema, further negatively impacting kidney function (i.e. congestive nephropathy) (Prowle et al., 2013). The use of hypotonic fluids (e.g. 0.45% sodium chloride solution) might be preferred in selected cases as a maintenance fluid, due to lower sodium and chloride content particularly in those veterinary patients that become hypernatremic.

Statement: Volume overload is life threatening and may be detrimental for organ function, including delayed kidney recovery and worsening hypertension, and therefore must be avoided (100% agreement).

Severe volume overload, defined as increase $\geq$ 10% in body weight resulting from fluid accumulation, must be avoided as it has been associated with poor outcomes in both people (Bouchard et al., 2009; Kim et al., 2017) and dogs (Cavanagh et al., 2016). Clinical signs associated with volume overload include a generalized, gelatinous texture to the skin due to peripheral edema, chemosis, and serous nasal discharge (Cowgill and Langston, 2012). Ultrasound evaluation may detect signs of volume overload such as cavitary effusion, enlarged left atrium, or pulmonary B-lines (Tan et al., 2022).

Statement: Some animals with AKI may become markedly polyuric in the recovery phase and need frequent reassessment and adjustment of fluid rate and type to maintain adequate volume status and prevent electrolyte abnormalities. This phase might take several days and should be followed by cautious de-escalation of fluid therapy (100% agreement).

In the recovery phases of AKI, polyuria is commonly identified (Rimer et al., 2022), and fluid rates should be matched to urine production to prevent intravascular volume depletion and kidney hypoperfusion. Polyuria can also cause substantial changes in serum electrolyte concentrations, thus close monitoring, typically at least twice daily, is indicated. Once an animal is consuming enough fluids (either voluntarily or via an enteral feeding tube) to maintain its hydration and sCr is trending down, intravenous fluid therapy can be tapered slowly whilst monitoring hydration status.

Diuretics

Statement: There is no solid evidence that use of diuretics changes the outcome of AKI in dogs and cats (100% agreement).

Statement: Anuria and oliguria are consistent risk factors for mortality. Attempting to convert anuric dogs and cats using diuretics may be beneficial in controlling some consequences of severe kidney dysfunction (e.g. hyperkalemia, volume overload). Diuretics might increase urine production but are not likely to facilitate the recovery of kidney function (91% agreement).

Statement: Diuretics should not be used until dehydration has been corrected (100% agreement).

Oligoanuria is a common feature of AKI in small animals (Langston, 2017), and has been associated with an increased risk of mortality in dogs with AKI (Behrend et al., 1996; Segev et al., 2008; Segev, 2012). Increasing urine production is often considered a therapeutic target, particularly when dialytic support is not an option. Yet, the use of diuretics has not been shown to improve outcome of AKI human patients (Patschan et al., 2019). Therefore, it is important to understand the indications and limitations of diuretics and not delay initiation of renal replacement therapy if indicated.

Loop diuretics

Statement: Potential beneficial effects of furosemide include increasing urine production to manage volume overload and consequently hypertension, decreasing the risk of volume overload when delivering therapies like nutritional support, and facilitating the clearance of potassium, aiding in the management of hyperkalemia. Increased intratubular flow might facilitate removal of luminal debris and obstructions (100% agreement).

In humans, loop diuretics have failed to protect patients at risk from

AKI or to improve renal recovery in established AKI (Ho and Sheridan, 2006). Loop diuretics are used in the management of fluid overload or to increase potassium excretion. Loop diuretics have also been shown to increase renal blood flow in healthy dogs (Nuutinen and Tuononen, 1976) and to reduce oxygen consumption and metabolic demands of injured tubular cells in rodent models (Heyman et al., 1994). Potential adverse effects such as ototoxicity, hypovolemia, and decreased GFR should not be overlooked (Oishi et al., 2012). In human medicine, the furosemide stress test is reported as a method to evaluate renal tubular integrity (McMahon and Chawla, 2021). In different demographics of AKI, urine production in response to a fixed dose of furosemide administered during the early stages of AKI has shown potential in predicting progression to later stages of AKI. The utility of the furosemide stress test has not been explored in dogs and cats.

Osmotic diuretics

Statement: Potential benefits of mannitol include promoting urine production and urea excretion. However, mannitol should not be used repeatedly in anuric veterinary patients due to risk of worsening electrolyte derangements, or in overhydrated or uncontrolled hypertensive veterinary patients (91% agreement).

Although mannitol has been shown to increase urine production and excretion of urea in healthy dogs (Segev et al., 2019), it has not been studied in animals in the AKI setting, and it may cause electrolyte disturbances, intravascular volume expansion, and tubular injury (Clabots et al., 2019). Repeated boluses of mannitol in animals with minimal excretory capacity might further worsen the aforementioned concerns.

Dopaminergic agonists

Statement: Based on the current literature, there is no indication for the use of low-dose dopamine in the management of AKI. Low-dose dopamine may have adverse effects resulting from α- and β-adrenergic receptor activation. (91% agreement).

As a catecholamine, dopamine has direct α- and β-adrenergic agonist activity and through its action on dopamine receptors, it induces arterial vasodilation of various vascular beds (Sigrist, 2007). In humans, dose-related response has been reported with dopamine-1-receptor mediated vasodilation at low dosages, β-effects at medium dosages, and α-effects at higher dosages (Sigrist, 2007). A low-dosage response of dopamine with increased renal blood flow and urine production has been the basis for its use in humans (Day et al., 2000; Ichai et al., 2000a, 2000b); however, beneficial effects in humans in terms of prevention or recovery from AKI were not demonstrated (Bellomo et al., 2000, Friederich et al., 2005). Even at low doses in humans, dopamine may cause severe adverse effects including renal vasoconstriction and worsening renal ischemia or systemic vasoconstriction and hypertension (Sigrist, 2007). Its preventive or therapeutic use in human, canine, and feline AKI is therefore strongly discouraged (Holmes and Walley, 2003; Sigrist, 2007).

Statement: Fenoldopam administration at high dosages increases GFR and urine production in healthy dogs and canine experimental models of hypoperfusion AKI . Fenoldopam did not affect the outcome of dogs and cats with spontaneous AKI, based on two studies. Based on the available evidence, fenoldopam cannot be recommended as part of AKI management in dogs and cats (80% agreement).

The specific dopamine-1 agonist fenoldopam, as an antihypertensive that maintains or improves renal perfusion, has raised interest as a renal protectant or for the management of established AKI in humans (Noce et al., 2019). Increased renal perfusion and kidney function have been reported in healthy dogs (Kelly et al., 2016), in hypoperfusion models (Aronson et al., 1991; Halpenny et al., 2001), and in AKI models (Brooks et al., 1991; Nichols et al., 1992; Halpenny et al., 2000; Murray et al., 2003). However, fenoldopam did not improve survival or kidney function in a large group of dogs and cats with AKI (Nielsen et al., 2015) and it failed to demonstrate an effect on kidney function in dogs with heatstroke related AKI (Segev et al., 2018).

Other diuretics

Diltiazem, a calcium channel blocker, has been suggested to improve renal recovery in dogs with AKI from leptospirosis based on the outcomes of a non-controlled small-scale case series (Mathews and Monteith, 2007), although findings of the case series failed to reach statistical significance. However, the intravenous administration of diltiazem did not improve markers of kidney function in healthy dogs in a prospective unmasked crossover study (Kelley et al., 2022a,b).

Electrolyte and acid-base status

Statement: Metabolic acidosis is common in severe AKI and increases in severity with AKI grade. It contributes to clinical deterioration and hemodynamic instability. Monitoring of acid-base status should be commensurate with AKI grade, performed at least once daily in hospitalized AKI veterinary patients and should continue until derangements are no longer of clinical concern without active management (100% agreement).

Metabolic acidosis is common in and is associated with AKI grade (Lippi et al., 2023). Metabolic acidosis in AKI results from increased acid generation, decreased bicarbonate reabsorption, and decreased acid secretion. High anion gap metabolic acidosis is also recognized with hyperlactatemia (associated with decreased tissue perfusion) in human and veterinary patients secondary to both diabetic ketoacidosis and toxin ingestion (e.g. ethylene glycol) (Hopper and Epstein, 2012; Leblanc, 2004). In humans, metabolic acidosis has been recognized as an independent risk factor for AKI, hence could contribute to clinical deterioration (Hu et al., 2017). Metabolic acidosis may lead to cardiac dysfunction and reduced catecholamine response with potential myocardial dysfunction and vasodilation (Huang et al., 1995). Given the clinical implications, acid-base status (including blood pH, base-excess, bicarbonate, and partial pressure of carbon dioxide) should be monitored on at least a daily basis until treatment is not required to maintain appropriate acid-base status.

Statement: Administration of balanced crystalloid solutions is expected to improve metabolic acidosis and hyperlactatemia when administered to correct volume status. However, acid-base derangements persisting beyond correction of volume status should be addressed with administration of bicarbonate, with a goal to normalize and maintain acid-base status (91% agreement).

Hyperlactatemic metabolic acidosis can be corrected with fluid resuscitation, guided by, and targeted to perfusion parameters (Langston, 2012). However, as lactate production can be multifactorial (i.e. type-A vs. type-B hyperlactatemia), lactate concentrations should only be used to guide fluid resuscitation in conjunction with a holistic clinical assessment of the veterinary patient (Seheult et al., 2017). Bicarbonate therapy in severe metabolic acidosis (pH <7.2) is associated with improved 28-day outcome in people with AKI and increased numbers of days free from renal replacement therapy and vasopressor use (Jaber et al., 2018). Therefore, it appears reasonable to treat metabolic acidosis with bicarbonate in AKI veterinary patients when pH < 7.2, with no evidence of respiratory acidosis and a bicarbonate concentration < 16 mmol/L, if other potential causes of acidemia have been ruled out and/or targeted. Many veterinary clinics do not have the facility to measure acid-base status. Due to the potentially harmful consequences of excessive intravenous bicarbonate administration (Wardi et al., 2023), its use in the absence close monitoring is not recommended in the

veterinary setting.

Statement: Electrolytes disorders are common in AKI both at presentation and during hospitalization, especially in oliguric and anuric animals. The most frequent electrolyte abnormalities in dogs include hypochloremia, hyperkalemia, and hypocalcemia and in cats hypochloremia, hyperkalemia, hyponatremia, and hypocalcemia. Electrolyte monitoring is recommended initially at least twice daily. In the presence of severe abnormalities, more frequent monitoring is required (100% agreement).

The most common electrolyte abnormalities reported at presentation in cats with severe AKI were hypochloremia (90%), hyperkalemia (76%), hyponatremia (54%), and hypocalcemia (37%) (Segev et al., 2013). In dogs, the most common electrolyte abnormalities reported were hypochloremia (28.9%), hyperkalemia (27%), hypocalcemia (25%), and hypernatremia (17%) (Segev et al., 2008).

In people with AKI, changes in sodium have been directly correlated with survival (Gao et al., 2019). In veterinary medicine, urological disease accounts for 55% of cases of hypernatremia in cats and 12.5% in dogs (Ueda et al., 2015a). In 62% of these cats and 50% of these dogs, the hypernatremia developed during hospitalization due to changes in volume status, fluid management and diuretic use. Hyponatremia also occurs commonly in small animals, with urological disease accounting for 30% and 18% of cases of hyponatremia in cats and dogs respectively (Ueda et al., 2015b). Intervention should be considered, in terms of choice of fluid therapy, when the sodium concentration is trending towards the upper or lower limit of the laboratory reference interval and should be implemented when the sodium concentration falls outside the laboratory reference interval. Treatment of moderate to severe hypo- and hypernatremia requires specific, case-dependent consideration, in terms of cause(s) and acuity of onset leading to different therapeutic strategies and rate of correction. The readers are directed towards other resources to optimize treatment of veterinary patients (Burkitt-Creedon, 2022).

Statement: Treatment of hyperkalemia should be tailored to its severity. Balanced isotonic crystalloids should be used in dogs and cats with fluid deficits as a first line treatment. If hyperkalemia is associated with arrhythmia, calcium gluconate with ECG monitoring should be administered. To reduce potassium concentration, administer dextrose bolus with or without regular insulin bolus. A constant rate infusion of dextrose is indicated when insulin is administered. Sodium bicarbonate administration should be administered in refractory hyperkalemic veterinary patients with severe metabolic acidosis, while monitoring acid-base status to avoid iatrogenic alkalemia. In refractory cases terbutaline can also be used. If conventional treatment for hyperkalemia fails to maintain potassium concentration lower than 6.5 mmol/L, dialysis is indicated (81% agreement).

Potassium abnormalities are common in animals with kidney diseases with hyperkalemia developing due to reduced excretion with the onset of oligoanuria. In a cohort study of 13,621 humans with AKI, presence of both hypokalemia and hyperkalemia were associated with excess mortality, and hyperkalemia at admission associated with increased risk of 90-day mortality (Gao et al., 2019). Reduction of GFR and tubular dysfunction can lead to reduced urinary potassium excretion and life-threatening hyperkalemia, which can be associated with arrhythmias (both brady- and tachyarrhythmias), thus should be monitored closely. Intervention is likely to be required for cats and dogs where potassium concentrations are predicted to exceed 6.5 mmol/L and is always indicated where cardiovascular manifestations are present. Management of hyperkalemia should start with appropriate fluid therapy in dehydrated or hypovolemic animals to re-establish kidney perfusion and increase potassium excretion. Where cardiac toxicity associated with hyperkalemia is identified, calcium gluconate (10% calcium gluconate 0.5–1.5 mL/kg IV slowly over 15–20 mins) should be administered with continuous ECG monitoring. Calcium administration increases the threshold potential in cardiac myocytes, resulting in reduced membrane excitability (Wigglesworth and Schaer, 2022). Additional interventions promote intracellular shifting of potassium, and include dextrose (50% dextrose 0.5–1 mL/kg, diluted 1:1 in saline or similar, IV over 5 min), dextrose and insulin (regular insulin at 0.25–0.5 U/kg combined with dextrose at 1 g/unit of insulin, diluted 1:1 in saline or similar, IV over 5 min; with continued 2.5%−5% dextrose in fluids for 4–6 h), sodium bicarbonate (1–2 mEq/kg IV slowly over 30 min; sodium bicarbonate should be diluted 1:3 with water for injection or 5% dextrose for peripheral administration) all with close monitoring of potassium and, where relevant, glucose concentrations. Terbutaline (0.01 mg/kg IV, IM, SC) can also be considered (Hopper, 2023; Wigglesworth and Schaer, 2022).

Hypokalemia can also develop, especially during the polyuric phase. Severe hypokalemia (<2.5 mmol/L) can lead to muscle weakness, cervical ventroflexion (cats), hypoventilation, and arrhythmias. In veterinary patients with persistent hypokalemia, potassium supplementation is required, and intravenous administration is preferable until potassium has normalized and nutritional support and oral supplementation can maintain potassium status. As magnesium is an important cofactor for intracellular ion exchange, if the hypokalemia is refractory to supplementation, ionized magnesium should be measured in whole blood. Where ionized hypomagnesemia is identified, intravenous magnesium supplementation should be considered, with magnesium sulfate or magnesium chloride given at 0.25–1 mEq/kg/day during the first 24–48 h (diluted in 5% dextrose and administered as a constant rate infusion) and with lower doses (0.3–0.5 mEq/kg/day) administered for the following 3–5 days if required (Martin and Allen-Durrance, 2023). Magnesium should be administered at concentrations of 20% or lower (Martin and Allen-Durrance, 2023). Parenteral administration of magnesium sulfate can result in hypocalcemia due to chelation of calcium and, in this scenario, consideration should be given to administration of magnesium chloride (Martin and Allen-Durrance, 2023).

Statement: Hyperphosphatemia is a common feature of AKI. The use of phosphorus binders is not indicated in dogs and cats with AKI until enteral feeding is initiated as phosphorus binders bind dietary phosphorus (100% agreement).

Hyperphosphatemia in AKI is a common feature of AKI (Segev et al., 2013; Rimer et al., 2022), and results from decreased renal phosphorus excretion and thus its prevalence is associated with the AKI grade. Evidence in humans suggests a correlation between hyperphosphatemia and the risk of AKI and mortality in hospitalized human patients (Moon et al., 2019). Initial management of hyperphosphatemia is focused on improving GFR, to increase phosphorus excretion. Intestinal phosphate binders are not indicated in the initial management of patients with AKI where focus should be on optimizing adequate nutrition.

Statement: Hypocalcemia is common in dogs and cats with AKI. Serial monitoring and treatment decisions should be based on ionized calcium concentrations. In the presence of either ionized or total hypocalcemia with compatible clinical signs (such as tremors, fasciculations, facial rubbing, weakness, or seizures) or in case of severe ionized hypocalcemia (<0.75 mmol/L), intravenous calcium supplementation should be administered even in the face of hyperphosphatemia. The main treatment goal is to eliminate clinical signs rather than normalizing the hypocalcemia. Oral calcium administration can also be used in animals with feeding tubes who fail to maintain normocalcemia and as a phosphate binder (81% agreement).

Calcium disorders may exacerbate clinical signs related to hyperkalemia and critical illness, including hypotension, decreased myocardial contractility, and arrhythmias (De Brito Galvo et al., 2023). Ionized calcium should be monitored at presentation and during hospitalization. Hypocalcemia may indicate ethylene glycol toxicity. Specific treatment

for hypocalcemia is only indicted if severe or if associated clinical signs are present (e.g. muscle tremors or fasciculations, ataxia, facial rubbing, abnormal mentation). Where parenteral calcium supplementation is initiated and dogs and cats are refractory to bolus administration (calcium gluconate 10% solution (9.3 mg of elemental calcium/mL); 0.5–1.5 mL/kg slow IV to effect), constant rate infusion of calcium can be initiated (calcium gluconate 10% solution; 5–15 mg/kg/h or 0.5–1.5 mL/kg/h IV) (De Brito Galvo et al., 2023).

Hypercalcemia is also another relevant electrolyte abnormality in animals with AKI as both cause and consequence. In a retrospective study, kidney diseases accounted for 1.2% of dogs and 13.4% of cats with hypercalcemia (Coady et al., 2019). Hypercalcemia can contribute to perpetuation of the AKI via a combination of afferent arterial vasoconstriction, natriuresis, and diuresis mediated by calcium-induced downregulation of the Na-K-Cl cotransporter, leading to reduced GFR and nephrogenic diabetes insipidus (Leaf and Christov, 2019). Hypercalcemia, where noted in veterinary patients with AKI, is often mild (Rimer et al., 2022) and may not require specific intervention beyond those therapies already being prescribed for management of AKI e.g. fluid therapy. However, where hypercalcemia is considered to be contributing to the primary pathogenesis of AKI (e.g. vitamin D intoxication), direct management is required. Readers are directed to resources that review this topic (Galvao et al., 2022).

Extra renal manifestations of AKI

Gastrointestinal

Statement: Uremia induced gastrointestinal disturbances are common in severe AKI and should be treated supportively to effect with multimodal anti-emetic, prokinetic, and gastroprotectant agents as necessary to alleviate discomfort, control vomiting and gastric bleeding when present, encourage voluntary food intake and enable enteral nutrition (100% agreement).

Uremia typically causes gastrointestinal (GI) signs including nausea, vomiting, diarrhea, anorexia, gastrointestinal and oral ulcerations, with glossitis and stomatitis, and halitosis (Cowgill and Langston, 2012; Nivy et al. 2021; Rimer at al, 2022). Clinical signs and consequences of uremia have a significant impact on well-being and typically prevent voluntary oral food intake in an already catabolic veterinary patient. Ongoing vomiting and diarrhea may contribute to continued fluid losses and, consequently, contribute to progression and perpetuation of the AKI. Vomiting may lead to esophagitis resulting in regurgitation, megaesophagus, and risk of aspiration pneumonia.

GI ulceration may lead to significant blood loss and contribute to the development of anemia, and therefore should be addressed. The use of proton pump inhibitors (e.g. omeprazole) has progressively replaced H2-blockers. For anti-emetic / anti-nausea therapy a multimodal approach may be necessary, depending on the severity of clinical signs, and may include a serotonin 5-HT3 receptor antagonist (e.g. dolasetron, ondansetron), dopamine (D2) receptor antagonist (e.g. metoclopramide), and / or neurokinin (NK1) receptor antagonist (e.g. maropitant). It is important to recognize that nausea can persist through maropitant therapy in situations where the chemoreceptor trigger zone may be stimulated (Kenward et al., 2017) and therefore multimodal anti-emetic and anti-nausea therapy can be beneficial.

Uremia may not be the only underlying cause for GI signs, particularly when azotemia is resolving. In such situations, it is advisable to exclude alternative differentials such as intussusception (especially in dogs with leptospirosis) or pancreatitis (Schweighauser et al., 2009).

Pancreatitis and liver injury

Statement: Pancreatitis and AKI often coexist and can exacerbate each other. Therefore, animals with intractable vomiting, abdominal effusion, and abdominal pain should be evaluated for presence of pancreatitis. Although most of the therapeutic interventions for uremic animals are commonly used in the management of pancreatitis; special consideration should be given to the dietary management, e.g. avoiding high-fat diets, of dogs with AKI and concurrent pancreatitis (100% agreement).

Pancreatitis was documented in 22% and in 62% of dogs with AKI (Takada et al., 2018; Rimer et al., 2022). Pancreatitis may be a manifestation of AKI due to hypoperfusion, volume overload, and systemic inflammation or may be an iatrogenic consequence of high-fat renal support diet, which should be avoided in the acute setting in dogs with AKI and pancreatitis (Gori et al., 2019). Potential contributing factors should be corrected as soon as possible. Severe pancreatitis may also cause AKI, likely in the context of an inflammatory insult due to systemic inflammatory response syndrome, hypoperfusion, or coagulopathy. Diagnosis of pancreatitis may be challenging particularly given that an edematous pancreas due to volume overload may be misinterpreted as pancreatitis.

Liver dysfunction in dogs and cats with AKI is typically due to the underlying etiology, e.g., leptospirosis, sepsis, or toxin (Schuller et al., 2015a, 2015b). In severe cases, it may need to be addressed therapeutically as a separate entity (e.g. choleretics, hepatoprotectants), whilst in most dogs with leptospirosis few to no additional treatment is needed (Sykes et al., 2023). However, the latter may be prone to mucocele formation during the course of their infection up to several months post-recovery (Sonet et al., 2018).

Arrhythmias

Statement: Arrhythmias are common in uremic veterinary patients. Arrhythmias due to severe hyperkalemia and arrhythmias (tachy- or bradycardia) causing cardiovascular compromise, should be addressed therapeutically. Ventricular premature complexes and accelerated ventricular rhythm are common and can be ignored unless causing cardiovascular compromise (100% agreement).

The prevalence of arrhythmias in uremic patients in unknown. The causes of arrhythmias in small animals with AKI are likely multifactorial. In human patients with AKI electrolyte and acid-base disorders, hypoxemia, inflammation, and pain, together with the underlying disease process contribute to the development of arrhythmias (Genovesi et al., 2023). In a study including 24 dogs with AKI (75% leptospirosis), ventricular premature complexes were the most common arrhythmias observed and their presence was associated with both high cardiac troponin concentrations and a negative outcome (Keller et al., 2016). However, the detected myocardial injury was reversible and did not require specific therapy.

Coagulation status and anemia

Statement: Veterinary patients with AKI may be in a hypo- or hypercoagulable state, or even in a combination of both, which cannot be predicted from the clinical presentation. The extent to which coagulation status should be assessed is based on the degree of azotemia, etiology of AKI, clinical signs of bleeding or thrombosis, and individual risk for hypo- and hypercoagulability. At a minimum, all veterinary patients with AKI should have a complete blood count, including reliable platelet count, performed. When the risk for bleeding or clotting is high, both primary and secondary hemostasis should be evaluated (100% agreement).

Veterinary patients may show hemostatic abnormalities such as (uremia-induced) thrombocytopathia, thrombocytopenia, or disseminated intravascular coagulation due to platelet activation, potential loss of anticoagulation factors (mostly with acute-onset protein-losing nephropathy), and / or vasculopathy (McBride et al., 2019, Brassard et al.,

1994, Dudley et al., 2017). Viscoelastic techniques could be considered to guide treatment in individual cases.

Anemia may occur due to blood loss (gastrointestinal bleeding, leptospirosis-associated pulmonary hemorrhage, excessive blood sampling), uremia-induced hemolysis due to red blood cell fragility, a transient decrease in erythropoietin production, and the effect of the inflammatory state on the bone marrow (Cowgill and Langston, 2012). Blood transfusion may become clinically indicated. If there is a progressive and ongoing non-regenerative anemia, with a PCV < 20% anticipated, prophylactic treatment with darbepoetin should be considered.

Respiratory system

Statement: Respiratory compromise occurs in approximately one third of the veterinary patients with AKI and is associated with worse outcome. Respiratory compromise results from pulmonary edema (e.g. due to iatrogenic fluid overload), pneumonia (e.g. aspiration or other), pulmonary hemorrhage, thromboembolism, and, less commonly, due to uremic pneumonitis in severe and long-standing cases (100% agreement).

Statement: Leptospirosis-associated pulmonary hemorrhage is a frequent and a severe manifestation in some geographic locations and is associated with worse outcome, thus should be anticipated in dogs with leptospirosis. Immune complex deposition in the alveolar membranes has been documented in dogs, possibly suggesting immune mediated mechanisms. Concurrent bleeding diatheses might worsen bleeding and should be evaluated and addressed. Treatment should be adjusted including strict prevention of volume overload, hypertension, and excitation. Mild sedation can be administered to limit excitation-associated bleeding exacerbation. Dogs that may require oxygen supplementation should be referred to an emergency center that can provide mechanical ventilation as rapid deterioration may occur (100% agreement).

Respiratory compromise occurs in approximately one third of the veterinary patients with AKI (Segev et al. 2008). Pulmonary hemorrhage is increasingly recognized in some areas in dogs with leptospirosis (Kohn et al., 2010; Major et al., 2014; Lippi et al., 2021) with preliminary evidence suggesting that this may be at least partly attributable to immune complex deposition (Schuller et al., 2015a, 2015b). Immunomodulation including therapeutic plasma exchange (TPE) has been reported to be a successful adjunctive therapy in humans with leptospirosis-associated pulmonary hemorrhage (Trivedi et al., 2010; Taylor and Karamadoukis, 2013; Herath et al., 2019; Kularathna et al., 2021). Therefore, TPE may be considered in severe cases. Other suggested treatments that have no published evidence base in dogs but which might be utilised include desmopressin (1 μg/kg IV once; dilute in 20 mL 0.9% saline and administer over 20 min) and weaker evidence for tranexamic acid (15–20 mg/kg orally or 10 mg/kg by slow IV infusion every 8 h) (Kelley et al., 2022a,b, Callan and Giger, 2002) which have reportedly been used in people in this situation (Pea et al., 2003; Lin et al., 2011; Niwattayakul et al., 2010).

Systemic hypertension

Statement: Systemic hypertension is a severe complication, commonly seen in dogs and cats with AKI regardless of the IRIS grade and underlying etiology. The prevalence of hypertension in dogs and cats with AKI is up to 80% and 60%, respectively. Systemic hypertension can be present at admission or develop and worsen during hospitalization and is considered multifactorial in the AKI setting. Iatrogenic fluid overload is a key contributor to hypertension, and should be avoided. The most commonly documented manifestations of systemic hypertension in AKI include seizures, encephalopathy, and retinal detachment and need to be avoided as they may negatively affect the outcome (100% agreement).

Statement: Measurement of blood pressure should be performed at least 2–4 times per day, with frequency based on clinical progression. Interpretation of the finding of systemic hypertension should include consideration of potential for situational hypertension (e.g. due to pain and stress) (91% agreement).

Statement: Systolic blood pressure should be maintained below 160 mmHg and antihypertensive therapy is recommended to proactively minimize risk of acute target organ damage. Amlodipine is the first line medication. Hydralazine is the second line medication. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be avoided in the AKI setting (91% agreement).

Systemic hypertension is a common and potentially life-threatening complication of AKI reported in up to 80% of dogs and 60% of cats (Cole et al., 2020, Cole et al., 2017) and has been negatively associated with the outcome (Acierno et al., 2018; Cole et al., 2020). Indirect blood pressure measurement can be performed using either Doppler or oscillometry following recommendations of the ACVIM hypertension guidelines (Acierno et al., 2018). When monitored pro-actively, manifestations of systemic hypertension may not be identified but can include seizures, encephalopathy and retinal detachment (Cole et al., 2020, Cole et al., 2017, Beeston et al., 2022).

In a study including 52 dogs with AKI, there was no association between systemic hypertension and IRIS AKI grade, oligoanuria, survival to discharge, duration of hospitalization, or proteinuria (Cole et al., 2020). However, there was a significant association between fluid overload and systemic hypertension on initial presentation to the referral center (Acierno et al., 2018; Cole et al., 2020).

Antihypertensive treatment should be individualized based on the veterinary patient's concurrent condition(s). Although there is limited evidence for the choice of antihypertensives in small animals with AKI, amlodipine (Acierno et al., 2018) is considered first line because it has been shown to be efficient at correcting blood pressure and does not influence GFR or worsen electrolyte disorders unlike inhibitors of the renin-angiotensin-aldosterone system (Geigy et al., 2011).

If treatment with first line antihypertensives is ineffective, increasing the dosage of the currently used agents or addition of an alternative agent is recommended. Other antihypertensives, used mostly in an emergency setting, include hydralazine and acepromazine (Acierno et al., 2018). Fenoldopam is used in human medicine but has not been critically evaluated for acute hypertension in either cats or dogs. Antihypertensives should be used with caution in dehydrated animals as GFR may decrease precipitously, thus monitoring is required (Acierno et al., 2018).

Central nervous system

Typical differentials for central nervous system signs in dogs and cats with AKI include a manifestation of the underlying disease (e.g. ethylene glycol poisoning, grape toxicity), severe uremia, systemic hypertension, side effects or overdose of drugs (e.g. metoclopramide, fluoroquinolones), complications of dialysis if applicable (dialysis disequilibrium), or others including local thrombosis or hemorrhage (Wolf, 1980; Stahlmann and Lode, 1999; Kosecki, 2003; Shi and Wang, 2008; Schweighauser et al., 2020).

Nutrition

Statement: When anorexia or inappetence have or are expected to persist > 48 h, nutritional support (enteral or parenteral) is indicated, as AKI results in a severe catabolic state (100%

agreement).

The nutrition of small animals with AKI is hampered by the dysorexia and anorexia resulting from central and peripheral effects of uremia and by the severe GI losses associated with vomiting and diarrhea. The resulting decreased nutrient intake and increased nutrient losses amplify the effects of the severe catabolism associated with AKI or its underlying etiology. Additional losses of amino acids and nitrogenous metabolites can be expected in patients with severe AKI that are receiving dialytic therapies. Protein-energy wasting and deficiencies in critical nutrients impair kidney parenchymal recovery, weaken the immune response, and worsen the azotemia and the metabolic acidosis due to breakdown of endogenous proteins (Fouque et al., 2008). In humans, protein energy wasting clearly contributes to increased morbidity and mortality (Fouque et al., 2008).

Quantitatively and qualitatively appropriate nutrition aims at providing adequate amounts of energy, protein, and nutrients to minimize catabolism and breakdown of endogenous proteins and to support overall body function (Fiaccadori and Cremaschi, 2009). Although difficult to assess, these needs should be based on an individualized nutritional assessment of the animal and the appropriateness of nutritional interventions should be re-evaluated as part of the daily monitoring (Ostermann et al., 2019). As most cases of moderate to severe AKI have a predictable clinical course, including a long duration of hospitalization, an early and proactive approach is recommended to avoid progressive clinical deterioration and additional morbidity. Generally, nutritional support should include the enteral route, to accelerate digestive recovery and to avoid intestinal bacterial translocation (Cowgill and Langston, 2012; Langston, 2017). Forced oral feeding is contraindicated as it is ineffective, can cause food aversion, and increases the risk of aspiration.

Statement: General anesthesia can be provided safely in most dogs and cats with AKI providing that renal perfusion (i.e. cardiovascular stability) is maintained during the procedure, therefore placement of an esophageal or gastrostomy tube is almost invariably feasible when indicated and not contraindicated for other reasons. If placement of an esophageal or gastrostomy tube / anesthesia is contraindicated, enteral nutrition using nasogastric tube or parenteral nutrition should be provided (100% agreement).

The use of enteral feeding is preferred, in association with antiemetics and prokinetics as needed. Common options include esophageal, naso-esophageal, gastric, esophago-jejunal, or gastro-jejunal tubes. When selected as standalone nutrition or as a complement to partial enteral feeding, parenteral nutrition should be given through a central venous access to prevent phlebitis (Queau et al., 2011).

Feeding dogs 1.3 times their resting energy requirement during initial AKI resulted in a weight loss of 1.2% body weight per day (Hinden et al., 2020). Caloric requirements should therefore exceed 1.5 times their resting energy requirement. Once nausea is controlled medically or by progressive recovery from the acute insult, voluntary oral food intake may be enhanced by appetite stimulating agents such as mirtazapine or capromorelin. Close monitoring of the caloric intake is important during this transition phase to ensure calculations accurately represent oral intake. Enteral and parenteral nutrition techniques are major sources of hidden water administration that can result in fluid overload and electrolyte shifts (Langston, 2017). This volume therefore needs to be accounted for in the fluid volume calculations, especially in oligoanuric animals (Langston, 2017).

Statement: Highly digestible diets should be favored during hospitalization with avoidance of high-fat content diets that might induce or aggravate pancreatitis in dogs. Protein restriction is not indicated in AKI veterinary patients initially and might even be detrimental to recovery due to high catabolic state (100% agreement).

Although scientific evidence is still lacking, highly digestible diets should be favored to avoid nausea, vomiting, and to reduce the risk of pancreatitis in initial AKI (Langston, 2017). There is no evidence for protein restriction in AKI. The administration of a high-protein recovery-type diet to dogs with AKI did not result in an increased urea generation rate compared to dogs fed a mildly protein-restricted diet, possibly suggesting an increased protein requirement in dogs with AKI (Hinden et al., 2020). Specific therapeutic renal diets should be considered only after discharge once pancreatitis, if present, has been resolved.

Adjustment of medications dosages

Statement: Nonsteroidal anti-inflammatory drugs, aminoglycosides, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and intravenous contrast agents should be avoided in veterinary patients with AKI. If a nephrotoxic drug is specifically indicated for a life-threatening condition without an alternative, close monitoring for adverse renal effects should be performed (e.g. cylindruria, worsening trend in azotemia, active injury markers) (100% agreement).

Statement: All medications to be administered to a dog or cat with AKI should be evaluated for their nephrotoxicity potential, the degree of renal elimination, and the window of safety. When possible, medications with potential nephrotoxicity should be avoided and drugs with wider margin of safety or predominant hepatic metabolism/excretion should be used. When specific veterinary studies are not available, human guidelines on suggested dose alterations (dosage or administration frequency) can be considered when similar pharmacokinetics exist (91% agreement).

Many drugs undergo renal elimination, tubular reabsorption, or renal biotransformation. Kidney disease leads to aberrations in all aspects of drug pharmacokinetics (adsorption, distribution, metabolism, and elimination). Therefore, all medications should be evaluated for their nephrotoxicity potential and pharmacokinetics.

Drugs that have predominant renal elimination will likely have prolonged elimination half-life when GFR is reduced (De Santis et al., 2022). This may lead to an increased plasma drug concentration unless the administered dose or schedule is adjusted. Most drugs lack pharmacokinetic evaluation in veterinary patients with kidney disease. In these situations, human guidelines can be reviewed and considered to be employed for veterinary species with similar pharmacokinetics. Augmented drug dosing for humans with kidney disease is based on their estimated GFR (Matzke et al., 2011). Such formulae have not been validated for dogs and cats. Serum creatinine, urea, and SDMA concentrations are surrogate markers of GFR, with limitations to their accuracy. If GFR needs to be confidently known, direct measurement should be performed. In the absence of GFR measurement, sCr may serve as a rough estimate for GFR and can be used to compare the recommended change in drug dosing in people with similar reductions in kidney function. As veterinary resources do not exist at this time, readers are directed to resources that cover drug dose alteration for humans with reduced kidney function (Aronof, 2007, Ashley and Dunleavy, 2018).

Normal estimated GFR in people is $>$ 100 mL/min and categories for the severity of reduction of kidney function is commonly established, and the estimated GFR categories may be roughly extrapolated to the IRIS AKI grading scheme (Langston, 2017), such that:

$>$ 50 mL/min → IRIS AKI grade III.

10–50 mL/min → IRIS AKI grade IV.

$<$ 10 mL/min → IRIS AKI grade V.

An estimate of the GFR is needed for calculating changes to drug dosing to account for decreased kidney function in AKI (Gabardi and Abramson, 2005). For drugs with a wide therapeutic index and a long elimination half-life, the dosing interval can be adjusted with the following formula:

New interval (h) = (normal GFR/measured GFR) x normal dosing interval (h)

This method preserves peak drug concentration but may result in subtherapeutic trough drug concentration. For drugs where a more consistent plasma drug concentration is needed, administering a reduced dose at the original dosing interval can be considered. This method is preferable to drugs with a narrow therapeutic window and shorter elimination half-life. The new dose can be calculated:

Reduced dose (mg/kg) = (measured GFR/normal GFR) x normal dose (mg/kg)

Therapeutic drug monitoring should be performed to evaluate whether dose and schedule adjustments still deliver target plasma drug concentrations.

Until species-specific pharmacokinetic studies are performed in veterinary patients with kidney disease, using these recommendations may be a reasonable starting point for guiding drug dosing in animals if similar renal elimination exists. Dogs and cats with significant glomerular component to their AKI may have additional derangements to normal drug pharmacokinetic (Joy, 2012). For example, increased diffusion of drug into the glomerular filtrate through the abnormally permeable glomerular basement membrane. Albuminuria may result in increased urinary loss of drugs that are highly protein-bound. Hypoalbuminemia would also result in an increased unbound fraction which may be excreted differently than the protein-bound drug.

Pain assessment and management

Statement: Dogs and cats with AKI should be evaluated for pain using a validated, standardized scoring system every 4–6 h and appropriate analgesia should be administered and adjusted accordingly. An appropriate first line analgesia is opioids. The use of NSAID's is contraindicated in dogs and cats with AKI (100% agreement).

The relationship between AKI and pain in dogs and cats is unclear, although pain can be present with nephroliths, ureteroliths, pyelonephritis, and nephromegaly, as well as with underlying conditions leading to AKI or comorbidities (e.g. pancreatitis). Specific canine and feline pain scoring systems should be used to standardize assessment for the requirement and refinement of analgesia using validated scoring systems (e.g. Glasgow Composite Measure Pain scale, UNESP- Botucatu Multidimensional Composite Scale, and the Feline Grimace Scale) (Morton et al., 2005; Reid et al., 2017; Della Rocca et al., 2018; Evangelista et al., 2019).

Opioids, such as pure agonists (e.g. methadone or fentanyl) or partial agonists (e.g. buprenorphine), are excellent analgesics, have minimal renal side effects and can therefore be used as first line treatment (Papich, 2000); however, the evidence base in cats and dogs is limited. The use of NSAIDs is contraindicated in AKI due to nephrotoxicity (Lomas and Grauer, 2015).

Recovery

Statement: AKI outcome collectively depends on reversibility of the initial injury, its severity, comorbidities, and the therapeutic options available (e.g. extracorporeal therapies) for the individual veterinary patient (100% agreement).

Statement: Discharge should be considered when sCr has stabilized and clinical signs controlled without the need for intravenous medication or fluid therapy. Long-term monitoring is indicated to evaluate further renal recovery and determine long-term outcome (100% agreement).

Statement: The expected hospitalization period for dogs and cats with severe AKI is approximately one week, but an extended hospitalization period of up to several weeks should be expected in some animals (100% agreement).

Hospitalization time of animals with severe AKI is approximately 1 week, with median time of 5 days (range 0–72 days) reported (Rimer et al., 2022). Hospitalization time is not only dictated by the improvement in kidney function, but is also influenced by presence of comorbidities and complications. Animals that become highly polyuric require extended hospitalization, even in face of complete normalization of azotemia, to permit successful weaning from fluids.

Statement: The inciting cause is a major determinant of the prognosis as some AKI tend to be reversible and other AKI tend to be irreversible (100% agreement).

Statement: The severity of azotemia (IRIS AKI grade) is not an accurate or consistent indicator of reversibility; therefore, prognosis should not be solely based on the AKI Grade (100% agreement).

The prognosis for veterinary patients with AKI is highly influenced by the underlying cause with superior outcome identified for infectious e.g. leptospirosis than other causes of AKI (Legatti et al., 2018, Adin and Cowgill, 2000). Since dialytic therapy to allow time for renal recovery is not available to many veterinary patients with high-grade AKI, mortality is likely overestimated. The degree of azotemia (i.e. AKI Grade) does not define the potential reversibility, but rather the window of opportunity for recovery. Yet, it has been shown that the severity of the injury is negatively associated with the proportion of dogs with normalization of sCr (Bar-Nathan et al., 2022).

Statement: The recovery phase from AKI takes days to months, depending on the severity of the injury and the etiology. Lack of an improvement in kidney function parameters within the first days of treatment does not indicate an inability to recover (100% agreement).

The recovery process of animals with AKI might take up to several months (Bar-Nathan et al., 2022). If recovery is only partial, compensatory mechanisms of remaining nephrons (i.e. compensatory hypertrophy) can occur, proportionally to the residual kidney function. At the time of discharge approximately 55% of the dogs with AKI have normalization of sCr; however, an additional 20% of the dogs normalize sCr after discharge and up to several months later (Bar-Nathan et al., 2022).

Statement: Short term outcome of dogs and cats with AKI on CKD is comparable to AKI without pre-existing CKD, but the long-term prognosis is worse (91% agreement).

In two studies of 100 dogs and 100 cats with acute on CKD, the short-term survival outcome was approximately 60%, comparable to animals with AKI without apparent prior CKD component (Chen et al., 2020; Dunaevich et al., 2020). As the pre-existing kidney function of animals with acute on CKD is expected to be substantially lower than the pre-existing kidney function of animals considered to have normal kidney function at the time of insult, a higher degree of nephron recovery would be needed in the acute on CKD group to achieve a positive outcome. It is possible that the etiologies of injury in animals with acute on CKD are more likely to be reversible (ischemic/inflammatory/infectious) with appropriate medical care (Chen et al., 2020, Dunaevich et al., 2020). However, the median long-term survival of dogs and cats with acute on CKD after discharge is relatively poor (median survival in dogs 105 days and cats 66 days) with 57% of dogs and 81% of cats surviving for 6 months and 13% of dogs and 8% of cats surviving for 12 months (Chen et al., 2020, Dunaevich et al., 2020). It has been hypothesized that this may be due to active ongoing damage, facilitating further progression and nephron loss.

Statement: Recovery may be partial or complete. However, even with apparent complete renal recovery, dogs and cats should be

considered as IRIS stage 1 CKD and monitored as such (100% agreement).

After an acute insult the kidney might recover completely with renal functional markers (e.g. creatinine, SDMA) returning to baseline serum values (Bar-Nathan et al., 2022). However, due to insensitivity of these markers, GFR may still be lower than prior to the AKI insult. Therefore, animals with apparently complete recovery should be monitored as IRIS CKD stage 1.

Long-term monitoring

Statement: First follow-up recheck should be scheduled based on the clinical state of the animal and the degree of kidney recovery, typically within a few days from discharge. Long-term monitoring includes regular rechecks of kidney function, at least every 3 months initially for 1 year, and subsequently based on IRIS CKD stage (100% agreement).

The IRIS AKI grading system allows veterinary patients to transition both up and down grades recognizing the capacity over time for both progression of acute injury and renal recovery (Langston, 2017). The timeline and degree of renal recovery that occurs in an individual veterinary patient is difficult to predict and likely multifactorial, such that careful individualized monitoring is required to optimize management. The point of maximal recovery is recognized by plateau of serum markers of kidney function (e.g. creatinine, SDMA) and, for some veterinary patients, return of urine concentrating ability (Bar-Nathan et al., 2022). The period of time until plateau of renal markers has high inter-individual variability with some veterinary patients appearing to reach maximal recovery within days, whilst in others continued improvement may occur over several months. Compensatory mechanisms resulting in nephron hypertrophy, may allow sCr to continue to decline for up to 3 months (Bar-Nathan et al., 2022). The proportion of dogs reaching a non-azotemic point is significantly associated with their maximal AKI grade, but long-term survival has not been significantly associated with sCr indicating that even dogs that remain azotemic can have equivalent survival (Bar-Nathan et al., 2022). Underlying etiology is an important factor in determining normalization of sCr, emphasizing the importance of reversibility of renal recovery rather than necessarily initial severity when considering outcome (Bar-Nathan et al., 2022).

All dogs and cats that have sustained an AKI transition through a period of acute kidney disease (AKD) between days 7–90 post-AKI (Bar-Nathan et al., 2022; Chawla et al., 2017), the pathophysiological response of the kidney to an insult or injury. Transition to CKD is based on the recognition that an AKI increases susceptibility of the kidney to future injury and disease progression (Patel and Gbadegesin, 2022). Staging of CKD after an AKI should only be performed once stability of renal parameters has been documented (Elliott, 2007).

Severity of azotemia and clinical status at the time of discharge will determine frequency of post-discharge monitoring. For most dogs and cats, re-examination for evaluation of kidney and other serum biochemical parameters, general clinical assessment, evaluation of tolerance and requirement for continued medical therapies, and assessment of nutrition will be required within the first week. Thereafter, frequency of monitoring and management can be guided by both disease progression and based on IRIS CKD stage guidelines but must also be commensurate with any change in clinical status, comorbid conditions, and requirement for adjustment of medications. Early detection of progression of disease is important, therefore, re-evaluation at least every 3 months initially and then every 6 months is recommended as a minimum, even for IRIS stage 1 CKD.

Referral guidelines

Veterinary patients with AKI should be promptly referred to a hospital with capabilities to perform 24 h monitoring and nursing care, blood pressure measurement, diagnostic imaging, and other advanced diagnostics. Referral should occur as early as possible to help determine underlying etiology to direct therapy and for intensive monitoring to minimize risk of complications. Veterinary patients with AKI are very dynamic, and their clinical status may change rapidly. Those with severe or oligoanuric AKI should be referred to a facility with capabilities to perform extracorporeal renal replacement.

Guidelines for the timing of initiation of renal replacement therapy have not been rigorously evaluated in humans or animals. Most dogs and cats with a sCr $<$ 5 mg/dL ($<$442 μmol/L) and blood urea nitrogen concentration $<$100 mg/dL (35.7 mmol/L) can be managed without the use of extracorporeal renal replacement therapy. Veterinary patients that will benefit from renal replacement therapies include those with uremia unlikely to controlled with medical management only. Consultation with clinicians providing renal replacement therapies should be performed early in the management of AKI and referral should always be offered when indicated.

Conclusions

This is the first guidelines document reviewing the diagnosis and medical management of dogs and cats with AKI. Whilst there has been continued expansion of knowledge in the AKI field in recent years, much of the evidence base that has and continues to be used in veterinary medicine has been extrapolated from human and experimental data. The generation of voting statements and consensus lead guidelines reviewed by international key opinion leaders in the field of veterinary nephrology therefore forms an initial baseline from which future guidelines documents can evolve with the goal of improving the management and outcome of dogs and cats that develop AKI.

Conflicts of Interest Statement

G. Segev and J. D. Foster are board members of the International Renal Interest Society but did not form part of the voting community in this document. None of the other authors of this paper had a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

CRediT authorship contribution statement

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