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Acute kidney injury in severe sepsis: Pathophysiology, diagnosis, and treatment recommendations

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Abstract

Objective – To review the unique pathophysiology of sepsis-induced acute kidney injury (AKI) and highlight the relevant aspects of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury that may apply to veterinary patients.
Data Sources – Electronic search of MEDLINE database.
Human Data Synthesis – Sepsis-induced AKI is diagnosed in up to 47% of human ICU patients and is seen as a major public health concern associated with increased mortality and increased progression to chronic kidney disease (CKD). Consensus criteria for the definition and classification of AKI has allowed for accurate description of the epidemiology of patients with AKI. AKI develops from a complex relationship between the initial insult and activation of inflammation and coagulation. In contrast to the traditional view, clinical and experimental data dispute the role of renal ischemia-reperfusion in the development of sepsis-induced AKI. Renal tubular dysfunction with activation of the tubuloglomerular feedback mechanism appears to be a crucial contributor to sepsis-induced AKI. Furosemide and n-acetylcysteine (NAC) do not appear to be helpful in the treatment of AKI. Hydroxyethyl starches (HES), dopamine, and supraphysiological concentrations of chloride are harmful in patients with AKI.
Veterinary Data Synthesis – Community and hospital-acquired AKI is a significant factor affecting survival in critical ill patients. Sepsis-induced AKI occurs in 12% of dogs with abdominal sepsis and is an important contributor to mortality. Early detection of AKI in hospitalized patients currently offers the best opportunity to improve patient outcome. The use of urinary biomarkers to diagnose early AKI should be evaluated in critical care patients.
Conclusion – Veterinary clinical trials comparing treatment choices with the development of AKI are needed to make evidence-based recommendations for the prevention and treatment of AKI.

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Keywords: acute kidney failure, kidney failure, organ dysfunction

Abbreviations

AKI	acute kidney injury
AKIN	acute kidney injury network
CKD	chronic kidney disease
CRRT	continuous renal replacement therapy
GFR	glomerular filtration rate
HES	hydroxyethyl starch
IHD	intermittent hemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
NGAL	neutrophil gelatinase-associated lipocalin
NAG	N-acetyl-β-(D)-glucosaminidase activity
NAC	N-acetylcysteine
ROS	reactive oxygen species
RIFLE	Risk, Injury, Failure, Loss of kidney function, End-stage Kidney Disease
RRT	renal replacement therapy

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Introduction

The development of organ dysfunction secondary to a septic insult is well recognized as a significant contributor to mortality in critical care patients, regardless of species, or underling septic focus.[1–3] Acute kidney injury (AKI) has been documented to occur in 12% of dogs

with naturally occurring abdominal sepsis with only 14% of affected dogs surviving to hospital discharge.[1] This compares to an 84% survival to discharge in canine patients that did not develop organ dysfunction. In people, AKI is seen as a significant public health concern affecting not only survival but also leading to worsening of chronic kidney disease (CKD) or the development of de novo CKD requiring long-term dialysis treatment or kidney transplantation.[4] The development of the RIFLE criteria (Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease) has allowed greater precision in predicting the healthcare costs and epidemiological characteristics of AKI in people but the ability to predict which patients are at the highest risk of developing AKI before the development of organ dysfunction remains a significant unmet need in sepsis research for both veterinary and human medicine. This review will outline the current definition and classification of AKI, and we will discuss the distinct mechanisms of AKI in patients with sepsis and how biomarkers of renal injury may assist clinicians in the early diagnosis of AKI. We will also discuss the current management recommendations of AKI in human patients as outlined recently in Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury [5] and suggest how these may be applied in the veterinary critical care unit.

Human and Experimental Research

Definition and classification

One of the major breakthroughs in AKI research has been the development of a standardized definition and classification. This standardization enabled implementation of streamlined study protocols, enabled comparisons to be drawn between studies, and provided the means for effective communication between clinical and research groups. The RIFLE criteria were developed through a consensus of experts in the fields of nephrology and critical care from around the world.[6,7] The RIFLE criteria stratifies patients based on the presence of risk, injury, or failure based on increases in serum creatinine or decline in urine output; the worst criterion within each domain is used (Table 1). The outcome criteria, loss or end-stage kidney disease, define the duration of kidney dysfunction. The criteria were intentionally developed to encompass the broad range of forms of AKI from patients with minimally impaired kidney function to those requiring renal replacement therapy. This approach has the benefit of focusing the clinicians' attention to preventing severe loss of kidney function rather than just dealing with the most severely affected.

The acute kidney injury network (AKIN) subsequently proposed minor modifications to the RIFLE criteria.[8] The "Risk" category was widened to include an absolute increased in creatinine of 26.5 μmol/L [0.3 mg/dL] or more, even if this is below a 50% increase from baseline as long as it is documented within a 48 hour period. In addition, the AKIN network ascribed "Failure" on any patient requiring renal replacement therapy regardless of the urine output or serum creatinine concentration. The AKIN criteria improves the sensitivity for diagnosing patients with AKI but this change only affects a small number of patients (typically <5%).[4] The RIFLE criteria have been extensively validated in over 500,000 human patients to date. The KDIGO AKI Clinical Practice Guidelines has recognized the need for a single common definition and has published a unified criteria largely based on the AKIN network (Table 2).

Table 1: RIFLE criteria (Risk of renal dysfunction, Injury to kidney, Failure or Loss of kidney function, and End-stage kidney disease) to classify AKI. Note: the original RIFLE criteria contained GFR measurements, these were subsequently removed as they do not accurately agree with changes in serum creatinine[6,7]

	Serum creatinine	Urine output
RIFLE – RISK	↑ sCr × 1.5	<0.5 mL/kg/h for 6 h
RIFLE – INJURY	↑ sCr × 2	<0.5 mL/kg/h for 12 h
RIFLE – FAILURE	↑ sCr × 3 or >0.5mg/dL if baseline ↑ sCreat > 4.0mg/dL	<0.3 mL/kg/h for 24 h or Anuria for 12 h
RIFLE – LOSS	Complete loss of function > 4 weeks	
RIFLE – END STAGE	End stage renal disease	

Table 2: KDIGO (Kidney Disease: Improving Global Outcomes) definition and classification of AKI developed through consensus of nephrology and critical care specialists[5]

	Serum Creatinine	Urine output
STAGE 1	↑ sCr × 1.5–1.9 from baseline or > 26.5 μmol/L (>0.3 mg/dL)	<0.5 mL/kg/h for 6–12 h
STAGE 2	↑ sCr × 2–2.9 baseline	<0.5 mL/kg/h for ≥12 h
STAGE 3	↑ sCr × 3 baseline *or* ↑ sCr ≥353.6μmol/L (≥4.0 mg/dL) or initiation of renal replacement therapy	<0.3mL/kg/h for ≥24 h or Anuria for≥ 12 h

AKI is defined as:
- Increase in SCr by ≥ 26.5 μmol/L (≥.3 mg/dL) within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to occur within the prior 7 days; or
- Urine output ≤ 0.5 mL/kg/h for 6 hours.

Epidemiology

Prior to the consensus definition for AKI and severity classification, "acute kidney failure" in critically ill

people was diagnosed in a variable fashion depending on differing criteria. This variability had a negative impact on the ability to assess treatment strategies in these patients. Since the wide acceptance and adoption of the RIFLE/AKIN criteria in people, the occurrence and cost of AKI has been evaluated with greater reproducibility.[7–10] The standardization of definition of AKI has the additional benefit of allowing accurate assessment of therapeutic interventions across studies.

One of the largest epidemiological studies of AKI in people involved 120,123 patients across 57 ICU facilities between January 2000 and December 2005.[11] In this population AKI was documented in 36.2%; 16.3% were classified as RIFLE-R, 13.6% as RIFLE-I and 6.3% as RIFLE-F. AKI was associated with an overall increase in hospital mortality with each RIFLE category independently associated with increasing odds of mortality (odds ratio: R 1.58, I 2.54, F 3.22). This population however was only classified on admission to the ICU, largely representing community acquired AKI. In established ICU patients, AKI was found to occur in 66% of patients; within this population only 22% would have been classified with AKI if they were assessed at admission alone.[12] In this study, AKI was associated with 1.6 (R), 2.1 (I), and 4.8-fold (F) increase in hospital mortality. What is clear from both these studies is the development of AKI regardless of when it occurs is an independent risk factor for mortality and the greater the severity of the AKI, as per RIFLE, the greater the risk of death, even after adjusting for multiple covariates.

When looking more specifically at sepsis-induced AKI in people it has been documented in up to 47% of ICU patients with a clinical diagnosis of sepsis.[13] In contrast, dogs with abdominal sepsis, AKI has been documented in only 16% of cases. This wide discrepancy may in part be due to the failure to include smaller changes in serum creatinine concentration or urine output in dogs with abdominal sepsis.[1]

Etiology

Sepsis-induced AKI is characterized by marked reductions in kidney function with only mild histological changes in the kidney. This is evident by post mortem studies of both clinical and experimental sepsis-induced AKI where there is mild to moderate, patchy tubular changes with little evidence of necrosis; this is in stark contrast to AKI due to many nephrotoxins or ischemia where there is diffuse glomerular and tubular damage with extensive necrosis.[14]

Ischemia/reperfusion injury

Traditionally the observation of AKI in association with "low flow" states including cardiogenic, hemorrhagic, or septic shock, provided reasoning for global renal ischemia playing an important role in the development of all causes of AKI. It follows that restoring and maintaining renal perfusion would be the target for preventing AKI in critically ill patients. Unfortunately, such treatments that included the use of dopamine, a renal vasodilator, have not proven beneficial in the treatment or prevention of AKI in septic patients.[15–19] Current evidence indicates sepsis-induced AKI can occur in the presence of normal or even increased renal blood flow.

However, while global kidney perfusion may be normal or increased, abnormal distribution of blood flow within the kidney may be occurring resulting in flow favoring the cortex. This was not the case, however, in a study by Di Giantomasso et al.[20] who demonstrated unchanged cortical and medullary blood flow in a sheep model of hyperdynamic sepsis, in conditions approximating clinical disease. This and other studies[21,22] suggest factors other than altered hemodynamics may be responsible for sepsis-induced AKI, although microvascular abnormalities cannot be completely excluded.

Inflammation

Evidence from both experimental models and clinical studies support the role of inflammation and associated inflammatory molecules as important factors in development of AKI, and this evidence has been reviewed by Wen et al.[23] Following tissue injury at the site of sepsis, cells release damage associated molecular pattern molecules that result in a further proinflammatory response in distant organs (including the kidney) through activation of immune cells such as T-cells and dendritic cells in these organs.[24] In people with community acquired pneumonia, risk of AKI is correlated with plasma IL-6 concentrations.[25]

Oxidative stress

Generation of reactive oxygen species (ROS) is associated with sepsis and may contribute to AKI. ROS scavengers have been shown to blunt renal tubular injury during endotoxemia indicating ROS generation induces tubular injury. In a murine model of sepsis-induced AKI, administration of the ROS scavenger superoxide dismutase, decreased mortality in those animals.[26] Serum concentrations of endogenous ROS scavengers including superoxide dismutase have been shown to be reduced in the same model of endotoxemia.[27]

Epithelial dysfunction

The poorly controlled inflammatory response within the kidney results in the widespread renal tubular epithelial dysfunction. The link between this tubular

dysfunction and reduction in glomerular filtration rate may be through activation of the tubuloglomerular feedback mechanism within the kidney.[28] The tubular dysfunction will result in a lack of sodium chloride reabsorption in the proximal tubule. This will be detected as an increase in sodium and chloride delivery to the macula densa cells located in the distal tubule. Through tubulo-glomerular feedback mechanism this increased tubular NaCl concentration will result in widespread vasoconstriction of the afferent arteriole and a subsequent drop in glomerular filtration rate (GFR) that ultimately gives rise to the clinical manifestations of AKI, decreased urine output, and increased serum creatinine.

Epithelial dysfunction is also seen with the disruption of tight junctions between renal tubular epithelial cells resulting in back leakage of tubular fluid across the epithelium.[29,30] Cellular injury may also result in loss of cellular adhesion to the basement membrane and shedding of the epithelial cells in to tubular lumen resulting in the appearance of tubular epithelial cell casts in the urine. This cellular debris may also block the renal tubules preventing forward flow of tubular fluid. However, for this mechanism to be one of the main contributing factors to sepsis-induced AKI there would need to be widespread tubular damage evident on histopathology. The absence of these findings cast doubt over both this mechanism and treatments aimed to "flush out" the tubules.

Sublethal injury

A sublethal cellular injury will result in disruption of cellular function particularly on the transport processes. These processes combine to produce renal dysfunction in the absence of histological abnormalities in the renal tubular cells. With a sublethal injury, the renal tubular cells undergo repair, regeneration, and proliferation. During the repair phase cells injured beyond recovery undergo death and exfoliation with an associated infiltration of mononuclear cells.[31] Many hibernating cells will enter the cell cycle to either undergo repair or death. This "choice" is carefully regulated with cyclin-dependent kinase inhibitors appearing to play a key role.[32] In the regeneration phase undifferentiated epithelial cells (stem cells) appear that are thought to reside in the kidney.[33] This is followed by marked proliferation of surviving tubular cells under the influence of growth factors followed by cellular differentiation to produce normal proximal epithelial cells.[34] Despite this, there is a growing amount of evidence to suggest that even mild cases of AKI, which have apparent complete clinical resolution, may be associated with long-term negative outcomes including progression to chronic kidney disease and cardiovascular disease.[35]

When proximal tubular cells have sustained a lethal injury or when the repair process is incomplete there may be persistent inflammation and tubulointerstitial fibrosis. This can occur without previous renal disease. The persistent tubulointerstitial fibrosis is characteristic of lost renal function and it has been demonstrated the severity of AKI has significant influence on the degree of functional recovery.[36,37]

Use of Biomarkers to Detect AKI

The diagnosis of AKI is based on small changes in serum creatinine concentration or by an acute decline in urine output. However, by the time these changes are recognized the opportunity to intervene with effective therapy may have passed. It should also be noted that the production of creatinine is decreased during sepsis that further limits the use of creatinine as an early indicator of AKI.[38] This situation has resulted in the hunt for an effective biomarker that can detect early renal tubular damage before increases in serum creatinine are detected. The reader is referred to some excellent review articles for an in depth discussion of biomarkers for AKI.[39–41] During this search it became apparent that septic-induced AKI has a distinct pathophysiology when compared to non-septic AKI which may result in distinct serum and urinary biomarkers for this population of patients.[42–44] For example urine concentrations of interleukin-18 (IL-18) are higher in septic patients with AKI compared to non-septic AKI patients.[45] Molecules such as neutophil gelatinase associated lipocalin, kidney injury molecule-1, cystatin C, and liver fatty-acid binding protein have demonstrated potential for both early detection of AKI, before increases in serum creatinine and reductions in urine output, as well as yielding prognostic value in terms of predicting renal recovery.[42] Finally, a recent discovery-validation study in a large, heterogeneous cohort of people has found that 2 novel biomarkers of G1-G0 cell-cycle arrest (tissue-inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7) are increased in the urine prior to clinical evidence of AKI.[46] These biomarkers appear to represent markers of risk for AKI and may allow for risk stratification of patients facilitating early management.

AKI in Veterinary Critical Care

Current publications on AKI in veterinary medicine have focused on community acquired AKI such as exposure to nephrotoxins or renal ischemia.[47–49] Sepsis-induced AKI poses many different challenges but may also potentially offer an opportunity for early intervention for maximum patient benefit.

Definition and classification

A RIFLE-like criteria, having the same classification as RIFLE used in people, have been evaluated in dogs suffering from AKI.[50] This study showed a progressive increase in mortality at 30 days associated with increasing severity of kidney injury. RIFLE-R dogs had 24% mortality, RIFLE-I dogs 41%, and RIFLE-F dogs a 79% mortality rate. Dogs in the "Failure" category also had the shortest median survival time of 3 days compared to the "Risk" category having a median survival of 9 days. Another classification system termed the "Veterinary AKI staging system" that grouped patients according to changes in serum creatinine in an identical manor to the AKIN criteria have also shown similar results.[51] Both these systems require a knowledge of the patients baseline creatinine if urine output is not measured that may limit their use to hospital acquired AKI; in human critical care and nephrology, baseline creatinine is estimated taking into account age, gender, and race when a laboratory measured baseline creatinine is not known. An important step in veterinary AKI research will be the development of a single definition and classification system that can be applied to both community and hospital acquired AKI patients. The International Renal Interest Society recently published a proposed AKI grading system for veterinary patients. IRIS AKI grades the severity of injury grom I–V; grade I is a non-azotemic AKI defined as serum creatinine <140 μmol/L(<1.6 mg/dL) with a rise in creatinine ≥26.3 μmol/L (0.3 mg/dL), grade II as creatinine 141–220 μmol/L(1.7–2.5 mg/dL), grade III as 221–439 μmol/L(2.6–5.0 mg/dL), grade IV as 440–880 μmol/L (5.1–10.0 mg/dL), grade V as >880 μmol/L(>10.0 mg/dL).

Epidemiology

One of the earliest studies to look at the occurrence of sepsis-induced organ dysfunction in veterinary patients showed AKI occurred in 12% of dogs with abdominal sepsis; although AKI was defined as an absolute increase in serum creatinine of 44.2 μmol/L (0.5 mg/dL) when postoperative values were compared to preoperative values.[1] This definition may have resulted in the exclusion of dogs fulfilling RIFLE-R and RIFLE-I and only included those with the most severe form of AKI, RIFLE-F. The veterinary studies to date that evaluate the RIFLE criteria in clinical small animal patients have not assessed the rate of AKI within a population with sepsis but did provide confirmation that small changes in creatinine, RIFLE-R, and RIFLE-I, can have significant influence on mortality.[50,51] It has also been documented in another clinical veterinary study that small increases in serum creatinine after a patient has been admitted to the hospital has a negative impact on mortality.[49] In this study, hospital acquired AKI showed similar characteristics to community acquired AKI with both dogs and cats being more likely to die with a rising creatinine was detected. The occurrence of AKI and its effect on a veterinary ICU population has yet to be fully established. With the adoption of a unified definition and classification system this important information can be uniformly gathered across veterinary establishments.

Biomarkers of AKI

In a recent clinical study in dogs[52] urinary neutrophil gelatinase-associated lipocalin (NGAL) was able to identify patients with AKI 12 hours before changes in serum creatinine or serum NGAL occurred. This study was designed to assess for postoperative AKI not AKI from sepsis but does show promise. It also highlights the need to assess urinary biomarkers in additional to serum biomarkers to enhance early detection.

Urinary cystatin-C has also been evaluated in dogs with preexisting renal disease.[53] Using urinary cystatin-C:creatinine Monti et al. were able to differentiated dogs with renal disease from those with nonrenal disease.[53] Other urinary biomarkers including N-acetyl-beta-D-glucosaminidase (NAG) and retinol-binding protein have also been shown to be increased prior to creatinine in dogs with chronic kidney disease.[54,55] These molecules have yet to be extensively investigated in veterinary critical care but offer exciting potential to detect changes early and allow for effective interventions before the animal is "off the cliff."

Management of AKI: Evidence from human and veterinary studies

The widespread use of consensus criteria for the definition and classification of AKI in people has enabled clinicians to develop evidence-based clinical practice guidelines for the treatment and prevention of AKI.[5] Some of these same recommendations may be appropriate to veterinary patients.

Primum nonnocere

The treatment of AKI remains largely supportive and while there is no magic bullet, there are interventions that clinicians can employ to help reduce the severity of injury and hopefully improve the patients' outcome. Discontinuation the use of nephrotoxic drugs such as aminoglycoside antimicrobials and nonsteroidal anti-inflammatory drugs (NSAIDs) from the treatment plan, iatrogenic damage to the kidney may be limited. The clinician should also re-evaluate the scale of objective monitoring this population requires and be prepared to react to small changes in physiological parameters. Optimizing treatment of the patient's underlying condition

will remain an important aspect of this care. For evidence base recommendations on the treatment of sepsis in people the reader is directed to the Surviving Sepsis Campaign.[56,57]

Hemodynamic monitoring and support

While sepsis may induce AKI without affecting systemic hemodynamics, shock superimposed on septic AKI may extend injury further. Hemodynamic monitoring in patients with or at risk for AKI is therefore vital. It is also of note that the injured kidney is unable to maintain autoregulation of blood flow making the kidney more vulnerable to changes in blood flow as blood pressure varies.

Fluid therapy

Management of blood pressure, volume status, and cardiac output requires judicious titration of fluid boluses and vasoactive drugs. Clinicians need to bear in mind that while vasopressors can result in reduced blood flow in the setting of volume depletion, patients that develop AKI will be at risk of volume overload and continued resuscitation can result in harm with a positive fluid balance associated with an increased mortality.[58–60] It is widely accepted that providing an optimal hemodynamic status and having a normal volume status will aid in minimizing any deterioration of kidney function. Current resuscitation recommendations in people include the use of isotonic crystalloids rather than colloids (albumin or starches) for intravascular volume expansion in patients with or at risk of AKI. This suggestion is based on studies showing although 4% albumin solutions to be safe it provided no benefit over isotonic saline [61] and others showing that hydroxyethyl starches (HES) have been associated with significant kidney dysfunction in addition to coagulation abnormalities.[62,63]

Despite wide spread use of both crystalloids and colloids in veterinary critical care units there are very few studies assessing the clinical effects of these fluids on patient outcomes. There is a growing body of evidence demonstrating coagulation defects associated with the use of HES in both healthy and critical ill dogs.[64–66] It has yet to be established if the use of HES in the management of sepsis in veterinary patients is of clinical benefit or if indeed causes harm. However, given the evidence of potential nephrotoxity of HES avoidance of these products in large or repeated doses is prudent.

Chloride restrictive versus chloride liberal fluid administration

A recent clinical trial by Yunos et al.[67] highlighted the important role chloride plays in the development of AKI during critical illness. This study compared 760 human patients given standard intravenous fluids and 773 patients given chloride restricted fluids such as a lactated solution (ie, lactated ringers solution), a balance solution (Plasma-Lyte 148) and chloride-poor 20% albumin. After adjustments for covariant, there was a significant association with incidence of RIFLE-I and RIFLE-F AKI and the use of chloride-rich fluids. One explanation for the observed increase in AKI may be due to higher concentration of sodium and chloride being delivered to the renal tubules, activating the macula densa and inducing renal afferent arteriole vasoconstriction. Although these findings need to be corroborated, avoiding fluids containing supraphysiological concentrations of chloride may be an important and cost effective method to reduced AKI in critical illness.

Vasoactive drugs

It is recommended to use vasopressors in conjunction with fluids in patients with vasomotor (ie, septic) shock. Septic shock is characterized by high cardiac output with low vascular resistance producing hypotension despite adequate fluid resuscitation or optimization of the vascular volume. With this clinical setting the only method to maintain or improve renal perfusion is to use vasopressors once intravascular volume status has been restored. It has yet to be discovered which, if any, vasopressors is most beneficial for the prevention or treatment of AKI and septic shock. The majority of studies compare dopamine, norepinephrine or vasopressin. Dopamine has been a historical drug of choice in this setting but has more recently fallen out of favor as it has not been shown to have any beneficial effects on the kidney and is associated with an increased number of adverse events.[68] There is a growing trend toward vasopressin for septic shock refractory to norepinephrine as it has been shown to increase blood pressure and urine output.[69] The current available evidence support the use of norepinephrine as a first line vasopressor given the potential detrimental effects of dopamine.

The use of diuretics in AKI

It is recommended that diuretics not be used to prevent AKI and suggested that diuretics not be used to treat established AKI, except to reduce volume overload. The prophylactic use of furosemide to prevent AKI has been shown to be ineffective and even harmful in critical illness.[70–72] There is also no evidence to support the use diuretics to reduce severity of AKI once established. Ho et al. [73,74] has published substantial reviews on using furosemide in the treatment of AKI. It was found that furosemide has no significant effect on patient outcome, need for renal replacement therapy (RRT), or even the percentage of patients with persistent oliguria. Given the lack of benefit and potential for harm we should question the continued use of diuretics in patients with AKI with the exception of regulating fluid balance in

hemodynamically stable animals until further evidence is provided to clarify their benefit.

Vasodilator therapy (eg, dopamine, fenoldapam)

Dopamine has historically been seen as having renoprotective properties in critical illness. When administered to healthy individuals at low doses (1–3 μg/kg/min) it causes renal vasodilation, increased GFR and diuresis. However, numerous negative studies[15–19] that include a randomized, double blinded, placebo controlled trial of appropriate size, and adequate power have resulted in its use in AKI being questioned. It has also been shown that these renal effects seen in healthy individuals are not preserved in patients with AKI. Leuschke et al[19] found that in patients with AKI, dopamine significantly increased renal vascular resistance and reduced renal blood flow. Additional negative effects of dopamine, even at low doses, include tachyarrythmias and myocardial hypoxia, reduced splanchnic blood flow, and suppressed T-cell function.[18] Currently, there is no evidence to support the use of dopamine in either the treatment or prevention of AKI. Fenoldopam mesylate is a pure dopamine type-1 receptor agonist that acts to cause renal vasodilation but without the α- and β-adrenergic activation seen with dopamine.[75] In experimental models of AKI there is evidence that fenoldapam may also have anti-inflammatory effects in AKI that are independent of its vasodilatory effects. It has taken prominence in recent years for the treatment of animals with oliguric AKI in the hope of converting them to nonoliguric AKI.[76] However, it is suggested that fenoldapam is not used for the treatment or prevention of AKI. The rationale for this suggestion comes from the absence of data from adequately powered trials with clinically significant endpoints. Two studies have analyzed the use of fenoldapam for the treatment of AKI in people.[77,78] Although these were small trials, fenoldopam did not reduce the requirement for RRT when compared to placebo. The recommendation also takes into account the potentially deleterious effects of causing hypotension when using vasodilatory drugs and the kidneys loss of autoregulation in disease states. The use of fenoldopam in veterinary critical care patients has yet to be evaluated to determine if the theoretical benefit and effects seen in healthy dogs hold true in disease states or if the drug has deleterious effects in our patients, therefore the use of fenoldopam should be restricted to clinical research at this time.

N-acetylcysteine (NAC)

NAC is a form of L-cysteine that can be used to regenerate glutathione store and is known to be potent scavenger of ROS within the body. It also enhances nitric oxide availability promoting vasodilation.[79] The increase in ROS and the loss of endogenous ROS scavengers documented in sepsis-induced AKI generated much interest in using NAC to prevent or treat sepsis induced AKI. Despite animal studies showing attenuated ischemic and nephrotoxic AKI these results have not translated in to human clinical trials. One study compared NAC to placebo in critically ill human patients with 30 consecutive minutes of hypotension or treatment with vasopressors.[80] There was no significant difference in the incidence of AKI between the two groups. The groups also had no difference in serum creatinine changes, recovery of renal function, necessity for RRT or length of stay. The current evidence does not support the use of NAC in AKI.

Renal replacement therapies

The goals of RRT in the treatment of AKI are: (1) to maintain fluid and electrolyte balance, and solute homeostasis; (2) to prevent further detrimental insults to the kidneys; (3) to permit renal recovery; (4) to allow concurrent supportive measures (eg, antibiotics and nutrition) to proceed without limitation or complication.[5]

Controversy ensues in both veterinary and human medicine as to the mode of RRT, continuous renal replacement therapy (CRRT) versus intermittent hemodialysis (IHD), is best suited to patients with AKI, with each mode having distinct advantages and disadvantages. Currently, the mode used in clinical practice is determined by the availability of, and experience with, a specific treatment as only a small number of veterinary institutions have both modalities available to them. There has been no clinical trials in veterinary medicine comparing the two modalities in AKI patients to date, however several randomized controlled trials have been performed in human patients, the most recent being a metaanalysis published by the Cochrane Collaboration. This study assessed 15 randomized controlled trials involving 1550 human patients with AKI. They found no difference in outcomes [hospital mortality (RR 1.01; 95% CI: 0.92–1.12; $n = 1{,}245$) ICU mortality (RR 1.06; 95% CI: 0.90–1.26; $n = 515$) and renal recovery defined as free of dialysis at discharge (RR 0.99; 95% CI: 0.92–1.07; $n = 161$)] when IHD was compared to CRRT.[82] These findings are similar to results reported in other metaanalyses.[83,84] We therefore recommend the use of continuous and intermittent RRT as complimentary therapies in patients with AKI.

Perhaps of greater importance to which mode of RRT is better, is the need to determine which patients require RRT or not, and when to start RRT in those patients that require it. In veterinary medicine, RRT has increased costs associated with its use and is often

delayed in the hope or expectation the patient will recover renal function on their own. This is confounded with the well-known risks of RRT including, hypotension, arrhythmias, and complications associated with vascular access and anticoagulation. This effect of timing of RRT has been examined in a large multicenter observational study involving 54 human ICUs in 23 countries, RRT was stratified into "early" and "late" by median BUN concentration when RRT was initiated and also categorized temporally from day of ICU admission into "early" (less than 2 days), "delayed" (2–5 days), and "late" (more than 5 days). No difference was found between the groups stratified by BUN, however significant temporal difference were present with the "late" group having a greater crude mortality and covariant adjusted mortality (OR 1.95; 95% CI: 1.30–2.92; $P = 0.001$). The "late" group was also associated with longer duration of RRT, longer hospital stay, and increased dialysis dependence.[85] A more recent study analyzed the timing of RRT in patient with AKI in a surgical ICU. This group showed the late initiation of RRT, defined as RIFLE-I and RIFLE-F was an independent predictor of mortality (HR 1.846; CI: 1.07–3.18).[86] The challenge facing clinicians is how to identify patients requiring RRT early while avoiding initiating RRT in patients that do not require it. Current routine clinical parameters do not allow for this distinction to be made but the use of novel biomarkers in AKI including tissue-inhibitor or metalloproteinases-2 and insulin-like growth factor-binding protein-7 may aid in this distinction.

Other important factors relating to RRT include the dose of RRT in AKI, anticoagulation, buffer solutions, vascular access, and dialyzer membrane design are outside the scope of this article but extensively discussed in the KDIGO Clinical Practice Guideline for AKI.[5]

Conclusions and Future Directions

There are many gaps in our knowledge of sepsis-induced AKI in veterinary patients. It is becoming clear however that a rise in serum creatinine concentration, even if relatively small, has significant implications for patient outcome. The IRIS AKI grading system will allow an improved understanding of the impact AKI has in patients and enable comparisons to be made between studies. This will identify the incidence of AKI and risk factors, both diseases and treatments, associated with the development of AKI. The long-term effects of AKI on kidney function in veterinary patients should also be studied. The administration of HES and fluids containing supraphysiologic chloride concentrations are important factors in the development of AKI in people. The safety of these solutions in veterinary critical illness needs to be determined and we recommend caution in using these fluids especially in large volumes or in repeated doses.

The urinary biomarkers NGAL, cystatin-C, and NAG show promise with chronic forms of kidney disease in veterinary patients and may represent key diagnostic markers in veterinary critical care patients. The use of novel biomarkers of cell-cycle arrest, tissue-inhibitor or metalloproteinases-2 and insulin-like growth factor-binding protein-7, may offer the ability to detect AKI in the very early stages.

The use of clinical studies to understand the pathogenesis of sepsis-induced AKI will prove challenging due to the practical issues in obtaining renal tissue. For this the use of experimental models of sepsis will remain necessary. Through an improved understanding of the pathogenesis, specific treatments aimed at reducing the degree of kidney injury or inducing renal recovery will likely be discovered.

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