Can we improve the diagnosis of early stages of acute kidney injury in hospitalised dogs?

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THE concept of acute renal failure (ARF) has undergone significant re-examination in recent years. Practitioners traditionally used the term to refer to patients presenting with clinical manifestations of uremic syndrome and severe acute azotaemia, and it was often considered to be synonymous with acute kidney disease (AKD). However, it is now accepted that AKD is more than just ARF.

AKD represents a spectrum of diseases associated with a sudden onset of renal parenchymal injury, which are clinically imperceptible at the earliest stages and often end in severe ARF requiring renal replacement therapy. As such, animals diagnosed with ARF represent only the subset of AKD patients with the highest morbidity and mortality.[1, 2]

In an attempt to better reflect the broad spectrum of AKD, the term 'acute kidney injury (AKI)' was coined, first in human medicine and then in veterinary medicine. In order to define and stratify the severity of AKI, several grading schemes have been proposed in human nephrology,[3] and these have subsequently been adapted for veterinary patients (Table 1).[1, 4] These grading systems also include prerenal and postrenal conditions that may be independent of, or coexistent with, intrinsic kidney disease.

In contrast to the 'stability' of chronic kidney disease (CKD) stages, AKI grades represent a moment in the course of the disease, and the grading will change as the condition worsens, improves or transitions to CKD.[2] Therefore, serial assessment and sequential grading are needed to monitor the course of the disease and to update therapeutic decisions and outcomes.[2]

Although AKI in companion animals typically develops outside of the hospital setting, there has been increasing recognition of this condition in veterinary emergency and critical care medicine in recent years.[2] In 2011, Thoen and Kerl[5] reported that 14.6 per cent (n=164) of dogs admitted to an intensive care unit developed AKI, as defined by an increase in serum creatinine (Cr) concentration of at least 150 per cent compared with baseline or an absolute Cr increase of 0.3 mg/dl or more, during the hospital stay. These authors considered that small increases in serum Cr concentrations might be clinically relevant, even when absolute values were within reference intervals.

In another retrospective study,[6] 15 to 20 per cent of dogs with at least two Cr measurements taken within a two-, three- or seven-day period (n=400, 476 and 645, respectively) developed AKI, as defined by an increase in serum Cr concentration of 0.3 mg/dl or more. The study concluded that the severity of azotaemia predicts mortality, with a positive relationship existing between serum Cr levels and mortality at 30 and 90 days.

A recent meta-analysis of dogs with AKI (n=800) has reported a pooled mortality rate of 45 per cent, regardless of treatment type

WHAT YOU NEED TO KNOW

- Acute kidney injury (AKI) represents a continuous process of potentially progressive renal damage, characterised by sudden and continuous functional and parenchymal kidney damage. This is clinically imperceptible at the earliest stages but often ends in severe acute renal failure requiring renal replacement therapy.
- AKI occurs frequently in hospitalised patients and, when severe or progressive, is associated with high mortality.
- Early diagnosis and therapeutic intervention may improve the prognosis of patients with AKI. However, diagnosing patients with grade 1 AKI is challenging for clinicians due to the lack of characteristic clinical signs, the need to demonstrate a progressive increment in serum creatinine within a 48 hour period and the need to measure urine production for at least six hours.
- Measurement of urinary γ-glutamyl transferase at admission may predict the development of hospital-acquired AKI, allowing earlier treatment of these patients, which might improve their outcome.

Table 1: International Renal Interest Society acute kidney injury (AKI) grading scheme for dogs and cats[4]

AKI grade *	Serum creatinine	Clinical description
1	< 1.6 mg/dl (< 140 µmol/l)	Non-azotaemic AKI: Documented AKI – historical, clinical, laboratory or imaging evidence of AKI, clinical oliguria/anuria, volume responsiveness † Progressive non-azotaemic increase in serum creatinine ≥ 0.3 mg/dl (≥ 26.4 µmol/l) within 48 hours Measured oliguria (< 1 ml/kg/h) or anuria over six hours
2	1.7 – 2.5 mg/dl (141 – 220 µmol/l)	Mild AKI: Documented AKI and static or progressive azotaemia Progressive azotaemic increase in serum creatinine ≥ 0.3 mg/dl (≥ 26.4 µmol/l) within 48 hours or volume responsiveness Measured oliguria (< 1 ml/kg/h) or anuria over six hours
3	2.6 – 5 mg/dl (221 – 439 µmol/l)	Moderate to severe AKI: Documented AKI and increasing severities of azotaemia and functional renal failure
4	5.1 – 10 mg/dl (440 – 880 µmol/l)	
5	> 10 mg/dl (> 880 µmol/l)	

* Each AKI grade is further subgraded on the basis of current urine production and on the requirement for renal replacement therapy
† Volume responsiveness is an increase in urine production to more than 1 ml/kg/h over six hours and/or a decrease in serum creatinine to baseline over 48 hours

and aetiology.[7] However, early recognition and therapeutic intervention may improve the prognosis of patients with AKI.[8] Unfortunately, diagnosing patients with grade 1 AKI is a challenge for practitioners due to the lack of characteristic clinical signs, the need to demonstrate a progressive increment in serum Cr within a 48 hour period and the need to measure urine production for at least six hours (Table 1, Fig 1).

In addition, serum Cr concentration is considered to be a poorly sensitive marker of renal function. Its value is affected by several extrarenal factors (eg, lean body condition), and it has a curvilinear inverse relationship with glomerular filtration rate (GFR) – progressively increasing in small increments in AKI grades 1 and 2 while significant reductions in GFR occur at these stages.[9]

The general consensus regarding the poor performance of serum Cr concentration for the early diagnosis of AKI has prompted the search for more sensitive markers of renal disease. To date, more than 30 candidate biomarkers have been evaluated, but no one of them fulfils the criteria to be considered an ideal biomarker.[10-12]

γ-Glutamyl transferase (GGT) – a membrane-bound enzyme that catalyses the transfer of glutamyl groups between peptides and is involved in glutathione reactions – is one of these biomarkers. Many cells have GGT activity, but biliary epithelial cells, pancreatic acinar cells and renal tubular epithelial cells (proximal tubule, luminal side) are considered to have the greatest activity.[13] As GGT is too large to be filtered through a normal glomerulus, a rise in its urinary activity is typically caused by acute damage to the tubules and leakage from the tubular cells.[13-14] Measurement of urinary GGT (uGGT) activity is simple, widely available and cost-efficient, so it can be easily applied in the clinical setting.

uGGT has been most extensively investigated in aminoglycoside-induced AKI in dogs,[15-16] but it has also been investigated in other conditions, including pyometra,[17] cisplatin-induced nephrotoxicity[18] and leishmaniosis,[19-20] and also in dogs with AKI of unknown aetiology.[21-22] However, the results of these studies are contradictory. While some authors concluded that uGGT was a sensitive, early urinary biomarker of kidney damage, whose increments precede changes in serum Cr,[15-19] others found that uGGT was not a useful biomarker for this purpose.[18,21,22]

These conflicting data may be a consequence of the lack of standardisation and validation of

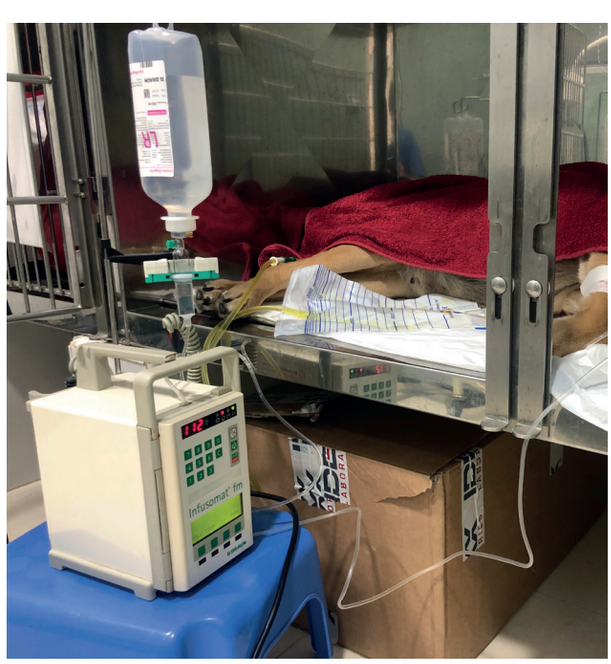

Fig 1: Assessment of urine production (ideally using an indwelling catheter and a closed collection system) is critical for properly grading the severity of acute kidney injury

the assays used in the different studies, the effect of different variables (ie, sample storage time, pyuria, urine pH, within-day variation), differing causes of AKI in the sampled populations or the variable periods of time elapsing between the occurrence of renal injury and the uGGT measurement in each study.[11,12,14,21,22] However, despite the conflicting data obtained in these studies, the authors seem to agree that the maximum benefit of using uGGT as an early marker of AKI would be obtained at the earliest stages of the disease – when the patient is first admitted to hospital and before increases in standard serum markers of kidney function are observed.[22-24]

In a study summarised on p xxx of this issue of *Vet Record*, Peronti and colleagues prospectively investigated the usefulness of measuring uGGT (in the form of the uGGT/urinary Cr [uCr] index) to predict the development of AKI in a cohort of non-azotaemic dogs admitted to an intensive care unit.[25] There are some interesting findings in this study that deserve to be considered and could be of interest for practitioners.

The first is the high prevalence of AKI in the studied population (63.9 per cent), which is significantly higher than that previously reported by other authors.[6-7] This discrepancy may be partly due to different classification criteria being used in this study compared with previous studies. However, this finding also suggests that hospital-acquired AKI may be underdiagnosed in veterinary medicine.

The second is that patients with progressive AKI have a high mortality rate (69.2 per cent). However, no statistically significant difference in mortality rate was found between the dogs with AKI grade 1 and those without AKI. This suggests that AKI mortality rates need to be considered with caution in the context of hospitalised animals.

Finally, but no less importantly, the uGGT/uCr index was found to predict the development of AKI with moderate sensitivity and specificity. Therefore, uGGT measurement at hospital admission could contribute to earlier diagnosis and therapeutic intervention in patients with AKI, thereby improving their outcome.[8,24] However, before this diagnostic approach may be routinely recommended, it would be advisable to standardise and validate the assays used to measure uGGT and properly evaluate all known variables that may affect the results obtained.

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