Acute kidney injury in cats part one – aetiology and prognosis

Author : NATALIE FINCH

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NATALIE FINCH BVSc, PhD, MRCVS in the first of a three-part article, introduces readers to this renal disease in feline patients by explaining its various potential causes as well as likely outcomes

ACUTE kidney injury (AKI) is characterised by sudden onset renal parenchymal injury, which can be clinically undetectable or result in generalised failure of renal function; that is, acute renal failure (ARF).

The term AKI has now replaced ARF as it is recognised there can be a spectrum of insult and injury to the kidneys without failure and that the injury, which may not necessarily result in failure, can be of great clinical significance.

There are classification schemes in human medicine to provide more uniform definitions of AKI. The most widely used are the Risk, Injury, Failure, Loss of Kidney Function and End-stage Kidney Disease; and Acute Kidney Injury Network schemes.

A clear advantage of one classification scheme over the other has not been demonstrated. Studies to evaluate these schemes have been performed in veterinary patients and a grading system has been proposed by the International Renal Interest Society (IRIS) to better define criteria for AKI in cats and dogs.

AKI leads to accumulation of uraemic toxins, fluid and electrolyte dysregulation, and acid-base imbalances. It is associated with high rates of morbidity and mortality.

There are four recognised phases of AKI.

• **Initiation.** The initiation phase begins with an initial insult to the kidneys and decline in glomerular filtration rate (GFR).

• **Progression.** The progression phase involves worsening of the initial insult due to ongoing hypoxia, ischaemia, inflammation and cellular injury. Ischaemia can lead to detachment of renal tubular cells, which can be recognised clinically as cast formation on urinalysis. Free radical production can contribute to cellular damage and inflammatory mediators can worsen kidney injury.

• **Maintenance.** The maintenance phase is characterised by stabilisation of renal blood flow (RBF) and GFR, and is considered a longer course than the initiation and progressive phases lasting several days to weeks.

• **Recovery.** The recovery phase is associated with an increase in GFR and cellular repair, during which renal tubular cells can reattach. AKI is generally diagnosed in veterinary patients during the maintenance phase, in the course of which overt clinical signs develop (Figure 1).

Aetiology

Historically, AKI in cats was most commonly associated with nephrotoxin exposure, which was thought to account for more than 50 per cent of cases[1]. However, the study population was from a US referral hospital, which may not represent the UK general population appropriately.

Ureteral obstruction is increasingly recognised as a significant cause of AKI in cats, affecting up to 35 per cent in a referral population of cats[2]. Some cases of AKI can be superimposed on pre-existing chronic kidney disease (CKD), which is termed “acute or chronic”. This is important to recognise clinically as cats experiencing an acute or chronic episode should be staged using the AKI grading system and not the one established for CKD. Furthermore, it may alter the management recommendation for the patient.

Acute on chronic episodes can occur as a complication of CKD and also as a result of uretero or nephroliths causing obstruction.

AKI can be considered to be pre-renal, intrinsic renal or post-renal in origin.

Pre-renal

Pre-renal injury results from a functional decline in GFR secondary to reduced RBF or perfusion pressure.

Pre-renal AKI is consequently the result of clinical conditions that disrupt the extracellular fluid

volume or systemic or renal haemodynamics, such as hypovolaemia, hypotension, reduced cardiac output or administration of angiotensin-converting enzyme inhibitors.

The kidneys are particularly susceptible to ischaemic damage. In normal patients the RBF decreases from the outer to inner cortex, with the medullary blood flow being approximately 10 per cent to 15 per cent of total RBF. Consequently, it is the inner medullar that is first affected by ischaemia and hypoxia. However, as the renal cortex receives most of the RBF, it is the cortex that is predominantly affected by toxins.

Hypoxia results in subsequent cell injury, with the tubular epithelial cells in the proximal tubule and ascending loop of Henle being most susceptible. Cell injury can progress to eventual cell death. This is generally termed “acute tubular necrosis”.

Hypoxia can also lead to generation of reactive oxygen species and free radicals, resulting in cell damage. In response to cellular injury, an inflammatory reaction with production of cytokines and chemokines ensues.

Cells that desquamate into the tubular lumen can form casts, causing obstruction within the tubules and resulting in back leakage of ultrafiltrate and increased glomerular back pressure, thereby contributing to further reduction in GFR.

Intrinsic

Intrinsic AKI is associated with renal damage and morphological changes within the renal tissue. This may result from prolonged ischaemia, immune-mediated disease, infectious disease, systemic disease such as pancreatitis or systemic inflammatory response syndrome, or nephrotoxins. The most common nephrotoxins in cats are considered to be ethylene glycol, lilies and NSAIDs (Figure 2).

Post-renal

Post-renal AKI is caused by urinary tract obstruction, such as urethral or ureteral calculi, severe pyelonephritis, neoplasia or urinary tract rupture and reabsorption of uraemic toxins. This will result in increased glomerular back pressure and hence reduction in GFR.

NSAIDs and renal function

NSAIDs inhibit cyclooxygenase (COX), which catalyses the formation of prostaglandins and thromboxane from arachidonic acid. Prostaglandins will preferentially cause afferent arteriolar dilation, which maintains renal blood flow and hence glomerular perfusion and GFR.

In normal healthy patients there is low potential for nephrotoxicity. However, when renal blood flow is decreased – for example, in anaesthesia, hypovolaemia or hypotension – then renal function is

more dependent on prostaglandin synthesis. Both isoforms of COX – COX1 and COX2 – are expressed in the kidneys and therefore COX2 selective NSAIDs are no safer for renal function than non-selective NSAIDs.

Reactive vs proactive detection of hospital acquired AKI

Diagnosis and management of AKI is generally reactive in veterinary patients. In humans, AKI typically develops while a patient is hospitalised and hospital-acquired AKI appears also to be common in veterinary patients.

In a retrospective study of dogs with hospital-acquired AKI, 72 per cent were exposed to a nephrotoxin, 41 per cent had cardiac disease, 35 per cent had pre-existing renal disease, 31 per cent had neoplasia, 28 per cent had pyrexia and 14 per cent had undergone anaesthesia[3].

Therefore, hospitalised patients that may be considered at risk should be closely monitored and proactive intervention implemented if necessary.

Implementing the IRIS grading system, which will be discussed in part two of this article, is likely to be important for detecting these patients and future studies evaluating the effect of early recognition and management are needed.

Prognosis

Urine output and, specifically, a nonoliguric state, has been shown to be an important prognostic indicator in cats with AKI[1].

A study reported the mortality rate at 20 days to be 64 per cent in cats with AKI[4]. Negative prognostic indicators in this study were low body temperature, low albumin concentration and low lactate dehydrogenase activity.

An earlier study reported a mortality rate of 47 per cent in cats; however, this was a referral population and mortality rates may be higher in general practice[1].

Potassium was an important prognostic indicator in this study, with each unit increase in potassium associated with a 57 per cent decrease in survival.

The prognosis is generally considered to be better for patients with AKI in which the tubular basement membrane is preserved.

Mortality rates in cats following lily ingestion is reported to be between 50 per cent and 100 per cent[5]. Patients with early stage AKI (IRIS grade I and II) may regain adequate renal function after several days; however, those in the more advanced stages may require several weeks of

hospitalisation and supportive care, or may die, despite treatment. Full renal recovery for cats with severe AKI may take several months.

The mortality rate increases and prognosis worsens in cats with increasing stage, of AKI[6]. However, other studies have reported no association between survival and degree of azotaemia[1,2,4].

Specifically, in post-renal AKI there is no association between severity of azotaemia and outcome, and therefore the prognosis following appropriate management is fair.

In human AKI patients, even a transient rise in creatinine concentration is associated with an increased risk of mortality[7] or the need for chronic dialysis in the future[8]. In cats that survive AKI, there is a high prevalence (approximately 50 per cent) of persistent CKD post-recovery[1].

Parts two and three of this article will discuss the diagnosis and management of AKI in cats.

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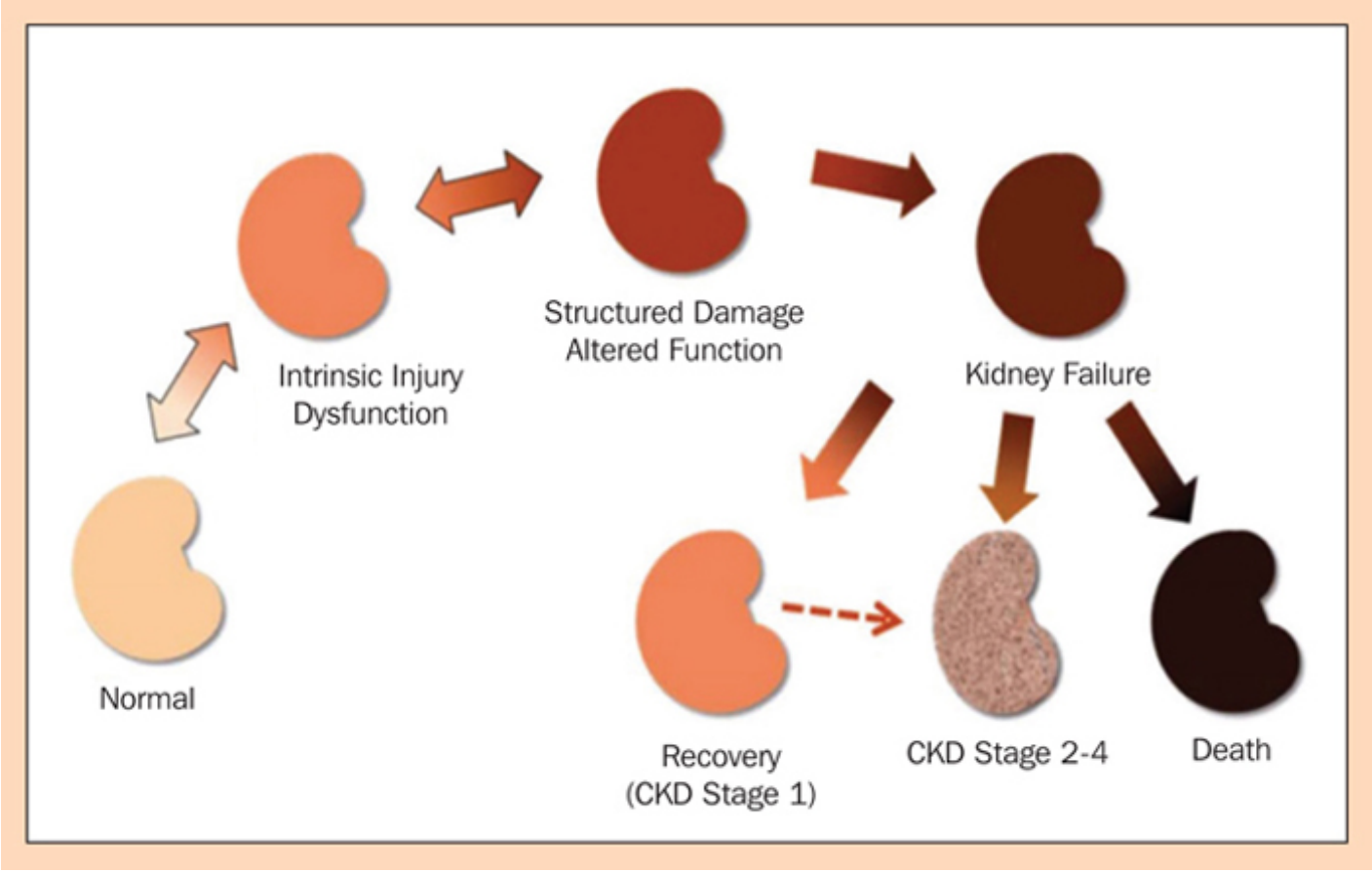

Figure 1. Spectrum of acute kidney injury (AKI) taken from International Renal Interest Society (IRIS) grading of AKI (2013; www.iris-kidney.com).

Figure 2. Lilies are a common nephrotoxin in cats.

IMAGE: Cesar Mayorga.