Acute kidney injury in cats: part two – diagnosis of AKI

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Part one of this article (VT44.48) discussed the pathophysiological process of acute kidney injury (AKI) and the varying aetiologies in cats. In addition, it also discussed prognosis, prognostic indicators and outcomes for cats.

The focus of part two will be the diagnosis of AKI in cats.

History and physical examination

The most common clinical signs in cats with AKI are generally non-specific and include anorexia, vomiting and lethargy. Other potential clinical signs could include polyuria and polydipsia, anuria, ataxia or seizures.

A complete and thorough physical examination should be performed in each patient (Figure 1). This should include assessment of hydration, cardiovascular and respiratory status. AKI patients can have fluid volume overload, which may manifest as conjunctival oedema, peripheral oedema, pleural effusion, pulmonary oedema or potentially, if very severe, hypertension.

Lung auscultation and respiratory rate can be helpful if there is a suspicion of pulmonary oedema or pleural effusion. Jugular distension or pulsation can also be assessed. Conversely, patients can be dehydrated secondary to vomiting and anorexia. Bradycardia or other dysrhythmias can be noted in patients that are hyperkalaemic. The urinary bladder should be palpated to ascertain if there is evidence of urine production. This should be assessed in conjunction with hydration status.

Neurological examination and assessment of mental status can be helpful in detecting uraemic or hypertensive encephalopathy. Renal palpation should be performed to detect changes or asymmetry in kidney size and also to assess if there is any pain. Oral examination can reveal oral ulceration or uraemic stomatitis and inspection of the cat’s coat may suggest lily exposure if there is evidence of pollen present.
**Diagnosis**

**Haematology**

Haematology may demonstrate anaemia or neutrophilia, but is generally non-specific. If there is moderate to severe anaemia present (with no obvious cause such as trauma or haemorrhage), the presence of chronic kidney disease (CKD) with the cat experiencing an acute or chronic episode should be considered.

**Biochemistry**

In terms of biochemistry:

- Assess severity of azotaemia.

- Screen to rule out any underlying or concurrent disease such as hepatopathy. Liver enzyme activity may be increased due to ischaemic or hypoxic injury or toxic insults.

- The presence of hyperglobulinaemia may be suggestive of feline infectious peritonitis (FIP).

- Include the electrolytes Na, K, Cl and iCa if possible as electrolyte abnormalities are common.

- Include phosphate as hyperphosphataemia is also very common in AKI patients due to reduced glomerular filtration rate (GFR). If this is severe it can lead to decreased ionised calcium due to an increase in complexed calcium.

- Total calcium is generally normal, except in ethylene glycol toxicity in which metabolisation of the toxin leads to oxalate formation, which chelates calcium, resulting in hypocalcaemia.

**Acid-base balance**

If practice facilities permit then acid-base status should also be assessed. Many patients with AKI have a metabolic acidosis due to reduced bicarbonate production in the kidneys, reduced ability to excrete hydrogen ions and an increased concentration of uraemic acids.

Intervention is only required if there is a severe metabolic acidosis (pH less than 7.1), which cannot be corrected with fluid therapy. Severe metabolic acidosis can cause cardiovascular depression and damage to enzymatic pathways.

An increased anion gap may also be identified on acid-base analysis due to increased phosphates and other organic acids, or in ethylene glycol toxicity.
**Additional testing**

Feline pancreatic lipase immunoreactivity may be helpful for excluding pancreatitis as an underlying cause. An in-house ethylene glycol test is available, although this is associated with false positives and false negatives.

These tests are only useful in the first few hours of toxicity. They are therefore of limited use in cats, which most commonly present many hours after ingestion when clinical signs start to manifest. False negatives are more of a concern in cats due to the lower limit of detection of the assay below which cats can exhibit nephrotoxicity.

Leptospirosis is a more common cause of clinical disease in dogs than cats; however, a study identified significantly higher seropositivity in cats with kidney disease compared to healthy cats. This could suggest it may play a role in the pathogenesis of kidney disease in cats, but remains to be further studied – particularly in AKI.

**Urinalysis**

Urine should be obtained prior to fluid therapy and measurement of urine specific gravity performed. This will assist in determining whether the azotaemia is prerenal in origin and potentially fluid volume responsive.

Urine culture should also be performed to exclude potential pathogenesis, such as pyelonephritis, and also to serve in forming an ongoing management plan. A urine sediment exam may be helpful in identifying an active sediment and for assessing the presence of casts that suggest tubular damage.

Other changes on urinalysis can include proteinuria, glucosuria and the presence of calcium oxalate monohydrate crystals in cats with ethylene glycol toxicity.

Glucosuria can result from acute tubular necrosis and proteinuria from tubular leakage or necrosis of tubular epithelial cells.

**Diagnostic imaging**

Abdominal radiographs can be helpful in identifying radio-opaque urinary tract calculi and for assessing renal and bladder size. Renal size in cats is generally considered to be 2.5 to 3.0 × height of the second lumbar vertebra.

Ultrasound is the diagnostic imaging modality of choice for evaluating the kidneys. An experienced ultrasonographer will be able to identify changes in renal architecture, pyelectasis or hydronephrosis. A less experienced ultrasonographer may observe changes in renal size or a
grossly irregular appearance to the kidneys.

Ultrasonographic changes in the acute stages of ethylene glycol toxicity can include markedly hyperechoic cortices, corticomedullary rim sign and renomegaly.

Ultrasonographic changes suggestive of lymphoma include generalised diffuse increase in echogenicity in both the cortex and medulla, reduced corticomedullary definition, and renomegaly. There can be focal masses with renal lymphoma, although this is uncommon in cats.

If renal lymphoma is suspected then fine needle aspirates of the kidney may be helpful in confirming this. Renal biopsy would not be indicated in cats with AKI.

Thoracic radiographs are helpful in ruling out any other underlying disease such as cardiac disease or metastatic disease, or for looking for evidence of fluid volume overload.

**Grading of AKI**

A staging system for CKD has been established for some time. This staging system was proposed by the International Renal Interest Society (IRIS) and is widely used in clinical and research work to promote uniform standardisation, aid diagnosis and management and predict prognosis. It is based on serum or plasma creatinine concentration, with sub-staging based on proteinuria and systolic blood pressure.

As discussed previously, in human patients with AKI there are two widely recognised staging systems (the Risk, Injury, Failure, Loss of Kidney Function and End-stage Kidney Disease; and Acute Kidney Injury Network). Veterinary studies have explored incidence, mortality and prognosis associated with AKI using modified versions of the human scoring systems\(^2,3\). However, the criteria that define the human staging systems are not always applicable in cats and dogs, such as documenting change in GFR or creatinine concentration from initial insult.

More recently, a grading system for AKI has also been proposed by IRIS for dogs and cats (Table 1). This is predominantly based on creatinine concentration and urine output. The aim of the IRIS AKI grading system is similar to that of the CKD staging system, which is to aid early recognition, diagnosis, management and prognosis of patients.

An important difference between the two systems is the AKI system can be used in patients with unstable kidney disease, whereas the CKD system is only applied to patients with stable disease. Grade III, IV and V defines cats with moderate to severe AKI with progressive greater degrees of renal parenchymal disease and functional damage (uraemia).

Future prospective studies validating the AKI grading system are required and further information can be found at [www.iris-kidney.com](http://www.iris-kidney.com)
Each AKI grade is sub-graded based on whether the patient is:

- oligoanuric (O; oliguria)
- non-oliguric (NO >1ml/kg/hr); or
- requires renal replacement therapy (RRT).

Urine production is important in the sub-grading of AKI patients due to its significance in therapeutics and outcome.

RRT (commonly referred to as dialysis) is not available in UK general practice, but could be used to manage severe azotaemia and hyperkalaemia, correct acid-base imbalances and fluid volume overload or, potentially, to eliminate nephrotoxins.

**Biomarkers for AKI**

There is interest in identifying and evaluating renal biomarkers, which may be useful indicators of early kidney damage prior to development of azotaemia. These biomarkers may be measured in urine and/or blood.

Such markers include neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, gamma-glutamyl transpeptidase, N-acetyl-?-glucosaminidase, ?1 and ?2 microglobulins, retinal binding protein and cystatin C (Table 2).

Studies evaluating these markers are ongoing and analysis of most markers is not offered at commercial veterinary laboratories. There is a useful and interesting review of the use of biomarkers for the assessment of acute and chronic kidney disease in dogs and cats by Cobrin et al (2013).²

Part three will discuss the management of AKI in cats.

**Acknowledgement**

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**References**

2. Thoen M E and Kerl M E (2011). Characterisation of acute kidney injury in hospitalised...


Figure 1. A complete and thorough physical examination should be performed in each patient for AKI.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Serum creatinine concentration (µmol/l)</th>
<th>Clinical description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;150</td>
<td><strong>Non-azotaemic AKI</strong></td>
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</tbody>
</table>
|       |                                        | a) Documented AKI – historical, clinical, laboratory or imaging evidence of AKI, clinical oliguria/anuria, fluid volume responsive (increase in urine production >1ml/kg/hr within six hours or decrease in blood creatinine concentration to baseline over 48 hours) and/or  
|       |                                        | b) Progressive non-azotaemic increase in creatinine concentration >26µmol/l within 48 hours  
|       |                                        | c) Documented oliguria (<1ml/kg/hr) or anuria over six hours |
| II    | 141-220                                | **Mild AKI**         |
|       |                                        | a) Documented AKI and mild static or progressive azotaemia  
|       |                                        | b) Progressive azotaemia (increase in creatinine concentration >26µmol/l within 48 hours; this may include cats with pre-existing CKD) or fluid volume responsiveness (increase in urine production >1ml/kg/hr within six hours or decrease in blood creatinine concentration to baseline over 48 hours)  
|       |                                        | c) Documented oliguria (<1ml/kg/hr) or anuria over six hours |
| III   | 221-439                                | **Moderate to severe AKI** |
| IV    | 440-880                                |                      |
| V     | >880                                   |                      |
Table 1. IRIS AKI grading system

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Description</th>
<th>Sample measured in</th>
<th>Evidence for use in AKI</th>
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<tbody>
<tr>
<td>Gamma-glutamyl transpeptidase (GGT)</td>
<td>Proximal tubular enzyme involved in protein processing</td>
<td>Urine</td>
<td>Increased in research dogs with gentamicin-induced AKI prior to increases in serum creatinine⁴. None in cats</td>
</tr>
<tr>
<td>N-acetyl-β-glucosaminidase (NAG)</td>
<td>Proximal tubule lysosomal enzyme</td>
<td>Urine</td>
<td>None in cats or dogs</td>
</tr>
<tr>
<td>α1 and β2 microglobulins</td>
<td>Proteins freely filtered at glomerulus and reabsorbed by proximal tubules</td>
<td>Urine</td>
<td>None in cats or dogs</td>
</tr>
<tr>
<td>Retinal binding protein (RBP)</td>
<td>Protein freely filtered at glomerulus and reabsorbed by proximal tubules</td>
<td>Urine</td>
<td>Increased in dogs with pyometra compared to healthy controls⁵. None in cats</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Cysteine protease inhibitor freely filtered at glomerulus and reabsorbed by proximal tubules</td>
<td>Urine and serum</td>
<td>None in cats or dogs</td>
</tr>
<tr>
<td>Kidney injury molecule-1 (KIM-1)</td>
<td>Type one cell membrane glycoprotein</td>
<td>Urine</td>
<td>Detected in cats with possible AKI (patients were not well defined), but not in clinically healthy cats⁶</td>
</tr>
<tr>
<td>Neutrophil gelatinase-associated lipocalin (NGAL)</td>
<td>Protein bound to gelatinase in neutrophils</td>
<td>Urine</td>
<td>Increased in dogs defined as developing AKI post-surgery prior to increases in serum creatinine⁷. Higher in dogs with AKI compared to healthy dogs or dogs with urinary tract infection or CKD⁸. None in cats</td>
</tr>
</tbody>
</table>
Table 2. Suggested biomarkers for AKI and evidence for use in cats