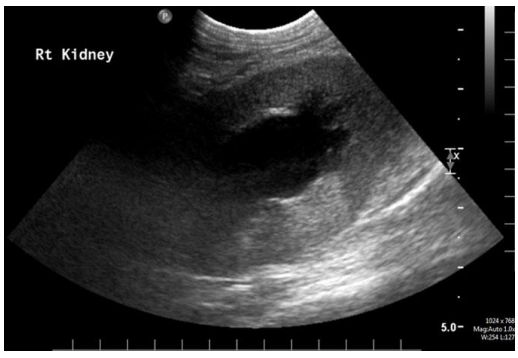
cpdsolutions
transferring knowledge through excellence in training

Urinary Tract Disease Mini Series

Session One: Recognising and Treating Acute Kidney Injury

Mayank Seth BSc(Hons) BVetMed(Hons) DACVIM(SAIM) DipECVIM-CA MRCVS
American, European and Royal College Specialist in Small Animal Internal Medicine



Introduction

Acute kidney injury (AKI) is an emergency condition that requires rapid identification and treatment to maximise patient outcome. This is in part because it is a highly dynamic condition that can rapidly progress and become fatal, but also because ongoing AKI causes progressive, irreversible kidney damage that can result in subsequent chronic kidney disease (CKD).

Similar to CKD (see other notes), the International Renal Interest Society (IRIS – www.iris-kidney.com) have produced a grading system to define the severity of AKI. This system is based largely on plasma creatinine concentration with sub-staging based on the degree of urine output and the use of renal replacement therapy. The utility of this grading system is unclear at this time as there is no related treatment or prognostic guidelines. The system does, however, highlight one important aspect of AKI – namely that an animal does not need to be azotaemic to have AKI and if other factors are identified that indicate the presence of AKI, the patient should still be considered and treated as such.

Azotaemia

Azotaemia refers to the build-up of nitrogenous compounds in the blood. Principally, it is used to refer to the build-up of urea and creatinine, as 2 of the most significant nitrogenous compounds found in plasma and those routinely measured on biochemistry panels. Whilst it is common to interpret the presence of azotaemia as “kidney failure” this is often not the case and numerous other explanations must be considered.

Urea is formed in the liver during the metabolism of amino acids and ammonia. It is filtered in the kidney and excreted in the urine but may be reabsorbed in the proximal tubule together with sodium and water in response to hypotension and activation of the sympathetic nervous system. Urea may also be reabsorbed from the nephron if a pressure build-up occurs within the nephron.

Decreases in urea therefore may be seen with low protein diets or hepatic insufficiency. Conversely, increases in urea may be seen with high protein diets (most notably gastrointestinal bleeding), or conditions associated with a reduction in glomerular filtration, including hypovolaemia, renal diseases or post-renal obstruction.

Creatinine is produced from the breakdown of creatinine phosphate in muscles. Its production is usually constant, but related to muscle mass. Creatinine is filtered in the kidneys but in contrast to urea no reabsorption takes place. In fact, small amounts of additional creatinine may be excreted in the proximal tubule.

Plasma or serum creatinine may be decreased with lack of musculature or increased in well-muscled athletic animals (sighthounds). Otherwise, creatinine is closely related to glomerular filtration rate (GFR) and as noted above, this can be affected by hypovolaemia, renal disease or post-renal obstruction. Holy Birman cats have been noted to have higher creatinine concentrations than other breeds of cat but it remains unclear if this represents normal breed variation or a high incidence of mild chronic kidney disease in this breed.

Causes of Azotaemia

From the above, it is clear that urea and creatinine are both primarily influenced by GFR and hence frequently change together BUT there are exceptions to this:

- Urea elevations with normal creatinine may be seen in association with gastrointestinal bleeding or high protein meals.
- Urea may be significantly more elevated than creatinine if there is decreased GFR and concurrent muscle wasting.
- In mild hypovolaemia urea MAY be more elevated than creatinine due to tubular reabsorption of urea and excretion of creatinine.
- In early/partial post-renal obstruction urea may be more elevated than creatinine due to tubular reabsorption of urea.

- Decreased liver function combined with decreased GFR is uncommon but may yield a lower urea compared to creatinine.
- Mild elevations in creatinine with a normal urea may be normal in sighthounds and Holy Birman cats.

Aside from the exceptions above, azotaemia generally represents a decrease in GFR. The causes of azotaemia and decreased GFR are then further divided into pre-renal, renal or post-renal.

Pre-renal azotaemia refers to a decrease in GFR secondary to decreased renal blood flow (hypovolaemia/ hypoperfusion). This may be clinically apparent if the patient appears to be hypoperfused (weak pulses, cold extremities etc.) but it can also be indicated by a relatively high urea compared to creatinine. Urine specific gravity is often used to indicate if azotaemia is pre-renal in origin and a high urine specific gravity (> 1.030 in a dog, > 1.035 in a cat) generally indicates that the nephrons are able to concentrate urine and thus the azotaemia is not renal in origin. **HOWEVER, urine specific gravity may be reduced with a pre-renal azotaemia if a concurrent cause of low specific gravity is present.** Examples of this are common, and include a diabetic ketoacidosis, where the patient is hypovolaemic but glucosuria causes the urine to be dilute and pyometra where the patient is again hypovolaemic but endotoxaemia prevents adequate urine concentration.

Renal azotaemia refers to azotaemia where the kidneys are unable to adequately balance nitrogenous waste excretion with water retention. Renal azotaemia is generally characterised by an inadequate urine concentration in the face of azotaemia (<1.30 in a dog, <1.035 in a cat). It is important to note that renal azotaemia does not necessarily equate to chronic kidney disease, or even necessarily to kidney disease at all. As noted above, many diseases can prevent adequate urine concentration and if coupled with hypovolaemia, this will lead to what may technically be considered a renal azotaemia. In addition to acute kidney injury and chronic kidney disease, an inability to concentrate urine may be seen with a wide range of systemic conditions including hyperadrenocorticism, hypoadrenocorticism, diabetes mellitus, diabetes insipidus, hypercalcaemia, endotoxaemia or administration of various drugs with diuretic effects (commonly ACE inhibitors or steroids). If a patient is euvolaemic, azotaemic and post-renal causes of azotaemia have been excluded then acute or chronic kidney disease can be suspected. It is often stated that only 25% of normal renal function is required to maintain normal nitrogen/water balance. Therefore, if renal azotaemia is present this indicates that less than 25% of normal renal function is present and both kidneys must be affected to some degree.

Post-renal azotaemia is caused by an inability to excrete nitrogenous waste that occurs distally to the renal pelvis. These conditions are characterized by a reduced urine output and concurrent hyperkalaemia is common. The commonest causes of post-renal azotaemia seen in companion animal medicine are due to urethral obstruction or internal urine leakage (eg traumatic uroabdomen). Unilateral ureteral obstruction may contribute towards the development of post-renal azotaemia but as noted above, the presence of azotaemia indicates renal function <25% of normal and therefore if a unilateral ureteral obstruction is present with azotaemia, the non-obstructed kidney must also have some degree of dysfunction.

Approach to the investigation of azotaemia

If a patient is found to be azotaemic, it is prudent to start by considering if a pre-renal component may be present:

- If the patient appears “well” – e.g. it is bright, eating, drinking and has strong pulses, moist mucus membranes etc. then it is unlikely to be hypovolaemic.
- In pre-renal azotaemia the urine specific gravity should be high, although consideration must be given to comorbidities that lower the USG as noted above.
- If the patient is “unwell” – (lethargic, inappetant, dehydrated, poor pulses or low blood pressure etc.) and a pre-renal component to the azotaemia is possible, a fluid bolus can be considered to normalise perfusion, with urea and creatinine re-measured once this is achieved. Unless congestive heart failure is present, this is often beneficial and rarely contraindicated.

Post-renal azotaemia should be considered early in the investigation as its presence often necessitates emergency treatment.

- Post-renal azotaemia is often accompanied by hyperkalaemia and a low urine output.
- Urethral obstruction may be associated with a turgid bladder and stranguria.
- Abdominal imaging (preferably ultrasound) should be used to rule out ureteral obstruction and uroabdomen if these are possible differential diagnoses.

Once pre-renal and post-renal considerations are excluded then investigation should focus on renal causes of azotaemia. The initial consideration should be if the patient has acute kidney injury or chronic kidney disease. This is an important distinction as acute kidney injury is much more dynamic, potentially worsening in a matter of hours but also with the potential to regain renal function. By contrast, chronic kidney disease is a slowly progressive, irreversible condition where the focus of ongoing therapy will be to palliate clinical signs and reduce progression. Acute kidney injury may cause permanent damage, leading to chronic kidney disease and thus it is important to make the distinction as soon as possible to maximise patient outcome. The distinction is often challenging but some of the common differences are described below:

Acute Kidney Injury	**Chronic Kidney Disease**
Good Body Condition	Poor Body Condition
Relatively Sick	Relatively Well
Normal or Large Kidneys	Kidneys often normal or small
Variable haematocrit	Non-regenerative anaemia
Polyuria, oliguria or anuria	Polyuria
Variable Potassium	Normal or Low Potassium
Normal bone density	Possible osteodystrophy

While the above serves as a useful guide, in practice it is often best to assume that there is at least a component of acute kidney injury present as the consequences of missing this may be permanent and severe. Additionally, it is possible for both acute and chronic kidney disease to exist concurrently – for example chronic kidney disease is a risk factor for the development of pyelonephritis. A table of common causes of acute kidney injury and the appropriate tests is listed below:

Injury	Test
Grapes, raisins (dogs) Chloroform, Lilies (cats)	History
Rodenticide or Psoriasis cream (Vit D)	History, serum calcium concentration, imaging (mineralisation), specific tests
Melamine (contaminated dog treats)	Urinalysis (crystaluria)
Heavy metals	History, specific blood/urine tests
Ethylene Glycol	Crystaluria (CaOx monohydrate) Increased anion gap Hypocalcaemia, hyperglycaemia Urine/coat flouresence Ultrasound Urine test kits (not recommended)
Envenomation, stings, bites	History, identified wound

Drugs: • NSAIDs • Diuretics • Aminoglycosides • Various cytotoxics • Bisphosphonates	History
Pyelonephritis	Urine culture (must be x 3) Ultrasound (NB Urine sediment not reliable)
Leptospirosis	Paired serology (Dark field microscopy or PCR but less sensitive) Concurrent liver enzyme elevations
Pigmenturia (haemoglobin/myoglobin)	Urinalysis
Prolonged hypoperfusion	History/clinical picture
Prolonged post-renal obstruction	History/clinical picture
Infarction	Ultrasound
Alabama Rot	Concurrent skin wounds Marked proteinuria Renal/skin biopsy
Sepsis	Concurrent clinical picture
Acute pancreatitis	Concurrent clinical picture, PLi, imaging
Neoplasia	Imaging Cytology/histology
Hyperviscosity syndrome	PCV/globulins

The above table clearly contains too many tests/injuries to consider in every case and there are many additional rarer causes too. A suggested standard approach to investigate acute kidney injury, which considers most of the major points above, therefore includes:

- A thorough history and physical examination.
- Complete haematology and biochemistry.
- Urine culture – at least one but preferably 3 on separate samples to minimise the chances of missing an intermittently shedding pyelonephritis.
- Urinalysis, including sediment examination.
- Abdominal imaging.
- Further tests based on findings from above.

Treatment of Acute Kidney Injury

The causes of AKI are many; if a specific cause of AKI is identified, this should be addressed as appropriate. The kidney has many different roles within the body and hence the possible consequences of AKI are many. The major problems seen relate to problems with fluid balance, electrolyte balance and nitrogenous waste excretion. These lead to the development of dehydration, hypovolaemia and uraemia and addressing these concerns is a principle aim of AKI treatment.

Fluid balance

Volume

At the time of initial evaluation, many patients with AKI are hypovolaemic due to hypodypsia, vomiting, diarrhoea and/or polyuria. Hypovolaemia itself can be a cause of AKI and will worsen AKI of any other cause by decreasing GFR. As such, it should be addressed with urgency. Hypovolaemia can be recognised by the presence of a delayed capillary refill time, weak peripheral pulses and poor arterial blood pressure. In dogs tachycardia is usually present but cats may be tachycardic or bradycardic.

Hypovolaemia should be addressed rapidly through the use of fluid boluses. A balanced crystalloid solution such as Hartmann's solution is generally preferred, unless there are specific indications for an alternative. I generally start with a bolus of 15-20ml/kg intravenous fluids given over 15 minutes and then reassess the patient. If some improvement in volume status is seen but the response remains inadequate, boluses can be repeated to effect with repeat assessment immediately after each one. If no response is seen then this may be because the dose was inadequate or it may be because the observed abnormalities are not due to hypovolaemia. Tachycardia may be due to pain or arrhythmias secondary to electrolyte disturbances. Hypotension may be due to cardiac problems or vasodilation (maldistributive shock). Mucus membrane moisture and CRT are generally reliable indicators of volume status in AKI so these may be used as a guide but caution should be applied to repeatedly fluid blousing animals that are showing minimal signs of response.
Conversely, animals with AKI may be oliguric or anuric. This assessment can only be made once volume status is adequate as it is physiologically appropriate for urine output to decrease during hypovolaemia. If patients truly have a decreased urine output that they are not able to upregulate, overzealous fluid administration may readily cause fluid overload, a form of congestive heart failure, and lead to respiratory distress. This may be particularly likely in cats that had some pre-existing cardiomyopathy, which is a common occurrence in association with other common comorbidities such as hypertension.
Once initial hypovolaemia has been addressed, fluid therapy should address dehydration and maintain euvolaemia in order to maintain renal perfusion, aiding in waste excretion and maximising renal blood flow to aid with recovery. Dehydration should be corrected over 6-12 hours using the formula:
Required fluid volume = (% Dehydration x Wt(kg))/100
This volume should be added to the ongoing maintenance requirements, accounting for fluid loss. Fluid losses in patients with AKI can be highly variable as gastrointestinal losses can vary, as can voluntary fluid intake and urine output. Patient with AKI may be highly polyuric (urine output in excess of 15 ml/kg/hr is occasionally seen- normal urine output is 1-2ml/kg/hr), or they may be oliguric (<1ml/kg/hr) or anuric. An appreciation of this variability is essential to match intravenous fluids with output. In addition to regular reassessment of volume and hydration status based on clinical parameters, patients should be regularly weighed to ensure rapid fluctuations are not occurring. Respiratory rate should be monitored to look for early indicators of circulatory overload. Placement of an indwelling urinary catheter to quantify urine output can be beneficial in dynamic cases but if this is not done then bladder size and semi-quantitative estimation of urine output should be monitored. Placement of a central venous catheter may be beneficial as monitoring trends in central venous pressure may indicate changes in fluid balance. Central lines also have the advantages of allowing repeated atraumatic blood sampling, being less irritating to patients compared to having bandaged legs and if appropriately maintained they can be left in situ for the days/weeks needed for treatment. In appropriate circumstances, a central line can also be used for nutritional support (see below).
If fluid therapy is successful and a patient's azotaemia improves and they begin to eat and drink, fluids should be continued until creatinine levels fall to a plateau. At this stage they should be cautiously tapered and discontinued over the following 48-72 hours with frequent re-assessment of fluid balance. Recurrence of azotaemia or hypovolaemia may represent ongoing disease but a small increase in creatinine is normal and acceptable as long as the patient appears euvolaemic and well. Rapid fluid discontinuation is discouraged as medullary washout is likely to have occurred, meaning even if the kidneys are well healed they will be unable to adequately concentrate urine immediately.

Electrolytes and Acid-Base Balance

Sodium and water balance are often decoupled in AKI, meaning patients may be hypo- or hypernatraemic and this may not be as tightly associated with the patient's volume status as with other conditions. Rapid fluctuations in sodium may cause irreversible neurologic complications and so these are to be avoided. The sodium concentration of the administered fluid should be as close to the patient's sodium concentration as possible during the volume expansion phase in order to minimise sodium fluctuations. Thereafter, cautious normalisation of sodium can occur by altering the sodium concentration of the fluid administered. Sodium should change by no more than 12mmol/L over 24 hours (0.5mmol/L/hr).

Potassium concentrations in patients with AKI can be highly variable and generally related to urine output, with hyperkalaemia in oliguric/anuric states and hypokalaemia in polyuric states. If hypokalaemia is present then potassium chloride supplementation can be used to normalise levels. Initially, this can go in the maintenance fluids using the guide below:

Patient's K^+ (mEq/l)	***Amount of K^+ to add per liter***
3.5 – 4	20 mEq
3.0 – 3.5	30 mEq
2.5 – 3.0	40 mEq
2 – 2.5	60 mEq
< 2	80 mEq

In some instances, this is not sufficient to address the ongoing losses and so more potassium must be added, either to the maintenance fluids or as a separate KCl infusion. If a separate infusion is to be used it is vital that this is diluted as per manufacturer's instructions. In any eventuality, K^+ should not exceed 0.5mEq/kg/hr without continuous ECG monitoring as the risk of arrhythmia development increases beyond this rate.
If hyperkalaemia is present, this may be addressed by volume expansion and fluid diuresis. If this is not sufficient and it is severe enough to be associated with arrhythmias (bradycardia with flattened/absent p waves and tall T waves), then it warrants direct treatment. Treatment options include:

- Intravenous glucose: 1ml/kg of 50% glucose given through a central line or diluted and given through a peripheral catheter
- (Regular insulin: 0.25IU/kg given intravenously – can be given in addition to glucose but must not be given without glucose)
- Calcium gluconate: 1ml/kg of 10% solution given intravenously over 20 minutes with continuous ECG monitoring. This is cardioprotective but will not actually lower potassium concentrations
- Sodium bicarbonate - (see below)
- Frusemide – (see below)

Another common problem in AKI is metabolic acidosis. In most cases this is mild but in severe cases blood pH can decrease below 7.1 and this may then be associated with further metabolic consequences, worsening the situation. If normalisation of perfusion does not improve the acidosis then cautious use of sodium bicarbonate may be indicated but this should only be used in severe acidosis and only if the patient's respiratory function is adequate to eliminate CO_2, otherwise severe complications may arise. If sodium bicarbonate is to be used, the suggested initial rate is to replace 1/3 of the base deficit over 6 hours:

$$\text{Bicarbonate dose required (mmol)} = \frac{0.3 \times \text{weight (kg)} \times \text{base excess (mmol/L)}}{3}$$

This volume of Sodium bicarbonate should be given as an intravenous infusion in the maintenance fluids or diluted and concurrent with maintenance fluids. It should be noted that this represents a significant amount of sodium and so fluctuations in this electrolyte should be carefully monitored.

Addressing decreased urine output

If fluid therapy alone does not promote urine output, then this should be addressed by other means to allow management of volume status, promote waste excretion and also flush out any toxins that may be contributing to AKI.

In the first instance, the loop diuretic frusemide is generally recommended. An initial dose of 2mg/kg IV is generally used, with assessment of effect 30-60 minutes later. If this is unsuccessful then 4mg/kg can be attempted, then 6mg/kg. If an effect is seen then this can be followed with a continuous rate infusion (CRI) of 0.1-1mg/kg/hr. CRIs are preferred over repeated intermittent blousing as it has been shown to be more effective and may also improve renal recovery for a variety of reasons. If a CRI is not possible, repeat dosing q4-6 hours can be used. Careful monitoring of volume and electrolyte status is important in cases where frusemide is effective as it may cause marked polyuria, hypokalaemia and hyponatraemia.
If frusemide is not effective then the osmotic diuretic Mannitol can be used (0.25-1g/kg IV over 20 minutes). Mannitol may promote diuresis, cause renal vasodilation and scavenge free radicals. Unfortunately it also expands intravascular volume by osmotically drawing fluid from the interstitium and so it may cause or worsen fluid overload, particularly if it does not rectify urine output. Use of mannitol must therefore be very cautious.
If urine output cannot be restored with the above therapies then renal replacement therapy is indicated. While peritoneal dialysis is possible at several institutions, it is generally considered to be inferior to haemodialysis or continuous renal replacement therapy and so referral to an institution that offers these services is recommended in this setting. In addition to improving volume balance and allowing waste excretion, renal replacement therapy may remove some nephrotoxins directly. These therapies are occasionally coupled with mechanical ventilation to allow better management of the patient's respiratory and acid-base status. If such options are a possibility for a patient with AKI, then one jugular vein should not be used for sampling or catheters so that it can be reserved for a dialysis catheter if needed.

Other therapies

Dopamine and diltiazam have both been used in order to improve renal blood flow in patients with AKI, and potentially improve urine output. Use of either is questionable based on the available evidence and use of diltiazam carries a risk of causing or worsening hypotension and so this author does not routinely recommend the use of either substance.
Other supportive therapies for patients with AKI can be guided by "The Rule of 20", developed by the criticalist Rebecca Kirby:

- Fluid therapy: See above
- Oncotic pull
- Glucose
- Electrolytes/Acid-Base: See above
- Oxygenation/Ventilation: depending on mental status and fluid balance – see above
- Mentation
- Blood Pressure: patients may be hypotensive or hypertensive. Hypotension may the the result of fluid or electrolyte disturbances or may be due to maldistributaive shock. In the latter case, use of pressor agents such as dopamine may be indicated. Colloid use should be very cautious due to risk of fluid overload and also as colloids may be nephrotoxic. If hypertension is identified then it should be addressed using amlodipine orally/rectally or nitroprusside or hydralazine given parenterally. Diltiazem may be considered in hypertensive cases.
- Cardiac Function: see above re risk of arrhythmia, fluid overload and pre-existing cardiomyopathy
- Albumin: May be reduced in cases of AKI associated with sepsis or glomerulonephritis but rarely warrants direct intervention. Alterations in albumin may have an effect on the kinetics of other drugs that are admisntered.
- Coagulation
- RBC Mass/haemoglobin: Anaemia may occur due to underlying cause, renal dysfunction or repeated sampling and should be treated if severe.
- Renal function

- Immune status/antibiotic selection: consideration should be given to antibiotics if the cause of AKI is suspected to be infectious or no other cause is found (given

pyelonephritis can be difficult to prove). Amoxicillin-clavulanate is generally appropriate in most cases.

- GI Motility and Mucosal Health: Gastric ulceration, nausea and ileus are common in patients with AKI and so antacids, antiemetics +/- prokinetics are generally recommended. The author uses omeprazole, maropitant and metoclopramide respectively. Metoclopromide use is generally reserved for cases of overt ileus as it may decrease renal blood flow.
- Drug Dosage and Metabolism
- Nutrition: Nutritional support is vital in patients with AKI. Appetite stimulants or not usually sufficient and so use of a feeding tube is preferred. This also allows for supplementation of water to help with fluid balance in a manner that is generally considered safer than intravenous fluids (reduced risk of fluid overload). If a feeding tube is not possible/appropriate then parenteral nutrition through a central line can be considered.
- Pain Control: Many causes of nephritis are painful and so analgesia is vital. Opioids are generally preferred. NSAIDs are contraindicated.
- Nursing Care
- Wound Care
- Tender Loving Care

Specific therapies

With so many potential causes of AKI, it is impossible to detail the specific investigation and treatment of them all. If a known toxin ingestion has recently occurred then gastric decontamination (emesis/lavage) may be helpful in some cases. In some common circumstances, however, there are specific therapies that are indicated:

- Leptospirosis: Several antibiotics are effective for treating the acute phase of leptospirosis but penicillins are generally used. This does not eliminate the carrier status of affected dogs and a course of doxycycline is required for this purpose. Doxycycline may also be used in the acute setting but its use is problematic as it is generally given orally.
- Ethylene glycol may be treated with alcohol if caught early (prior to the development of oliguria). It may be given orally but is generally not well tolerated. Intravenously medical grade alcohol or clear spirits (vodka) may be used. A 7% alcohol solution should be used (eg 175ml of 40% vodka added to 825ml saline to make 1 litre). An initial dose is 8.6ml/kg IV over 30 minutes then 1.43ml/kg/hr for a further 24 hours. A specific therapy 4-MP is available in some countries but it is often cost-prohibitive, has a short shelf life and is only effective if given within a few hours of toxin ingestion.
- If vitamin D intoxication is confirmed (known ingestion or marked elevation in calcium/phosphorus with evidence of mineralization) then calcitonin can be given to reduce calcium concentration. It should be noted that mild total calcium elevations are commonly seen in AKI and this should not be confused with the marked ionised hypercalcaemia seen in vitamin D toxicosis.