RECOGNITION AND TREATMENT OF ACUTE KIDNEY INJURY (AKI)

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Causes of intrinsic kidney injury and failure:
Renal function impairment results from cell damage and/or death most likely after diminished renal blood flow or oxygen delivery. Diminished blood flow e.g. as in shock, prevents sufficient delivery of nutrition and oxygen to the cells and consequently, metabolic disturbances can lead to cell apoptosis if not remedied. Molecular changes activate destructive enzymes cascades and the sodium-potassium-pump is influenced, this changes intracellular electrolyte concentrations and cellular function. As a trigger for the inflammatory cascade this leads to neutrophil activation and cytokine release thereby altering vascular permeability. Cell oedema contributes to tubular obstruction and oxygen free radical substances can lead to direct toxic substances that continue to cause progressive cellular injury to the renal architecture, this diminishes GFR and results in leakage of fluid through tight junctions, loss of urine concentration ability and further cell lysis and death follows.

Conditions leading to kidney injury
Further examples can be reviewed within Mugford et al 2013:

- Ischaemia (e.g. hypoperfusion, infarct)
- Sepsis
- Toxins
  - Ethylene glycol,
  - Lily intoxication (cats),
  - Grapes/raisin intoxication (dogs)
  - Heavy metals
  - Haemoglobinuria
- Drugs
  - NSAIDS
  - Contrast agents
  - Aminoglycosides
- Infectious
  - Pyelonephritis
  - Leptospirosis
- Hypercalcaemia
- Hyperviscosity

Management of acute kidney injury
Patients with acute kidney injury (AKI) present with a wide variety of symptoms renal function impairment leads to uraemia, hyperphosphataemia and isosthenuric urine, when gastrointestinal bleeding occurs, the BUN:Crea ratio can be significantly increased. Retained acids due to excretion impairment can increase the anion gap and result in severe acidosis. Other significant changes can occur with electrolytes including rapid changes in serum sodium and potassium concentration. Many conditions can ultimately lead to severe kidney injury; the most effective treatment is to address the underlying disease process to
Acute kidney injury (AKI) can be divided pathophysiologically into four stages

Initiation phase
The initial insult results in some renal tissue damage.

- **Extension phase:** Damage from the initial insult extends due to spreading inflammatory response. Clinically, there might be no indication of renal impairment, no azotaemia, no casts within the urinary sediment, no glycosuria etc. Decreasing glomerular filtration rate, increasing renal analytes (urea and creatinine), decreasing or inappropriate urine output can occur. (48-72 hours)

- **Maintenance phase:** The initial insult and resulting inflammatory response are well established and maintain damage to the cellular structures of the kidney. Azotaemia and later significant oliguria/anuria occurs (7-21 days).

- **Recovery phase:** Repair processes are active, some renal tubules might return to function which improves azotaemia and we might see a marked increase in urine output (polyuric AKI) due to osmotic diuresis of accumulated solutes, medullary wash out can occur due to loss of the normal counter current mechanism of urine concentration in the loop of henle. (1-2 months)

We should aim for early intervention within this cascade it is recommended to review Brown, S. A (2016) for diagnostic criteria. Thoen et al categorized AKI via Veterinary Acute Kidney Injury Score (VAKI) mortality rate was greater in stage 1-3 than in stage 0 (54% vs 16%) whereas the length of hospital stay, general anaesthetics, number of diagnoses, mean survival prediction scores were not significant 21% of stage 1 dogs had a creatinine within reference, therefore small increases can be important even if overall creatinine is within reference level. It has been shown in human medicine that these criteria when used alone can be insensitive and incorrectly classify patients due to over hydration and or the effects of high volume fluid resuscitation so we should still not rely on these alone to monitor for AKI. Note that acute renal failure (ARF) should now be used to describe the highest grades of AKI only.

**PRINCIPLE ONE:** Address/Treat the initiating problem
Discontinue nephrotoxic medications e.g. non-steroidals. Perform a urinary culture and start antibiotic treatment for pyelonephritis. In ethylene glycol intoxication (prior to onset of azotaemia) consider ethanol/fomepizole treatment. Significant hypercalcaemia (ionized calcium >1.6 mmol/l) should be managed to decrease levels as soon as possible. The inciting cause needs to be dealt with and removed, otherwise supportive care will be inefficient it is therefore most challenging when this cannot occur rapidly in disease processes such as SIRS due to severe pancreatitis and AKI due to sepsis and in congestive heart failure treatment (cardio-renal syndrome).

**PRINCIPLE TWO:** Supportive care
Fluid therapy: Most patients will have a hydration deficit and this should be replaced as soon as possible. The deficit, maintenance needs, and ongoing losses should be taken into account with calculation. Compound sodium lactate is a good solution as an initial choice for replacement, but after re-hydration this may need reassessment based on electrolyte, acid-base status and body weight. Caution should be exercised with attempting to drive urine output with fluid therapy not all the infused fluid might be filtered through the glomeruli with oliguric AKI and will then lead to over hydration.

There is a body of evidence in human medicine, that over hydration is detrimental to outcome. Optimisation of fluid therapy with the aim to achieve sufficient renal perfusion without over hydration is recommended. To avoid the scenario of positive fluid balance cautious monitoring of hydration and fluid volume parameters is essential. This would include monitoring mucous membranes for moisture (without hypersalivation), capillary refill time, heart rate, blood pressure, haematocrit/total solids, urine output (ideally via catheterization and a closed collection system), Creatinine, Urea, Potassium, Sodium, phosphate measurement and acid base status.
If oliguria continues after appropriate fluid therapy and restoration of adequate renal perfusion (urine output should be in excess of 2mls/kg/hr when receiving IVFT) first recheck that hydration has truly been restored to exclude that the lower urine output is physiological (fractional excretion of electrolytes are used in this situation if readily available) rather than due to worsening AKI. Careful calculations of “ins-and-outs” in ml/kg/hr and ensuring that the urinary catheter is unobstructed (bladder ultrasound can be helpful in this situation) are recommended. If concern is present review average UOP over serial measurements and patient body weight trends. Attempt to match the urine produced by an appropriate intravenous fluid rate to avoid over-hydration whilst an adequate UOP is restored. If significant hypotension remains present after adequate volume resuscitation this will continue to impede adequate UOP. Severe metabolic acidosis can occur in these patients and it is tempting to consider therapy to correct this, however due to the possible significant effects of bicarbonate therapy (paradoxical CSF acidosis, hypernatraemia, hypocalcaemia, excessive volume administration) it should only considered in severe acidosis after re-hydration (persistence of pH < 7.0).

There are different therapies available to attempt to increase urine output:

**Furosemide:** Aims to diminish fluid overload by acting diuretically on the tubules, no increase in renal blood flow or GFR occurs directly. Theoretically, as described above, if urine output ceases we should stop fluid therapy to avoid fluid overload. The administration of furosemide makes a continuation of the supportive care possible when urine output diminishes i.e. to prevent a significant worsening in hyperkalaemia. Instead of bolus administration, furosemide can also be administered as a CRI (one study showed increased diuresis by CRI in comparison to intermittent injections, but this was investigated only in normal dogs. The recommended dose is 0.5-1mg/kg/hr. The use of furosemide to restore UOP however has not been shown to improve outcome in human patients. It theoretically reduces renal metabolic rates, but it also has the potential to be nephrotoxic and needs to reach the luminal membrane to be effective. Therefore in the situation of complete persistent anuria it may be unlikely to make a significant impact. However its use is important in veterinary medicine due to the cost implications and lack of wide spread access to haemodialysis to address fluid balance and electrolyte changes by more advanced therapy.

**Mannitol:** can be considered but care should be taken. As an osmotic diuretic it can contribute to over hydration with oligo-/anuria. At high dosages (>2g/kg) it has been reported to contribute to kidney injury. Usual dosages (0.5-1g/kg/over 20-30 minutes) can not only increase urine output, but also purportedly acts as a free radical scavenger, and has other positive effects that might contribute to diminish renal injury via improvements in fluid flow.

**Dopamine:** Had been recommended due to theoretically increasing renal blood flow and GFR, leading to an increase in urine output, several studies (other than in normal dogs) showed negative results and species differences may have significant implications. Wohl et al. JVECC 2007 investigating the effect of low dose dopamine in healthy experimental anaesthetized cats. They received Dopamine at 3 mcg/kg/hr and there was no significant difference in UOP, sodium excretion, HR or creatinine clearance. Only a transient decrease in MAP was noted. In human medicine, dopamine is no longer recommended in the treatment of acute kidney injury and excessive vasoconstriction may worsen renal ischaemic injury.

**Fenoldopam:** Has been shown to be renoprotective in human studies, but is controversial in veterinary medicine due to lack of efficacy in clinical studies. It is a selective dopamine (DA1) receptor agonist, Simmons et al. JVIM 2006 studied the diuretic effects of fenoldopam in healthy cats and showed that at 0.5 mcg/kg/min it induces diuresis in a delayed manner, It was also thought to have the potential to induce positive changes in GFR. Recent clinical studies however by Nielsen et al (JVECC 2015) Segev et al JVIM (2017) have failed to show benefit, Nielsen administered fenoldopam to critically ill small animal patients with AKI 28 dogs and 34 cats received fenoldopam at 0.8 µg/kg/min in dogs and 0.5 µg/kg/min in cats it appeared relatively safe but was not associated with improvement in survival to discharge, length of hospital stay, or an
improvement in renal biochemical parameters when compared to patients with AKI not receiving fenoldopam. It should be noted that more than 2/3 of the patients in the fenoldopam group were euthanised. Nearly ¼ of the cats in the study were also noted to suffer hypotension and currently it is challenging to obtain in some part of the EU. No benefit was again found in in a study of its use in dogs with AKI due to heatstroke by Segev.

Diltiazem had been considered due to its possible effect to reverse renal vasoconstriction and by causing natriuresis. It has been used in human medicine and one veterinary study showed an increase in urine output in dogs suffering from leptospirosis and more rapid reduction in creatinine, however there was no statistically significant effect.

Prognosis
It has been shown that for oliguric cats for each increase per mEq/L in K+ leads to a 57% decrease in survival. Other negative prognostic indicators at diagnosis were decreased albumin and decreased bicarbonate. Importantly in this study and those subsequent to it BUN, creatinine and other variables were NOT prognostic.

There was a 53% overall survival rate, 53% had persistent azotaemia at discharge. Study numbers were small and other studies have shown improved survival rates and if financially viable CRRT or IHD may improve outcomes further improvement could be seen up to 50 days post injury.

Care should also be taken to not only monitor absolute values of sodium but also rapid changes within the reference range. This is due to the risk of Central pontine myelinolysis (osmotic demyelination syndrome) and shifts in intracranial fluid balance as a result of changes in serum osmolality a consequence from rapid loss of free water in the polyuric phase of AKI which once UOP has returned can become extreme.

The aim is to minimise the rate of change to no more than 0.5 mmol/hr or 12 mmol/l in 24 hours. Rapid changes from hyperkalaemia with oliguria/anuria to severe hypokalaemia with polyuria occur. Questions come to CVS Stand 124.

REFERENCES


