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Fluid Therapy in Acute Kidney Injury of Dogs and Cats

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List of abbreviations

ACE angiotensin converting enzyme

AKI acute kidney injury

AMP adenosine monophosphate

ATP adenosine triphosphate

BUN blood urea nitrogen

CBC complete blood count

CKD chronic kidney disease

CRI continuous rate infusion

CRT capillary refill time

CVP central venous pressure

EG ethylene glycol

FFP fresh frozen plasma

GFR glomerular filtration rate

LRS lactated Ringer solution

NSAIDs non steroidal anti inflammatory drugs

PGs prostaglandins

PPIs proton pump inhibitors

PU/PD polyuria/polydipsia

RBF renal blood flow

ROS reactive oxygen species

RRT renal replacement therapy

USG urine specific gravity

UTI urinary tract infection

Introduction

Acute kidney injury (AKI) causes various hemodynamic changes: disturbances in fluid balance, electrolytes and acid-base balance, reduced clearance of toxic waste products. As such, AKI significantly benefits from treatment with fluid therapy. However, some elements in fluid therapy of AKI and in fluid therapy in general, are under debate in veterinary literature. Thus, in this thesis I will review the existing literature of AKI in small animals, its pathophysiology, diagnosis and treatment guidelines. The thesis will highlight fluid therapy guidelines as described in current literature, and discuss the differences between the various approaches to fluid therapy found in veterinary literature. In addition, I will present clinical cases of AKI to show how fluid therapy plays a role in AKI management, and how the recommendations reviewed in the thesis are manifested in the different cases.

1. What is Acute Kidney Injury (AKI): causes and pathophysiology

AKI is by definition a rapid and a potentially reversible state of reduced kidney function, characterized by a sudden increase in blood urea nitrogen concentration (BUN) and/or decreased urine output (oliguria) and reduced glomerular filtration rate (GFR). This results in fluid maintenance problem, electrolyte and acid-base alterations, as well as azotemia. The term AKI has been coined in human medicine and is now being used in most recent veterinary publications instead of its predecessor "ARF- Acute Renal Failure". The new term allows for more explorative room in regards to diagnosis and prognosis, and is better understood by clients [1]. Various causes can lead to AKI, essentially leading to damage in the kidney's functional units, the nephrons. It is emphasized in several publications that the prognosis and outcome of AKI will depend on the cause of injury, thus every attempt to identify the cause should be made [1,2,3]. In general, it can be said that all causes primarily lead to direct damage on tubular cells and ischemia [1].

1.1 Ischemia and Inflammatory Processes as Main Events in AKI

The cause of decreased renal function includes many factors, but the main culprits are *reduced intrarenal blood flow* and *cellular damage*. The kidney is supplied with 20-25% of the cardiac output, thus is very sensitive to ischemia. Mechanisms of blood flow maintenance in the kidney include the decrease in resistance by prostaglandins (vasodilation) on the afferent arteriole and vasoconstriction of the efferent arteriole caused by Angiotensin II. If ischemia continues, vasoconstriction will occur in the afferent arterioles as well, leading to a decrease in GFR and a further decrease in blood flow to the renal tubules. This results in tubular cell damage, desquamation of cells which in turn obstruct the tubular lumen and cause back leak [2]. In more detail, ischemia causes degradation of intracellular adenosine triphosphate (ATP) to adenosine monophosphate (AMP). AMP is further degraded into nucleotides that diffuse out of the cell and this prevents the re-synthesis of ATP. The state of decreased ATP within cells leads to: 1. increased intracellular calcium which in turn may activate proteases and phospholipases which then cause further damage to the cells. 2. Decreased activity of intracellular Na+ K+ ATPase causing a change in concentration gradient and leading to water movement into the cell, subsequently causing cell swelling. This swelling can lead to tubular obstruction. Nitric oxide produced in tubular cells during ischemia, is another factor to note; it can react with superoxide and have a direct oxidative effect on different molecules which can delay the regeneration ability of tubular cells.

Once cell integrity is damaged and structural changes occur in the cells, altered solutes handling takes place. Cells lose their microvilli and polarity. Na+ K+ ATPase lose their location on the basolateral cell membrane and transferred to the apical cell membrane. Tight junctions are lost and cell debris and desquamations occurs, potentially leading to back leak and tubular obstruction [3].

Inflammation also plays its part in the onset of AKI. Neutrophil granulocytes release inflammatory mediators, proteases and cytokines which worsen the initial inflammatory response. Neutrophil infiltration into the interstitium damages tubular cell integrity in addition to accumulation in blood capillaries in a tissue that is already hypoxic. Both necrosis and apoptosis occur in AKI, necrosis happens due to ischemia and elicits an inflammatory reaction. Apoptosis occurs when there is a less severe injury. Different causes of injury may lead to either one [3].

The changes in cellular structure are illustrated in the image 1.

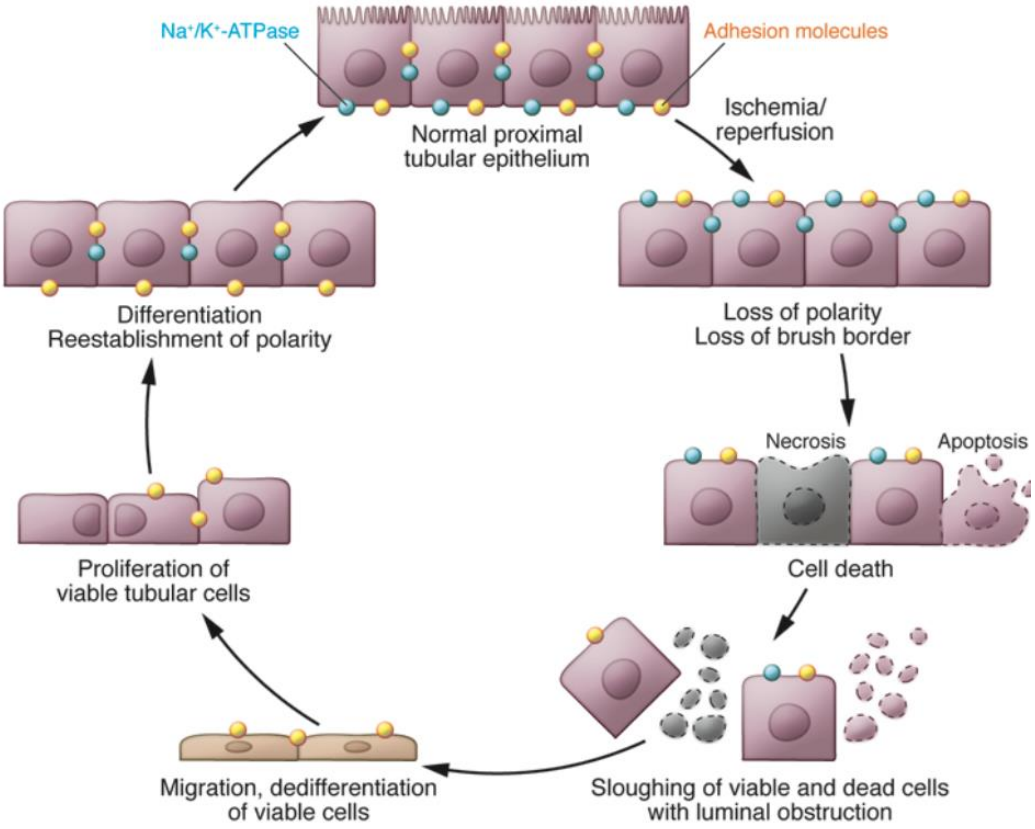


Image 1: borrowed from Joseph V. Bonventre and Li Yang's "Cellular Pathophysiology of Ischemic Acute Kidney Injury" 2011 [5].

1.2 The phases of AKI

AKI can be described in 4 clinical phases; initiation phase, extension phase, maintenance phase and recovery phase. The *initiation phase* (also known as the *latent* phase) describes the time from the initial insult by toxins or ischemia and until there is a noticeable change in renal function. This phase can be variable in duration depending on the cause and severity of the injury. This phase is not detected because clinical signs are absent or minimal. At this phase, an early action may prevent the progression of the injury. The *extension phase* follows if the cause is not removed. At this phase, hypoxia and inflammatory responses to the initial insult facilitate further damage and cellular structural changes previously described (see 1.1). The structures that are most sensitive to ischemic and toxic insults are the proximal tubules and loop of Henle. This is because these structures are highly metabolic and require a significant percentage of the renal blood flow. The third phase is the *maintenance phase.* This phase describes the time when a significant injury has occurred. 1-3 weeks of treatment will be required before restoration can occur. If the cause is removed at this phase, it will not lead to a fast return of normal function. Anuria, oliguria (<0.5 ml urine/kg/hour), normal urine production or polyuria are possible depending on the cause and severity. Anuria and Oliguria are observed in patients with most severe injuries, while normal urine output or polyuria are seen in patients with aminoglycosides nephrotoxicity. There can be a persistent increase in serum creatinine despite correction attempts and the patient may not survive this phase. The *recovery phase* describes GFR and RBF recovery, the return of diuresis and the decrease of BUN and creatinine. Partial repair of renal tubules leads to polyuria due to the concentration of solutes. Polyuria is typical clinical sign of the recovery phase. At this phase, there is still a reduction in the number of functional tubules and sodium transporters, which can lead to sodium loss and consequently volume depletion. This can interfere with renal recovery and cause a delay in regeneration. Restoration may lead to complete recovery, or remain partial. Restoration may be partial and lead to chronic kidney disease (CKD), especially in injuries with long lasting hypoxia due to injury of peritubular microcapillaries and chronic activation of immune cells and immune mediators. All these may contribute to post-ischemic fibrosis which results in CKD (illustrated in image 2) [2, 3, 4, 5].

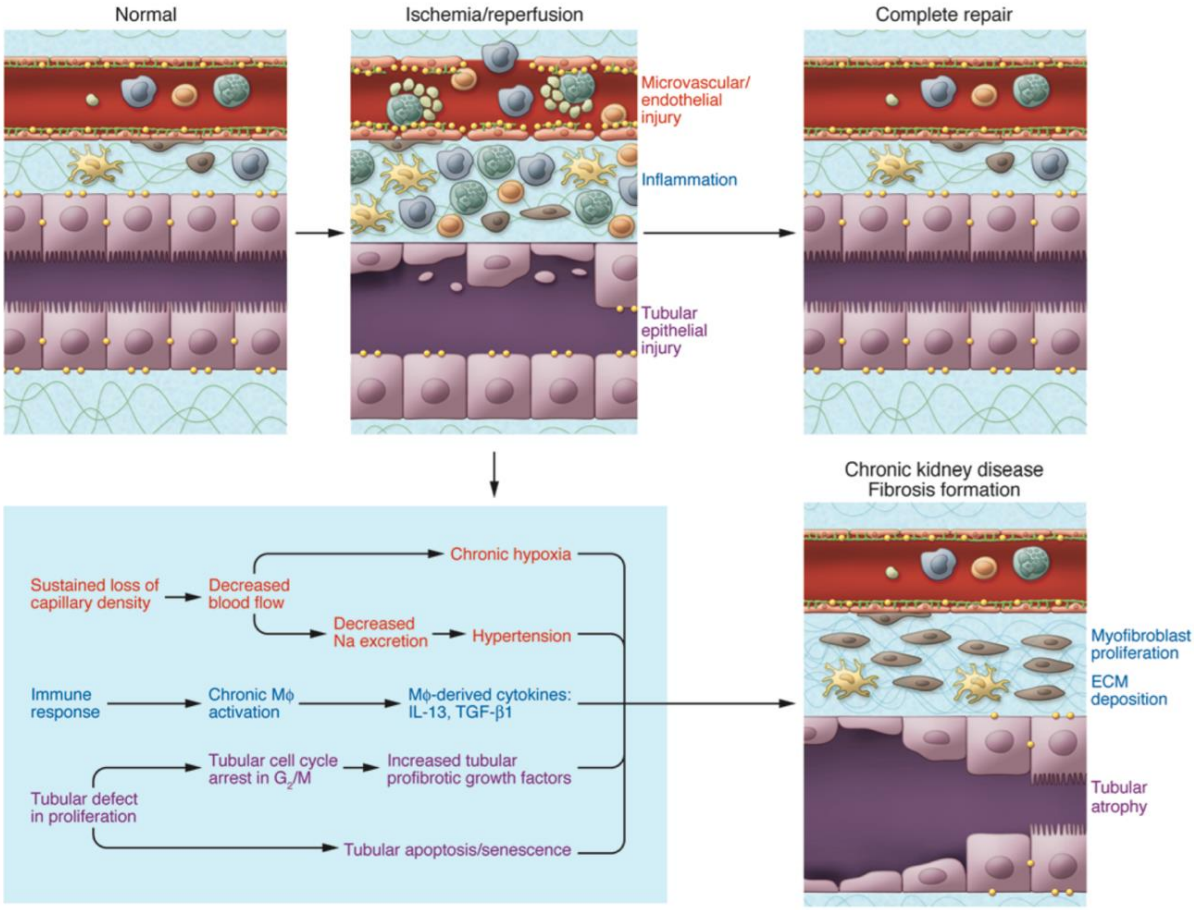


Image 2: borrowed from Joseph V. Bonventre and Li Yang's "Cellular Pathophysiology of Ischemic Acute Kidney Injury" 2011 [5].

1.3 Causes of AKI

The potential causes for AKI are traditionally classified into three main locations; prerenal, (intrinsic) renal and post renal. Recently it has been suggested that the term 'volume-responsive' or 'hemodynamic' azotemia should be used instead of 'prerenal' [4].

Table 1: Causes of AKI [3]

Prerenal / Volume-Responsive: blood perfusion to the kidney is reduced	
Infarction/ thromboembolism	
Hypovolemia: blood loss, burns, severe diarrhea and vomitus, dehydration	
Reduced cardiac output: heart failure, septic shock, hypovolemia, hypotension	
Renal: injury initiated in the kidney due to nephrotoxins or an infectious cause, leading to ischemia, infarction, glomerulonephritis, vasculitis, acute tubular necrosis	
Lily plants (only in cats)	Mannitol
Envenomation	Vitamin D
Grapes, raisins (only in dogs)	Melamine, cyanuric acid
Ethylene glycol	Hypercalcemia
Heavy metals	Pigmenturia, hemoglobinuria/myoglobinuria
Radiographic contrast agents	Pyelonephritis
Aminoglycosides	Feline infectious peritonitis
Doxorubicin	Leptospira (only in dogs)
Amphotericin B	Borrelia
NSAIDs	
Post renal: damage to the kidney due to urine flow obstructions	
Calculi	
FLUTD	
Mucous plug/ dried solidified blood	
Tumors (lymphoma, adenocarcinoma, sarcoma, nephroblastoma, TCC)	
Blood clots	
Urethral / ureteral strictures	

1.3.1 Volume-Responsive Azotemia

Volume responsive azotemia is a term used to better describe prerenal azotemia; namely, any process that causes decreased RBF (as listed in Table 1). Reduced RBF essentially prevents clearance of waste products and solutes. This is characterized by increased BUN, creatinine and a concentrated urine specific gravity (USG). Volume-responsive azotemia, as the term itself suggests, can be corrected by fluid therapy and will be reversed by replacement of fluid deficits and stabilization of mean arterial pressure > 80 mmHg. If the underlying cause for decreased RBF is not treated, this state can progress to volume-nonresponsive azotemia [4].

1.3.2 NSAIDs

In healthy patients without pre-existing renal conditions, NSAIDs will not cause AKI. But in patients with an existing state of reduced blood flow, NSAIDs will exaggerate that state by blocking prostaglandins E_2 and I_2 production [1]. These PGs are meant to function as vasodilators in order to maintain the renal blood flow. In the absence of these prostaglandins, an ischemic state can develop. During renal ischemia, vasoconstriction occurs in the renal cortex. If ischemia is severe or prolonged, tubules with high metabolic activity are in more risk of injury [2]. Excessive use of NSAIDs may also cause gastrointestinal signs and AKI may only be apparent 3-5 days later. All NSAIDs should be used with caution in risk patients, as they all pose a risk to the maintenance of normal RBF [1].

1.3.3 Ethylene Glycol

Ethylene Glycol is a highly nephrotoxic substance found in antifreeze. This substance is used not only in car radiators and different thermal units, but also in paints, decorative snow globes and other stationary supplies. Stationary supplies may contain only a few milliliters of EG containing fluid, but the EG is in high concentration and can pose a risk to cats or kittens, as cats are twice more sensitive to EG than dogs. Toxic does of pure EG in cats is 0.5- 2.5ml/kg, where the lower value results in ataxia and lethargy that may be resolved with no further effects and return to normalcy in 48 hours, and the high value of 2.5ml/kg may result in coma followed by death within 36 hours [6]. The minimal lethal dose of pure EG is is 6.6 ml/kg in dogs, and 1.5 ml/kg in cats [7]. It is commonly believed that animals choose to lick EG due to its sweet taste, however in a study that was conducted on 50 rats and 4 dogs, water containing EG in different concentration were only ingested in a water deprived state of the animals, and the water containing the lowest concentration of EG were mostly chosen [7]. It is most likely that dogs and cats ingest EG after chewing through an object, a spill, or licking their fur after walking through a spill. EG is a gastrointestinal irritant, causes depression of the CNS and diuresis, and is not as toxic in its original form. Its metabolites are the ones responsible for the systemic toxic effects. After ingestion, EG is absorbed fast from the stomach and within 1 hour reaches peak level of concentration in the blood. In the liver, EG is metabolized by alcohol dehydrogenase into glycoaldehyde, glycolate, glyoxylate and oxalate: these metabolites are the cause of severe metabolic acidosis, and are directly harmful for tubular epithelium, in addition to the calcium oxalate crystals deposition in tubular lumen and interstitium [7].

1.3.4 Aminoglycosides

Aminoglycosides are the most well known antibacterial group to cause renal damage. They bind to the brush border of tubular cells where they are endocytosed. They accumulate in intracellular lysosomes until those rupture and induce cellular damage and tubular necrosis. Thus, aminoglycosides should not be used in risk patients. In non risk patients, they should be used alongside hydration and volume resuscitation, one time daily for no more than 5-7 days, in order to avoid accumulation in lysosomes and prevent tubular cell injury. In addition, a urine analysis prior and during the treatment with aminoglycosides should be made, so that treatment can be stopped if casts are found in the urine [1].

1.3.5 Lily Plants

All Lilies (*Lilium*) and Daylilies (*Hemerocallies*) are considered toxic to cats. Although the dose and compound are still unknown, the compound is known to be water soluble. The flower is more toxic than other parts of the plant, but every part of the plant should be considered toxic. The lily toxins elicit diffuse tubular necrosis, proximal tubular cell injury, desquamation, debris and severe azotemia. An early urinalysis will show isosthenuria, glucosuria, proteinuria and casts prior to a clinically noticeable azotemia [1].

1.3.6 Leptospirosis in Dogs

Leptospirosis is a zoonotic disease caused by *Leptospira* genus. There are at least 10 Leptospira serovars that are important for pets and can induce diseases in the kidneys, liver or lungs. The route of infection is through skin abrasion/cut contact with contaminated urine, or urine-contaminated water [8]. After incubation and hematogenous spread, it is enough that a small amount of bacteria reaches the kidneys. There, the organisms attach to the luminal side of the tubular epithelial cells and replicate already at 10-days post infection [9]. The bacteria's attachment to the cells causes a cellular increase in reactive oxygen species (ROS). Increased oxidative stress intracellularly, in turn leads to apoptosis of tubular cells [10].

1.4 Prognosis of AKI

The prognosis of AKI depends greatly on the etiology of the disease, making the cause a prognostic factor. Additionally, access to dialysis in severe cases is also a factor that can affect the outcome, because 40-60% of AKI patients that are treated with hemodialysis survive. In the case of cats with nephrotoxic AKI, one study showed a 50% survival rate, and a 75% survival rate for cats with ischemia. In other studies, the survival rate for AKI of infectious origin was 58-100%, while only 20-40% of patients with toxic AKI survived. Many factors were studied to evaluate whether they can be associated with mortality; the

severity of azotemia is not predictive, whereas decreased urine output suggests poor prognosis. In another study, an increase of serum potassium was found to be associated with decreased survival (57% decrease in survival rate for each unit of increase potassium). Another study showed that lower body temperature, serum albumin and lactate dehydrogenase are factors that predict mortality. It can be said that the mortality of both hospital-acquired and community-acquired AKI is generally high [4].

Table 2: Survival Rates by Etiology [4]

Etiology	Nondialytic Therapy	Hemodialysis
Obstructive	91%	70-75%
Infectious	82%	58-86%
Hemodynamic	66%	56-72%
Other	50%	29-56%
Toxic	43-69%	18-35%

2. How is AKI diagnosed

As was mentioned in the previous chapter, prompt diagnosis is crucial for the treatment of AKI. Clinical signs may not be seen at early stages but they can escalate quickly. The treatment plan will depend on the cause of injury thus the focus of diagnosis should be finding the underlying cause, the severity of the disease and the state of the patient. This

chapter will discuss the staging schemes and other important points in establishing a diagnosis.

2.1 Establishing a Diagnosis

2.1.1 History

History should be obtained from the owner. The owner may say that the patient is lethargic, vomiting, inappetent and may or may not have noticed reduction in urine output. The time course depends on the cause of injury, but the owner may only notice changes in behavior when BUN elevation has been significant enough to cause the above mentioned signs, and when urine output is reduced. In EG toxicosis the first clinical signs (ataxia, depression, vomiting) can appear very quickly after ingestion (30 minutes to some hours). It is important to ask the owner regarding any previous treatments. Recent trauma, shock, surgery, or general anesthesia suggest ischemia. Medication history, as well as possible exposure to toxins (such as chemotherapy or prolonged use of cox-inhibitors, lily plants in cats) should also be investigated [2].

2.1.2 Physical Examination Findings

In clinical presentation, animals with AKI commonly show after several days to a week of inappetence, lethargy, nausea, vomiting, diarrhea, PU/PD, oliguria/anuria and weakness. Thus the clinical signs can be variable and they include dehydration or overhydration in oliguric patients who received intravenous fluids, uremic breath and oral ulceration- if azotemia is severe and has been present for some days already. Melena suggests gastrointestinal ulceration, and pale mucous membranes due to anemia that may be present, but not at early stage. During abdominal palpation, abdominal pain may suggest renal pain, the kidneys may be normal or enlarged and painful. Urinary bladder size may suggest obstruction or hint towards urine output. Bradycardia can be a sign of hyperkalemia and other electrolytes imbalance, while fever can point towards an infectious AKI. Body condition is generally good, except in patients with preexisting chronic conditions. In EG toxicosis, if a patient arrives at early stages, central nervous system signs may be noticeable [2,4].

2.1.3 Assessment of Hydration Status

The well assessed hydration status is a crucial point before starting fluid therapy. Dehydration: less than 5% fluid deficit is clinically undetectable, 5-6% leads to sticky mucous membranes while 6-8% leads to dry mucous membranes and decreased skin

elasticity. When evaluating mucosal membranes, we have to keep in mind that xerostomia can be caused by uremia as well, unrelated to hydration status. 8-10% deficit will present with sunken eyes, prolonged CRT, tachycardia and weak pulse. Over 12% deficit is already life threatening - with dull mentation, dry cornea, impaired perfusion.

The signs of overhydration include wet mucous membranes, increased skin elasticity (heavy or gelatinous), shivering, nausea, vomiting, restlessness, serous nasal discharge, edema, tachypnea, cough, dyspnea, pulmonary crackles and edema, pleural effusion, ascites, diarrhea, or subcutaneous edema (especially hock joints and intermandibular space). Hypoalbuminemia and vasculitis can cause interstitial fluid accumulation despite an intravascular volume deficit. Thus dehydration may be present but these manifestations can make it challenging to asses. Emaciating or geriatric patients may also present decreased skin elasticity [11].

2.1.4 Blood Evaluation

Blood evaluation should include a Complete Blood Count (CBC) and biochemistry, where findings may include anemia if gastrointestinal ulcers are present and cause blood loss. Leukocytosis may indicate infectious AKI. BUN and creatinine may be elevated or progressively rising. AKI should not be ruled out if azotemia is not present. The evaluation should also include an assessment of acid-base status, and evaluation of electrolytes imbalance and hydration status. The findings may reveal metabolic acidosis, hypo/hyperkalemia, increased phosphate and hypocalcemia [2,4].

It is important not to take blood from the jugular vein, if hemodialysis would be an option at any point of worsening, and especially before having a full picture on the state of the patient. This area should be preserved for the dialysis catheter [3].

2.1.5 Urine Evaluation

Urinalysis is important in the diagnosis of AKI, together with blood evaluation and clinical signs it can confirm some of the suspicions. Urinalysis may reveal isosthenuria, or low concentration in urine specific gravity (USG). Proteinuria, hematuria, glucosuria and casts may also be found. Casts are cylindrical in shape and are molded by the shape of the renal tubules, they are formed in the ascending loop of Henle and distal tubules due to high acidity, high concentration of solutes and very low renal flow. They are composed of proteins and cells, and they indicate an injury to the kidney. Hyaline and granular casts can be an occasional, isolated yet normal finding but if found higher in number, they are considered abnormal. Granular casts (image 4) represent cell degeneration and when found in urine

sediment it can suggest ischemic or nephrotoxic tubular injury. Cellular casts (image 3) should never be found in normal urine, these include red or white blood cells and renal epithelial cells. Renal epithelial cells suggest tubular necrosis or pyelonephritis [12]. Calcium oxalates can be found in case of EG toxicosis (images 7 and 8). Urine culture is necessary if bacteria are present, in order to explore the possibility of infectious pyelonephritis and for an accurate choice of antibiotics [4,12]. Assessment of urine output should be made as well, to check whether the patient is oliguric, anuric or is producing normal urine output. However, this assessment can only be made after hydration deficits have been sufficiently restored [1,2,3].

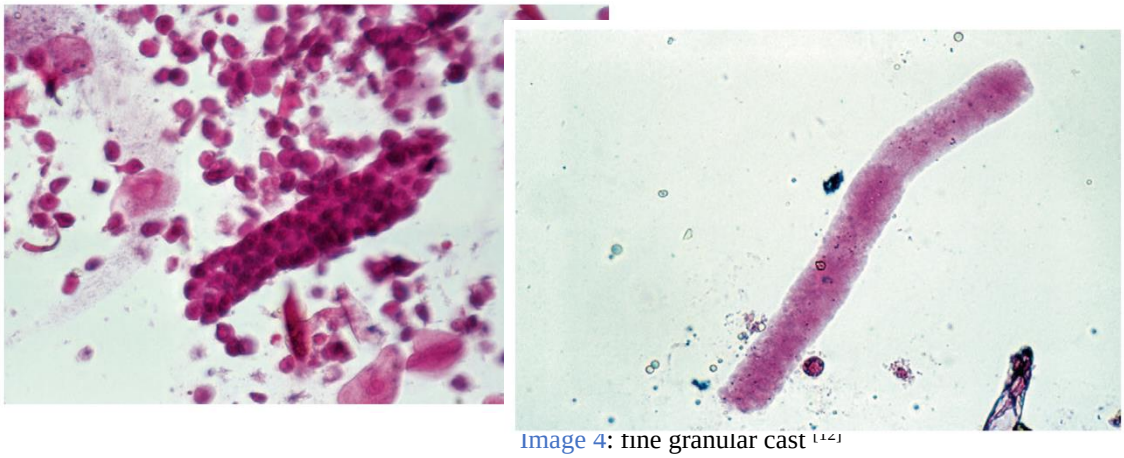


Image 4: fine granular cast [12]

2.1.6 Imaging

Radiography can help evaluate the size of kidneys, the urinary bladder and presence of uroliths [3,4]. Normal length of kidneys is measured on the ventrodorsal view; 2.5 to 3.5 times the length of the second lumber vertebra in dogs and 2 to 3 times, in cats [3]. Ultrasonography allows a more accurate measurement of kidneys, the kidneys' echogenicity and presence of masses, cysts or uroliths, signs of pyelonephritis. In pyelonephritis, renal pelvic size increases and a diffuse thickening of the cortex may be visible [3]. In AKI, increased cortical or medullary echogenicity is possible. Normal ultrasonographic findings do not exclude

AKI [2].

2.1.7 Renal Biopsy

Renal biopsy can be used to confirm that azotemia is of renal origin and can help in characterization of the lesions as acute/chronic. Findings include tubular degeneration, tubular necrosis and intratubular casts. Intact tubular basement membranes with evidence of tubular regeneration is a good prognostic sign while disrupted basement membranes suggest a worse prognosis. Absence of fibrosis is a good supportive evidence that rules out CKD [2]. However, in patients with AKI, this diagnostic option is not commonly used, it is more likely to be used if there is a suspicion of neoplasia (and in that case, fine needle aspiration may also be enough) [1].

2.1.8 Tests for Infectious Causes [4]

- Leptospirosos (serology -microagglutination test, PCR – blood, urine)
- Babesiosis (microscopic blood smear evaluation, PCR – blood)
- Lyme borreliosis (serology test)
- Ehrlichiosis, Anaplasmosis (serology test)
- Dirofilariosis (D. immitis, Knott, PCR, serology test)

2.1.9 Findings in Ethylene Glycol Toxicosis

In case of EG toxicosis, an abdominal ultrasound examination may show renal hyperechogenicity attributed to calcium oxalate crystals [2]. The urine will be minimally concentrated or isosthenuric within 3 hours from ingestion, with an acidic pH. Calcium oxalate crystalluria can be observed within 3 hours in cats and 6 hours in dogs, where monohydrate calcium oxalate crystals (image 7) are more abundant than calcium oxalate dihydrate crystals (image 8). EG detection in urine is possible 1-2 hours after ingestion. Blood and acid-base examination will reveal a normochloremic metabolic acidosis with an increased anion gap, within 3 hours of ingestion of EG. Serum osmolality can be 100 mOsm/kg above normal (280–310 mOsm/kg). Hyperglycemia is possible due to stress and inhibition of glucose metabolism by EG metabolites. EG is detectable in blood 1-2 hours after ingestion, commercial test kits are available in some countries and can detect EG concentration ≥50 mg/dL [1,14].

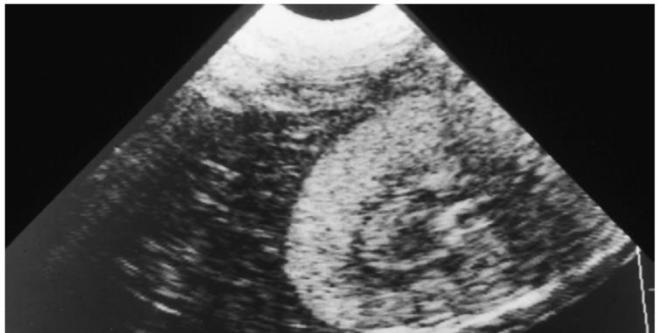


Image 5: hyperechoic renal cortex in EG poisoning, dog [2]

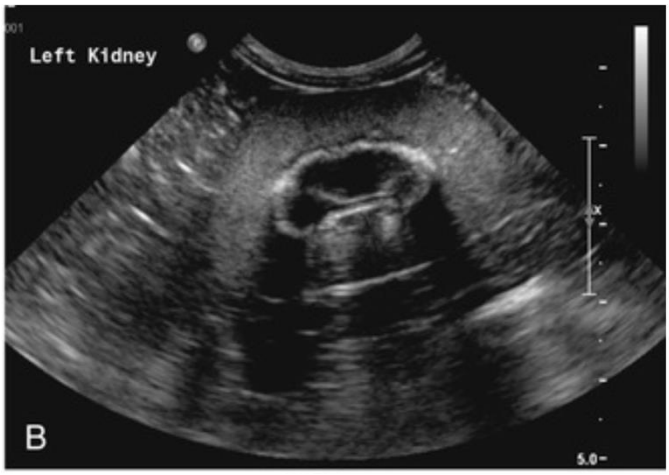


Image 6: hyperechoic medullary rim in EG poisoning, dog [13]

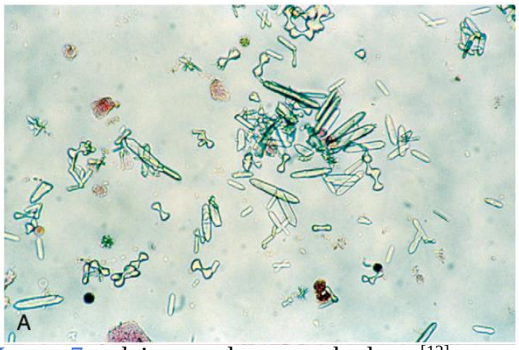


Image 7: calcium oxalate monohydrate [12]

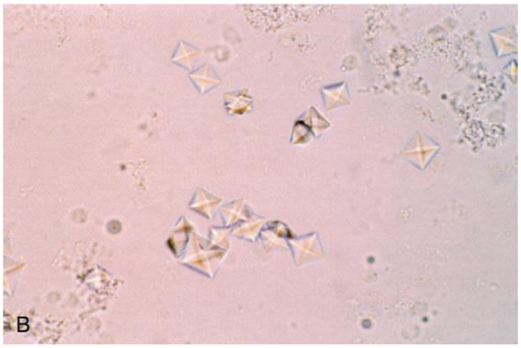


Image 8: calcium oxalate dihydrate [12]

2.1.10 Differentiation between Volume-Responsive Azotemia and AKI

As was mentioned in chapter 1, volume-responsive azotemia is caused by various hemodynamic alterations that lead to reduced RBF. If left untreated, the prolonged state of reduced RBF may lead to ischemic AKI. This means that in a state of volume-responsive azotemia, kidney functions remain normal; urine output will be decreased, but the kidneys will clear creatinine and will be able to retain chloride and sodium as there is no injury to tubular cells yet. USG in volume-responsive azotemia thus will be increased, whereas in AKI isosthenuria is expected [3].

Table 3: Selected Urinary Parameters in Volume-Responsive Azotemia and AKI [3]

Test	Volume-Responsive Azotemia	AKI
Urine sodium	<20 mEq/L	>40 mEq/L
Urine chloride	<20 mEq/L	>40 mEq/L
Urine creatinine/plasma creatinine	>40	<20
Fractional excretion of sodium	<1%	>2%
USG	increased	isosthenuria

2.2 Grading [15]

The International Renal Interest Society (IRIS) has established guidelines for the grading of AKI. The grading system describes five stages that are based on fasting blood creatinine and urine output (see Table 4). The purpose of grading is to pinpoint changes in the course of the disease, whether the condition is worsening, improving, or changing into CKD. Grade I: non azotemic, with historical/ clinical/ imaging findings of AKI and/or oliguria/anuria. This grade includes animals with a progressive increase in blood creatinine ≥ 0.3 mg/dl or ≥ 26.4 µmol/l but still within the non azotemic range in 48 hours. This grade also includes animals who are fluid responsive and present >1ml/kg/h of urine over 6 hours of treatment, and/or decreased creatinine to baseline concentration within 48 hours. Grade II: this grade includes the same definitions of Grade I, in addition to mild azotemia. This grade also includes patients with a pre-existing CKD whose creatinine ≥ 0.3 mg/dl or ≥ 26.4 µmol/l from their baseline concentration.

Grade III, IV, V: animals with documented AKI and progressively greater degrees of parenchymal damage and functional failure.

Subgrade: each grade of AKI is further subgraded based on urine output. O- oliguria <1 ml/kg/hr, Anuria, NO- nonoliguric >1ml/kg/h. Subgrading can also include the requirement of renal replacement therapy.

Table 4: IRIS AKI grading criteria [15]

AKI GRADE	Blood Creatinine
Grade I	<1.6 mg/dl or <140 µmol/l

Grade II	1.7-2.5 mg/dl or 141-220 μmol/l
Grade III	2.6-5.0 mg/dl or 221-439 μmol/l
Grade IV	5.1-10.0 mg/dl or 440-880 μmol/l
Grade V	>10.0 mg/dl or >880 μmol/l

3. AKI Treatment

The main goals of the treatment should be to correct acid-base and electrolyte imbalances, to restore fluid household, to promote diuresis, to remove toxic waste products from the blood and to give supportive treatment to secondary injuries (for e.g. ulcers and nausea). The treatment should be initiated as soon as possible while searching for the underlying cause. The patient must be intensively monitored for any changes in order to avoid complications (such as fluid overload). Conservative treatment consists of fluid therapy (including corrections of acid-base and electrolyte changes), diuretics, gastroprotection, antiemetics, management of hypertension and nutritional support. Disease specific treatment can be applied in some cases e.g. leptospirosis, EG toxicosis. When conservative and disease specific treatment are insufficient, renal replacement therapy should be started.

Fluid therapy is a significant part of the treatment due to the nature of the kidneys physiology; fluid therapy is needed in order to restore losses, expand volume, induce diuresis and thus remove some of the toxins, correct acid-base and electrolyte imbalance, essentially aiming to resolve most of the disorders caused by AKI. Due to its significance, the topic of Fluid Therapy will be discussed later in two chapters, while this chapter will discuss other aspects of AKI treatment. Fluid overload, hypertension and the use of diuretics will also be discussed in later chapters dedicated to fluid therapy, due to its relevance and proximity to the topic.

3.1 Gastroprotection

Gastrointestinal complications are common in AKI patients, and they are mostly associated with uremia. The kidneys also take part in elimination of gastrin (stimulator of gastric acid secretion), thus a patient with AKI faces hypergastrinemia, which leads to gastric ulceration and inflammation [1].

To treat and prevent ulceration and hyperacidity, proton pump inhibitors (PPIs) should be the first choice of treatment. PPIs are more efficient than H_2-blockers in increasing the gastric pH, preventing gastric ulcers and promoting their healing process [16]. Omperazole can be used at 0.7 mg/kg q 24h PO, or lansoprazole at 0.6–1.0 mg/kg q 24h IV [3].

Therapy with H_2-blockers such as famotidine, cimetidine or ranitidine can also be used (famotidine at 0.5–1.0 mg/kg q 24h). In severe cases, sucralfate can be used for mucosal protection in addition to the abovementioned can complement this therapy.

3.2 Antiemetics

Due to decreased renal function, uremic toxins accumulate and stimulate peripheral and central receptors that trigger nausea. Thus, patients suffering from AKI suffer from nausea and vomiting. To treat this, antiemetics can be used; maropitant (1 mg/kg SC or IV q 24h, or PO 2mg/kg q 24h) and ondansetron (0.5-1mg/kg PO/IV q 12h) are very effective in decreasing vomiting and nausea [1]. Metoclopramide continuous rate infusion (CRI) of 1–2 mg/kg/day is also an option. It should not be given with concurrent dopamine use, as it is a dopamine antagonist [17].

3.3 Nutrition

The goals of nutritional therapy are to meet the energy and nutrient requirements of the animal, correct protein-energy wasting, alleviate the azotemia, minimize disturbances in

fluid, electrolyte, vitamin, mineral, and acid base balance, and aid renal regeneration and repair. There is no evidence which diet is best for AKI patients. Johnson recommends for the patients who eat voluntarily a low-protein, carbohydrate-rich diet (e.g. renal or hepatic veterinary diets) [17], other authors recommend diets made for critically ill patients with high caloric content. Animals with AKI that are anorexic are at risk of becoming malnourished if the lack of food intake persists beyond several days, as AKI is a highly catabolic state. Enteral tube feeding is the preferred route of nutritional support and is recommended in animals whose gastrointestinal health will tolerate feeding but fail to meet nutritional goals voluntarily. Esophageal feeding tubes are the most effective and safe enteral feeding device and generally are preferred over nasoesophageal or percutaneous gastrostomy tubes. Esophageal feeding tubes can be placed quickly under short general anesthesia and facilitate either short-term or indefinite feeding for dogs or cats with
AKI [18]. In patients who are anuric or oliguric, the volume instilled, whether enterally or parenterally, must be taken into consideration [11]. Appetite stimulants can also be used; mirtazapine at 1.87mg/cat PO q 48 hours, 3.75-30mg/dog PO q 24 hours can make a significant change on appetite in addition to its antiemetic effect [19, 20].

3.4 Treatment of Ethylene Glycol Toxicosis

Treatment of EG toxicosis may include ethanol, fomepizole and/or dialysis with intensive fluid therapy and additional supportive therapy [1,21].

Ethanol is one of the oldest methods. The enzyme that metabolizes both ethanol and EG has higher affinity to ethanol, thus by administering ethanol, alcohol dehydrogenase will be occupied and the metabolism of EG will be prevented [1]. 20% ethanol is given 9 times intravenously (5.5 ml/kg every 4 hours 5 times, then the same dose every 6 hours 4 times). Treatment with ethanol has the disadvantage of causing CNS depression, sedation, bradycardia, hypoventilation, metabolic acidosis, hypothermia and hypoglycemia. Ethanol is not the proffered treatment for EG toxicosis but is in some case the more accessible and affordable option.

Fomepizole is an alcohol dehydrogenase blocker, and its usage is preferred over ethanol treatment. However, it is an expensive option, and its usage is time limited. In dogs, the time frame that allows the efficiency of fomepizole is within 8-12 hours of exposure, while in cats, only within 3 hours of exposure. Thus, if fomepizole is not available or the time frame has been missed, ethanol can be used. If the patient has already developed azotemia, dialysis should be employed otherwise the prognosis is very poor [21]. Fomepizole treatment for dogs should start with 20mg/kg IV, followed by 15mg/kg IV at 12 and 24 hours from the initial

dose, followed by additional 5mg/kg IV at 36 hours. 3mg/kg IV q 12 hours can be continued until clinical signs and metabolic acidosis subside. Fomepizole treatment for cats should start with 125mg/kg IV, followed by 31.3mg/kg IV at 12, 24 and 36 hours after the initial dose [21].

3.5 Treatment of Leptospirosis

In addition to supportive treatment of clinical signs, the current recommendation for the treatment of leptospirosis is doxycycline. Doxycycline can clear the organism from the blood and organs. The dosage for dogs is 5mg/kg PO q 12 hours or 10mg/kg PO q 24 hours for 14 days. If doxycycline is not tolerated due to gastrointestinal signs, it is recommended to start the treatment with penicillin or penicillin derivatives until it can be replaced with doxycycline. Long term monitoring is required for dogs who survive the acute phase, because renal damage and decreased renal function may appear during the first year and sometimes longer than a year after discharge from the hospital [22].

3.6 Renal Replacement Therapy (RRT): Hemodialysis and Peritoneal Dialysis

Renal Replacement Therapy is used to when it is necessary to artificially remove toxins from the blood. The kidneys are responsible for many crucial activities such as acid base balance, electrolyte balance, disposal of waste products, fluid maintenance, hormone production and maintenance of blood pressure together with other organ systems. As such, many conditions can benefit from RRT [23]. In veterinary medicine, dialysis has been primarily used to treat patients with AKI, CKD, poisonings, drug overdose or fluid overload. The use of RRT allows to treat many of the problems caused by AKI while buying time for the return of kidney function [4, 24]. There are two main routes of dialysis; Hemodialysis is a form of blood purification using *external filters*, while Peritoneal Dialysis (PD) is based on *the patient's own peritoneum* function as a semipermeable membrane [4].

3.6.1 Hemodialysis

The most important part of the hemodialysis machine and the part which essentially functions as an artificial kidney, is the dialyzer. This is the part that functions as an external filter. The dialyzer is comprised of thousands of straw-like semi-permeable membranes. Blood will flow through a venous catheter from the body, through the dialyzer. There are two ways through which the blood can be purified and balanced in the dialyzer: diffusion and convection. During diffusion, the membranes are found in a fluid called dialysate. This fluid contains very low amounts of waste molecules, to ensure these solutes will diffuse from

the blood through the membrane based on concentration gradient principle (solutes move from high concentration to low concentration). In the same way, beneficial substances like bicarbonate are found in higher concentration in the dialysate, ensuring their movement across the membrane and into the blood. The dialysate is discarded and the purified, corrected blood is returned to the patient. Convection is based on pore size of the membranes through which certain particles can pass through. Small blood constituents such as uremic toxins, electrolytes and excess fluid are filtered through the pores while vital blood constituents such as blood cells, are unable to pass through this pore size. The ultrafiltrate is discarded and a sterile, balanced electrolyte solution is then added to the blood to replace what has been lost with the ultrafiltrate, and the blood can be returned to the body [4, 24].

3.6.2 Peritoneal Dialysis

This method is based on the peritoneum as the filtering membrane. The abdomen can be filled with the dialysate through an abdominal catheter, and as result of diffusion, waste molecules will pass from the blood across the peritoneum into the dialysate. This ultrafiltrate is then drained and discarded, and the abdomen can be refilled with fresh dialysate to repeat the process until urine production and renal function are adequate [25]. PD has the advantage of being a straight forward, simple method of blood purification without the need of additional expensive equipment and equipment maintenance. Once the patient's condition improves, if the patient is stable and no longer requires intensive care and monitoring, the patient can be sent home with supportive medication, and the owners can be trained to perform the PD refill and drainage. It requires the owner's cooperation and willingness, as it may be required several times a day before it can be gradually reduced (if the patient's condition improves).

4. Fluid Therapy – General

Fluid therapy is a cornerstone in veterinary medicine and particularly in AKI. Many conditions and medical situations can benefit from the use of fluid therapy administration such as hypotension, dehydration, electrolytes and acid base imbalance, promoting urine output and maintenance fluid homeostasis in sick and hospitalized patients. It is also a useful route for drug administration in patients that are hospitalized or undergoing a surgical procedure. Because of the expansive usage of fluid therapy, it is fundamental to understand and consider the role of fluids and the consequences of disturbances in fluid volume, content and distribution.

4.1 Fluid Distribution and Fluid Loss

Fluids in the body are distributed over two main compartments; 2/3 in the intracellular compartment and 1/3 in the extracellular compartment. Of the extracellular volume, 3/4 of the fluid is in interstitial tissue, and 1/4 is in the intravascular space. Body fluids move back and forth between these compartments via semipermeable cell membranes [26]. The forces that are responsible for water movement between compartments are: 1. hydrostatic pressure

which is provided by the heart and the vascular tone, 2. oncotic pressure which is opposed to hydrostatic pressure and is created by plasma proteins and 3. osmotic pressure provided by blood solutes [27]. Fluids can be depleted from the body due to excessive loss or decreased intake. Intravascular fluid depletion results in decreased perfusion, tissue hypoxia and consequently decreased clearance of toxic waste products. Extravascular fluid depletion results in clinical signs of dehydration [28]. The terms hypo/hypervolemia and dehydration also refer to volume loss in the different compartment; hypo/hypervolemia refer to volume decrease/increase in the intravascular space, while dehydration refers to whole body fluid loss. In a healthy patient, fluid loss occurs through urine and fecal excretion, respiration, panting and sweat (in some species). Abnormal losses can happen as result of vomiting, diarrhea, polyuria, blood loss, ascites and effusions [30]. Fluid loss can be labeled as sensible or insensible loss, namely measurable and not measurable losses. Fluid lost through urine for example is a sensible loss, while fluid lost through respiration and through the skin are insensible [29].

4.2 Distribution of Solutes

Body fluids contain different solute concentrations, that are not distributed homogenously in body fluids. This is due to variations in permeability of cell membranes to different solutes throughout the body. Thus intracellular solute concentrations differ greatly form the extracellular solute concentrations. The concentration of solutes and the number of osmotically active particles in the different compartments greatly affect the distribution of fluids intra and extracellularly [26]. It is thus important to take into account the status of electrolytes and other molecules taking part in homeostasis (such as chloride and bicarbonate) when planning fluid therapy. Different states and imbalance in the different electrolytes will require different choice of fluid solution and at times different administration rates.

Table 5: Plasma Concentrations of Electrolytes in Dogs and Cats [26]

Substance	Units	Dog	Cat
Sodium	mEq/L	145	155
Potassium	mEq/L	4	4
Total Calcium	mg/dL	10	9
Total magnesium	mg/dL	3	2.5
Chloride	mEq/L	110	120

Bicarbonate	mEq/L	21	20
Phosphate	mg/dL	4	4
Proteins	g/dL	7	7
Lactate	mg/dL	15	15

4.3 Types of Fluids

4.3.1 Crystalloids

This category refers to solutions that are water based and contain electrolytes and other solutes. Fluid types in this category are able to enter all water compartments and are the most commonly used in veterinary medicine as maintenance fluids. They are fit for restoration of intravascular volume as well as in shock, interstitial fluid losses and in dehydration. Crystalloids can be further subcategorized as hypotonic, isotonic and hypertonic solutions. Isotonic crystalloids are known as *replacement fluids*, as their sodium concentration is similar to that of plasma (140 mmol/l). These are classified as acidifying, like normal saline or buffering, like Ringer Lactate or Normosol-R. Saline is considered as acidifying due high chloride concentration and lack of buffering solutes [31]. Hypotonic fluids are known as *maintenance fluids*, they contain more free water and have lower osmolarity than plasma (sodium concentration is about 70 mmol/l). They are commonly used when there are no fluid deficits, but the patient is not able to eat and drink (for example when recovering from a jaw fracture). Hypertonic crystalloids are strictly used for short term, when there is a need for a fast intravascular volume expansion. The hypertonicity of these fluids cause movement of interstitial and intracellular water into the intravascular space due to the difference in concentration gradient. Consequently, these fluids lead to dehydration and must be followed by isotonic fluids [31].

The use of isotonic fluids in comparison to hypotonic fluids as maintenance fluids is under debate both in veterinary and human medicine due to their higher/lower sodium content in relation to daily need. Hypotonic fluids administration as maintenance fluids, may pose a risk of hyponatremia, while isotonic fluids used as maintenance fluids contain higher concentrations of sodium and chloride. These solutions exceed the daily requirements and are also restricted to extracellular fluid compartments. The sodium content requires higher renal clearance, and thus posing the risk of fluid overload and hypervolemia in patients who are critically ill, as renal clearance is reduced due to stress response to illness (and other pathologies that may be renal-associated). Immobile patients who are experiencing an inflammatory process which increases blood vessels permeability, are also at risk of edema

formation [28]. This emphasizes the need for a thoughtful plan of fluid therapy and frequent reevaluation of the patient's changing status.

Table 6: Composition of Commonly Available Crystalloids Used in Dogs and Cats [27]

Fluid	pH	Na+ mEq/L	Cl- mEq/L	K+ mEq/L	Mg^{2}+ mEq/L	Ca^{2}+ mEq/L	Glucose g/L	Osmolarity mOsm/L	Buffer mEq/L
0.9% NaCl	5.0	154	154	0	0	0	0	308	0
Normosol-R	6.4	140	98	5	0	3	0	296	Acetate 27
Vet. Plasma-Lyte A	7.4	140	98	5	3	0	0	294	Acetate 27
LRS	6.5	130	109	4	0	3	0	272	Lactate 28
0.45% NaCl	5.0	77	77	0	0	0	0	154	0
D5W	4.0	0	0	0	0	0	50	252	0
Normosol-M in 5% dextrose	5.5	40	40	13	3	0	50	364	Acetate 16
Plasma-Lyte M in 5% dextrose	5.5	40	40	16	3	5	50	376	Acetate 16

4.3.2 Colloids

Colloids are essentially crystalloid based solutions, that contain large molecules that cannot cross the capillary membrane thus they are retained in the intravascular space. Colloids can be classified as natural or synthetic, based on the protein molecules they contain. For example, a synthetic colloid can be HES solution which contains Hydroxyethyl starch, and a natural colloid can be whole blood, fresh frozen plasma (FFP) or albumin solution. Colloids are used when large volumes are needed intravascularly for resuscitation. Crystalloids are not appropriate for this need because their content of solutes is relatively free to move across membranes, they may lead to interstitial edema and fluid overload. Colloids are more restricted to the intravascular space and so they are longer lasting in their effect. Thus, colloids are useful when there is not only a need in expanding the intravascular volume, but also improve blood flow and maintain oncotic pressure [32]. Colloids can also be used when there is a need to increase tissue perfusion and oxygen delivery to tissues, when there is a decrease in oncotic pressure or when total protein is below 35g/L, or albumin is

below 15g/L [33]. It is also possible to administer colloids in a combined therapy with crystalloids if there is a need to both expand intravascular volume or increase oncotic pressure together with a need to replace interstitial deficits. That being said, it is also important to note that the use of HES has been under debate in human medicine and was questioned due to adverse effects that were documented in clinical trials. These adverse effects include coagulation alteration, immunologic reactions, higher risk of AKI and need for RRT. However, there is still no study in cats and dogs that shows an acute kidney injury due to HES administration, but there are studies that document adverse effects on platelet function and coagulation, although their clinical relevance is undetermined [27].

4.4 Fluid Additives

Because of the limitation in availability of different fluid solutions and the varied needs of different medical conditions, it is often necessary and useful to alter the content of fluid bags to fit to each individual case more accurately. Thus, electrolyte solutions, amino acids and vitamins can be added to fluid bags to answer the changing requirements of a patient. It is recommended to start with general fluid therapy until lab results can reveal in detail what abnormalities are present and fluid therapy can be tailored according to the patient's needs [33]. *Potassium* is one of the most common supplements, especially in patients that require intensive fluid therapy and replacement fluids. Gastrointestinal fluid losses, diuresis, administration of bicarbonate, insulin and dextrose can all lead to a hypokalemic state [27]. Potassium chloride can be added to fluid bag; it is important that it is mixed well to avoid unintentional potassium overdose. In case of concurrent hypophosphatemia, potassium phosphate can be used [33]. Potassium supplementation should not be given at a higher rate than 0.5 mEq/L/kg/hr and must be accompanied by strict monitoring of the patient [27]. In case of hyponatremia, *Sodium* supplementation can be used in the form of fluid containing a similar sodium concentration to that of plasma. Sodium is an osmotically active solute thus changes in serum concentrations must occur slowly.

Dextrose can be included in the course of fluid therapy in the form of dextrose-containing fluid solutions, or a concentrated dextrose solution can be added to an isotonic balanced electrolyte solution for example, and the wanted concentration of dextrose can be adjusted [33].

Table 7: Potassium Supplementation [34]

Serum Potassium (mEq/L)	mEq KCl to Add to 1 L Fluid	Maximal Fluid Infusion Rate (mL/kg/hr)
<2.0	80	6

2.1-2.5	60	8
2.6-3.0	40	12
3.1-3.5	28	16

4.5 How to Plan Fluid Therapy?

Fluid therapy must be planned thoughtfully according to the patient's needs. Different conditions will dictate different needs; the choice of fluids, whether fluids require adjusting, the rate and volume should all be individually tailored, and reevaluated over the course of therapy [33]. Essentially, fluid therapy may be comprised of three main parts: resuscitation, replacement and maintenance. Resuscitation addresses the critical state (i.e hypovolemia), allowing to progress to further replacement of dehydration deficits and ongoing losses, aiming to achieve a state where only maintenance fluids (and additional fluids for ongoing losses) can be given.

4.5.1 Patient Assessment

Patient assessment should include history, complaint and physical examination. The physical examination can reveal many details regarding the fluid needs of the patient and so fluid therapy can start right away if the patient requires stabilization, while waiting for lab results. Lab results will show the alterations in content and then fluid therapy can be finely tuned. It is first necessary to determine what fluid deficits are present; if the patient is hypovolemic, fluid therapy should start with volume restoration, even if there is a concurrent dehydration. For assessment of hydration status see '2.1.3 Assessment of hydration status' and table 8: Estimation of Dehydration Based on Clinical Signs.

4.5.2 Hypovolemia and Shock

Clinical signs of hypovolemia are dull mentation, hypotension (-systolic blood pressure <80 mm Hg), poor perfusion to the periphery (-cold extremities), weak peripheral pulse, pale-gray mucous membranes (not always) and prolonged CRT, hypothermia, tachycardia in dogs and normal heart rate or bradycardia in cats [27, 28]. When dull mentation and collapsed veins appear, hypovolemia is severe [27]. To correct hypovolemia, crystalloids at 60 to 90 ml/kg for dogs and 45 to 60 ml/kg for cats can be used. The first ¼ of the fluid should be given within 5-15 minutes. If there is no improvement after the first ¼ of fluids, another ¼ should be given [28], and reassessment is necessary after each bolus given [27]. Combining synthetic colloids (such as HES) with crystalloids is another option, that will reduce the total amount of volume needed. Colloids will also shorten the time it takes to restore euvolemia, reduce

the risk of fluid overload as with colloids there is a better intravascular fluid retention [35]. HES can be used alone if hypovolemia is hypoproteinemic at 5-20 ml/kg for dogs and 2-10ml/kg for cats over 20-30 minutes and then we have to reassess [27]. Treatment of hypovolemia should not take longer than 1-2 hours [27]. If there is any suspicion of a cardiac pathology, these should be assessed before bolusing any type of fluids, and prolonging the period of restoration over 6-12 hours or even 12-24, depending on the patient's dehydration status and cardiac ability [17, 27, 35].

Resuscitation should aim to restore normal vital signs, mentation, systolic blood pressure to >80-90 mmHg, restore serum lactate to <2.5mmol/L, improve central venous oxygen saturation to >70%, PCV >25%, urine output to >1ml/kg/h. These parameters can be checked between each bolus. Once resuscitation efforts effectively reach these goals, resuscitation can be stopped and the next step would be to assess hydration status and address dehydration deficits [27].

4.5.3 Replacement Fluids

Replacement of fluid deficit (dehydration) is calculated as the percentage of estimated dehydration multiplied by body weight in kg and multiplied by 10; estimated dehydration % x BW x 10 = fluid deficit [27, 33]. At this point it is important to remember that below 5% dehydration, there are no clinical signs, so a 5% or lower percentage may be presumed by history of vomiting or diarrhea (see '2.1.3 Assessment of hydration status' and table 8). If fluids were given in bolus for resuscitation of hypovolemia, that amount should be deducted from the total of dehydration deficit correction [28]. Ongoing losses and maintenance volume can be added to dehydration deficit volume and this total volume can be administered over a period of 4-24 hours depending on the patient's cardiovascular abilities and risk of hypovolemia. After replacement of deficits, fluid therapy can be reevaluated and changed according to patient's maintenance needs and presence of ongoing losses [27].

Table 8: Estimation of Dehydration Based on Clinical Signs [27]

Dehydration %	Clinical Signs
<5	No specific signs, history of fluid loss
6-8	Enophthalmia, dry mucosal membranes, decreased skin turgor
10-12	Enophthalmia, dry mucosal membranes, decreased skin turgor, weak peripheral pulse, depression, significantly decreased skin turgor

12-15	Stupor, coma, death

4.5.4 Maintenance Needs

Maintenance fluid therapy is indicated for patients that are not eating or drinking, but do not have volume depletion, hypotension, or ongoing losses.

Maintenance needs are determined by insensible and sensible water losses. The requirements of water and electrolytes change with age, activity level, temperature, humidity and diet [29]. Maintenance requirements of dogs and cats are based on caloric needs because in healthy animals, a significant amount of the water comes from voluntarily ingested water and water derived from metabolism of food.

Table 9: Water Derived from Oxidation of Food [29]

100g of substrate	Water derived from oxidation (ml)
Protein	41
Fat	107
Carbohydrates	60

As can be seen in table 9, a significant amount of water is derived from food in healthy animals, thus evaluation of maintenance fluids must take under account whether the patient is eating or not [29]. It is important to note that the estimates of water needs have been studied on healthy and partially active animals in laboratory conditions, whose activity level is *higher* than that of a sick hospitalized patient [29].

The formulas used to assess how much maintenance fluids a patient should receive are under debate in veterinary literature (table 11). In "2013 AAHA/AAFP Fluid Therapy Guidelines for Dogs and Cats", Davis et al suggest an estimate of 80 x BW $(kg)^{0.75}$ for cats and 132 x BW $(kg)^{0.75}$ for dogs [33]. Hansen et al suggest an estimate of 97 x $BW^{0.655}$ for sick, inactive patients and a higher estimate for active animals of 140 x $BW^{0.73}$, and reports that this estimate provides sufficient amount of water to promote mild diuresis [29].

In sick patients, there are many more factors to consider that may increase or decrease their water requirements. Examples for reduced water requirements include stress response to a critical condition resulting in reduced renal clearance of both water and sodium, excessive ADH production as response to certain drugs, ventilation and stress, and oliguria in AKI. Examples for increased water requirements include animals that eat dry food, abnormally high body temperature or fever, increased respiration or panting and stress (table 10), extensive burns and many others [28, 29].

Table 10: Respiratory Water Losses of Panting Dogs and Cats [26]

Species	Weight	Respiratory water losses	
		g/min	g/day
Dogs	16	0.326	469
Cats	3.5	0.029	41.2

Table 11: Maintenance Fluid Equations

60 ml/kg per day [28]
50 ml/kg per day – cats [28]
1 ml water per kilocalorie of energy required [28]
140 x BW(kg)$^{0.75}$ [28]
80 x BW (kg)$^{0.75}$ – cats 132 x BW (kg)$^{0.75}$ – dogs [33] 2-3 ml/kg/h cats – cats 2-6 ml/kg/h – dogs [33]
97 x BW(kg)$^{0.655}$ – sick and inactive patients 140 x BW(kg)$^{0.73}$ – active patients [29]
30 x BW(kg) +70ml = ml/day / 80 x BW (kg)$^{0.75}$ = ml/day [27]

4.5.5 Route of Administration

The common routs of fluid administration in dogs and cats are intravenous, subcutaneous, enteral, intraosseous and intraperitoneal. Venous access is the most common and preferred. When venous catheterization cannot be achieved in hypovolemia, intraosseous route (proximal femur or cranial tibial crest) may be used until venous access can be made. The subcutaneous route is sufficient only for replacement of mild dehydration deficit at 10-20ml/kg per site. Dextrose should not be administered by this route, and potassium may cause discomfort if administered subcutaneously. Enteral fluids may be considered if there is a need to prevent villous atrophy, and can be combined with enteral nutrition [27].

4.6 Monitoring the Response to Fluid Therapy

It is necessary to monitor the response to fluid therapy and reassess whether the signs that indicated fluid therapy, are resolved. The following parameters can be checked frequently in order to adjust the therapy to the changing needs and avoid complications. *Prolonged CRT* >2 seconds suggests reduced tissue perfusion, and reduced tissue perfusion is commonly caused by hypovolemia. Improved CRT indicates that tissue perfusion has improved. *Dry*

mucosal membranes are frequent in dehydrated patients; thus the return of moisture suggest restoration of hydration. *Skin turgor* is another easily accessible parameter that can be checked, if skin turgor has a gelatinous appearance then it is most likely that the patient is overhydrated and developed edema. If skin turgor is still reduced it may suggest the patient has not been sufficiently rehydrated. In geriatric or anorexic patients, this is not a sufficiently reliable indicator, because it is common for them to have reduced skin turgor. The same can be said on skin turgor of obese/overweight patients, who may have increased skin turgor. *Heart rate* should be monitored frequently; compensatory mechanism of hypovolemia in dogs will increase heart rate and tachycardia can be expected. This can sometimes be seen in cats but not always. If resuscitation of hypovolemia is adequate, tachycardia should be resolved. *Blood pressure* can also be measured; hypovolemia may result in hypotension (<60 mmHg). Hypotension may also occur without hypovolemia if the patient's cardiac contractility or vascular resistance is reduced. *Body weight* is another easily accessible and non invasive way to evaluate fluid gain or fluid loss. Although there are insensible losses that cannot be measured, the measurement of body weight can still be helpful evidence together with the other parameters. Measuring *urine output* is an important way to not only reassess the 'ins and outs' but also indicate normal urine output, oliguria or anuria (Normal:1-2ml/kg/h, oliguria: 0.5-1ml/kg/h, anuria <0.3ml/kg/h). *Central Venous Pressure (CVP)* is another measurement that can indicate the status of circulating volume. In dogs and cats the normal CVP range is 0-10 cm H_2O. In order to efficiently utilize this evaluation method, CVP must be recorded several times a day and compared to previous results. *Lactate* is another parameter that can be evaluated, its increase in hypovolemia suggests tissue hypoxia, thus this increase should be resolved once volume resuscitation is achieved. Lactate may also be increased due to a decrease in vascular resistance, cardiac output and arterial oxygen concentration without hypovolemia, thus should be evaluated with caution. Lungs may also be assessed; respiratory rate and effort, edema and crackling sounds suggest fluid overload [27, 33, 34].

4.6.1 Fluid Overload and Hypervolemia

Healthy animals are normally tolerant to a mild excess in fluid administration, but patients who suffer from renal or heart disease are at risk of fluid overload [33]. The parameters described previously (4.6 Monitoring the Response to Fluid Therapy) are useful indicators for tracking of the patient's response to therapy, and if monitoring is performed routinely, it should help to avoid such complications. Signs that indicate fluid overload also include weight gain, restlessness, tachycardia (gallop rhythm in cats), increased respiratory rate and

effort (tachypnea, dyspnea), crackling lung sounds, serous nasal discharge, chemosis in cats, coughing and jugular venous distension [27].

5. Fluid Therapy in AKI

The most significant part in management of AKI is fluid therapy. When fluid therapy is well planned, it can correct the alterations in homeostasis caused by AKI while also promoting diuresis in early stages of the disease.

Fluid therapy should be carefully planned and reassessed frequently due to changes that are affected by the progress of the disease and the treatment itself. The plan of fluid therapy should aim to 1. Restore fluid deficit and intravascular volume to improve perfusion and acid-base balance and to correct electrolyte changes, 2. Maintain euvolemia and promote diuresis without causing fluid overload and accumulation [4,17, 28].

Therapy should start with correction of the most life-threatening conditions (i.e hypovolemia, hyperkalemia) and ensuring the prevention of further damage to the kidneys. Ultimately, the goal is to provide enough support and stabilization to allow time for recovery [2].

5.1 Restoration of Fluid Deficits and Intravascular Volume

If the patient is hypovolemic at presentation, the first step is to restore volume and correct shock to prevent further damage to organs, especially the compromised kidneys of an AKI patient. The options for resuscitation of hypovolemia are described in the previous chapter (see 4.5.2 Hypovolemia and shock). Once hypovolemia is resolved, replacement of fluid deficit (dehydration) should be started. Dehydration deficits should be calculated as described in chapter 4, by calculating the estimated dehydration % x BW x 10. In patients with AKI that do not show clinical signs of dehydration, a 5% deficit is assumed. Volumes that were given for resuscitation of hypovolemia, should be deducted from the total volume of dehydration deficit correction [28]. The restoration of dehydration deficit should occur over a period of 6 hours, because in patients with AKI, the dehydration occurred over a short period of time. Rapid restoration will also reveal whether urine output is appropriate or if oliguria is present. Oliguria is to be expected in a dehydrated patient, but once deficits are corrected, the urine output will determine the next steps of the treatment. Thus, this phase of

the treatment has some potential to reveal the severity of the injury. A volume-responsive azotemia will typically resolve after correction of the hypovolemia. When intrinsic kidney injury has already occurred, further fluid therapy will be needed. Replacement fluids can be administered over a longer period if there is any suspicion of a cardiac pathology. Thus replacement can be done over 6-12 hours or even 12-24, depending on the patient's condition [4,17]. It is important to note that urine output can only be indicative of oliguria/anuria once replacement of deficit is sufficiently achieved and the signs of dehydration are resolved (see chapter 4).

5.2 Maintenance Fluids

Once the intravascular volume is replaced and dehydration is corrected, the next goal of fluid therapy is to maintain fluid balance. As was mentioned in chapter 4, there are several formulas by which the volume of maintenance fluids can be calculated. However, these formulas assume normal urine output, and do not take into account an oliguric state, which is often the case with AKI patients. Furthermore, if the patient's urine output is normal, the kidneys still may not be able to make the required alterations in order to excrete any excess fluids. Here lies the challenge in managing fluid therapy in AKI patients; maintaining an optimal hydration rate to provide proper renal perfusion without causing deficits by administering less than what is required, or at a too slow rate, and without overhydrating by administering too much or too fast [2, 4]. Several publications suggest to accurately measure and document all fluids going in and out of the patient (known as 'Ins and Outs', see table 12). By doing so, we can have a more accurate picture on the fluid status and thus adjust it precisely according to the patient's needs. However, if some measurements are not accurate or have not been documented correctly, an estimate of these losses can be counted [4, 28]. These calculations should include insensible losses as 22 ml/kg/day, urine losses of the past hours, and other ongoing losses such as vomiting or diarrhea. If any fluids were administered for any other purpose (transfusions, medications or feeding), these should be included in the calculation as well. It is advised to calculate fluids for intervals of 4-6 hours and reevaluate [3, 4]. If a patient is anuric, fluids should be given only to replace the insensible loss and ongoing losses. In an overhydrated patient, insensible loss should not be included. In an overhydrated patient that is anuric or oliguric, where attempts to induce diuresis have failed, the next option is dialysis [4].

Table 12: Sample Calculations of 'Ins and Outs' [4]

Insensible loss: 4.5(kg BW) x 22ml/kg/day = 100ml/day, 100 ml/day ÷ 24 = 4ml/h

Urine loss: 30 ml urine output over previous 6 hours ÷ 6 = 5ml/h
Ongoing loss: vomiting 3 times a day, 8ml each time= 24ml, 24ml/24= 1ml/h
4 + 5 + 1 = 10ml/h

5.3 Acid-Base and Electrolyte Balance

Metabolic acidosis and alteration in electrolytes are common in AKI patients due to reduced kidney functions and the kidneys role in maintenance of homeostasis. The choice of fluids should be made after the assessment of acid-base and electrolytes status, and this should be continuously reevaluated to avoid causing more disturbances or exacerbating the existing disturbances. If a patient is hyponatremic, 0.9% NaCl solution can be the right fluid choice. In case of higher serum sodium concentrations, lower sodium fluids can be chosen (i.e 0.45% NaCl with 2.5% dextrose, or ½ strength LRS with 2.5% dextrose) [2, 4].

If hyperkalemia is severe or life threatening, and the patient is anuric or oliguric, there are several possibilities to resolve the hyperkalemia; 1. sodium bicarbonate at 1–2 mEq/kg slowly intravenously, which may induce an exchange of potassium and chloride but may not be successful in acidosis, 2. Insulin and glucose may promote intracellular potassium uptake and 3. 10% calcium gluconate (if life threatening hyperkalemia) at 0.5 to 1 ml/kg slowly IV while monitoring EKG for arrhythmias [3,17].

In case of metabolic acidosis, there is no indication for bicarbonate supplementation unless blood pH is below 7.2 or serum bicarbonate is below 14mEq/L after fluid deficits have been corrected. When necessary, bicarbonate can be supplemented according to the following formula: BW(kg) x 0.3 x (24: measure bicarbonate) = mEq bicarbonate deficit. ¼ of this deficit can be administered over a period of 12 hours [3]. Another formula is recommended by DiBartola: 0.3 x body weight (kg) x base deficit. 1/4 to 1/2 dose is given slowly IV and the rest is given with IV fluids over the next 2 to 6 hours [36]. Acid – base balance should be then reevaluated before any further administrations [3].

5.4 Diuresis in Oliguric/Anuric Patients

In a dehydrated, hypovolemic patient, oliguria is expected due to fluid retention. This is a part of normal renal response. This is why oliguria and anuria can only be determined once all fluid deficits are corrected. In an animal that is properly hydrated and receiving fluid therapy, urine output is expected to be 2-5ml/kg/h [2, 3]. Thus, urine output <1ml/kg/h can be considered absolute oliguria while < 2ml/kg/h is considered relative oliguria [2, 4]. If urine output is insufficient, the first step should be to reassess the patient's hydration status and also arterial blood pressure and CVP. If deficits are still present, this can explain lower urine

output. If the patient is normally hydrated or overhydrated, fluid administration rates should be slowed in order to prevent fluid overload. The next step is employment of diuretics. There is no evidence that diuretics improve GFR or the outcome of AKI, but they may improve urine output, and by doing so they allow the continuation of fluid therapy [3, 4]. In addition, because the use of diuretics may convert oliguria to nonoliguria, the risk of overhydration, hyperkalemia, and accumulation of toxic waste products greatly reduces when diuretics are successful [2]. If attempts to transform oliguria to non oliguria have failed, RRT is indicated [3, 4].

5.4.1 Loop Diuretics

The first diuretic agent to administer should be Furosemide. An initial dose of 0.66 mg/kg, followed by continuous rate infusion (CRI) of 0.66 mg/kg/h has been shown efficient in dogs and can be adjusted between 0.25-1.0 mg/kg/h in CRI [3, 4]. Furosemide does not increase GFR and when is successful in increasing urine output, it suggests that the renal injury may be less severe with better recovery chances. Furosemide is contraindicated in aminoglycoside-AKI [4].

5.4.2 Osmotic Diuretics

If there is no response to furosemide, it should be stopped, and osmotic diuretics may be considered. Mannitol, as an osmotic diuretic agent can inhibit renal Na absorption, increase tubular flow which can release occlusion by casts and debris. It also decreases vascular resistance and cellular swelling, increases GFR and RBF while promoting excretion of solutes. It also has potential to tone down the inflammatory processes by preventing vascular congestion and RBC aggregation, reduction of ROS. It induces PGs production and vasodilation and atrial natriuretic peptide release which in turn increases GFR [4]. 20% mannitol can be administered as a slow IV bolus over 15-20 minutes (0.5-1.0 g/kg), urine output should increase within one hour if mannitol is successful. Further bolus doses can be repeated every 4-6 hours only if initial dose is successful, or as CRI at 1–2 mg/kg/min. Doses higher than 2mg should be avoided as they can actually cause AKI [3, 4]. Mannitol should not be used in dehydrated patients as it can worsen the dehydration intracellularly, and it is also contraindicated in overhydrated patients as it may induce or worsen pulmonary edema. 20% dextrose solution can be used if mannitol is not available at 2-10 ml/min for 10-15 minutes, followed by 1-5 ml/min. Total daily dose may be 22-66 ml/kg. 20% dextrose should be alternated with polyionic solution to prevent dehydration, and urine should be tested for glucose to evaluate if the treatment is successful [3, 4].

5.4.3 Dopamine and Fenoldopam

Dopamine was traditionally used in the past to increase RBF and urine output by stimulating DA-1 and DA-2 receptors as well α– and ß–adrenergic receptors. However, it is no longer recommended for treatment in AKI patients, as several studies failed to show any clinical benefit or efficacy in dogs and cats. Fenoldopam, a DA-1 receptor agonist has been shown to increase urine output, but one study in dogs and cats showed no difference in urine output between dogs who received Fenoldopam or saline. There are no clinical studies in dogs and cats in regards to treatment with fenoldopam for AKI management, thus its role in oliguric AKI patients is undetermined [3].

5.4.4 Calcium Channel Blockers

Calcium channel antagonists such as diltiazem are presumed to reverse preglomerular vasoconstriction and promote natriuresis independent of GFR. These are used in human medicine to prevent AKI in renal transplant patients. Their use has been studied in dogs with leptospirosis-AKI but the results did not show a significant difference [3, 4].

5.4.5 Polyuria

Patients who are recovering from an oliguric or anuric state and patients who had a mild injury often become polyuric over long periods (from days to weeks). As such, they should be continuously monitored for changes in electrolytes. Hypokalemia and hyponatremia are common due to significant increase in urine output while the kidneys are still recovering and may not be able to retain and alter the proper concentrations [3] (see 1.2 The phases of AKI).

5.5 Avoiding Fluid Overload and Hypertension in AKI

Hypertension is a potentially serious and common complication associated with fluid overload and aggressive fluid therapy in AKI patients. As have been repeatedly noted due to its significance, frequent monitoring in critical patients is a necessity, and is especially crucial in AKI patients who face frequent hemodynamic changes and very often receive fluid therapy in an oliguric state. Monitoring is thus essential for appropriate adjustment of therapy to avoid complications, but also for prompt recognition of a trend towards dehydration or fluid overload. The patient should be clinically assessed on a regular basis for hydration, CRT, heart rate, respiratory rate and sounds, arterial blood pressure, CVP, packed cell volume and plasma total solids, serum biochemistry parameters (BUN,

creatinine, sodium, potassium, chloride, phosphorus) [3]. Body weight measurements should be taken at least three times a day in order to evaluate fluid gain or fluid loss where 1 kg is equal to 1 L of fluid [1, 37]. It is important not to overlook the body weight measurements because they can reveal a change in hydration status before clinical signs appear. Urine output measurement is one of the most important measurements and should be done in coordination with the reassessment of the fluid plan every 4-6 hours to ensure proper volumes of fluid are administered [37]. A urinary catheter may be the most convenient way to accurately monitor urine output, but it requires well trained staff and ensuring daily cleaning and disinfecting, and possibly replacing the catheter every 3 days to avoid ascending infections [3].

If signs of hypertensions or fluid overload are spotted, fluid therapy must be stopped or slowed, and action should be taken towards stabilizing the patient. Diuretics can be employed to induce diuresis, and if the patient is severely oliguric or anuric, dialysis should be considered to assist in removal of excess fluid and toxins. As most antihypertensive drugs are used PO, they may not be beneficial for patients who suffer from severe nausea and vomiting. Parenteral antihypertensive medication may be considered (accompanied by very close monitoring of blood pressure); nitroprusside at an initial dose 1–2 mcg/kg/min CRI, titrating the dose every 5 minutes to achieve desired blood pressure, or hydralazine at 0.5–3 mg/kg every 12 hours intravenously or an initial dose of 0.1 mg/kg IV, then 1.5–5 mcg/kg/min CRI [3].

Hypertension may be controlled with oral amlodipine besylate at 0.1–0.25 mg/kg every 12–24 hours PO in dogs, 0.625–1.25 mg/kg every 24 hours PO in cats [3,38]. It is also possible to give amlodipine rectally [38].

Angiotensin-converting enzyme (ACE) inhibitors may also be considered, such as enalapril at 0.25–0.5 mg/kg every 12–24h PO, or benazepril at 0.25–0.5 mg/kg every 24h, PO [3].

6. AKI Cases

In these case presentations, I will have a short overview of the history, physical examination findings, diagnostic workup and medical therapy of three AKI patients. The main goal of this chapter is to show how fluid therapy is done in real life; how the calculations, decision making and monitoring plays a role in the management of AKI patient, and how this literary review is reflected from these cases.

The cases were collected from the Small Animal Clinic of the University of Veterinary Medicine Budapest.

6.1 Case #1: Bly

Signalment

Name: Bly

Identification number: 270285

Species: dog

Sex: female

Breed: Border Collie

Age: 5 years

Color: blue-merle

Body weight: 17,8 kg

History

During the day the dog was alone in the garden. It was a hot, sunny day. When the owners arrived home in the evening they found the dog laying on the side, not able to stand up. The dog had diarrhea.

They called a vet, who examined the dog at home. Her body temperature was 39,5 °C. The vet suspected a heat stroke, so they cooled the dog. He also gave imidocarb (against babesia infection), dexmethasone injection and vitamin B complex injection. The vet referred the patient to the Small Animal Clinic. On the way to the clinic the dog vomited big amount of water but then was able to walk.

First clinical evaluation: T: 39,2 °C (on the high-normal end), mild tachycardia (150/min), prolonged CRT (3 sec), dry mucous membranes, suffusions appeared when shaved for the IV catheterization.

Day 1 (arrived in nightshift) – 05.24.2018

1) Acid-base examination showed mild metabolic acidosis (pH 7,29; HCO_3 15,6 mmol/l; BE -10,7 mmol/l, CO_2 33,1 mmHg) and moderate azotemia (creatinine 475 µmol/l), mildly increased PCV (52%) normal electrolytes and lactate level.

2) Initial fluid therapy:

- The dog was moderately hypovolemic, but not dehydrated.
- Shock rate was calculated: 80-90 ml/kg = 1424 – 1602 ml
  recommendation: 25% to be given quickly (350 – 400 ml), the rest (1000 – 1200 ml) through 6-8 hours.
- As clinicians suspected anuria (the dog's bladder was empty, and the owners haven't reported any urine in the evening) they didn't dare to give the whole dose (to avoid overhydration), only 2/3 of the calculated dose was given and they gave it at a slower rate; 500 ml Ringer-lactate infusion given through 3 hours (9 ml/kg/h) and another 500 ml through 7 hours (until the morning) (4 ml/kg/h).
- Mannitol (0,5 g/kg) was given as a diuretic.

Day 2 – 05.25.2018

1) The dog's general condition was acceptable; she was weak but able to walk. Vomited twice and had diarrhea. Had anuria in the last 12 hours.

2) Body temperature (38,2 °C) and CRT (1 sec) normalized. Petechiae appeared on the abdominal skin.

3) Bloodwork showed thrombocytopenia (64 G/l), azotemia (creatinine 625 µmol/l) hyperkalemia (6,4 mmol/l), hyponatremia (132 mmol/l), hypochloremia (107 mmol/l)

4) Coagulation parameters (APT, PTT) were within the normal range.

5) Urinalysis showed urinary tract infection (increased number of red blood cells, white blood cells, lot of bacteria) and renal tubular epithelial casts (it also confirms tubular injury).

6) On abdominal ultrasound the only alteration found was in the kidneys: they appeared enlarged with hyperechogenic cortexes.

7) Blood pressure (measured with HDO method on the tail): 172/103 mmHg – mild hypertension.

8) Fluid therapy:

- Insensible losses were estimated: 22 x body weight (BW=17,8 kg) = 391 ml/day
- As there was no urine production during the day the dog received 400 ml Ringer-lactate/24 h.

- Hyperkalemia (6,4 mmol/l) was not life-threatening, but needed intervention: 40% glucose was added to the infusion to get a 5% solution (62,5 ml 40% glucose in 500ml Ringer-lactate)
- Furosemide (2 mg/kg) was given to increase urine output and to help eliminate potassium

9) Medical therapy:

- Maropitant (1 mg/kg SID) – as antiemetic
- Pantoprazol (1 mg/kg SID) – as gastroprotectant
- Amoxicillin-clavulanic acid (20 mg/kg BID) – antibiotics for urinary tract infection

10) A permanent urinary catheter was inserted to measure urine production.

- The dog started to produce urine in the evening (after 24 hours of anuria).
- During the night the urine production was 520 ml (2,4 ml/kg/h).

Day 3 – 05.26.2018

1) The dog became polyuric: urine production was 4 ml/kg/h during the day (1600 ml urine).

2) Fluid therapy:

- Maintenance need was calculated: $132 \times 17{,}8^{0{,}75}$ [33] = 1144 ml/24h = 48 ml/h = 2,67 ml/kg/h
- *Additional maintenance sample calculations (chapter 4 Table 11):*
  1) $97 \times 17{,}8^{0.655} = 639$ ml/24h
  2) 30 x 17,8 + 70ml = 604 ml/24h
  3) $80 \times 17{,}8^{0.75} = 693$ ml/24h
- 1000 ml Sterofundin B (hypotonic solution) was given over 24 hours
- Ongoing losses were estimated: 2 ml/kg with urine (800 ml)
  800 ml Ringer-lactate was given over 24 hours

3) Medical therapy was continued with maropitant, amoxicillin-clavulanic acid, pantoprazol.

Day 4 – 05.27.2018

1) Bly started to drink voluntarily.

2) She was not tolerating the urinary catheter anymore, so it was removed.

3) Obvious polyuria was seen on the walks.

If 'Ins and Outs' cannot be measured, it makes fluid therapy more challenging in AKI patients. The most helpful measurement in this case is body weight measurement.

4) Bly's BW was measured 2 times daily.

5) Blood examination showed deteriorating azotemia (urea: 67,1 mmol/l, creatinine: 851 µmol/l), hyperphosphatemia (5,13 mmol/l), and thrombocytopenia (18 G/l) (which explained the petechia). Electrolytes normalized (K+: 4,5 mmol/l), and there was no more metabolic acidosis.

6) Fluid therapy:

- The clinicians decided to give only the calculated maintenance fluids (1000 ml) expecting the dog drink the 'ongoing losses' and they had a close eye on the BW and physical exam changes.

Day 5 – 05.28.2018

1) Bly was apathic, but able to walk.
2) It was drinking a lot of water and took some food from syringe (received 'critical care' diet).
3) BW: 17,5 kg.
4) The vet found signs of hypervolemia on physical exam: nasal discharge, small volume of subcutaneous edema on the sternal region.
5) Blood results: urea: 74,3 mmol/l; creatinine: 889 µmol/l.
6) BP was normal: 130/69 mmHg.
5) Fluid therapy:

- Maintenance fluids were stopped.
- 80 ml (5 ml/kg/24 h) hetastarch was started to help maintaining the intravascular volume.

Day 6-7 – 05.29–30.2018

1) Bly's general condition improved a little bit, but was still apathic.
2) She was drinking well and eating small amounts voluntarily.
3) BW: 17,2-17,5 kg
4) Urinalysis showed inactive sediment (UTI was handled), and borderline proteinuria (UPC 0,2).
5) Creatinine was stable: 919 µmol/l on day 6, 801 µmol/l on day 7.
6) Therapy:

- No infusions!
- Maropitant (until 05.30), amoxicillin-clavulanic acid (until 06.01.), pantoprazol (until 06.07.)

Day 8 – 05.31.2018

1) The subcutaneous edema had absorbed. On physical examination the clinician found its fluid balance good.

2) BW kept decreasing as it was expected with insufficient calorie intake: 16,9-17,2 kg.

3) Creatinine decreased: 619 µmol/l

Day 9 – 06.01.2018

1) BW:17,2 kg

2) Creatinine decreased: 473 µmol/l

3) As kidney parameters kept decreasing and the dog's general condition got better the dog was discharged from the intensive care unit.

Day 15 – 06.07.2018

1) On the control examination Bly was doing well with no changes on the physical exam.

2) The owners reported good appetite.

3) BP was normal (155/65 mmHg).

One Month after Kidney Injury – 08.22.2018

1) The owners reported that Bly is back to normal in every aspect.

2) Blood test showed no alterations: urea 9,0 mmol/l; creatinine 117 µmol/l; P 1,19 mmol/l

3) Urine was well concentrated (USG 1030) without proteinuria.

4) SDMA (symmetryc dymethylarginine) test was also performed which was at the upper normal range: 14 ug/dL (reference value <0-14)

One Year after Kidney Injury – 09.05.2019

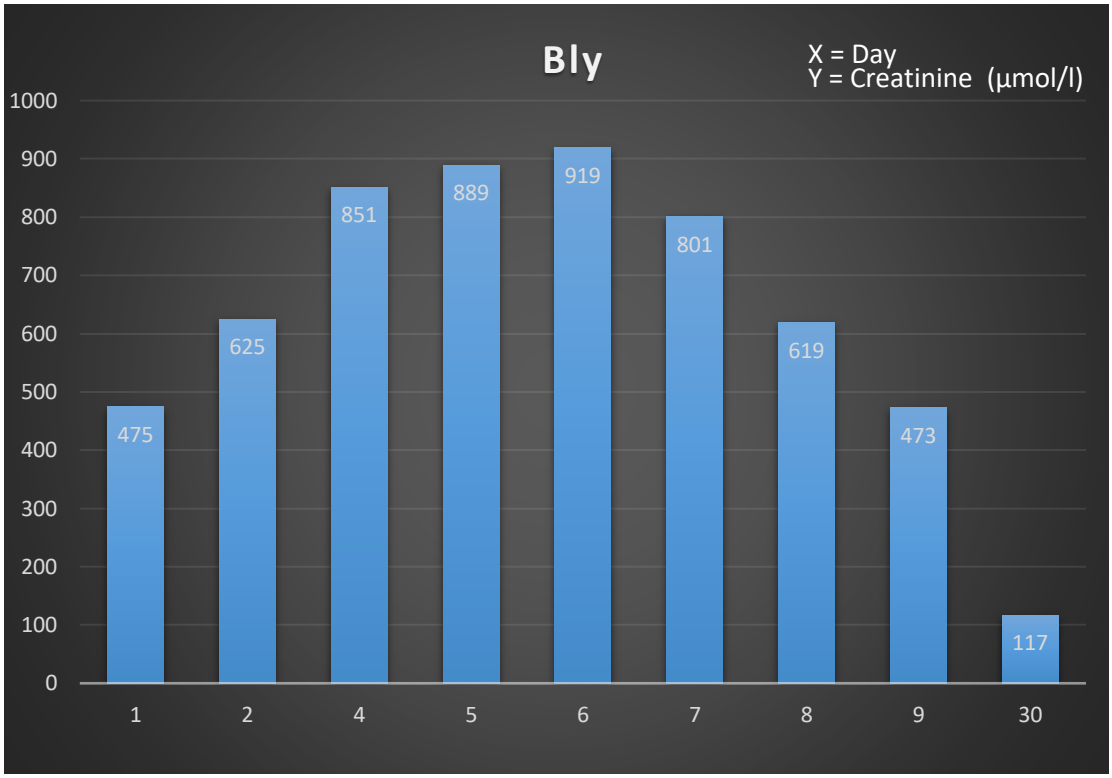
Bly showed no symptoms and the laboratory results haven't changed either.

6.1.1 Conclusion Case #1: Bly

- *This dog's kidneys were able to manage fluid and electrolyte balance before the resolution of the azotemia.*

- *Sometimes 'less is more', aggressive fluid therapy is not the answer in AKI but rather accurate fluid therapy. Although fluid therapy is the most important part of the treatment of AKI sometimes the right decision is not to give any fluids.*
- *If it was not monitored that closely, fluid therapy wouldn't have been stopped for sure, and have caused hypervolemia which would have aggravated the AKI.*
- *Bly's serum creatinine over the course of therapy shows that an AKI takes time to resolve, and one of the main therapeutic goals is to give enough supportive care to allow time for the kidneys to recover.*

Graph 1: Bly's serum creatinine over the course of therapy



6.2 Case #2: Irma

Signalment

Name: Irma

Identification number: 271623

Species: dog

Sex: female

Breed: Greyhound mix

Age: 6 years

Color: black

Body weight: 23,5 kg

History

Symptoms started 4 days prior to presentation with apathy, vomiting, diarrhea, inappetence and polyuria.

Alterations on physical exam: Irma was in bad general condition, was weak, apathic, body condition score was decreased (1,5/5). Hypothermia (36,8 °C) and mild dehydration was also present.

Bloodwork showed severe azotemia (urea 110,8 mmol/l; creatinine 1667 µmol/l), hyperphosphatemia (7,43 mmol/l) and moderate metabolic acidosis (pH 7,25; HCO_3 12,6 mmol/l; BE -14,5 mmol/l; CO_2 28,8 mmol/l).

Urinalysis showed isostenuria (USG:1012), inactive sediment and no proteinuria.

On abdominal ultrasound the the kidneys showed a picture of AKI: enlarged size, increased cortex/medulla ratio, with diffusely hyperechogenic cortexes, medullary rim (a distinct hyperechoic line in the renal medulla parallel to the corticomedullary junction) and halo sign (a hypoechoic zone at the corticomedullary junction).

Blood pressure was high (measured with HDO method on the tail): 202/80 mmHg.

Day 1 – 07.24.2018

1) Fluid therapy:

- The dog arrived in the evening. During the night the correction of the dehydration was the plan and to observe whether there is any urine production.
- 5 (% of dehydration) x 10 x 23,5 kg = 1175 ml Ringer-lactate was administered through 14 hours (80 ml/h, 3,4 ml/kg/h fluid rate)

2) Medical therapy:

- Maropitant (1 mg/kg SID) – as antiemetic
- Pantoprazol (1 mg/kg SID) – as gastroprotectant
- Famotidine (1 mg/kg SID) – as gastroprotectant
- Amlodipine (0,2 mg/kg SID) – as antihypertensive medication

- Vitamin B complex – as appetite stimulant
- CaCO3, chitosan powder – as phosphate binder

Day 2 – 07.25.2018

1) Irma was doing somewhat better; she was clinically not dehydrated.

2) She was drinking and eating small amounts.

3) She had diarrhea and polyuria (as ongoing fluid losses).

4) Irma's kidney parameters were extremely high (urea 129,7 mmol/l; creatinine 1563 µmol/l; P 8,0 mmol/l)

5) Fluid therapy:

- Maintenance fluids: 132 x $23,5^{0,75}$ [33] = 1409 ml/24h = 60 ml/h = 2,5 ml/kg/h
- *Additional maintenance sample calculations (chapter 4 Table 11):*

  1) 97 x $23,5^{0.655}$ = 767 ml/24h

  2) 30 x 23,5 + 70ml = 775 ml/24h

  3) 80 x $23,5^{0.75}$ = 854 ml/24h
- 1400 ml Sterofundin B hypotonic solution was used for maintenance needs.
- Ongoing losses: polyuria and diarrhea were estimated around 1-2 ml/kg/h but as the dog was also eating and drinking small amounts, only 0,5 ml/kg/h was added to the maintenance infusions (300 ml/24 h = 12 ml/h)
- 300 ml Ringer-lactate solution was used to correct dehydration.

Day 3-7 – 07.26 – 07.29.2018

1) Irma's general condition was mostly unchanged, she was weak, but eating and drinking small amounts and vomiting sometimes.

2) Kidney values were still very high, but decreasing:

- Day 3: creatinine 1774 µmol/l; urea 129,6 mmol/l; P 8,30 mmol/l
- Day 4: creatinine 1563 µmol/l; urea 129,7 mmol/l; P 8,0 mmol/l

3) The blood pressure normalized with amlodipine therapy: 157/82 mmHg

4) The owners wanted to take the dog home, so fluids were tapered to 1000 ml on day 7 and then the dog was released from the hospital with the instruction to try to make the dog drink a lot and bring it back 2 x daily for infusion therapy.

Day 8 – 07.31.2018

1) Irma was brought back for infusion therapy where she received 2 x 250 ml of Ringer-lactate and medical therapy.

Day 9 – 08.01.2018

1) Irma was doing worse, she was very weak and apathic, not eating and vomiting. She was still drinking a lot.

2) On the physical examination she was 8% dehydrated and showed pain in the epigastric region. She also lost a lot of weight. BW= 21,0 kg (previously 23,5 kg).

3) The reduction of the amount of infusions seemed to be too quick, Irma's kidneys were managing fluid balance poorly.

4) Kidney values were better but still very high (urea 121,6 mmol/l; creatinine 1249 µmol/l; P 4,7 mmol/l).

5) Irma was readmitted to the ICU.

6) She was put back to the previously calculated fluid dose and rate (1700 ml/day).

7) Medical therapy was continued and completed with tramadol as pain killer because of suspected gastric ulcerations.

Day 10-13 – 08.02–08.05.2018

1) Irma was receiving the calculated fluid dose (1700 ml/day maintenance + ongoing losses).

2) After rehydration Irma's BW was 22,1 kg(gained 1,1 kg), and after, it was decreasing slowly day by day as she was not eating properly.

3) Kidney values were decreasing:

- Day 11: creatinine 1025 µmol/l; urea 99,3 mmol/l; P 4,11 mmol/l
- Day 13: creatinine 864 µmol/l; urea 81,3 mmol/l; P 4,11 mmol/l

Day 14 – 08.06.2018

1) Irma was doing better. She had more strength, she was more alert, drinking well and eating frequently small portions of high caloric critical care food.

2) As kidney parameters were also decreasing the clinicians started to taper down the infusions for 1000 ml/day (40% decrease), consisting of 500 ml Sterofundin B and 500 ml Ringer-lactate.

3) BW: 21,4 kg

Day 15 – 08.07.2018

1) With this reduction of the fluids Irma was not showing signs of dehydration but its body weight dropped from 21,4 kg to 20,6 kg through one night *(which is an obvious fluid loss)*, so the fluids were increased back to 1500 ml/day.
2) Kidney parameter also increased with the dehydration: urea 86,2 mmol/l; creatinine 963 µmol/l.
3) *The 40 % reduction of the infusions seemed to be too quick.*

Day 16-22 – 08.08-08.14.2018

1) Irma's general condition was improving, it was alert.
2) Irma still had severe pulyuria and polydipsia.
3) Her appetite was getting better and she had no diarrhea anymore.
4) On these days the clinicians tried judicious tapering of the infusions with body weight measurement 2x daily. Every day the infusions were tapered with 10%.
5) When BW dropped suddenly, the infusion rate was increased back to the previous dose, kept for one more day and then decreased again by 10%.
6) On day 20, the clinicians changed the route from IV to subcutaneous fluid administration, as Irma's veins were inflamed after 3 weeks of intensive therapy.
7) Kidney parameters keep decreasing:

- Day 18: urea 75,6 mmol/l; creatinine 700 µmol/l
- Day 22: urea 74,1 mmol/l; creatinine 658 µmol/l

Day 23 – 08.15.2018

1) Irma was released from the hospital.
2) The owners were instructed to give daily 500 ml Ringer-lactate subcutaneously for one more week and then try to decrease the amount every day by 10%.
3) Medical therapy was continued with pantoprazol, amlodipine and phosphate binder.
4) Renal diet was suggested.

Day 25 – 08.17.2018

1) Irma was doing fine, eating and drinking a lot.
2) On acid-base examination the pH was normal (7,35) and all electrolytes were within reference range.
3) Kidney values kept decreasing (urea 59,6 mmol/l; creatinine 543 µmol/l; P 2,45 mmol/l).

Two Months after Kidney Injury – 09.13.2018

1) The owners stopped the subcutaneous infusions.
2) Kidney values were mostly unchanged (urea 30,4 mmol/l; creatinine 560 µmol/l; P 2,06 mmol/l).

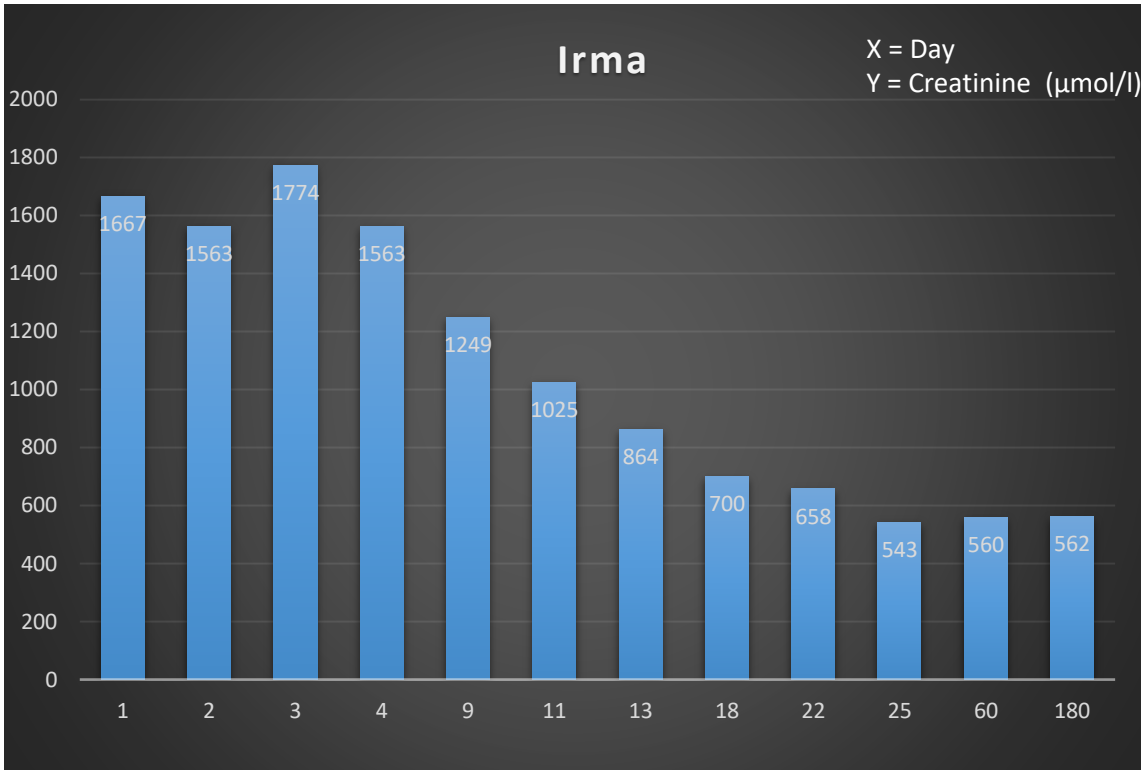
Six Months after Kidney Injury – 01.17.2019

1) Kidney values were mostly unchanged (urea 46,5 mmol/l; creatinine 562 µmol/l; P 2,7 mmol/l).
2) Irma's kidneys did not regenerate perfectly and she sustained a chronic kidney disease.

6.2.1 Conclusions Case #2: Irma

- *Irma had a very severe AKI.*
- *At the beginning dialysis therapy could have been started but as at that time there was no hemodialysis available in Hungary and the owners didn't want to try peritoneal dialysis. Irma was treated only with conservative therapy although the time of treatment could have been shortened significantly with dialysis therapy.*
- *Irma's kidneys were not able to maintain fluid balance for a long time after the kidney injury, she needed fluid therapy for almost 2 months.*
- *Irma's case showed how important frequent BW measurements are, because sudden drop in BW can show dehydration before clinical signs of dehydration appear.*
- *This case shows that complete recovery of the kidneys is not always possible.*

Graph 2: Irma's serum creatinine over the course of therapy



6.3 Case #3: Holly

Signalment

Name: Holly

Identification number: 271378

Species: dog

Sex: female

Breed: Bichon Havanese

Age: 1 years

Color: beige-white

Body weight: 6,6 kg

History

Symptoms started 10 prior to hospital admission with vomiting, lethargy and inappetence. The dog was diagnosed with AKI possibly due to ethylene-glycol toxicosis at another veterinary clinic. At that time, it was oliguric. It received daily fluid therapy (1-2 hours), and medical therapy (furosemide, famotidine). The dog's general condition was getting worse, developed subcutaneous edemas and ascites and creatinine level was already 1900 umol/l. Her normal BW was 5 kg, at presentation it was 6,6 kg. Holly was referred for intensive care.

Alterations on first physical examination: The dog showed severe overhydration, had subcutaneous edemas all over the body and the abdomen was distended. She was weak, lethargic and had yellowish diarrhea. Urine production was present.

Bloodwork showed severe azotemia (urea 102,1 mmol/l, creatinine 1184 µmol/l), severe hyperphosphatemia (7,8 mmol/l) very severe metabolic acidosis (pH 7,01; HCO_3 7,4 mmol/l; BE -23,6 mmol/l; CO_2 29,2 mmol/l), and hyperchloremia (135 mmol/l).

Urinalysis showed isosthenuria (USG 1010), glucosuria, kidney urothelium cells and proteinuria (all of these can be caused by tubular cell injury).

On abdominal ultrasound the kidneys had highly hyperechogenic cortexes. There was a lot of free abdominal fluid which was tapped for further diagnostics.

The cytological diagnosis of the abdominal fluid was transudate.

Blood pressure (measured with HDO method on the tail) was normal (152/83 mmHg).

Day 1 – 07.12.2018

1) Fluid therapy:

- As the dog was overhydrated only bicarbonate therapy was initiated to help compensate the severe metabolic acidosis.
- This calculation was used [36]: 0,3 x BE (23,6) x BW (5 kg – the original BW) = 35,4 ml
- 15 mmol $NaHCO_3$ (diluted with 20 ml of NaCl) was given over 15 minutes and then:
- 20 mmol $NaHCO_3$ (4 mmol/kg) diluted with 30 ml of NaCl infusion was given over 5 hours.

2) Medical therapy:

- furosemide (1,5 mg/kg BID) and mannitol (0,5 g/kg only once) – as diuretics to help eliminate the extra fluid
- famotidine (1 mg/kg SID) – as gastroprotectant
- maropitant (1 mg/kg SID) – as antiemetic

3) Measuring the urine production was well manageable with this patient. At walks the urine was caught in a bowl and measured, and the pads in the cage were measured when the dog urinated on them.

4) Holly urinated 530 ml in the first 16 hours, 6 ml/h/kg which means polyuria.

Day 2 – 07.13.2018

1) Holly's BW decreased to 5,5 kg, but was still overhydrated.

2) Urine production was 7 ml/kg/h.

3) Acid-base examination showed improvement (pH 7,13; HCO_3 9,9 mmol/l; BE -19,2 mmol/l; CO_2 30,3 mmol/l) although there was still severe acidosis.

4) Creatinine level was 1243 µmol.

5) Fluid therapy was continued with only NaHCO3 (4 mmol/kg = 20 mmol) diluted with 30 ml of NaCl solution, and was given over 3 hours (the 2/3 of the previous day's calculated dose).

Day 3 – 07.14.2018

1) Holly's BW decreased to 4,5 kg. All the edemas and the ascites disappeared.

2) Holly's general condition improved, she was more alert, drinking but not eating.

3) Furosemide was stopped.

4) Maintenance fluids were started: (400 ml/day Sterofundin B):

- 132 x $4,5^{0,75}$ [33] = 408 ml/24h = 17 ml/h = 3,7 ml/kg/h
- *Additional maintenance sample calculations (chapter 4 Table 11):*

  1) 97 x $4,5^{0.655}$ = 260 ml/24h

  2) 30 x 4,5 + 70ml = 205 ml/24h

  3) 80 x 4,5 = 360 ml/24h

5) Creatinine level had slightly decreased: 1117 µmol/l

Day 4-5 – 07.15 - 07.16.2018

1) BW decreased to 4,2 kg but there was no dehydration present, it was more likely weight loss because of insufficient calorie intake.

2) Holly started to eat small amounts.

3) Maintenance fluids were continued.

4) Kidney parameters started to decrease: urea 89,8 mmol/l; creatinine 816 µmol/l; P 4,5 mmol/l.

5) Metabolic acidosis got better as well, without bicarbonate therapy (pH 7,3; HCO_3 20,9 mmol/l; BE -5 mmol/l; CO_2 44,2 mmol/l).

Day 6 – 07.17.2018

1) As Holly's general condition improved and it started to eat better, there was no need to continue the maintenance fluids.

2) Ongoing losses with due to polyuria were estimated:

- Holly's urine production was about 4,2 ml/kg/h. Normal urine production would be 2 ml/h, so fluid therapy was set for this difference 2 ml/kg/h=2 x 4,2 x 24 = 200 ml
- Ringer-lactate was used
- Hypokalaemia was found: 3,1 mmol/l *(due to increased loss with polyuria)*. Potassium supplementation was added as it is recommended by DiBartola [34] (Table 7): 28 mmol/L potassium was added into the Ringer-lactate solution.

Day 7-8 – 07.18.-07.19.2018

1) As Holly was eating and drinking well, the clinicians started to decrease the fluid rate:
   - on day 7 to 150 ml
   - on day 8 to 100 ml
   - on day 9 to 50 ml
2) Polyuria decreased to 3 ml/kg/h.
3) Special attention was on the BW, but it decreased only until 4,1 kg, and the dog was not showing signs of dehydration.
4) Kidney parameters kept decreasing: urea 65,7 mmol/l; creatinine 479 µmol/l; P 3,61 mmol/l.

Day 9 – 07.20.2018

1) Holly was feeling, eating and drinking well so it was discharged from the hospital.
2) Creatinine 425 µmol/l

One Month after Kidney Injury – 09.03.2018

1) Holly was doing well.
2) BW was 4,5 kg.
3) She vomited twice in the previous 2 weeks but otherwise was eating and drinking well.
4) Kidney parameters kept decreasing: urea 15,0 mmol/l; creatinine 240 µmol/l; P 1,78 mmol/l.
5) Urine examination showed isosthenuria (SG: 1012) and mild proteinuria (UPC 0,55).
6) Renal diet and enalapril (0,4 mg/kg BID) were prescribed.

Four Months after Kidney Injury – 12.12.2018

1) Holly was doing well.
2) BW was 4,5 kg.
3) She vomited twice in the last 2 weeks but otherwise was eating and drinking well.

4) Kidney parameters: urea 11,9 mmol/l; creatinine 235 µmol/l; P 1,48 mmol/l

5) Urine examination showed isosthenuria (SG: 1012) and mild proteinuria (UPC 0,75).

6) BP was normal: 153/88 mmHg

One Year after Kidney Injury – 09.06.2019

1) Holly was doing well.

2) BW was 5 kg.

3) There is mild polydipsia (0,5 l water/day) and polyuria.

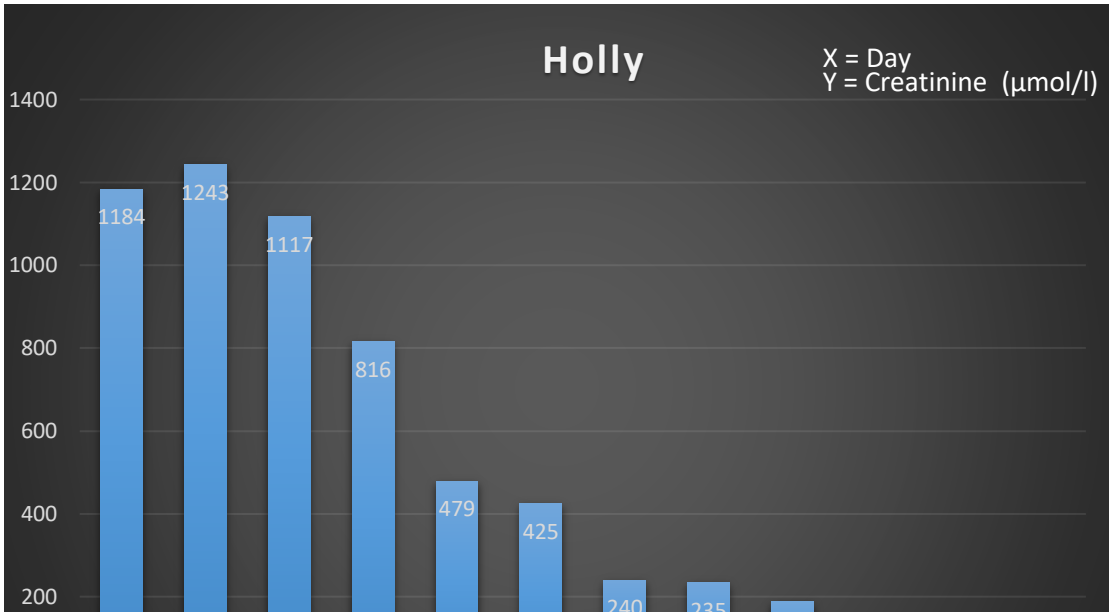
4) Kidney parameters: urea 11,1 mmol/l; creatinine 188 µmol/l; P 1,5 mmol/l

5) BP was normal: 118/66 mmHg

6.3.1 Conclusion case 3: Holly

- *With Holly's case I could show how important is measure (or at least to estimate) urine production.*
- *This case showed how easy it is to overhydrate a patient if clinicians don't take urine production into consideration.*
- *We have to pay special attention to fluid calculations in case of anuria and oliguria to avoid overhydration.*
- *Frequent BW measurements are also a crucial part of the management of overhydration.*

Graph 3: Holly's serum creatinine over the course of therapy



Conclusions

The main treatment of AKI other than supportive treatment is fluid therapy. Fluid therapy has the potential to resolve most of the disorders arising from AKI. The thesis reviewed the general guidelines for fluid therapy, and found that these guidelines are under an ongoing debate in veterinary literature; the recommendations for maintenance fluids calculations are mostly based on studies that were conducted on healthy animals. As such, they may represent a higher maintenance volume than sick and hospitalized patients often need. Thus, this should be taken under account when planning fluid therapy. Furthermore, the thesis found that when these guidelines are applied on AKI patients, they may or may not be appropriate because the fluid needs of AKI patients vary greatly. In a state of reduced kidney function,

the kidneys are not able to alter fluid volume and solute content. Thus, the guidelines that may fit many different conditions, may not always fit in AKI. The author's opinion is that the distinction between maintenance needs of hospitalized patients that are more active and less active is an important one. It is necessary to take into account the different factors that were described in detail in this thesis, when planning fluid therapy, for a more 'accuracy oriented approach' rather than using the general guidelines of maintenance fluids. It is possible that over a short period of hospitalization, differences arising from these factors can be minor, but that would rarely be the case in AKI patients, who may require between 1-3 weeks of hospitalization where fluid therapy is the main treatment. It would still be more proper to consider these differences when planning the course of fluid therapy than completely disregarding them and using a generalized formula. In addition to a careful, thoughtful and inclusive fluid therapy, frequent and deliberate monitoring is of great importance, as was seen in the last section of the thesis; the cases.

With the cases I could show how to manage hyperkalemia, hypokalemia, metabolic acidosis, dehydration, overhydration, and how to use calculations in the clinical setting. The cases show real life examples of the challenges in planning fluid therapy in AKI patients.

It can be seen from Bly's and Irma's cases why fluid therapy should be planned very carefully: Bly did not need any fluid therapy after 5 days while Irma needed extra fluids for 2 months.

There are several formulas available for calculation of maintenance therapy as I have shown in chapter 4. Some formulas are similar to one another while some formulas result in reduced volumes. The formula that was used for Bly's calculation, together with having to remove her urinary catheter and consequently not being able to measure 'ins and outs' to a tee, may have resulted in administration of larger fluid volumes than was needed, but in Irma's and Holly's case, the same formula was appropriate. These cases show that the need for fluid therapy can be very different between AKI patients, and no general calculation can be used in all cases. Therefore, frequent reassessments and close attention to monitoring and body weight are of highest significance. In Bly's case, the clinicians have spotted the changes on time thanks to close monitoring. In Irma's case, while she was at home for 2 days, severe dehydration occurred because she didn't receive the right amount of fluids. In Holly's case, exact monitoring of 'ins and outs' was possible, thus, setting the fluid therapy was easier.

These cases show it is absolutely crucial to monitor the patient as frequently as possible; body weight measurements should not be disregarded, 'ins and outs' should be measured with aiming for accuracy. There can be very rapid changes in fluid household of AKI, it is

important that the clinician is aware of that and will dare to make the necessary changes, as these cases show.

Summary

This thesis reviews the current literature of Acute Kidney Injury (AKI), its pathophysiological background, diagnosis and treatment recommendations. The thesis then reviews the subject of fluid therapy in general and the common guidelines, and highlights the special elements found in fluid therapy in AKI.

The thesis also presents three clinical cases to point out the conclusions and recommendations for the treatment of AKI patients. In the first case, fluid therapy had to be stopped very early in the course of the disease, in the second case clinicians could not stop fluid therapy for a very long time and, in the third case, severe overhydration had to be managed. This shows that the needs of fluid therapy differ between AKI patients and there is no singular course of treatment, but every case must be assessed individually and planned

carefully. Through the cases I could show how to manage the challenges (e.g. dehydration, overhydration, hyperkalemia, hypokalemia, metabolic acidosis) that may appear in the course of treating AKI in a clinical setting.

The conclusion of the thesis is that no generalized formula can be used in AKI, because the needs of AKI patients vary significantly. Due to that, fluid therapy must be planned cautiously and inclusively, with frequent reassessments and monitoring. I have also shown that the measurements of urine output and body weight are fundamental in the management of AKI.

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I hereby confirm that I am familiar with the content of the thesis entitled Fluid Therapy in Acute Kidney Injury of Dogs and Cats

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dr. Fruzsina Fales

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