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IRIS-Stage 4 CKD in a Dog: Diagnostic Approaches and Staging of Chronic Kidney Disease: A Case Study

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Glomerular filtration

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ABSTRACT

Chronic kidney disease (CKD) is a devastating disease of the kidneys that often arise from unresolved acute injury. As a chronic disease, CKD is challenging to diagnose, thus it needs a good combination of a comprehensive understanding of the kidney's anatomy and physiology and thorough planning for a framework of diagnostic tools to be utilized. This study is intended to provide the diagnostic planning used to determine CKD in an approximately 5-year-old intact male dog that was brought to My Vets Animal Clinic for a check-up visit. On presentation, the dog was emaciated, mildly dehydrated, halitotic, and infested with ticks. A complete blood count (CBC) indicated a normocytic, normochromic, non-regenerative anemia, and lymphopenia. The blood chemistry panel indicated azotemia, elevated symmetric dimethylarginine (SDMA), hypocalcemia, and hyperphosphatemia. Elevated SDMA level (64 µg/dL, reference value: 0-14 µg/dL) and hypercreatinemia (5.9 mg/dL, reference value: 0.5-1.8 mg/dL) indicated impaired glomerular filtration. Physical and clinical pathological findings signified the presence of CKD in this dog, with a stage-4 severity based on International Renal Interest Society (IRIS) CKD staging criteria. The prognosis of this case was highly guarded, and the dog eventually passed away on the sixth day of hospitalization. In a case with an uncertain outcome, accuracy in both diagnosis and staging of CKD in dogs will aid the therapy regimen planning, which may improve the patient's conditions.

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1 Introduction

Chronic kidney disease (CKD) refers to irreversible pathological alteration that most often arises from unresolved acute injury of the kidney. As a disease of chronicity, diagnosis can be challenging. Clinical symptoms is often subtle when results from diagnostic tools (*e.g.,* abdomen ultrasonography, clinical pathological evaluations) may indicate otherwise. Likewise, other chronic diseases such as metabolic disorders due to endocrinopathy and malignancy may present with the same symptoms as CKD. Therefore, it is important to rule out any other diseases, either being a different entity or concomitant, complicating disease, to diagnose CKD properly. This paper will discuss a case work-up of CKD in a dog, staged as a stage-4 CKD based on International Renal Interest Society (IRIS) CKD staging guideline.

2 Case Reports

A male, intact, mixed-breed dog was presented to My Vets Animal Clinic, BSD City, Indonesia. The dog was recently rescued by the client, approximately 2 weeks before the presentation, and had been brought to another veterinarian who diagnosed the dog with IRIS-stage-2 CKD. The dog had ongoing treatment with oral sodium bicarbonate, keto acids/analog (Aminoral®), and renal diet (Royal Canin Veterinary Diet® RenalTM dog formula).

Based on physical examination, cachexia (body condition score 2/9, Nestlé PURINA Body Condition System), mild dehydration (~6% based on slightly delayed skin turgor and tacky mucous membrane), and halitosis were identified. The characteristic "ammoniac breath" was suspected as uremic fetor. However, calculi were evident on the dog's teeth, hence it could not be ruled out as the possible cause of halitosis. Palpation of the body and auscultation of the heart and lungs were unremarkable, especially the urinary bladder, ruling out any post-renal urinary obstructions. Kidneys could not be appreciated due to thoracic cavity conformation. Because the clinical findings were not conclusive of any diseases with pathognomonic features, the use of other diagnostic tools was warranted. Analysis of complete blood count (CBC, IDEXX ProCyte Dx® Hematology Analyzer) and blood chemistry (IDEXX Catalyst One® Chemistry Analyzer, Chem 15®, SDMA test®) was done on the same day of presentation. Hemogram indicated normocytic, normochromic, non-regenerative anemia (RBC 4.42, reference range 5.65-8.87 x 10^6/µL; Hct 30.5, reference range 37.3-61.7%; Hb 10.2, reference range 13.1-20.5 g/dL; RDW 12.9, reference range 13.6-21.7%) and lymphocytopenia (0.80, reference range 1.05-5.10 x 10^3/µL). The blood chemistry panel indicated elevated serum symmetric dimethylarginine (SDMA, 64, reference range 0-14 µg/dL), creatinine (5.9, reference range 0-14 mg/dL), blood urea (>130, reference range 7-27 mg/dL), phosphate (>16.1, reference range 2.5-6.8 mg/dL) and decreased serum calcium (7.3, reference range 7.9-12.0 mg/dL). Both increased serum SDMA and creatinine indicated acute or chronic kidney injury. The dog, despite the serious increment in SDMA and creatinine levels, was relatively asymptomatic. Hyperphosphatemia and hypocalcemia, along with normocytic, normochromic, and non-regenerative anemia, also hinted at electrolyte disturbance and anemia of CKD, as discussed in the next section of this paper. Although the trends of BUN, creatinine, and SDMA levels in this dogs were not available, based on the serum SDMA and creatinine value, the dog was diagnosed with stage-4 CKD [Chronic Kidney Disease Guidelines, International Renal Society Interest (IRIS)].

Abdominal ultrasonography and blood pressure (BP) monitoring were conducted on the second day after the dog's initial presentation. Ultrasonography revealed narrowed renal medullar space and increased echogenicity of the renal cortex. No active inflammation was indicated, especially on the renal hilus connecting to the renal pelvis. The renal size was not unmeasured during the evaluation. Another abnormal finding from the ultrasonography was biliary sludge, covering up to 80% of the cystic lumen. BP monitoring revealed marked systolic hypertension (197, reference 90-140 mmHg; high-risk individuals, according to IRIS, are those with >40 mmHg above breed-specific blood pressure reference value). Macroscopic, chemical, and sedimentation urinalysis were performed the next day after the dog was admitted as an inpatient. The macroscopic feature of the urine was indicative of hypo- to isosthenuria (*i.e.,* clear urine with no turbidity, urine output was seen to be markedly increased, although quantification was not performed). Isosthenuria was then confirmed through refractometry (urine specific gravity of 1.012). Unstained urine sediment microscopic evaluation was performed, but it showed no apparent abnormalities, which ruled out lower urinary tract infection (UTI) and crystalluria.

During hospitalization, the dog was quiet, alert, and responsive. Polyuria and subsequent polydipsia were noticed, even though urine output quantification was not performed. The dog had postprandial vomiting for the first two days. The use of serotonin (5HT3) receptor antagoniston the first day of hospitalization, ondansetron (0.5 mg/kg IV q24h), was inadequate to suppress the emesis on the second day. Ondansetron was substituted with maropitant (1 mg/kg SQ q24h), and vomiting stopped the following days.

This dog was hospitalized for further evaluation and a timely treatment regimen. The treatment regimen was made specific to abnormalities found during diagnostic tests, though the use of some medications like sodium bicarbonate was not based on laboratory findings (*i.e.,* blood gas analysis), particularly bicarbonate and hydrogen concentration. Due to the mild nature of the dog's anemia, the use of hematopoietic hormone was postponed pending another CBC examination. The dog was treated

with a proprietary blend of calcium carbonate and chitosan (Yochito®) to treat hyperphosphatemia, antiemetics as previously described, and intravenous lactated Ringer's solution (500 mL per day). Other anecdotal drugs used in this case were proprietary keto acids (Aminoral®) and sucralfate (Inpepsa® 100 mg/ml). Other pharmacological agents were administered later, namely enalapril (0.56 mg kg-1 q24h) and ursodeoxycholic acid (Urdafalk® 250 mg, 1 capsule q24h), after hypertension and biliary sludge from abdominal ultrasonography were discovered, as mentioned previously. The dog died 6 days post-hospitalization. Postmortem evaluation was not conducted, thus making the cause of death undeterminable.

3 Discussion

3.1 Pathophysiology of CKD

CKD, as mentioned in the previous part, is characterized by the nearly irreversible damage of the kidney's functional units, nephrons. CKD, or chronic renal failure, is reported when the kidney loses one or more of its physiological functions including (1) metabolic waste excretion through urine formation, (2) acid-base regulation through reabsorption of bicarbonate and excretion of hydrogen, (3) conservation of water, (4) maintenance of intra- and extracellular electrolyte equilibrium, and (5) control of endocrine function, including renin-angiotensin-aldosterone (RAA) axis, calcitriol [1,25-(OH)2-D], and erythropoietin (Breshears and Confer, 2016). A nephron consists of an encapsulated glomerulus, proximal convoluted tubule, Henle's loops, distal convoluted tubule, and collecting tubule. Any disruptions in one or multiple parts of the nephron will subsequently cause renal failure. It takes a severely damaging insult to cause acute renal failure. This acute injury, if unresolved for more than three months, progresses into a chronic state of renal failure (Bartges 2012; Kovarikova 2015).

Damage to the kidney can happen both intrinsically (*e.g.,* renal ischemia, exposure to nephrotoxins) and extrinsically (*e.g.,* any circulation-related disorders that reduce kidney perfusion, any postrenal anomalies that may cause blockage of urine output). Decreased renal perfusion induces the kidneys into an ischemic state that, if it is severe and/or prolonged enough, causes acute necrosis of tubular cells which need high energy to meet the metabolic demand. The outer medulla of the kidney is at the greatest risk of hypoxia and subsequent necrosis due to the already hypoxic nature of the structure. Renal ischemia can be induced by non-steroidal anti-inflammatory drugs (NSAIDs), as any drugs of this class will cause a diminution of intrinsic prostaglandin E2 (PGE2) synthesis, an eicosanoid compound that is responsible for vasodilation of the afferent arteriole when the volume of circulating intravascular decreases (Wilson 2019). It should be noted that dehydration, or other causes of reduced intravascular volume, will cause vasoconstriction of the afferent arteriole which can result in the exacerbation of the renal ischemia and resultant uremic crisis due to the diminished intraglomerular pressure (DiBartola and Westropp 2014). Other nephrotoxic agents are more direct – drugs like aminoglycosides and mycotoxins such as aflatoxins may cause degenerative to necrotic damage of glomerulus and/or renal tubules (Yilmaz et al. 2018). The dog presented to My Vets Animal Clinic, BSD City, Indonesia was recently rescued, hence the cause of renal failure was not possible to be determined, although, according to Ross (2011), previous UTI, arthropod-borne infections (particularly ehrlichiosis, as tick infestation were apparent in this dog), prolonged dehydration, and ingestion of moderately nephrotoxic agents (e.g. chronic exposure of melamine, heavy metals, or organic compounds) may be attributed as the possible etiologies of early renal failure in this dog. Positive serological tests for *Ehrlichia* antibodies have been reported in multiple studies in Indonesian stray dogs (Bagus and Ardana 2017; Nesti et al. 2019; Putra et al. 2019), but further studies are imperative to determine the epidemiology of ehrlichiosis in Indonesian dogs to appropriately determine its risk factor. Serological testing for ehrlichiosis detection was not conducted in this dog, so this hypothesis is unproven. A recent retrospective study has indicated a 2.12 relative risk of CKD acquirement in dogs with ehrlichiosis, a 112% greater risk compared to those in the unexposed group (Burton et al. 2020).

During the initial phase of renal failure, there is latency when clinical signs are absent or minimal. If any kidney insults are removed, renal function will return rapidly. If the insult continues, renal failure enters its maintenance phase, indicating that a significant amount of injury has occurred in renal glomeruli and/or tubules. This phase can persist for 1-3 weeks until restoration happens. It is imperative, therefore, to promptly identify the type of injury (*e.g.,* nephrotoxins, renal ischemia due to decreased intravascular volume, nephrolith, or infection) and resolve the determined issue, although immediate removal of the inciting cause may not guarantee swift renal function restoration if an injury has progressed to the maintenance phase. Some etiological agents are more severe at inducing renal failure. For instance, lily and ethylene glycol induce severe kidney injury with very poor prognosis, even when a treatment like fluid therapy for correction of renal blood flow (RBF) is initiated. Serum creatinine and blood urea nitrogen (BUN) concentration usually will go down during the recovery phase because GFR is restored, ensuring normal diuresis in patients with clinical signs of oliguria or anuria (DiBartola and Westropp, 2014). However, most often than not, acute renal failure induces cellular maladaptation, causing an irreversible structural change in the nephrons (Breshears and Confer 2016).

As an organ responsible for fluid and electrolyte homeostasis, any disorders of the kidney will disturb this balance. This consequence

results from an orchestra of reduced GFR due to afferent arteriole vasoconstriction, leakage of filtered fluid across destroyed tubular epithelial cells into the interstitial space and/or occlusion of intraluminal space by dislodged damaged cells, casts or crystalloids, and/or reduction in glomerular permeability due to contraction of mesangial cells and its subsequent decrease in several fenestrations formed by podocytes, causing a significant reduction of effective filtrating surface area (DiBartola and Westropp 2014). Glomerulonephritis can also cause glomerular proteinuria, as intact glomeruli are responsible for the selective permeability of the filtrate so that protein greater than 70 kDa cannot be filtrated (Breshears and Confer 2016). Proteinuria, in renal failure, has been associated with further deterioration of the remaining renal function (Harley and Langston, 2012). Fluid disturbance was evident in this dog, and this abnormality is possibly attributable to the prevailing deterioration of kidney function. Proteinuria was detected based on a dipstick test (VET-10® urine test strips, KRUUSE). However, diagnostic acumen should be taken because proteinuria, especially in free-catch samples such as in this case, can be falsely positive in the presence of genital disease and other artifacts (*e.g.*, alkalized urine due to prolonged storage, presence of penicillin metabolites, microscopic hematuria). Urine sedimentation was done after initial dipstick evaluation and the result did not show active sediment (*i.e.*, presence of pus, erythrocytes, and/or casts). Therefore, proteinuria was concluded to be of intrarenal origin. Unfortunately, this finding was not evaluated further by the measurement of the urine protein-to-creatinine ratio. This evaluation is useful to determine the risk of any further renal damage that should be carefully addressed in the treatment regimen.

Potassium is a main intracellular cation and its concentration in extracellular space is tightly regulated. Patients with CKD may present with hypo- or hyperkalemia. Hypokalemia is usually associated with reduced renal reabsorption in the proximal tubules and abrupt reduction to elimination of sodium that results in activation of the RAA system and subsequent enhancement of potassium secretion from distal tubules (Palmer 2015; Polzin 2011). Renal failure, especially in stage-4 CKD, may cause renal hyperkalemia. Although common, hyperkalemia usually develops in patients with impaired renal excreting ability and/or concomitant disorders such as urine obstruction, adrenal insufficiency, and diabetes mellitus (Pak 2000). In humans, decreased renal function causes metabolic acidosis through increased retention of hydrogen cation and decreased reabsorption of bicarbonate anion, another renal metabolic disorder that may exacerbate hyperkalemia due to diminished potassium excretion by cortical collecting tubules in low blood pH (Breshears and Confer 2016; Krapf et al. 2008). Hyperkalemia-related clinical symptoms including muscle weakness and lethargy with clinical findings such as dysrhythmia and electrocardiograph (ECG) anomalies such as peaked T waves, increased PR intervals, and widened QRS complexes, indicating heart conductivity disorder (Parham et al. 2006). However, hyperkalemia can have a biphasic effect on conduction and excitation, dependent on the resting membrane potential level and the difference between the resting and the threshold potential. Indeed, the increased serum potassium level may initially speed up the ventricular repolarization due to less negativity of atrial myocytes' resting membrane potential and its subsequent elevated excitability threshold, then followed by a diminution in the cell membrane's depolarization ability due to increased resting membrane potential (Johns et al. 2011). ECG and serum potassium were not evaluated in this dog. However, the absence of arrhythmia based on heart auscultation indicated normal cellular electrical conductivity and possibly normal serum potassium level.

3.2 Other Consequences of CKD

There is a myriad of consequences that can happen in patients suffering from CKD. Reduction of RBF induces activation of the RAA axis which can cause systemic hypertension through increased heart preload volume and myocardial contractility exertion. Through this mechanism, other clinical consequences such as retinopathy, encephalopathy, myocardial hypertrophy, and further remaining renal function destruction ensue. Management of hypertension in CKD patients should be done and monitored periodically (Acierno et al. 2018). Due to the association between morbidity-mortality rate and hypertension, BP monitoring is critical. BP also can be used to determine the prognosis of CKD. This dog had severe systolic hypertension, indicating a high risk of multiple organ damage and further renal deterioration.

Tubular epithelial cells, especially the proximal convoluted tubule, synthesize cytochrome P450 enzyme (CYP27B1), and tubular degeneration and/or necrosis lessens the production of which substance is needed to hydroxylate 25-(OH)-D (calcidiol) into calcitriol. Calcitriol induces tubular and small intestinal calcium reabsorption. Phosphate, an anion that is mostly stored inside the bone, and to a lesser extent in the extracellular compartment, is mainly eliminated through renal excretion. In case of renal failure, serum phosphate is retained. Hypocalcemia and hyperphosphatemia may present with the sequelae of secondary hyperparathyroidism. Hyperparathyroidism leads to increased resorption of the bone, eventually worsening the hyperphosphatemia and hypocalcemia, as serum phosphate complexes with serum calcium. The blood chemistry panel of this dog indicated hypocalcemia and hyperphosphatemia, both of which are the causative agents of secondary hyperparathyroidism in CKD patients. Osteodystrophy and heterotopic ossification have been reported in CKD patients (Hruska et al. 2008; Polzin 2011; Stillion and Ritt 2009). This dog, however, was ambulatory with no gait anomalies, thus osteodystrophy was not indicated.

Metabolic acidosis is another clinical-pathological finding in patients with CKD. Renal function is essential to maintain the equilibrium of serum bicarbonates and hydrogen concentration. Bicarbonate is one of the main chemical buffers that are readily used to offset the fluctuation of hydrogen ions. Although the compensation is delayed in comparison to chemical buffer and respiratory compensation, renal compensation remains vital in maintaining blood pH value. In acidic blood, normal renal parenchyma, especially the proximal convoluted tubules, will increase their bicarbonate reabsorption and hydrogen secretion through Na^+/H^+ exchangers, H^+-ATPases, and Na^+/HCO_3^- co-transporters. Another key player of renal metabolic acidosis is the increased retention of acid anions (*i.e.*, uremic acidosis, marked by elevation of organic acid concentration such as phosphoric acid), contributing to the diminution of blood pH, marked by high serum anion gap (Ha et al. 2013; Kraut and Madias, 2010). When metabolic acidosis happens respiratory compensation entails where carbon dioxide is actively exhaled, thus decreasing the carbon dioxide partial pressure (PCO2). About 1.0 mmHg of PCO_2 will be reduced to offset the 1 mEq/L decrement of bicarbonate concentration. This compensatory mechanism starts immediately when pH drops and usually completes within hours, and it should be noted that this compensatory mechanism will eventually get overwhelmed if acidification continues (DiBartola 2012).

3.3 Staging and Sub-Staging of CKD

Once CKD has been determined as the definitive diagnosis, staging and sub-staging entail. Staging and sub-staging are done in accordance to the IRIS' chronic kidney disease guidelines that have been approved by the American and European Societies of Veterinary Nephrology and Urology (Kovarikova 2015; Polzin 2011). Based on laboratory results, the dog, in this case, was diagnosed with stage-4 CKD with a high risk of multiorgan damage due to severe systolic hypertension. Proteinuria had been screened with dipstick, and was not evaluated by UP/C, hence characterization of proteinuria in this dog is not available. To stage CKD, both serum creatinine and SDMA are used. IRIS' chronic kidney disease guideline recommends both parameters to be assessed together. However, in many instances where SDMA quantification is unavailable, staging based on fasted serum creatinine level is also possible. However, early detection may be impossible when serum creatinine level was used as a sole parameter of staging. Care must be taken that, if possible, serum creatinine level is measured on two separate occasions, all of which should be done in fasted and hydrated state, to rule out prerenal azotemia (Polzin 2011; Kovarikova 2015; Sargent et al. 2021). Staging of CKD in this dog was done immediately after the hematological evaluation dog was first presented. Sub-staging of this dog was conducted on the second day of hospitalization. Although UP/C was not evaluated in this case, the authors strongly encourage all clinicians to perform UP/C when presented with a confirmed case of CKD in their patients.

Table 1 IRIS stages of CKD in cats and dogs

Parameters	Dog	Cat
Creatinine (mg/dL)		
Stage 1	< 1.4	< 1.6
Stage 2	1.4 – 2	1.6 – 2.8
Stage 3	2.1 – 5	2 – 5
Stage 4	> 5	> 5
SDMA (µg/dL)		
Stage 1	> 18	> 18
Stage 2	18 – 35	18 – 25
Stage 3	36 – 54	26 – 38
Stage 4	> 54	> 38

SDMA has been gaining recognition as a novel endogenous biomarker that offers sensitivity in early renal failure detection in comparison with creatinine. Creatinine has been used both in human and veterinary medicine to assess renal function, in particular renal clearance. However, a steep curvilinear relationship between GFR and serum creatinine revealed no significant increase in serum creatinine until a significant diminution of GFR occurs, making creatinine a less sensitive renal biomarker to signify early renal failure. It is estimated that 75% of nephron loss will result in a value that is higher than the upper-limit value. Therefore, several measurements need to be taken to detect any subtle changes in serum creatinine levels (Kovarikova 2015; Hall et al. 2016). Serum creatinine is also affected by an extrarenal factor, especially the percentage of lean body mass and biological age of the patient. SDMA is an N-methylated form of arginine residue methylation, a post-translational modification that aids in its detection after release through proteolysis. SDMA has a renal clearance of up to 90% and even a slight elevation from its serum concentration reference range readily alerts for renal damage. Previously, its measurement had always been done by use of liquid-chromatography-mass spectrometry (LC-MS). Presently, SDMA assay is offered by a commercial veterinary diagnostic laboratory, IDEXX, through high-throughput immunoassay, thus offering less analytical variability. It should be considered, however, that SDMA may be affected by the patient's age and breed. One study indicated that a healthy, young dog had serum SDMA of up to 16 µg/dL, a concentration that otherwise will indicate mild elevation in adult dogs. It has been discovered that greyhounds have significantly higher mean serum SDMA concentrations in comparison to other dog breeds. Conclusively, it is advised to interpret serum SDMA concentration in both juvenile animals and greyhound dogs carefully, especially if other

Table 2 IRIS sub-stages of CKD in cats and dogs

	Dog	Cat
UP/C		
Proteinuria	Proteinuria	Proteinuria
Borderline proteinuria	Borderline proteinuria	Borderline proteinuria
Non proteinuria	Non proteinuria	Non proteinuria
Mean arterial blood pressure (dog, systolic; cat, diastolic) (mmHg)		
Minimum risk	< 150	< 95
Low risk	150 – 160	95 – 99
Moderate risk	160 – 179	100 – 119
High risk	≥ 180	≥ 120

diagnostic tools such as urinalysis and ultrasonography are at the clinician's disposal (Sargent et al. 2021). SDMA algorithm has been excellently provided by IDEXX and can aid in the early detection of renal failure[1].

Sub-staging of CKD facilitates the determination of prognosis and clinical reasoning necessary for pharmacological intervention that should be used on the patient. IRIS recognizes two sub-staging parameters, UP/C and BP. UP/C is a gold-standard test to determine risk factors associated with proteinuria and should be done after the dipstick test indicated a trace of increased protein in the urine. After urine sedimentation has been evaluated and the presence of active sedimentation has been ruled out, UP/C will help to distinguish the degree of proteinuria in the patient. BP, as already mentioned in the previously in this paper, needs to be monitored because renal failure will subsequently increase the activation of the RAA axis. Hypertension significantly increases the mortality rate in CKD patients. It is recommended that both parameters are evaluated at least twice over several weeks to accurately sub-stage the CKD (IRIS 2019).

3.4 Planning the treatment regime

Once staging and sub-staging have been done, choosing the right treatment regimen is the next thing a clinician should do. According to IRIS' Treatment Recommendations for CKD in Dogs[2], treatment in CKD patients is used to (1) impede the progression of CKD, hence the remaining renal function is spared, and (2) improve the life quality of the patient by correcting any CKD-associated clinical abnormalities. The former treatment goal is especially important in stage 1 and 2 patients, emphasizing the earlier the diagnosis, the better the prognosis. In CKD patients, it is important to identify any other intrarenal factors that potentially exacerbate renal failure. Identification and elimination of exposure to nephrotoxic agents, concomitant UTI, and/or urolithiasis, particularly nephroliths, and treatment of extrarenal abnormalities are important to preserve the remaining renal function and improve the life quality of the patient (Polzin 2011). In addition to CKD-associated clinical consequences, the dog, in this case, was also diagnosed with biliary sludge through abdominal ultrasonography. With this regard, the use of drugs unrelated to renal failure will also be discussed in this paper.

Correction of dehydration and maintenance of hydration ensure euvolemia and adequate renal perfusion. Therefore, it is important to provide an ample quantity of fresh water for the patient. However, it should be underscored that CKD patients might have impaired renal ability to appropriately concentrate the urine. It is of utmost importance, therefore, to quickly correct any clinical dehydration and/or hypovolemia with intravenous fluid administration. Lactated Ringer's solution (273 mOsm/L) was used (500 mL, dripped over 9 hours, q24h) to correct dehydration in this dog. Because the dog was still drinking, administered volume was estimated based on dehydration level and ongoing loss that was vomiting and polyuria. Vomiting happened twice a day for the first two days before finally being managed using a maropitant. It was noted, however, that the volume of fluid administered might have not been adequate because tacky mucous membranes and slightly delayed skin turgor were persistent throughout the dog's hospitalization. According to Polzin (2011), the use of crystalloid isotonic solution should be adjusted based on the patient's response. In other words, an increase in the volume administered would have been appropriate to correct the hydration status of the patient. It is also greatly suggested that ongoing loss (*e.g.*, urine output, vomiting, diarrhea) needs to be measured in the future, as it will help with the prudent calculation of fluid therapy that will be administered to the patient (DiBartola and Bateman 2012).

[1]IDEXX. https://ca.idexx.com/en-ca/veterinary/reference-laboratories/sdma/interpreting-your-sdma-results/
[2]IRIS. (2019). http://www.iris-kidney.com/pdf/IRIS-DOG-Treatment_Recommendations_2019.pdf

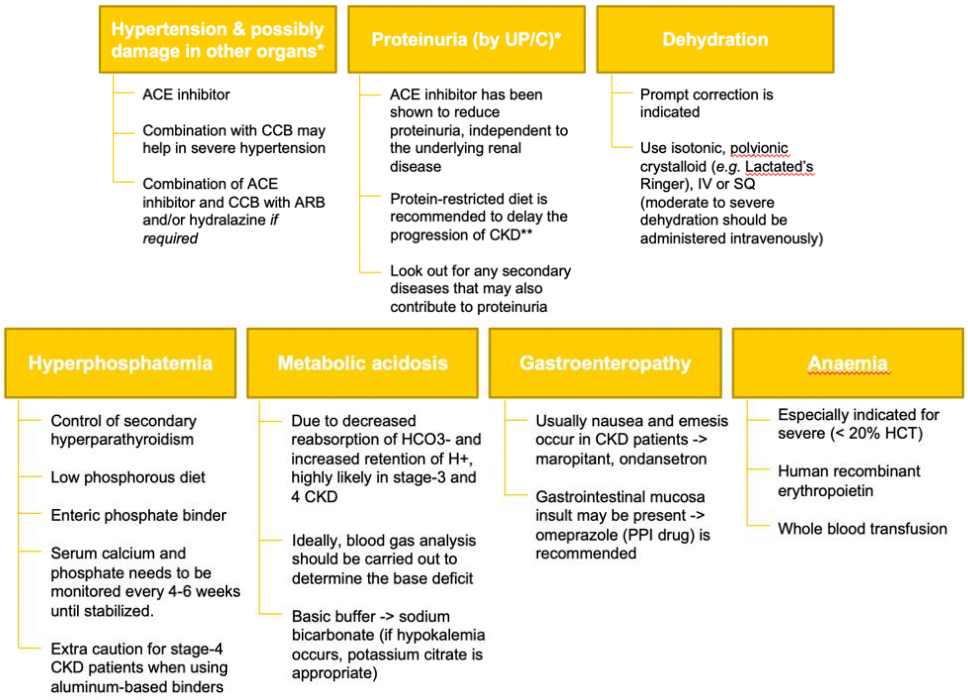

Figure 1 Approach to treatment of CKD patients (adopted from IRIS)
** In conjunction with low phosphorus dietary plan

Compared to human medicine, BP monitoring remains challenging for veterinarians on the account of differences in subject populations, measurement techniques, and handling methods. Hound dogs are found to naturally have higher arterial blood pressure than other dog breeds. In dogs, males have higher arterial BP, even when the males subjected to BP readings are already castrated, whereas intact females have lower BP. In contrast, neutered male cats have higher BP than females and even their intact counterparts (Acierno et al. 2018). In addition to those differences, the endpoint of antihypertensive drug administration in cats and dogs remains a moot point (Polzin 2011). Therefore, judicious use of antihypertensive drugs is necessary. ACEI is beneficial in reducing intraglomerular hemodynamics and its subsequent degree of proteinuria. Although ACEI can inhibit RAA system activation and its following elevation in systemic vascular resistance, its ameliorating effect is thought to be more attributed to its vasodilating effect in efferent arterioles, notwithstanding its lack of data to prove its efficacy and superiority against other antihypertensive agents in advanced CKD, at least in human (Hou et al. 2006; Ahmed et al. 2016). Nonetheless, the use of ACEI is recommended as the first-line antihypertensive drug according to IRIS, hence the use of enalapril (0.5 mg/kg q24h) in this dog. The efficacy of this drug in managing the dog's hypertension and suspected proteinuria could not be assessed. However, an increase in dosing frequency from q24h to q12h is recommended when enalapril is used, especially in severely hypertensive patients, and the addition of renal diet as an adjunct is shown to be more efficacious than the use of enalapril alone (Zatelli et al. 2016). Enalapril should never be used unless dehydration has been corrected and long-term monitoring is advised due to increased elimination half-life as the kidney plays a major role in the drug's metabolite excretion (Plumb 2011).

As mentioned in the previous part, hyperphosphatemia is detrimental due to its induction of secondary hyperparathyroidism and further exacerbation of renal failure. Secondary hyperparathyroidism and inhibition of calcitriol production will worsen the hypocalcemia state, if present, in CKD patients (Hruska et al. 2008; Stillion and Ritt 2009). In this case, the dog was treated with a proprietary blend of chitosan and calcium carbonate (q12h, with meal). In addition to the administration of the previously mentioned phosphate scavenger, the dog also received a renal diet that is low in phosphorus. Although hyperphosphatemia management in stage-3 and 4 CKD gives no merit in slowing down CKD progression, it can, at least, improve the patient's life quality. Aluminum (in hydroxide, oxide, or carbonate form), lanthanum (in carbonate form), and calcium (in acetate, carbonate, or citrate form) are used, although the use of aluminum-based phosphate binder is discouraged because of its nephrotoxicity (Segev et al. 2008; Polzin 2011).

Amelioration of renal metabolic acidosis is preferably done upon confirmation through blood gas analysis which can provide information regarding the patient's blood pH value and the serum

level of bicarbonate, so bicarbonate deficiency can be identified and calculated. The calculation is therefore advised by using the following formula[3]: [(n of the desired HCO3-) – (n of measured HCO3-)] x 0.5 x BW (kg), although patients with confirmed metabolic acidosis may require an additional dose of bicarbonate. When blood gas analysis is performed, it should be noted that aerobic handling of blood samples does not affect dissolved bicarbonate concentration while it affects carbon dioxide concentration (DiBartola 2012). Administration of bicarbonate has been used in human patients with a satisfactory result in the retardation of CKD progression and improvement of nutritional status (Bartges 2012). Sodium bicarbonate (500 mg, q12h) was used to treat presumptive metabolic acidosis in this dog, even though blood bicarbonate concentration is unknown. Care should be given to avoid overzealous alkalization of the blood (*i.e.*, not exceeding 19-23 mEq/L of bicarbonate), as no recommended dose of sodium bicarbonate in cats and dogs with CKD has been established (Zatelli et al. 2012). In an experimental setting, a dose of 0.01 g/kg body weight, divided into two daily administrations with a meal was seen to be beneficial for increasing serum bicarbonate levels in dogs with advanced CKD. However, considerations should be taken because the administration of sodium bicarbonate in this study used a proprietary amalgam of other substances such as calcium lactate gluconate, calcium carbonate, and chitosan (Martello et al. 2020).

Constant vomiting can exacerbate the existing fluid and electrolyte imbalances in CKD patients. This is particularly induced by uremia and the clinical presage is not limited to nausea and vomiting. Stomatitis, uremic fetor, gastrointestinal ulceration and hemorrhage, diarrhea, and hemorrhagic colitis are common alimentary tract signs in patients with stage-3 and 4 CKD. Reduced GFR also results in increased gastrin half-life, causing upregulation of hydrochloric acid by parietal cells of gastric fundus and corpus, consequently exacerbating gastrointestinal symptoms by directly insulting gastric mucosa (Santacoloma Osorio et al. 2017). Therefore, the use of gastric acid blockers and antiemetics is recommended in CKD patients. In this study, ondansetron (0.5 mg/kg, IV, q24h) and sucralfate (1 g/30 kg, q12h before meal) were used in this patient. However, ondansetron administration, in this case, may not be sufficient to suppress nausea and vomiting due to the under-frequency of drug administration (therapy regimen, in this case, was 0.5 mg/kg IV q24h, but its pharmacokinetic property, particularly its half-life and elimination rate, warrants for a constant rate infusion administration of 0.5 mg/kg/h up to 6 hours) (Plumb 2011). Sucralfate administration in CKD patients remains debatable due to the increased risk of aluminum toxicity, particularly in long-term use (Hemstreet 2001; Segev et al. 2008). Nevertheless, Polzin (2011) suggests that the use of sucralfate may be beneficial for gastric lining protection. Administration of a proton-pump inhibitor, omeprazole (0.5 mg/kg, q24h, IV), was started the day after initial gastrointestinal drugs were given. In addition, due to refractory postprandial vomiting, ondansetron was substituted with another antiemetic agent with a longer half-life and potentially more central action (neurokinin-1 antagonist compared to 5-HT3 antagonist), maropitant (1 mg/kg, q24h, SQ). Vomiting was resolved afterward.

Anemia, in this case, was treated with hematopoietic factor supplementation (Sangobion®) that contains ferrous gluconate. Iron supplementation has been associated with the alleviation of anemia by increasing the production of heme and subsequently hemoglobin (Naigamwaila et al. 2012). As anemia of chronic disease, erythrocytes in CKD patients are usually fragmented with/without the presence of Howell-Jolly bodies if a microscopic blood smear evaluation is performed. CBC finding characteristic of anemia of chronic disease is its poorly non-regenerative state as indicated by reticulocyte count and red blood cell distribution width (RDW) (Lippi et al. 2021). An erythropoiesis-stimulating agent such as human recombinant erythropoietin (not approved for veterinary use) and darbepoetin is indicated when anemia is severe enough, as manifested through hematocrit value (< 20%). Erythropoiesis-stimulating agent administration needs to be monitored for the risk of hypertension exacerbation in animals with CKD has been reported (Acierno et al. 2018).

The use of keto acids (Aminoral®) was another empirical therapy that was given to this dog. Keto acids or keto analogs are precursors of essential amino acids so through the process of amino acids transfer, ammonia (NH_3) can be consumed. In human medicine, with the addition of a low protein diet, administration of keto acids has been shown to impede the deterioration of renal function, though it should be noted that a review study suggested no significant differences in serum creatinine and blood urea nitrogen (BUN) between control (untreated) group and treatment groups (Jiang et al. 2016). Albeit that, in veterinary medicine, the study of keto acid administration remains polarized. According to a study conducted by Zatelli et al. (2017), supplementation of keto analogs might prevent the decrement of proteinuria (UP/C) and serum urea concentration, although the supplemented group did show improvement in terms of body condition score (BCS) and serum albumin. Another study conducted in dogs with stage-3 CKD indicated no improvement in terms of BUN and serum creatinine value (Linguori et al. 2018). Therefore, further studies are warranted before keto acid supplementation is recommended in dogs.

Conclusion

Appropriate diagnosis of CKD and its entailing staging and sub-staging play a crucial factor in the determination of a patient's life expectancy through meticulous treatment regimen planning and

[3]Dodam, J. (n.d). *Sodium bicarbonate*. https://www.vetstream.com/treat/canis/generics/sodium-bicarbonate

periodic monitoring. Not every drug recommended is necessary to be administered – sagaciousness to discriminate clinical and laboratory findings are advised.

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References

Acierno, M. J., Brown, S., Coleman, A. E., Jepson, R. E., Papich, M., Stepien, R. L., & Syme, H. M. (2018). ACVIM consensus statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *Journal of Veterinary Internal Medicine*, *32*(6), 1803. https://doi.org/10.1111/JVIM.15331

Ahmed, A., Jorna, T., & Bhandari, S. (2016). Should We STOP Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers in Advanced Kidney Disease? *Nephron*, *133*(3), 147–158. https://doi.org/10.1159/000447068

Bagus, I., & Ardana, K. (2017). Laporan Kasus : Ehrlichiosis Pada Anjing Kintamani Bali. *Indonesia Medicus Veterinus*, *6*(1), 68–74. https://doi.org/10.19087/imv.2017.6.1.71

Bartges, J. W. (2012). Chronic Kidney Disease in Dogs and Cats. *Veterinary Clinics of North America - Small Animal Practice*, *42*(4), 669–692. https://doi.org/10.1016/j.cvsm.2012.04.008

Breshears, M. A., & Confer, A. W. (2016). The Urinary System. In J. Zachary & M. McGavin (Eds.), *Pathologic Basis of Veterinary Disease* (6th ed.). Elsevier.

Burton, W., Drake, C., Ogeer, J., Buch, J., Mack, R., McCrann, D., & Coyne, M. J. (2020). Association Between Exposure to Ehrlichia spp. and Risk of Developing Chronic Kidney Disease in Dogs. *Journal of American Animal Hospital Association*, *56*. https://doi.org/10.5326/JAAHA-MS-7012

DiBartola, S. P. (2012). Introduction to Acid-Base Disorders. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice*, 231–252. https://doi.org/10.1016/B978-1-4377-0654-3.00016-0

DiBartola, S. P., & Bateman, S. (2012). Introduction to Fluid Therapy. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice*, 331–350. https://doi.org/10.1016/B978-1-4377-0654-3.00021-4

DiBartola, S. P., & Westropp, J. L. (2014). Urinary Tract Disorders. In R. W. Nelson & C. G. Couto (Eds.), *Small Animal Internal Medicine* (5th ed., p. 629). Elsevier.

Ha, Y. S., Hopper, K., & Epstein, S. E. (2013). Incidence, Nature, and Etiology of Metabolic Alkalosis in Dogs and Cats. *Journal of Veterinary Internal Medicine*, *27*(4), 847–853. https://doi.org/10.1111/jvim.12122

Hall, J. A., Yerramilli, M., Obare, E., Yerramilli, M., Almes, K., & Jewell, D. E. (2016). Serum Concentrations of Symmetric Dimethylarginine and Creatinine in Dogs with Naturally Occurring Chronic Kidney Disease. *Journal of Veterinary Internal Medicine*, *30*(3), 794–802. https://doi.org/10.1111/JVIM.13942

Harley, L., & Langston, C. (2012). Proteinuria in dogs and cats. *Canadian Veterinary Journal*, *53*(6), 631–638.

Hemstreet, B. A. (2001). Use of sucralfate in renal failure. *The Annals of Pharmacotherapy*, *35*(3), 360–364. https://doi.org/10.1345/APH.10117

Hou, F. F., Zhang, X., Zhang, G. H., Xie, D., et al. (2006). Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency. *New England Journal of Medicine*, *354*(2), 131–140. https://doi.org/10.1056/nejmoa053107

Hruska, K. A., Mathew, S., Lund, R., Qiu, P., & Pratt, R. (2008). Hyperphosphatemia of Chronic Kidney Disease. *Kidney International*, *74*(2), 148. https://doi.org/10.1038/KI.2008.130

Jiang, Z., Zhang, X., Yang, L., Li, Z., & Qin, W. (2016). Effect of restrictd protein diet supplemented with keto analogues in chronic kidney disease: a systematic review and meta-analysis. *International Urology and Nephrology*, *48*(3): 409-418. https://doi.org/10.1007/s11255-015-1170-2

Johns, S. M., Stern, J. A., & Nelson, O. L. (2011). ECG of the Month. *Journal of the American Veterinary Medical Association*, *238*(8), 982–984. https://doi.org/10.2460/javma.238.8.982

Kovarikova, S. (2015). Urinary biomarkers of renal function in dogs and cats: A review. *Veterinarni Medicina*, *60*(11), 589–602. https://doi.org/10.17221/8527-VETMED

Krapf, R., Seldin, D. W., & Alpern, R. J. (2008). Clinical Syndromes of Metabolic Acidosis. In R. J. Alpern & S. C. Hebert (Eds.), *Seldin and Giebisch's The Kidney* (4th ed., pp. 1667–1720). Academic Press. https://doi.org/10.1016/B978-012088488-9.50062-0

Kraut, J. A., & Madias, N. E. (2010). Metabolic acidosis: Pathophysiology, diagnosis and management. *Nature Reviews Nephrology*, *6*(5), 274–285. https://doi.org/10.1038/NRNEPH.2010.33

Lippi, I., Perondi, F., Lubas, G., Gori, E., Pierini, A., D'addetta, A., & Marchetti, V. (2021). Erythrogram patterns in dogs with chronic kidney disease. *Veterinary Sciences*, *8*(7). https://doi.org/10.3390/vetsci8070123

Liguori, T.T.A., Melchert, A., Takahira, R.K., Ramos, P.R.R., Padovani, C.R., Barretti, P., & Guimarães-Okamoto, P.T.C. (2018). Randomized controlled clinical trial of ketoanalogues supplementation in dogs with chronic kidney disease. *PesquisaVeterinariaBrasileira,*, *38*(3): 489-495. http://doi.org/10.1590/1678-5150-pvb-5245

Martello, E., Perondi, F., Capucchio, M. T., Biasato, I., Biasibetti, E., Cocca, T., Bruni, N., & Lippi, I. (2020). Efficacy of a new dietary supplement in dogs with advanced chronic kidney disease. *PeerJ*, *8*. https://doi.org/10.7717/peerj.9663

Naigamwaila, D. Z., Webb, J. A., & Giger, U. (2012). Iron deficiency anemia. *The Canadian Veterinary Journal*, *53*(3), 250. /pmc/articles/PMC3280776/

Nesti, D. R., Baidlowi, A., Ariyanti, F., & Tjahajati, I. (2019). Deteksi Penyakit Zoonosis Ehrlichiosis pada Pasien Anjing di Klinik Hewan Jogja. *Jurnal Nasional Teknologi Terapan (JNTT)*, *2*(2), 191. https://doi.org/10.22146/jntt.42966

Pak, S. I. (2000). The clinical implication of sodium-potassium ratios in dogs. *Journal of Veterinary Science (Suwon-Si, Korea)*, *1*(1), 61–65. https://doi.org/10.4142/jvs.2000.1.1.61

Palmer, B. F. (2015). Regulation of Potassium Homeostasis. *Clinical Journal of the American Society of Nephrology*, *10*(6), 1050. https://doi.org/10.2215/CJN.08580813

Parham, W. A., Mehdirad, A. A., Biermann, K. M., & Fredman, C. S. (2006). Hyperkalemia Revisited. *Texas Heart Institute Journal*, *33*(1), 40. /pmc/articles/PMC1413606/

Plumb, D. C. (2011). *Plumb's Veterinary Drug Handbook* (7th ed.). PharmaVet Inc.

Polzin, D. J. (2011). Chronic Kidney Disease in Small Animals. *Veterinary Clinics of North America - Small Animal Practice*, *41*(1), 15–30. https://doi.org/10.1016/j.cvsm.2010.09.004

Putra, W. G., Widyastuti, S. K., & Batan, I. W. (2019). Laporan Kasus : Anaplasmosis dan Ehrlichiosis pada Anjing Kampung di Denpasar , Bali. *Indonesia Medicus Veterinus*, *8*(4), 502–512. https://doi.org/10.19087/imv.2019.8.4.502

Ross, L. (2011). Acute Kidney Injury in Dogs and Cats. *Veterinary Clinics of North America - Small Animal Practice*, *41*(1), 1–14. https://doi.org/10.1016/j.cvsm.2010.09.003

Santacoloma Osorio, M., Giraldo, G. C., Santacoloma Osorio, M., & Giraldo, G. C. (2017). Gastrointestinal manifestations of chronic kidney disease. *Revista Colombiana de Nefrología*, *4*(1), 17–26. https://doi.org/10.22265/ACNEF.4.1.266

Sargent, H. J., Elliott, J., & Jepson, R. E. (2021). The new age of renal biomarkers: does SDMA solve all of our problems? *Journal of Small Animal Practice*, *62*(2), 71–81. https://doi.org/10.1111/jsap.13236

Segev, G., Bandt, C., Francey, T., & Cowgill, L. D. (2008). Aluminum toxicity following administration of aluminum-based phosphate binders in 2 dogs with renal failure. *Journal of Veterinary Internal Medicine*, *22*(6), 1432–1435. https://doi.org/10.1111/j.1939-1676.2008.0206.x

Stillion, J. R., & Ritt, M. G. (2009). Renal Secondary Hyperparathyroidism in Dogs. *Compendium*, E1–E11. http://vetfolio-vetstreet.s3.amazonaws.com/mmah/79/c1332da0b74423883f86f1d932c022/filePV0709_Stillion_0.pdf

Wilson, D. N. (2019). *Prostaglandins and Kidney Function : A Comparison Between the Cortical and Inner Medullary Collecting Duct on Prostaglandin Production PROSTAGLANDINS AND KIDNEY FUNCTION : A COMPARISON BETWEEN THE CORTICAL AND INNER MEDULLARY COLLECT*. University of Nebraska Medical Center.

Yilmaz, S., Kaya, E., Karaca, A., & Karatas, O. (2018). Aflatoxin B 1 induced renal and cardiac damage in rats: Protective effect of lycopene. *Research in Veterinary Science*, *119*, 268–275. https://doi.org/10.1016/J.RVSC.2018.07.007

Zatelli, A., Pierantozzi, M., D'Ippolito, P., Bigliati, M., & Zini, E. (2012). Effect of dietary supplements in reducing probability of death for uremic crises in dogs affected by chronic kidney disease (Masked RCCT). *The Scientific World Journal*, *2012*. https://doi.org/10.1100/2012/219082

Zatelli, A., Roura, X., D'Ippolito, P., Berlanda, M., & Zini, E. (2016). The effect of renal diet in association with enalapril or benazepril on proteinuria in dogs with proteinuric chronic kidney disease. *Open Veterinary Journal*, *6*(2), 121–127. https://doi.org/10.4314/ovj.v6i2.8

Zatelli, A., D'Ippolito, P., Roura, X., &Zini, E. (2017). Short-term effects of dietary supplementation with amino acids in dogs with proteinuric chronic kidney disease. *The Canadian veterinary journal = La revue veterinairecanadienne*, *58*(12), 1287–1293.