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RENAL HEALTH *in* VETERINARY MEDICINE

Making the most of available renal health markers for optimizing kidney health in canine and feline patients

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INSIDE

Renal health evaluation is critical

Kidney disease and injury are common in veterinary patients and cause significant morbidity and mortality, especially in senior pets. The International Renal Interest Society (IRIS) has established helpful guidelines for staging and treating kidney disease, but identifying cases early remains challenging. Detecting renal dysfunction in the initial stages is critical for slowing progression and improving patient longevity and quality of life. This booklet details the importance of evaluating renal health in canine and feline patients and explains new tests that may help guide your diagnostic and therapeutic planning.

Meet the Experts

Several key opinion leaders in veterinary renal health contributed their expertise to this booklet to provide the most up-to-date information.

JD Foster, VMD, DACVIM (SAIM), MS (Pharmacology and Toxicology)
Director of the Extracorporeal Therapies Service at Friendship Hospital for Animals in Washington, DC

Dr. Foster is a founding member of the American College of Veterinary Nephrology and Urology, an IRIS board member, and previous president of American Society of Veterinary Nephrology and Urology. He has lectured around the world on various renal and urinary diseases and authored numerous manuscripts and book chapters on these topics.

Christine Kirnos, VMD, CVA
Owner and Medical Director of The Cat Hospital of Media in Media, PA

Dr. Kirnos has worked exclusively in feline veterinary practices since 2003 where she routinely sees cats affected by kidney disease. She is a member of the American Association of Feline Practitioners, Veterinary Information Network, and the International Veterinary Academy of Pain Management, and serves on the Board of Referring Veterinarians for the University of Pennsylvania School of Veterinary Medicine.

Gregory F. Grauer, DVM, MS, DACVIM (Small Animal Internal Medicine)
Professor Emeritus of Small Animal Internal Medicine, Department of Clinical Sciences at Kansas State University College of Veterinary Medicine

Dr. Grauer's clinical and research interests involve the small animal urinary system. He serves on the board of directors for IRIS and previously served on the board of directors for the North American Society of Veterinary Nephrology and Urology, and he has published numerous research articles focused on kidney disease.

Sarah Sweet, DVM
Global Medical Affairs Specialist for the Renal and Cardiac franchises at IDEXX

Dr. Sweet practiced small animal medicine in Massachusetts, New Hampshire, and Maine. She is a past president of the Maine Veterinary Medical Association and was named Maine's Emerging Leader by the AVMA in 2011. She joined IDEXX Laboratories in 2018 and has extensive knowledge about canine and feline renal health as well as IDEXX's newest tools to help diagnose and monitor kidney disease.

Renal health's effect on overall pet wellness

Kidney function is essential for life, and kidneys play an integral role in a patient's overall health status. The nephron is the kidney's basic functional unit—dogs have an estimated 400,000 nephrons per kidney, while cats have about 200,000 per kidney. The kidneys receive approximately 25% of the cardiac output, which makes them susceptible to injury from hypo- and hypertension.[1]

Important Kidney Functions

- **Toxin removal** — The kidneys filter metabolic waste from the body, but major damage to the nephron can lead to the accumulation of waste products in the bloodstream, leading to uremia.
- **Water conservation** — The kidneys react to the amount of water consumed and produce dilute or concentrated urine to keep the body properly hydrated. Water and small particles pass through the nephron's filtration units, creating a urine filtrate that then travels through the nephron's tubular system. Urine concentration is determined by how much water and/or solutes are resorbed during this process. When the kidneys malfunction, they lose the ability to concentrate urine.
- **Blood pressure regulation** — The kidneys are part of the renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure by balancing fluids and electrolyte levels and regulating vascular tone and resistance. Hypertension is a common complication of kidney disease and can result in secondary damage to the eyes, heart, and nervous system.
- **Red blood cell maintenance** — The kidneys produce erythropoietin, which triggers the bone marrow to maintain red blood cell (RBC) volume. Patients with kidney disease have decreased erythropoietin production resulting in anemia.
- **Protein conservation** — A healthy kidney filters waste products and conserves important proteins. Damage to the glomerulus can result in protein loss, detected as proteinuria (i.e., increased protein concentration in the urine), which is a sequela to kidney disease. Nephrons are further damaged when the glomerulus and tubules are exposed to increased protein concentrations during the glomerular filtering process.

"In all states of health and disease, we rely on the kidneys to do their job, and they perform amazingly well, except when they can't."

—JD Foster, VMD, DACVIM (SAIM), MS (Pharmacology and Toxicology)

- **Drug processing** — Many medications are processed and removed through the kidneys.
- **pH balance** — The kidneys maintain acid-base balance by reabsorbing bicarbonate from the urine back to the blood and secreting hydrogen ions into the urine, adjusting the amounts absorbed and secreted to balance the blood's pH.
- **Calcium-phosphorus balance** — When the number of nephrons declines, glomerular filtration is impaired, resulting in decreased excretion of phosphorus. Increased phosphorus concentration stimulates the production of parathyroid hormone (PTH), which can lead to metabolic bone disease and potentially to the mineralization of soft tissues such as the gastrointestinal (GI) tract, the vascular system, or even the kidneys themselves (i.e., nephrocalcinosis).
- **Sodium-potassium balance** — When sodium concentration is too low, the kidneys stimulate the adrenal glands to secrete the hormone aldosterone, which results in the retention of sodium and excretion of potassium. Damaged kidneys may eventually excrete too much potassium, which is critical to maintaining cellular function. Effective treatment of kidney impairment often necessitates potassium supplements.
- **Maintain homeostasis** — In the face of extra-renal systemic disease, the kidneys are critical to maintaining homeostasis as the patient's clinical condition changes. For instance, a patient experiencing vomiting or blood loss may become significantly volume-depleted, resulting in downstream ischemic injury to other organ systems. The kidneys respond via the RAAS by increasing vascular resistance to maintain perfusion. Impaired kidneys are less effective at maintaining this homeostasis, which may exacerbate the underlying condition. This can lead to additional complications for the patient and extra expense and worry for the client. Maintaining optimal kidney health is imperative to the overall health status of the patient.

"If you name any organ system, we can figure out a way that kidney health impacts it. Renal function really affects the entire pet."

—Christine Kirnos, VMD, CVA

We have established that kidneys play a critical role in the overall health of our patients. One key interaction is between the kidneys and the heart. Each organ system is dependent on the other to function properly. When one or both systems are impaired, this is referred to as cardiorenal syndrome.

With cardiac dysfunction, there is decreased blood flow to the kidneys, which can lead to impaired GFR or tubular injury. Reduced renal blood flow triggers the RAAS, which serves as a compensatory mechanism to maintain cardiac output. The kidneys respond by upregulating the RAAS, resulting in increased hydrostatic pressure to maintain perfusion. Similarly, when there is primary renal dysfunction, the adaptive response to maintain blood flow through the glomerulus is dilation of the afferent arteriole with commensurate constriction of the efferent arteriole to maintain hydrostatic pressure. This kidney-mediated hypertension increases afterload and may lead to structural changes in the heart, including ventricular hypertrophy and mitral insufficiency.

The importance of routine renal health screening

Evaluating kidney health during routine pet wellness examinations is critical for detecting kidney dysfunction early, which is important because:

- **Pets hide illness**
  Pets are adept at hiding vulnerabilities, including illness, and they typically exhibit no clinical signs until kidney disease is advanced.

> Kidney disease is extremely common, and incidence increases significantly as pets age, to the point that 50% of geriatric cats and dogs have some degree of kidney dysfunction.[2]

- **Early intervention helps slow progression**
  Evidence indicates that early intervention may help slow kidney disease progression and provide patients with a better quality of life and improved longevity.[3-5]

- **Trend tracking is possible**
  The kidneys' unique ability to compensate in the face of decreased GFR means substantial changes don't occur on lab work until significant kidney function is lost. By monitoring trends, such as a steady increase in kidney functional parameters, veterinarians are better equipped in routine evaluations to address changes early, rather than waiting for results to move outside the established reference interval.

- **Clients are educated**
  Many pet owners are unfamiliar with the kidneys' role in health and disease. An early diagnosis allows veterinarians time to educate the owner about kidney function and disease. An educated owner who understands the management plan may more likely be compliant about administering treatments and scheduling follow-up visits.

- **The human-animal bond is improved**
  End-stage kidney disease can require owners to administer numerous treatments, which can fracture the human-animal bond and play a significant role in euthanasia decisions. Eearly detection provides opportunities to help preserve kidney function, which may prevent or delay the long-term need for multiple medications. Early detection can help inform owners of treatment options allowing them to take a more proactive role in ongoing disease management.

"If we just look at the red numbers on our blood work, we can think everything's OK, when really we are missing the CKD stage ones and twos. We as veterinarians can do better by looking at the values and the trends versus normals and abnormals alone."

—Christine Kirnos, VMD, CVA

Evaluating kidney health as part of a routine wellness examination provides the best opportunity to slow disease progression and give the patient the best quality of life.

"Pets don't speak our language, and they aren't able to articulate how they feel. Incorporating routine testing and preventive care into regular annual visits allows us to do what I call the 'internal exam' and uncover problems before they may become clinically evident."

—Sarah Sweet, DVM

"If you diagnose kidney disease late during the continuum when the patient has several clinical signs, quality of life is adversely affected, you have reduced ability to change or influence the outcome of disease progression. In addition, you don't have the luxury of time to educate the owner about kidney function and disease. Most clients know little about what the kidneys do in health and what happens with nephron loss. Client compliance with medication administration and follow-up rechecks will likely be improved if they have a better understanding of kidney function."

—Greg Grauer, DVM, MS, DACVIM

"Acute kidney injury (AKI) has the potential to be reversible for two reasons. Nephrons that are not irreversibly damaged can potentially repair themselves, and nephrons that aren't affected and/or repaired can undergo compensatory hypertrophy.

In the chronic kidney disease state, (the) repair and compensation has had at least three months to occur and has failed to maintain normal renal function."

—Greg Grauer, DVM, MS, DACVIM

Kidney injury

Kidney injury is defined as an abrupt decline in kidney GFR, with or without immediately recognizable function loss. As injury progresses, it is typically characterized by increased serum creatinine concentration, uremia, and changes in urine output. Chronic kidney disease (CKD), on the other hand, is defined as kidney dysfunction for at least three months, meaning anything less than three months, from hours to days to weeks, may be considered an acute kidney injury (AKI). Causes can be categorized as prerenal, renal, and post renal.

Causes of Kidney Injury

Prerenal causes

Since the kidneys receive 25% of cardiac output, any failure in the general circulation or isolated failure involving intrarenal circulation can profoundly impact kidney perfusion. Prerenal causes of kidney injury include (but are not limited to):

- Dehydration
- Hemorrhage
- Prolonged anesthesia
- Congestive heart failure
- Heatstroke
- Decreased renal perfusion caused by gastric dilatation volvulus (GDV)

The kidneys typically respond to prerenal injury by concentrating the urine and maximizing sodium reabsorption in an attempt to maintain or increase intravascular volume and normalize kidney perfusion.

Renal causes

Renal causes affect the kidneys directly, involving the tubules, glomeruli, interstitium, and/or intrarenal blood vessels. Renal causes of kidney injury include:

- Tubular damage (i.e. acute tubular necrosis) — Two major causes of acute tubular necrosis are:
  - Ischemia — Any severe or prolonged decrease in kidney perfusion (e.g., prolonged anesthesia) can result in ischemic kidney injury.)

"Because kidneys are so much a part of the overall systemic health of the patient, we shouldn't only be assessing for kidney injury when we suspect primary kidney insult. We need to think about those patients with chronic vomiting or diarrhea or other conditions that interfere with their hydration status, which could lead to perfusion changes in the kidney."

—Sarah Sweet, DVM

- Nephrotoxicity — Nephrotoxic injury is caused by exogenous compounds, such as aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic drugs, diuretics, grapes or raisins, lilies, ethylene glycol, and vitamin D, and endogenous compounds, such as hemoglobin or myoglobin that are toxic to the kidneys in increased concentrations.
- Glomerular damage — Glomerular damage may occur due to inflammation, infection or immune-mediated response to name a few cases of acute glomerulonephritis.

Cystatin B

Cystatin B is a small intracellular protein that can be found in almost all mammalian cells. Cystatin B concentration increases in urine when renal tubular epithelial cells rupture or are destroyed.

Cystatin B does not circulate in high concentrations systemically, and increased levels found in the urine indicate kidney tubular epithelial injury. This kidney injury marker is specific to renal tubular damage and not dependent on changes in GFR. Measuring cystatin B can help determine if kidney injury has occurred, which is especially helpful when subclinical kidney injury may have occurred before kidney functional markers change.[6-7] This test is intended for unwell patients and is not meant to be a screening test. Kidney injury may occur as a primary insult or secondary to other disease processes, so monitoring cystatin B in all sick patients is appropriate.[6-7]

"[Cystatin B] could be a great tool to provide more confidence that a bump in creatinine is acceptable, or that bump is actually associated with some intrinsic kidney injury, and we need to think about regrouping on our drug therapy, changing the dose, or giving the patient a drug holiday to try to prevent additional kidney injury."

—JD Foster, VMD, DACVIM (SAIM), MS (Pharmacology and Toxicology)

"Many tubular cells must die before the nephron is lost, and many nephrons must be lost before kidney function is reduced. If we wait for changes in the kidney function markers, we miss when those cell deaths are occurring. Cystatin B can detect when the tubular cells are injured and dying, potentially allowing earlier AKI detection."

—JD Foster, VMD, DACVIM (SAIM), MS (Pharmacology and Toxicology

- Interstitial damage — Kidney injury from interstitial damage typically results from acute interstitial nephritis caused by an allergic reaction or an infection such as leptospirosis, ehrlichiosis, Lyme disease, or pyelonephritis.
- Vascular damage — Kidney injury from vascular damage occurs when intrarenal vessels are damaged, decreasing renal perfusion and GFR. Causes may include hypertension, ischemia, toxin exposure and/or preeclampsia/eclampsia.

Possible scenarios for cystatin B measurement include:

- A pet known or suspected to have ingested a toxin
- Patients with pancreatitis or heatstroke, since these conditions can cause a systemic vasculitis that can lead to kidney injury and increased mortality rates
- Gastric dilatation volvulus (GDV) with profound hypotension, which may affect kidney perfusion
- A patient in cardiogenic shock after being hit by a car, which could lead to kidney hypoperfusion
- When administering potentially nephrotoxic medications to a high-risk patient
- After prolonged anesthesia
- To monitor recovery in a patient with known kidney injury
- To monitor CKD progression, especially in the early stages

Although cystatin B is a reference lab test, it is still useful in emergency situations, because the results can help determine the patient's prognosis and guide further treatment.

"If you have a patient receiving a potentially nephrotoxic antibiotic, measuring cystatin B on a daily basis would be helpful, so as soon as that level starts to climb, you can stop or decrease the medication and potentially better support the patient's renal perfusion."

—Greg Grauer,DVM, MS, DACVIM

Post-renal causes

Post-renal causes include situations that result in urethral or ureteral obstruction. These conditions increase intratubular pressure, decreasing GFR. In addition, acute urethral or ureteral obstruction can impair kidney blood flow and trigger inflammatory processes that contribute to diminished GFR. Post-renal causes of kidney injury include:

- Urethral plugs
- Stricture
- Urolithiasis
- Neoplasia

Kidney injury has four disease stages related to cellular events that occur during the injury and recovery process.[8]

- **Initiation phase**
  The initiation phase involves the initial injury or insult to the kidneys, and occurs when kidney blood flow decreases to the point that cellular adenosine triphosphate (ATP) is severely depleted, leading to acute cell injury and dysfunction. The extent of injury depends on the severity and duration of the ischemic event. Injury that occurs during the initiation phase may not result in cellular destruction, but the insult disrupts the ability of renal tubular epithelial cells and vascular endothelial cells to maintain normal kidney function. Disease progression can often be prevented if the underlying cause is identified and addressed at this stage.

- **Extension phase**
  During the extension phase, kidney injury continues because of persistent hypoxia following the initial ischemic event and ongoing inflammation, involving chemokine and cytokine production. Cells undergo apoptosis and necrosis, and GFR continues to decline. Interrupting the inflammatory cascade during the extension phase may be therapeutically beneficial.

- **Maintenance phase**
  The maintenance phase involves cellular repair, migration, apoptosis, and proliferation as the tissue attempts to reestablish and maintain cellular and tubular integrity. GFR stabilizes depending on the severity of the initial injury. Blood flow normalizes, and intra- and intercellular homeostasis is established by epithelial cells. Signs of uremia, such as vomiting, diarrhea, and polyuria and polydipsia, typically become more noticeable during this phase when the diagnosis of kidney injury is typically made.

"[Cystatin B] could be a great tool to provide more confidence that a bump in creatinine is acceptable, or that bump is actually associated with some intrinsic kidney injury, and we need to think about regrouping on our drug therapy, changing the dose, or giving the patient a drug holiday to try to prevent additional kidney injury."

—JD Foster, VMD, DACVIM (SAIM), MS (Pharmacology and Toxicology)

- Recovery phase
  The final recovery phase can last for months or years. Continued cellular repair leads to improved GFR, and cellular and organ function may return to baseline. However, in some cases, injury may lead to fibrosis and eventual chronic changes. The severity and duration of the kidney injury may be related to the number of sublethally damaged cells that maintain viability and contribute to restoring kidney structure and function. Further kidney injury should be avoided during this stage to prevent relapse.

Clinical signs of kidney injury are typically seen in the maintenance phase and are usually nonspecific.

Signs of Kidney Injury

- Lethargy
- Anorexia
- Scleral injection
- Polyuria
- Bradycardia
- Vomiting
- Dehydration
- Oliguria
- Polydipsia
- Enlarged, painful kidneys
- Diarrhea
- Halitosis
- Anuria
- Seizures

Kidney function is most accurately measured using GFR, and surrogate markers of kidney function, such as SDMA, creatinine, and blood urea nitrogen (BUN), facilitate this assessment.[9] Kidney injury, on the other hand, may be subclinical or can occur before changes in functional markers can be observed. Renal tubular epithelial cells that are injured release a protein called cystatin B which can be measured in the urine. This intracellular protein has been identified as a novel kidney injury biomarker, enabling veterinarians to identify kidney injury without having to rely on functional markers alone.

Once kidney injury has been identified, the underlying cause should be addressed if possible and supportive care instigated to minimize further renal damage. Since urine output can be variable in patients with kidney injury, fluid therapy should be aimed at restoring normovolemia while closely monitoring urine output in order to avoid further damage secondary to overhydration.

Chronic kidney disease

Chronic Kidney Disease (CKD) is functional or structural kidney dysfunction that has been present for at least three months, resulting in progressive, irreversible damage. In response to nephron loss, compensatory mechanisms such as glomerular hypertension and hyperfiltration can exacerbate CKD, potentially exacerbating the original injury. Potential causes of CKD include urethral obstruction, familial kidney disease, infection, inflammation, ischemia, and vascular injury. However, in the majority of cases, the underlying cause is unknown. Signs are nonspecific, and they typically do not occur until later in the disease process.

Signs of Chronic Kidney Disease

- Weight loss
- Lethargy
- Decreased appetite or anorexia
- Intermittent vomiting
- Oral ulcerations
- Halitosis
- Increased thirst and urination
- Increased or decreased urine volume
- Uncoordinated movements

The diagnosis of CKD includes:

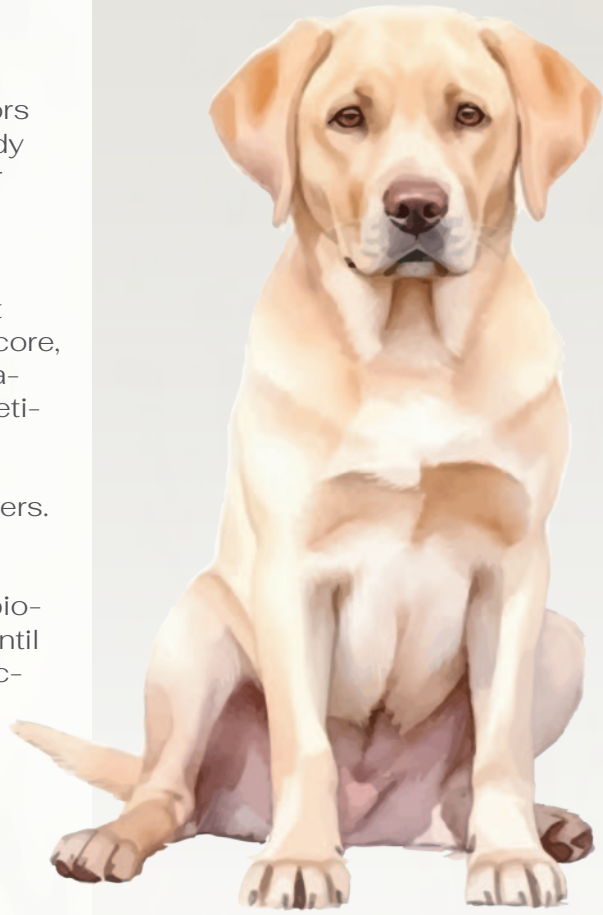
- **History**
  A thorough medical history is imperative to assess factors such as polyuria/polydipsia, diet, appetite, change in body mass, and energy level. This also provides a baseline for comparison following therapeutic intervention.

- **Physical examination**
  Important aspects to consider when evaluating a patient with known or suspected CKD include body condition score, cardiovascular status, hydration status, and kidney palpation. A fundic exam helps assess vessel tortuosity and retinal health, which may indicate systemic hypertension. A rectal examination may also be necessary to screen for melena or hematochezia, which may indicate uremic ulcers.

- **Creatinine**
  Creatinine is the most commonly used kidney function biomarker, but concentrations aren't persistently elevated until about 75% of nephrons are lost. In addition, extrarenal factors such as muscle wasting can alter creatinine levels.

"We sometimes let the perfect be the enemy of the good. Even if you can only get a urine specific gravity, that will provide much more information about what your creatinine or SDMA level means. You can get a much more comprehensive picture of your patient if you use tests that complement each other."

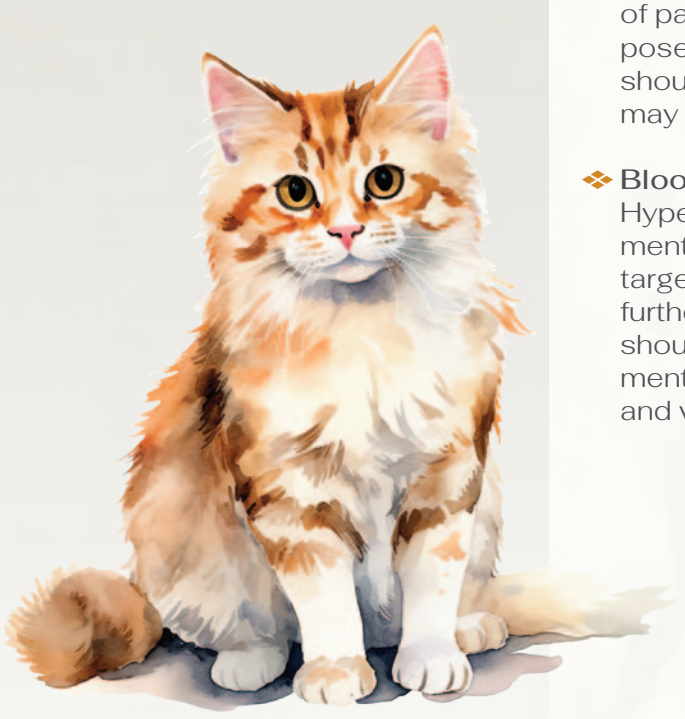
—Sarah Sweet, DVM



Monitoring matters: SDMA persistence

Following a **SINGLE mild increase in SDMA** concentration (15-19µg/dl), there is a 72% risk of further GFR impairment within one year.

Michael HT, Mack RM, Hegarty E, McCrann DJ, Grauer GF. A longitudinal study of the persistence of increased creatinine and concordance between kidney biomarkers in cats and dogs. The Vet J. 2021. 276:105729



Blood urea nitrogen (BUN)

BUN, which has traditionally been used to evaluate GFR, is not a sensitive or specific indicator of kidney dysfunction and should be used only in conjunction with creatinine and SDMA.

SDMA

SDMA is a more sensitive surrogate GFR marker than creatinine, increasing on average with 40% kidney function loss and as little as 25% function loss.[10-12] Elevated SDMA indicates diminished GFR, which could be caused by prerenal dehydration, kidney injury, or CKD.

Urine specific gravity

Patients with kidney dysfunction resulting in damage to approximately two-thirds of the nephrons are typically unable to adequately concentrate urine.[13] However, some cats with persistently increased creatinine and SDMA concentrations may retain some ability to concentrate urine.

Proteinuria

Renal proteinuria occurs when protein concentrations increase in urine as a result of glomerular or tubular dysfunction. Persistent proteinuria in the presence of an inactive sediment is considered a relevant finding and should be pursued.

Urine protein creatinine ratio (UPC)

A UPC quantifies the protein lost in the urine. A UPC greater than 0.2 is considered borderline proteinuric for both dogs and cats and a UPC greater than 0.4 for cats and 0.5 for dogs is considered proteinuric and warrants intervention.[14]

Urine culture

Urinary tract infections often complicate the clinical picture of patients with CKD as less concentrated urine may predispose patients to repeat infections. Antibiotic selection should be based on urine culture results and repeat cultures may be necessary.

Blood pressure

Hypertension is common in patients with CKD, and management of the condition is important to help prevent injury to target organs, such as the eyes, brain, and heart, as well as further damage to the kidneys. Ideally, two measurements should be taken at least two hours apart. Systolic measurements higher than 160 mmHg are considered hypertensive and warrant treatment.[14]

Imaging

- Abdominal radiographs can evaluate kidney structure and size, identify and locate calculi, and examine the kidneys and other organs for the presence of neoplasia. Radiographically, a normal canine kidney is 2 to 2 ½ times the length of the adjacent vertebra, and a normal feline kidney length is 2 to 3 times the adjacent vertebrae.[15]
- Ultrasound is a noninvasive means to evaluate kidney structure and can assist in biopsy or fluid sample collection. The urinary tract should be examined clockwise, from the left kidney, to the urinary bladder and proximal urethra, and then to the right kidney. Each kidney should be evaluated in its long and short axis, from medial to lateral, dorsal to ventral, or cranial to caudal. Static images or short video clips should be used to document abnormalities.[16]

IRIS has developed detailed guidelines to stage CKD to facilitate appropriate treatment and patient monitoring. Staging is performed following a CKD diagnosis based initially on fasting blood creatinine and SDMA levels, and assessed on at least two occasions in the stable, well-hydrated patient. Substaging is then performed based on proteinuria and systemic blood pressure measurements. IRIS provides empirical recommendations to guide treatment according to the patient's disease stage.

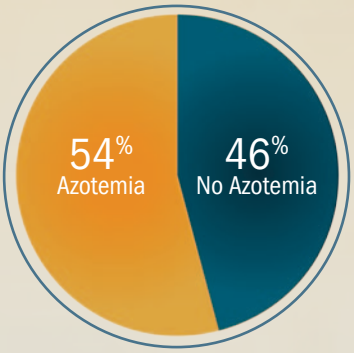
See **IRIS Staging of Chronic Kidney Disease Based on Blood Creatinine and SDMA Concentrations** on the next page.

CKD management should be tailored specifically to the individual patient and their disease stage. General management strategies include:

Maintaining hydration

Correcting and preventing dehydration is critical in patients with CKD to prevent worsening kidney function. Decreased GFR as a result of CKD is permanent. Hypovolemic or dehydrated patients experience prerenal GFR reduction which further exacerbates already compromised renal perfusion. Patients should always have access to fresh, clean water from several water sources throughout the home, and should ideally be fed wet food. If the patient cannot maintain adequate hydration, subcutaneous fluid therapy may be needed every one to three days depending on tolerance and the condition of the patient.

A mild increase in SDMA is a medical turning point



More than half of patients with two increased SDMA results were azotemic within 18 months

Michael HT, Mack RM, Hegarty E, McCrann DJ, Grauer GF. A longitudinal study of the persistence of increased creatinine and concordance between kidney biomarkers in cats and dogs. The Vet J. 2021. 276:105729.

IRIS Staging of Chronic Kidney Disease Based on Blood Creatinine and SDMA Concentrations

	Dogs	Cats	Comments
Stage 1	Blood creatinine <125 µmol/l <1.4 mg/dl	Blood creatinine <140 µmol/l <1.6 mg/dl	Normal blood creatinine or normal or mild increase blood SDMA. Some other renal abnormality present, such as inadequate urinary concentrating ability without identifiable non-renal cause (in cats, not dogs), abnormal renal palpation or renal imaging findings, proteinuria of renal origin, abnormal renal biopsy results, or increasing blood creatinine or SDMA concentrations in samples collected serially. Persistently elevated blood SDMA concentration (>14 µg/dl) may be used to diagnose early CKD.
	SDMA <18 µg/dl	SDMA <18 µg/dl	
Stage 2	Blood creatinine 125–250 µmol/l 1.4–2.8 mg/dl	Blood creatinine 140–250 µmol/l 1.6–2.8 mg/dl	Normal or mildly increased creatinine, mild renal azotemia (lower end of the range lies within reference ranges for creatinine for many laboratories, but the insensitivity of creatinine concentration as a screening test means that patients with creatinine values close to the upper reference limit often have excretory failure). Mildly increased SDMA. Clinical signs are usually mild or absent.
	SDMA 18–35 µg/dl	SDMA 18–25 µg/dl	
Stage 3	Blood creatinine 251–440 µmol/l 2.9–5.0 mg/dl	Blood creatinine 251–440 µmol/l 2.9–5.0 mg/dl	Moderate renal azotemia. Many extrarenal signs may be present, but their extent and severity may vary. If signs are absent, the case could be considered early Stage 3, while presence of many or marked systemic signs might justify classification as late Stage 3.
	SDMA 36–54 µg/dl	SDMA 26–38 µg/dl	
Stage 4	Blood creatinine >440 µmol/l >5.0 mg/dl	Blood creatinine >440 µmol/l >5.0 mg/dl	Increasing risk of systemic clinical signs and uremic crises
	SDMA >54 µg/dl	SDMA >38 µg/dl	

The blood creatinine concentrations apply to average size dogs; those of extreme size may vary.

The recommendations for SDMA are based on published literature which utilizes proprietary IDEXX technology for measuring SDMA. At this time, it is not known if other assays will provide equivalent results.

Table acquired from http://www.iris-kidney.com/guidelines/staging.html.
Reference: IRIS International Renal Interest Society. IRIS Staging of CKD (modified 2023).

Addressing underlying issues

Extrarenal disease processes must be identified and treated to ensure they do not contribute to further kidney injury.

Feeding a renal diet

Therapeutic kidney diets are typically low in protein, phosphorus, and sodium, with enhanced levels of omega-3 polyunsaturated fatty acids, fiber, and vitamin D, and a neutral pH. These diets are formulated to address the nutritional needs of patients with CKD and have been shown to maintain or improve nutrition compared with maintenance diets. Instruct clients to introduce the renal diet gradually to help improve patient acceptance.

Ensuring adequate nutrition

Failing to address issues such as uremic gastritis, uremic stomatitis, and periodontal disease can exacerbate anorexia. Avoid force feeding new diets, trying novel diets on hospitalized patients, or administering treatments around feeding times. If a patient refuses food, consider a feeding tube to ensure adequate calorie and water consumption.

> Malnutrition is a major cause of morbidity and mortality in patients with CKD. Ideally, patients should ingest sufficient calories from an appropriate diet to maintain at least a 4/9 body condition score (BCS).[17]

FGF-23

A decline in GFR secondary to CKD results in decreased phosphorus excretion interfering with phosphate-calcium homeostasis. Chronic kidney disease-mineral bone disorder (CKD-MBD) involves numerous factors, including fibroblast growth factor 23 (FGF-23) which increases in response to rising phosphate concentration. FGF-23 helps regulate phosphate metabolism as well as calcium-phosphate homeostasis. FGF-23 rises before serum or plasma phosphorus concentrations increase, alerting veterinarians to changes in phosphate metabolism before the onset of overt hyperphosphatemia.

FGF-23 is validated for use in feline patients diagnosed with IRIS CKD Stages 1 and 2 to help guide treatment decisions. Feline patients who have an elevated FGF-23, despite having a serum phosphate concentration within the IRIS target range indicate that FGF-23 is compensating in an effort to normalize phosphate concentration and prevent the onset of CKD-MBD.[18-20] Increased FGF-23 suggests the patient may benefit from further phosphate restriction, either through implementing a therapeutic renal diet or enteric phosphate binder.[18-19]

FGF-23 testing is indicated when the patient's CKD diagnosis has been established, ideally before they become overtly hyperphosphatemic. If you have a feline patient who is already

- **Maintaining serum phosphorus concentrations at an appropriate level**
  High serum phosphorus levels may contribute to progressive kidney injury. As GFR declines, phosphate retention increases; hyperphosphatemia stimulates parathyroid hormone (PTH) production, leading to chronic kidney disease-metabolic bone disease (CKD-MBD). IRIS details target phosphorus concentrations for each stage of CKD. Renal therapeutic diets and phosphate binders can help restrict phosphorus intake and may be necessary to maintain appropriate systemic phosphate concentrations. Monitor the patient's serum calcium concentration when using calcium-based phosphate binding agents, and consider measuring ionized calcium concentrations, particularly when increased calcium concentrations or decreased serum albumin concentrations are present. Once therapeutic targets are met, reevaluate the patient every three to four months to ensure continued therapeutic success.

- **Maintaining serum potassium levels in the target range**
  Hypokalemia in patients with CKD is presumed to be caused by inadequate potassium intake and enhanced urinary losses, and possibly enhanced RAAS activation in response to low sodium intake. Clinical ramifications may include skeletal, smooth, and cardiac muscle weakness and further impairment of kidney function. Increasing potassium intake by feeding a renal therapeutic diet and/or administering potassium supplements is recommended in patients with hypokalemia.

"FGF-23 alerts us to potential upstream changes that may result in metabolic bone disease, acting as the canary in the coal mine with these CKD cats. FGF-23 helps to alert us to changes before we see the cascade of events that results from what we used to think of as renal secondary hyperparathyroidism."

— Sarah Sweet, DVM

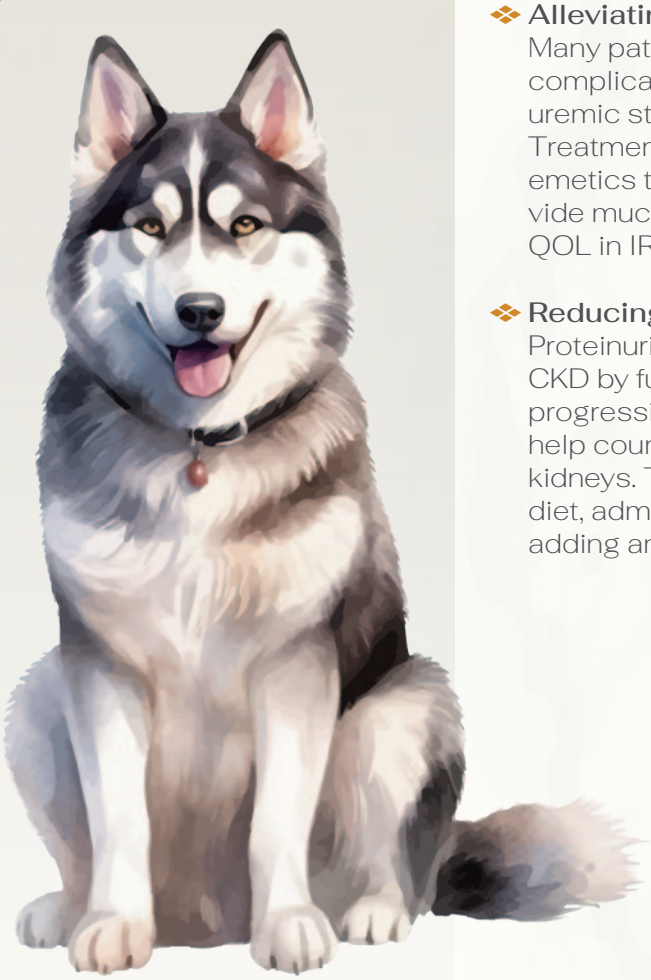
hyperphosphatemic, the FGF-23 will likely already be elevated, however, you can use the FGF-23 concentration to monitor the cat's response to phosphate restriction. FGF-23 is contraindicated in cats with uncontrolled hyperthyroidism, cardiac disease, systemic inflammation, neoplasia, lytic bone lesions, and significant anemia, since these conditions can affect FGF-23 levels. FGF-23 should be measured no more frequently than every two to three months, as it may take that long for treatment effects to be realized.[20]

Advances in veterinary medicine improve veterinarians' ability to detect disease and provide more timely treatment to help improve the patient's QOL and extend their life.

Tools that provide more accurate assessment of renal health can help enhance your diagnostic and monitoring protocols. Functional markers including SDMA, creatinine, BUN, and complete urinalysis provide insight into overall kidney health. Novel biomarkers such as cystatin B and FGF-23 are additional tests that can inform treatment decisions in patients with renal injury or disease. Cystatin B can help identify kidney injury before changes in functional markers, allowing for intervention that may prevent long-term consequences. FGF-23 can provide better phosphorus monitoring in cats with CKD, allowing for the addition of appropriate therapeutics that may improve prognosis. These tests may make a significant difference in your patients' renal health, and in your overall treatment success.

"The big outcome we strive for is to give our patients a great quality of life for as long as possible. We want them to be comfortable, be able to keep themselves well hydrated, eat well, and still enjoy playing with their ball, going for car rides, and sleeping in the sun. The problem with kidney disease is it can sometimes take a lot of medications to put a Band-Aid on the problem to allow the patient to do that."

—JD Foster, VMD, DACVIM (SAIM), MS (Pharmacology and Toxicology)



Conversely, during IRIS Stage 4, patients may develop hyperkalemia when the kidneys can no longer effectively excrete potassium, potentially leading to cardiotoxicity. Treatment at this point involves reducing potassium intake.

Correcting metabolic acidosis

Metabolic acidosis is a result of impaired bicarbonate reabsorption or impaired urine acidification. This may result in progressive renal injury, increased protein catabolism, and lean tissue loss. Oral sodium bicarbonate is the most commonly used treatment for metabolic acidosis in patients with CKD. Potassium citrate may also be used to address both hypokalemia and acidosis, particularly in cats.

Correcting anemia

Patients with CKD who have clinically signficant anemia may benefit from erythropoietin replacement therapy, and a molidustat oral suspension is FDA approved for feline use which may also be helpful, while other potential underlying causes of anemia such as blood loss, iron deficiency, poor nutrition, hyperparathyroidism, and infections must be ruled out.[21-22] Patients should be monitored weekly until desired targets are reached. Once therapeutic targets are achieved, the packed cell volume (PCV) should be evaluated monthly and dosages adjusted or supplemental iron provided as needed.[17]

Alleviating gastrointestinal signs

Many patients diagnosed with Stage 3 or 4 CKD exhibit GI complications, such as reduced appetite, nausea, vomiting, uremic stomatitis, halitosis, diarrhea, and GI hemorrhage. Treatment includes H_2blockers to reduce gastric acidity, antiemetics to suppress nausea and vomiting, sucralfate to provide mucosal protection, and appetite stimulants to improve QOL in IRIS stage 2 or earlier.[17]

Reducing proteinuria

Proteinuria adversely affects the outcomes of patients with CKD by further injuring the kidney tubules, promoting CKD progression. Suppressing the RAAS to reduce proteinuria can help counteract the negative effects of excess protein on the kidneys. Treatment may involve feeding a renal therapeutic diet, administering an angiotensin receptor blocker (ARB), or adding an angiotensin converting enzyme inhibitor (ACEi) if

necessary. Monitor the urine protein-creatinine ratio monthly until target levels are attained, and then every three to four months.[14]

- **Minimizing systemic hypertension**
  The objective of treatment is to reduce and maintain systolic blood pressure below 160 mmHg. Calcium channel blockers, ACE inhibitors, and ARBs are often used to manage hypertension in dogs and cats with CKD. In addition, ACE inhibitors are helpful because they reduce intraglomerular pressure even when systemic blood pressure is not effectively managed.

Frequent monitoring is essential to ensure the treatment plan for patients diagnosed with CKD, and can be modified when necessary. Creatinine, SDMA, phosphorus, packed cell volume, electrolytes, calcium, urine specific gravity, UPC, and blood pressure should be evaluated regularly according to IRIS CKD stage.[23]

- **Stage 1**
  CKD stability or progression should be assessed by monitoring patients every six months. Those who have borderline hypertension or proteinuria should be monitored more frequently.

- **Stage 2**
  For patients in CKD Stage 2, monitoring should include serum bicarbonate or total CO2 measurements to check for metabolic acidosis. CKD stability or progression should be monitored every three to six months in these patients.

- **Stage 3**
  CKD patients in early Stage 3 should be monitored every three months, while those in late stage three should be assessed every one to two months.

- **Stage 4**
  CKD patients in Stage 4 are at high risk for a renal crisis and should be monitored closely, depending on their condition.

For more in-depth guidance concerning treatment and monitoring, consult IRIS's Treatment Recommendations for Dogs and Cats.

New tests, including Cystatin B and FGF-23, may also be useful for monitoring CKD patients.

"Getting a blood pressure reading on a cat in a clinical setting can be really challenging, but I think we need to get ourselves in the habit of remembering some of those ancillary tests which are going to give us a better picture of what that CKD patient looks like."

—Sarah Sweet, DVM

"Numerous treatments can be overwhelming for pet owners. As you add all of these modalities to support the pet, you could interfere with the human-animal bond. This is why early intervention is key to preserve kidney function, so the patient doesn't need multiple medications for a long time period."

—Christine Kirnos, VMD, CVA

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