

## CKD vs AKI – So many markers, so little time, so much confusion!

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#### **Disclosure:** Full-time Employee of IDEXX

The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical exam and presentation, and laboratory data. With respect to any drug therapy or monitoring program, you should refer to applicable product insert(s) for complete description of dosage, indications, interactions, and cautions. Diagnosis, treatment, and monitoring should be patient specific and is the responsibility of the veterinarian providing primary care. (2024)



#### Learning outcomes

O1 What is the function of kidneys?
+ Recall the role the kidneys play in overall health

02

03

#### How do we assess kidney health?

+ Describe the different biomarkers for glomerular filtration rate (GFR) and what they tell us

#### What is kidney disease?

- Recognise the difference between acute kidney injury (AKI) and chronic kidney disease (CKD)
- + Review IRIS CKD guidelines and the utility of FGF-23
- + Describe the AKI and CKD continuum
- + Discuss kidney injury and the value of cystatin B

## How has our understanding of kidney health evolved?

 Recognise the importance of staging and managing changes in kidney function



## Timeline of kidney biomarkers





### Function of the kidneys

#### **Key responsibilities:**

- + Fluid balance in the body
  - + Blood pressure
  - + Hydration
- + Electrolyte balance in the blood
  - + Integral to cellular and organ function
- + Removal of nitrogenous waste
  - + Ammonia and urea
- + Excretion of drugs
- + Production of erythropoietin
  - + Stimulates red blood cell production





#### Comorbidities or disease states can heavily impact kidney health

				ST P
Heart disease Cardiorenal or renocardial syndrome	Liver disease Hepatic disease, congestion	Gastrointestinal disease Inflammatory effect, hypoproteinemia	Endocrinopathy Hormone imbalance, catabolic state	Infectious Inflammatory/ immune (acute or chronic)
NT-proBNP Troponin SDMA	CRP Iron	CRP Microbiome	Aldosterone PTH Vitamin D Iron	Regional infectious disease testing Leishmaniasis Ehrlichiosis Lyme disease



## How do we measure kidney health?



### Diagnosing kidney disease is more than diagnostics



**Clinical decision points** 



#### Where is the problem?





### Function versus injury



- + SDMA
- + Creatinine
- + Urea
- + Measured in serum or plasma
- + May **not** change with injury



#### **Injury markers**

- + Indicate damage
  - + Usually proximal tubules
  - + Tubules are the most metabolically active segment of the kidney
- May increase before or without functional marker change
- + Measured in urine



## Anatomy of a nephron

- + Glomerulus
  - + Filtration
    - + Water
    - + Small solutes
- + Proximal convoluted tubule
  - + Resorbs 60%–65% of filtrate
  - + Secretes cations, anions, H+
- + Loop of Henle
  - + Produces ultrafiltrate
- + Distal tubule
- + Collecting tubule
- + Collecting duct
  - + Electrolyte balance
  - + Acid-base balance
  - + Water resorption





How do we assess kidney function?

**Glomerular filtration rate (GFR)** 



Gold standard

Expensive











#### **GFR Biomarkers**

IDEXX SDMA	<sup>a</sup> 12	0 - 14 µg/dL	
📫 🖴 Creatinine	1.3	0.9 - 2.3 mg/dL	
💷 🜭 BUN	34	16 - 37 mg/dL	
BUN: Creatinine Ratio	26.2		
🛄 ∿ Phosphorus	4.5	2.9 - 6.3 mg/dL	

#### The biochemistry panel

#### BUN

- + Late marker—up to 75% loss of function before changes noted
- + Impacted by other factors including diet and liver disease

#### Creatinine

- + Late marker—up to 75% loss of function<sup>4</sup> before changes noted
- + Impacted by other factors, including muscle mass<sup>2,4</sup>

#### **SDMA**

- Earlier marker—SDMA increases on average with a 40% loss and as little as 25% loss of kidney function versus creatinine, which does not increase until 75% of kidney function.<sup>1-3</sup>
- + Not impacted by diet, muscle mass, liver disease

#### References

- Hall JA, Yerramilli M, Obare E, Yerramilli M, Yu S, Jewell DE. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in healthy geriatric cats fed reduced protein foods enriched with fish oil, L-carnitine, and medium-chain triglycerides. Vet J. 2014;202(3):588–596. doi:10.1016/j.tvjl.2014.10.021
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## Urinalysis

1				E G
	Collection	Free Catch		en al antes
	Color	Pale Yellow		
	Clarity	Slightly Cloudy	IDEXX SedIVue Dx	
	Specific Gravity	1,026		o <b>o</b>
Ш	White Blood Cells	3 /HPF		
Ш	Red Blood Cells	5 /HPF		а ал 1981 г. и
ш	Bacteria, Cocci	None Detected		- B
Ш	Bacteria, Rods	None Detected		and the second se
m	Squamous Epethelial Cells	<1 /HPF	-	
Ш	Non-Squamous Epethelial Cells	1-2 /HPF		
m	Hyaline Casts	None Detected		
	Urine Creatinine	50.3 mg/dL		
	Urine Protein	198.8 mg/dL		•//•
<u>ш</u> •	Urine Protein: Creatinine Ratio	4.0		1 3
	Color	e Yellow		

#### **Urine analysis**

- Evaluates many aspects of renal function including glomerular, tubular, endocrine, fluid balance, and acid-base functions
- Includes Urine specific gravity (USG), Chemical analysis (glucose, ketones, pH), and Sediment evaluation (manual or automated)
- Affected by other factors, including endocrine disease and lower urinary tract disease

#### Urine protein:creatinine ratio (UPC)

- Evaluates glomerular filtration barrier health and renal tubular function
- May increase earlier than Creatinine, Urea or SDMA or be the only abnormality in some types of renal dysfunction
- Required by IRIS for substaging and monitoring all dogs and cats with CKD



### Kidney function: creatinine versus GFR



Graph used with permission from Dr. Sheri Ross.

Source: Braun JP, Lefebvre HP, Watson ADJ. Creatinine in the dog: a review. Vet Clin Pathol. 2003;32(4):162–179. doi:10.1111/j.1939-165x.2003.tb00332.x



### How to interpret SDMA with creatinine

- + SDMA should always be interpreted along with creatinine and urinalysis.
- + Diagnostic algorithms and interpretive comments promote complete kidney evaluation.



## The importance of monitoring results

#### Establish a baseline:

- + Allows for personalised care
- + Informs decisions in a crisis
  - + Preanaesthetic choice
  - + Fluid rate
  - + Post-op pain management
- + Guides decision-making as pet ages
  - + NSAIDs for degenerative joint disease?
  - + Diet change?





## What is kidney disease?



#### What is kidney disease?

#### Active kidney injury (AKI) Potentially reversible

#### Ongoing kidney injury

#### Caused by:

- + Toxin exposure
- + Nephrotoxic drugs
- + Infectious diseases, such as leptospirosis in dogs
- + Dehydration
- + High blood pressure

#### Chronic kidney disease (CKD) Irreversible

#### Caused by:

- + Kidney infections
- + Kidney and ureteral stones
- + Toxin ingestion
- + Infectious diseases, such as Lyme disease in dogs
- + Hereditary conditions



#### Acute kidney event and chronic disease continuum





#### Chronic kidney disease

## Early CKD symptoms are often nonspecific

- + Decreased appetite
- + Weight loss
- + Decreased activity level
- + Vomiting
- + Lethargy

## Symptoms in later stages may include the following

- + Drinking and urinating a lot
- + Loss of appetite
- + Vomiting
- + Bad breath
- + Oral ulcers
- + Marked weight loss



Pet owners may not recognise subtle changes





## Kidney disease is common in both dogs and cats

- + Chronic kidney disease is a **leading** cause of suffering in both dogs and cats.<sup>1</sup>
- + Prevalence increases with age.<sup>2</sup>
  - + With pets living longer, uncovering disease earlier can improve quality and lifespan.
- + Including SDMA in every chemistry profile **can improve outcomes** for your patients.

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- 1. Lulich JP, Osborne CA, O'Brien TD, Polzin DJ. Feline renal failure: questions, answers, questions. *Compend Contin Educ Pract Vet.* 1992;14(2):127–153.
- 2. Brown CA, Elliott J, Schmiedt CW, Brown SA. Chronic kidney disease in aged cats: clinical features, morphology, and proposed pathogeneses. *Vet Pathol.* 2016;53(2):309–326. doi:10.1177/0300985815622975
- 3. Brown SA. Renal dysfunction in small animals. The Merck Veterinary Manual website. www.merckvetmanual.com/mvm/urinary\_system/noninfectious\_diseases\_of\_the\_urinary\_system\_in\_small\_animals/renal \_dysfunction\_in\_small\_animals.html. Updated October 2013. Accessed December 6, 2024.



In time, at least **1** in **3** cats<sup>1</sup> and **1** in **10** dogs<sup>3</sup> will develop kidney disease.



## Chronic kidney disease



#### To diagnose IRIS CKD Stage 1 and early IRIS CKD Stage 2 One or more of these diagnostic findings



#### Abnormal kidney imaging



#### Persistent renal proteinuria

Urine protein to creatinine (UPC) ratio

- > 0.5 in dogs
- $\sim$  > 0.4 in cats



Reference

International Renal Interest Society (IRIS). IRIS Staging of CKD. IRIS website. www.iris-kidney.com/guidelines/staging.html. Accessed December 6, 2024.



#### To diagnose more advanced CKD (late IRIS CKD Stage 2-4) **Both of these diagnostic findings**



hydration status.

\*Some cats can produce hypersthenuric

Feline

urine in the face of renal azotemia.

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#### Reference

International Renal Interest Society (IRIS). IRIS Staging of CKD. IRIS website. www.iris-kidney.com/guidelines/staging.html. Accessed December 6, 2024.



1.008

1.008

### Staging CKD using IRIS guidelines











Substage based c blood pressure

Note: In the case of staging discrepancy between creatinine and SDMA, consider patient muscle mass and retesting both in 2-4 weeks. If values are persistently discordant, consider assigning the patient to the higher stage.

\*SDMA = IDEXX SDMA® Test result

See www.iris-kidney.com for more detailed staging, therapeutic, and management guidelines.



### Treatment of CKD using IRIS guidelines

			R		
Treatm	nent	Stage 1	Stage 2	Stage 3	Stage 4
recom	mendations	Use nephrotoxic drugs with caution	Same as Stage 1	Same as Stage 2	Same as Stage 3
		Correct prerenal and postrenal abnormalities	Renal therapeutic diet	Keep phosphorus < 5.0 mg/dL (< 1.6 mmol/L)	Keep phosphorus < 6.0 mg/dL (< 1.9 mmol/L)
Routine chemistry monitoring		Fresh water available at all times	Treat hypokalemia in cats	Treat metabolic acidosis	Consider feeding tube for nutritional and hydration support and ease of medicating
including SDMA, urinalysis, and UPC ratio		Monitor trends in creatinine and SDMA to document stability or progression	Treat inappetence and nausea if present	Consider treatment of anemia	
		Investigate for and treat underlying disease and/or complications		Treat vomiting, inappetence, and nausea	
FGE-23 in cate		Treat hypertension if systolic blood pressure persistently > 160 or evidence of end-organ damage		Increased enteral or subcutaneous fluids may be required to maintain hydration	
with IRIS CKD Stages 1 and 2		Treat persistent proteinuria with renal therapeutic diet and medication			
		Keep phosphorus < 4.6 mg/dL (< 1.5 mmol/L)			
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See <u>www.iris-kidney.com</u> for more detailed staging, therapeutic, and management guidelines.

### Regulation of phosphorus in CKD

#### Hyperphosphatemia

- + Other relevant players: phosphatonins
- + Fibroblast growth factor 23 (FGF-23)
- + Released from osteocytes in response to increased phosphorus, calcitriol, and PTH concentrations
- + Decreases phosphorus and calcitriol concentrations



### Chronic kidney disease-mineral bone disorder (CKD-MBD)



#### Decreased GFR

#### Reduced phosphorus excretion

Calcium-phosphorus imbalance

**CKD-MBD** 



### CKD-MBD

#### Hyperphosphatemia

One of the most important risk factors for CKD progression of disease and survival in cats and dogs

- + Reduced phosphate excretion in CKD  $\rightarrow$  CKD-MBD
  - + Abnormalities of calcium-phosphate homeostasis, bone disease, and soft tissue calcification
    - + Renal secondary hyperparathyroidism
    - + Accelerated progression of CKD
    - + Increased mortality rate
    - + Renal osteodystrophy
    - + Extraskeletal calcification
    - + Hypo- or hypercalcemia, and hypo- or hypermagnesaemia





FGF-23

a. 19 0 - 14 µg/dL Cats diagnosed with 🛤 😘 IDEXX SDMA IRIS CKD Stage 1 or 2 🛤 😘 Creatinine 2.0 0.9 - 2.5 mg/dL BUN 34 16 - 37 mg/dL M 14 **BUN:** Creatinine 17.0 .... Ratio Phosphorus < 4.6 mg/dLL M M Phosphorus 2.9 - 6.3 mg/dL 3.7 (1.5 mmol/L)





#### FGF-23 identifies phosphorus overload before overt hyperphosphataemia

Feline     Feline,       Oct 27     Sep 29	Mixed Breed <b>Jun 9</b> J	Female   6 y   Profile un 9 Mar 4 Mar	∽ 3 Jan 18 Jan 17 Jan 14	+	Feline   SH	northair, Domes	tic   Female   5 y   <b>Prof</b>	île 🗸
				Res	ult Details 🗸			
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Chemistry	3:17 AM	<i></i>		88 V	Glucose	80	72 - 175 mg/dL	
🛤 😘 IDEXX SDMA	a. 14	0 - 14 µg/dL		R V	IDEXX SDMA	a. <b>15</b>	0 - 14 µg/dL	
🛤 🐝 Creatinine	1.7	0.9 - 2.3 mg/dL		III V	Creatinine	2.2	0.9 - 2.3 mg/dL	
nn 🐝 BUN	29	16 - 37 mg/dL		III V	BUN	24	16 - 37 mg/dL	
BUN: Creatinine Ratio	17.1			88	BUN: Creatinine Ratio	10.9		
🛤 ∿ Phosphorus	4.3	2.9 - 6.3 mg/dL		III V	Phosphorus	4.3	2.9 - 6.3 mg/dL	
🛤 😘 IDEXX FGF-23	b. <b>1,098</b>	0 - 300 pg/mL		88	IDEXX FGF-23	b. Less tha	n 300 pg/mL	
🛤 😘 Calcium	8.6	8.2 - 11.2 mg/dL		III V	Calcium	9.8	8.2 - 11.2 mg/dL	
🛤 😘 Sodium	150	147 - 157 mmol/L		III V	Sodium	153	147 - 157 mmol/L	
🛤 🖴 Potassium	4.9	3.7 - 5.2 mmol/L		III V	Potassium	4.7	3.7 - 5.2 mmol/L	
🛤 😘 Na: K Ratio	31	29 - 42		III V	Na: K Ratio	33	29 - 42	
en es chiede	115	114 - 126 mmol/l		III V	Chloride	118	114 - 126 mmol/L	



## **Algorithm:** Identifying and managing phosphorus overload in cats diagnosed with CKD





FGF-23 fills a diagnostic gap for when to institute a therapeutic kidney diet in CKD for cats



## Active/acute kidney injury



#### Potential causes of AKI

Prerenal	Intrarenal	Postrenal
<section-header><section-header><list-item><list-item><list-item><list-item><list-item><list-item></list-item></list-item></list-item></list-item></list-item></list-item></section-header></section-header>	<ul> <li>+ Tubular disease</li> <li>+ Acute tubular necrosis (ATN)</li> <li>+ Toxic</li> <li>+ Ischemic</li> <li>+ Ischemic</li> <li>+ Glomerular disease</li> <li>+ Primary immune</li> <li>+ Secondary immune</li> <li>+ Amyloid</li> <li>+ Interstitial nephritis</li> <li>+ Drug</li> <li>+ Infectious</li> <li>+ Vascular disease</li> </ul>	<section-header><list-item><list-item></list-item></list-item></section-header>





#### Mechanisms for pathogenesis of AKI in cats and dogs

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### Stages of AKI



Healthy tublar spithelium: Normal urine output

Courtesy of Dr. Sherri Ross

Initial insult: Cellular damage/death Urine output may be unchanged Progressive swelling with or without death of epithelial cells: Oligoanuria possible Cell lysis/sloughing Debris occluding tubule Back leak and inflammation Oligoanuria



### 4. Recovery (hopefully)



**Sad renal tubule** If basement membrane intact, recovery possible Cell regeneration begins Some function returns **Tubular epithelial cells mature** Varying return of function

Courtesy of Dr. Sherri Ross



Cystatin B is a very small protein that is contained in the epithelial cells of the renal tubules



#### References

- Hall JA, Yerramilli M, Obare E, Yerramilli M, Yu S, Jewell DE. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in healthy geriatric cats fed reduced protein foods enriched with fish oil, L-carnitine, and medium-chain triglycerides. *Vet J.* 2014;202(3):588–596. doi:10.1016/j.tvjl.2014.10.021
- Hall JA, Yerramilli M, Obare E, Yerramilli M, Almes K, Jewell DE. Serum concentrations of symmetric dimethylarginine and creatinine in dogs with naturally occurring chronic kidney disease. J Vet Intern Med. 2016;30(3):794–802. doi:10.1111/jvim.13942
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During active or acute injury to the kidney, the cells that line the tubules can become damaged or necrotic





**Increased cystatin B** can occur with or without functional marker increase, **alerting to earlier, ongoing, and unresolved** injury to the kidney.



The types of active and acute injury that can cause cystatin B to leak into urine include both primary and secondary insults to the kidney





### The IDEXX Cystatin B Test

#### Novel kidney injury marker

- + Urine-based test
- + Cystatin B is very stable within urine when refrigerated/stored properly\*
- + Indicated for use on unwell dogs and cats
- + Available from IDEXX Reference Laboratories and with IDEXX Anywhere Urinalysis with SediVue Dx<sup>®</sup> Urine Sediment Analyzer codes





## When to use **Examples**

#### Use case

- + Veterinarian suspects a toxin exposure and is looking to confirm active injury
- Monitoring treatment/recovery from an injury event
- + Dogs with IRIS CKD Stage 1
- Patients that may be at higher risk when taking an NSAID
- + Shock (heat stroke, acute pancreatitis)
- + Anesthetic hypotensive event

#### **Potential action**

- + Confidence that treatment course is the correct one
- + Feedback that treatment is working or not; is the insult ongoing?
- IDEXX Cystatin B Test can provide indication of CKD progression; if disease is progressing, consider more aggressive treatment
- + If ongoing injury is occurring, consider NSAID alternatives
- Assess if injury occurred/is ongoing to determine next steps
- + Assess if injury occurred/is ongoing to determine next steps





#### Renal health in the sick pet



#### **Emergent cases**

- + Vehicular trauma
- + Hemoabdomen
- + Gastric dilatation and volvulus (GDV)
- + Uroabdomen
- + Toxin exposure
- + Seizures
- + Hyperthermia

#### **Hospitalised patients**

- + Post-op hospitalisation
- + Sick diabetic
- + Addisonian crisis
- + Pancreatitis
- + Urethral obstruction



### Kidney's role in renal monitoring in the sick pet



+ Pancreatitis

- 1. Sharp CR, Rozanski EA. Cardiovascular and systemic effects of gastric dilatation and volvulus in dogs. *Top Companion Anim Med* 2014;29(3):67–70. doi:10.1053/j.tcam.2014.09.007
- Maddens B, Heiene R, Smets P, et al. Evaluation of kidney injury in dogs with pyometra based on proteinuria, renal histomorphology, and urinary biomarkers. *J Vet Intern Med.* 2011;25(5):1075–1083. doi:10.1111/j.1939-1676.2011.0772.x
   Stern A. Canine environmental hyperthermia: a case series. *J Vet Med Sci.* 2019;81(2):190–192. doi:10.1292/jvms.18-0586
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## IDEXX Cystatin B Test: interpreting normal results

Cystatin B < 100 ng/mL There is a decreased potential of kidney injury

SDMA or creatinine within reference intervals Appropriately concentrated urine

Evidence of renal injury not present at this time SDMA or creatinine outside reference intervals Inappropriately concentrated urine

Previous history of kidney disease

## IDEXX Cystatin B Test: interpreting increased results



Subclinical kidney injury may be

HIDEXX VetConnect P	PLUS Home	Directory of Services Imagi	ng Telemedicine	
BELLA FI Canine Mixe 2023 Dec 21	TZPATRICK 2 ed Breed   Female	203AB Patient Manageme 8y	ent Y	
Result details 🗸				
Chemistry	12/21/23 5:13 AM			11/2/22 6:32 AM ▲
🛤 🍤 Glucose	92	63 - 114 mg/dL		88
🛤 \infty IDEXX SDMA	7	0 - 14 µg/dL		15
🛤 😘 Creatinine	1.4	0.5 - 1.5 mg/dL		1.2
🛤 🐃 BUN	14	9 - 31 mg/dL		13
<ul> <li>IDEXX Cystatin B (Urine)</li> <li>Learn More</li> </ul>	65	0 - 99 ng/mL		
-	The IDEXX Cystatin B Test			•
• • •	omarker that indicates itive and/or acute injury caused by current and ongoing insult. It is best			
	performed on sick patients patients with known kidne disease.	y and the second s		
Introducing IDEXX Cysta	tin B			

With the IDEXX Cystatin B Test, IDEXX's kidney health suite is more comprehensive than ever. Never before have veterinarians been able to detect active or acute injury to the kidneys with a kidney injury marker. Now with the IDEXX

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n B (Urine)
t values Result note
The IDEXX Cystatin B Test
datects a urinary kidney
omarker that indicates itive and/or acute injury caused by current and ongoing insult. It is best performed on sick patients or patients with known kidney disease.
Image: second

#### Introducing IDEXX Cystatin B

With the IDEXX Cystatin B Test, IDEXX's kidney health suite is more comprehensive than ever. Never before have veterinarians been able to detect Cystatin B  $\geq$  100 ng/mL: There is an increased potential of active kidney injury

- + Injury MAY RESOLVE
- + Injury may NOT be permanent
- + Consider ALL factors including
  - + Age
  - + Breed
  - + History

Patient presented for wellness visit	In a well patient, subclinic cannot be ruled out Subclinical kidney injury a single acute inciting ever result in overt clinical sign functional markers
SDMA and creatinine within reference intervals	A comprehensive histor medications, supplement travel, and other information obtained.
Appropriately concentrated urine	<b>Consider</b> rechecking cyskidney markers, including weeks or sooner if clinical apparent

#### Possible subclinical kidney injury

ical kidney injury

may be caused by ent and may not ns or changes in

ry, such as diet, ts, preventives, tion, should be

statin B and other g SDMA, in 1–2 al signs become



## Traditional diagnostics only allow for case evaluation by functional markers

**High/Abnormal** 

Markers **SDMA** 

Creatinine **BUN** 



#### Low/Normal



# Addition of an injury marker provides better case discrimination and management





Urine Cystatin B

Low/Normal



#### Diverse renal health portfolio





### Questions?



+ + + + + + CREATING CLARITY

##