Cystatin B: when and how should I use it in practice?

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Disclosure:

Bill Saxon is a full-time employee of IDEXX.

What the @#$% is Cystatin B?!

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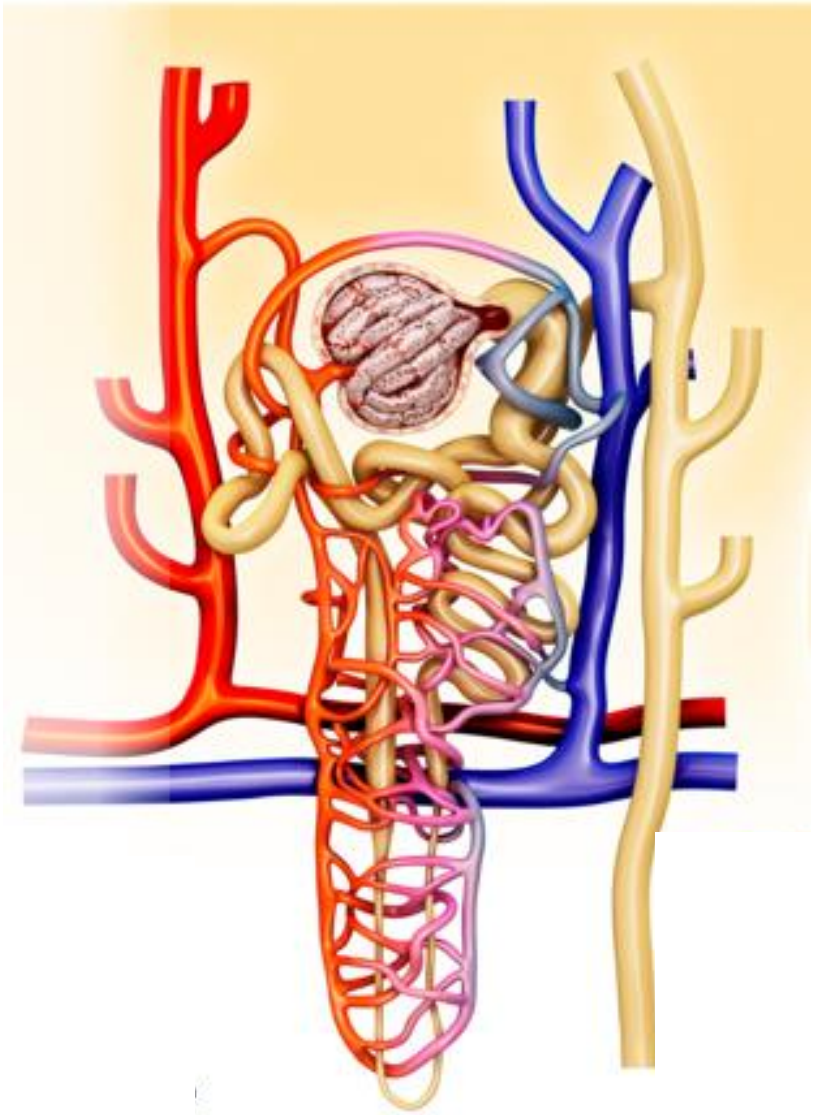
Tubules are the most vulnerable part of the nephron

Dogs
400K/kidney

Cats
200K/kidney

Humans
1 million/kidney



Tubular injury markers are earlier indicators of damage than functional markers.

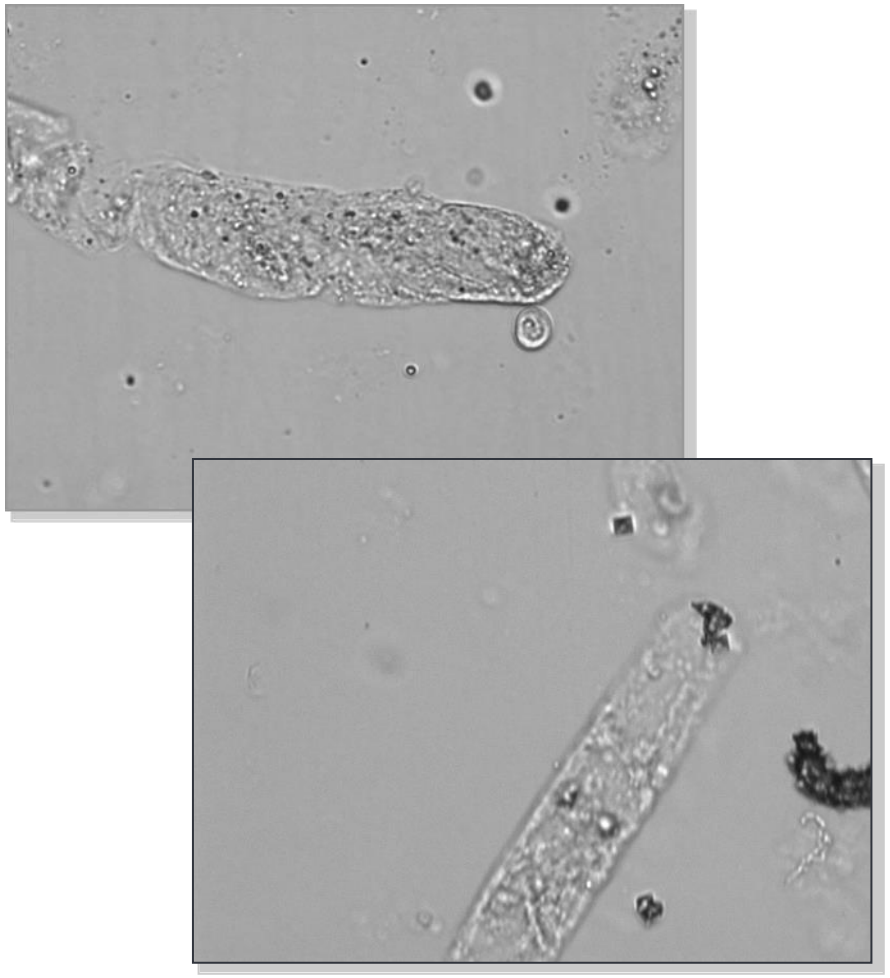
By up to 2 days….

Traditional injury markers okay but…

- **Granular casts ≈16%**
- **Euglycemic glucosuria**

} **30%**

- Proteinuria
- Hematuria
- Pyuria
- Bacteriuria
- Positive urine culture
- Renal epithelial cells
- *Non-physiologic* oliguria/anuria
- Decreased USG



Cystatin B fills a gap in detecting early active renal damage.

“The development and validation of Cystatin-B as an **active kidney injury biomarker** in dogs (and cats) that will be readily available to veterinarians has the potential to reshape the future diagnostic and therapeutic directions of kidney disease. As nephrologists*, we anxiously await this new era of early disease discovery and management.”

*Segev, Vaden, Cowgill (IRIS board members)

Cystatin B

- 11 kD (small) intracellular protein
  - Cysteine protease inhibitor (controls function and fate of proteins)
- Freely filtered at glomerulus
- Present in many cells in body
- In tubular epithelial cells in kidney
- Not present in urine of normal animals
- Increased urine concentration indicates active ongoing tubular damage
- Urine test recommended in sick patients to identify early kidney damage

Cystatin B = ALT

SDMA, creat = bile acids

Injury markers in urine.

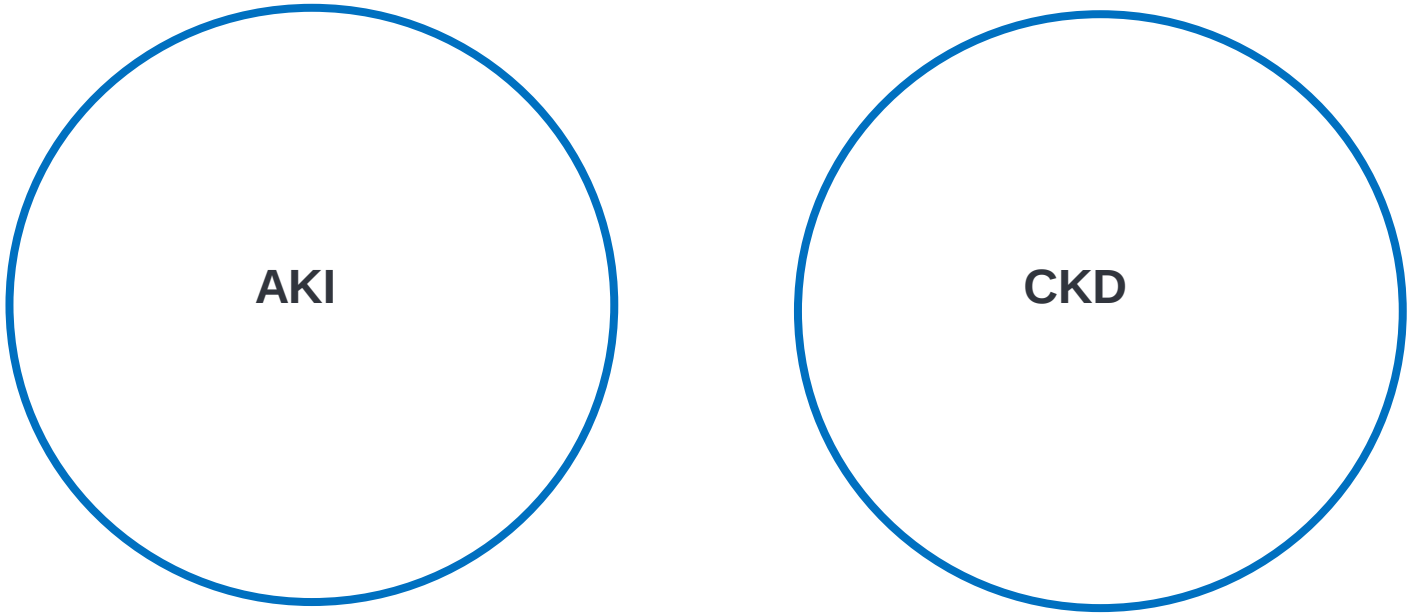
Functional markers in blood.

Need both to fully assess kidney.

The ideal dog or cat to run a cystatin B on…

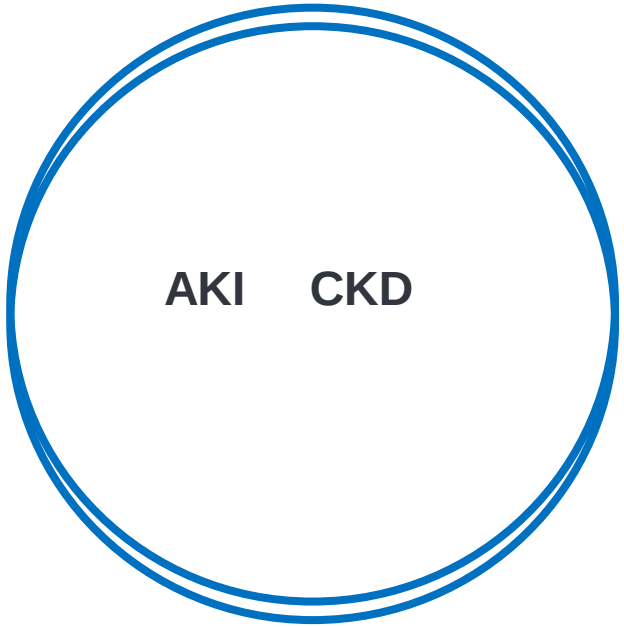
- AKI present or possible
  - Acutely ill with supportive lab results +/- non-physiologic oliguria/anuria
  - Known or possible exposure to nephrotoxin
  - Chronic NSAIDs
- Systemic disease present resulting in:
  - Renal hypoperfusion
  - Cytokine storm
- Early CKD to predict risk of progression
  - Is there a concurrent active injury component

It used to be…



Now it’s…

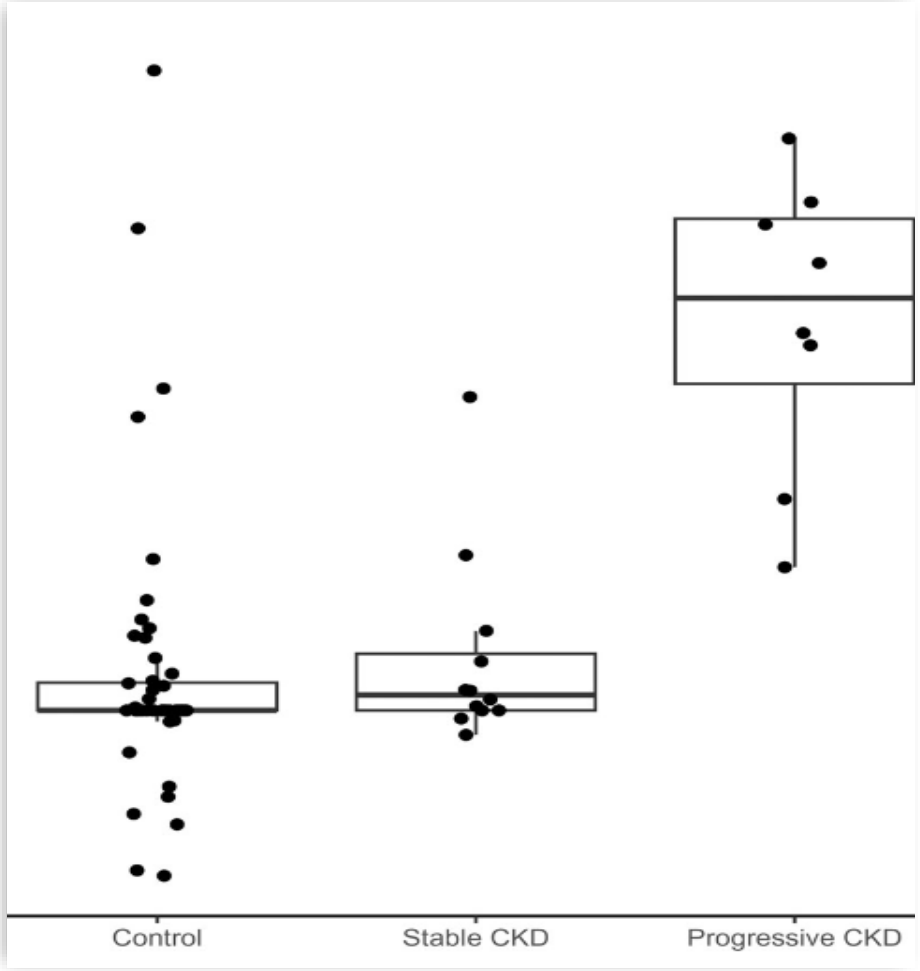
An AKI patient may have or develop CKD.



A CKD patient may have concurrent active kidney injury.

Cystatin B detects active ongoing injury with CKD

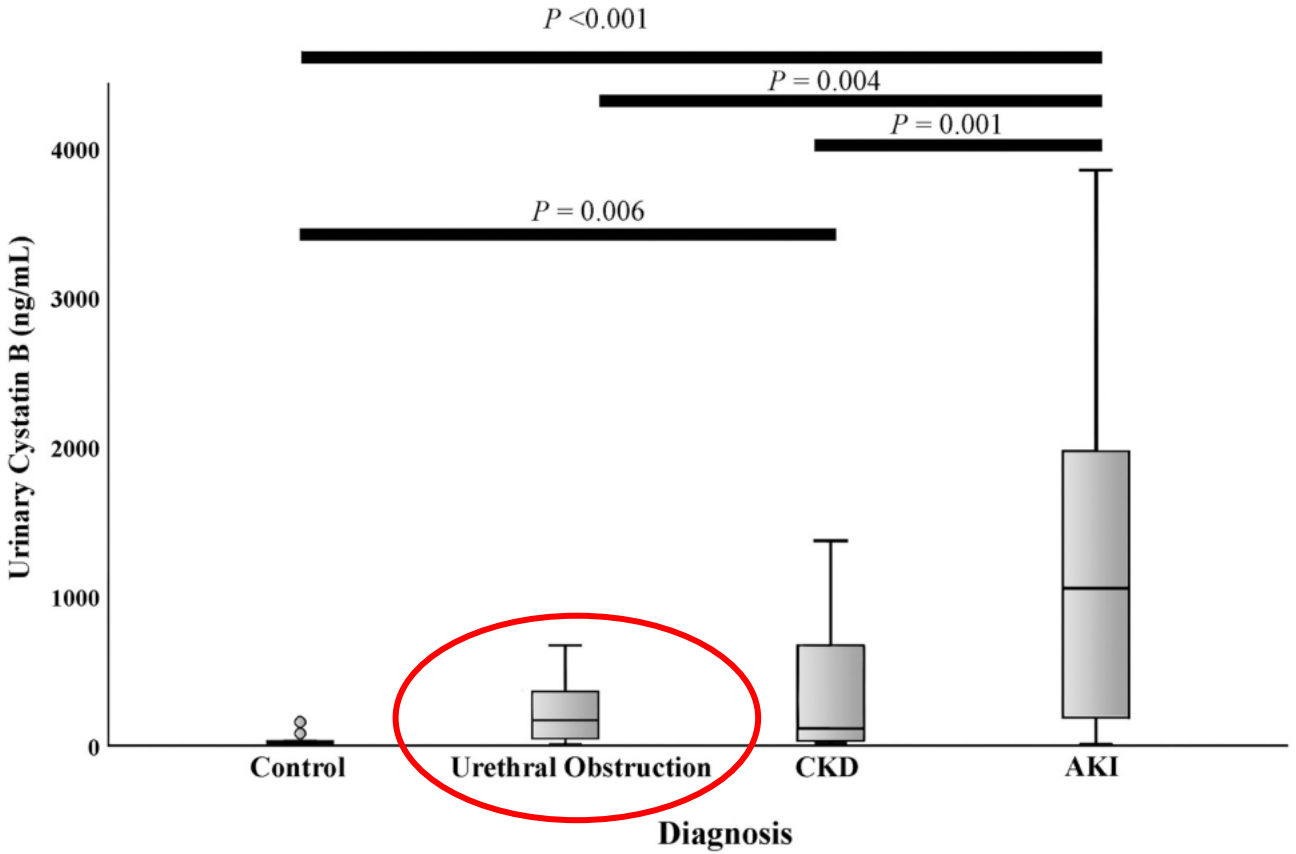
- CKD progressive and irreversible
- ***Rate*** of progression unpredictable
- Cystatin B identifies active ongoing injury in dogs and cats with CKD
- Increased Cys B in dogs with IRIS Stage 1 CKD predictive of more rapid progression
- Identifies which pets need more frequent monitoring



Segev, et al. J Vet Intern Med 2023

Chen, et al. Vet Journal 2024

Starting to see cat studies...



Chen et al. Vet Journal 2024

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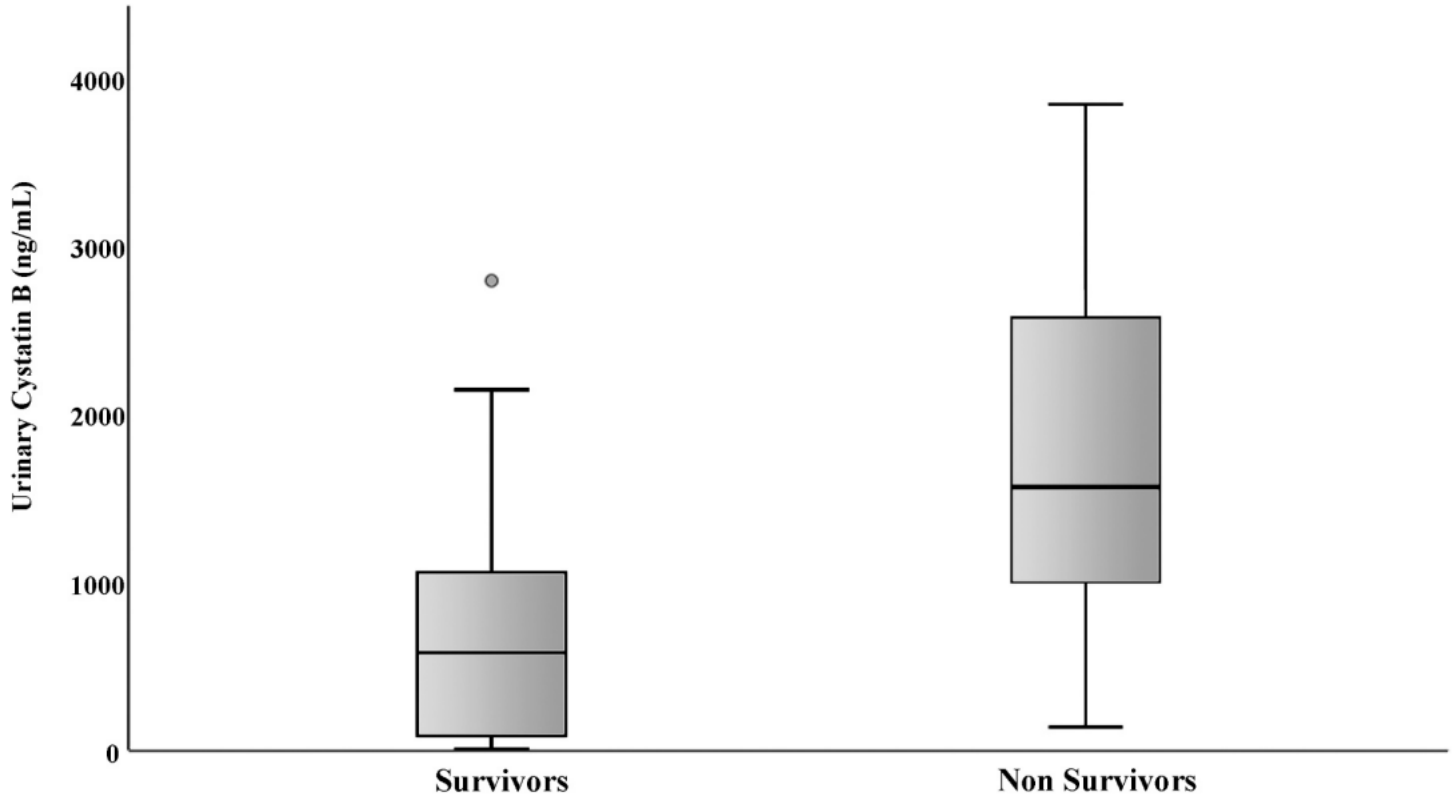


Chen et al. Vet Journal 2024

If Cystatin B increased:

Tubular epithelial cell damage is happening.

Do *something*.

Serial cystatin B to monitor.

Functional markers may be normal.

What to do with increased cystatin B depends…

- Did you request it or did it just show up in results?
  - You requested → increase more concerning
  - Just showed up → review history
  - *Not recommended if healthy and no concern of kidney injury*

- How high is it?
  - What would you do with similar ALT?
  - If only mild increase worth repeating at least once.

- Creatinine, SDMA, urinalysis normal or abnormal?

Presents for wellness, cystatin B increased:

Possible subclinical kidney injury

In a well patient, subclinical kidney injury cannot be ruled out

Subclinical kidney injury may be caused by a single acute inciting event and may not result in overt clinical signs or changes in functional markers

Ask questions!

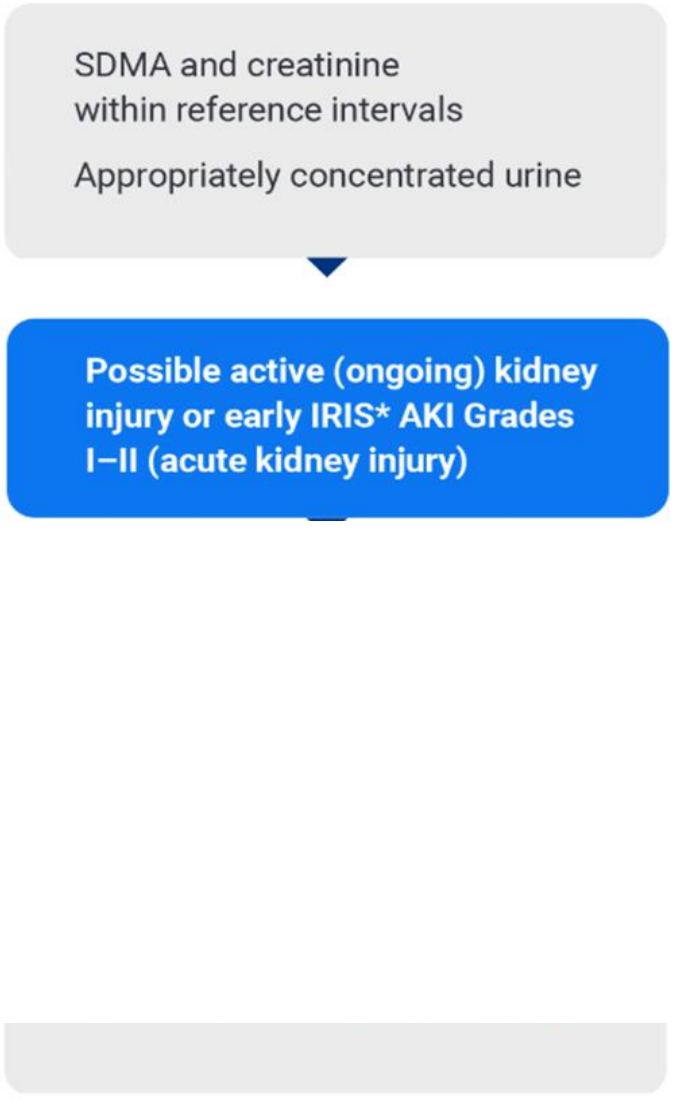
Current or past:

- Drugs
- Toxins
- Anesthesia
- Diet/treats
- Disease
  - CKD
  - AKI
  - Pyelo
  - Obstruction
  - Pancreatitis
  - Trauma
  - …

Recheck 1-2 weeks

Sooner if signs occur

Presents for non-wellness. Sick *or* nonclinical. No azotemia.



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  - …

Treat your patient

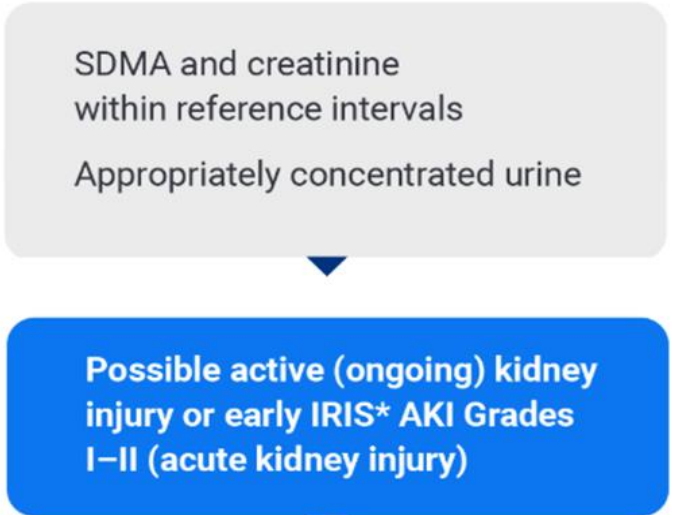
Other diagnostics prn

If hospitalize

- IRIS AKI grading q24h
- AVOID excess fluids
- Weigh 2-4 x/d

Recheck values in 24-48h

Presents for non-wellness. Sick *or* nonclinical. No azotemia.



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Treat your patient:

Other diagnostics prn

Outpatient tx

If hospitalize

- IRIS AKI grading q24h
- AVOID excess fluids
- Weigh 2-4 x/d

Recheck values in 24-48h

IRIS AKI grading and subgrading criteria. Apply daily.

Table 1: IRIS AKI Grading Criteria

AKI Grade	Blood Creatinine	Clinical Description
Grade I	<1.6 mg/dl (<140 µmol/l)	Nonazotemic AKI: a. Documented AKI: (historical, clinical, laboratory, or imaging evidence of AKI, clinical oliguria/anuria, volume responsiveness‡) and/or b. Progressive nonazotemic increase in blood creatinine: ≥ 0.3 mg/dl (≥ 26.4 µmol/l) within 48 h c. Measured oliguria (<1 ml/kg/h)# or anuria over 6 h
Grade II	1.7 – 2.5 mg/dl (141 – 220 µmol/l)	Mild AKI a. Documented AKI and static or progressive azotemia b. Progressive azotemic: increase in blood creatinine; ≥ 0.3 mg/dl ≥ 26.4 µmol/l) within 48 h),or volume responsiveness‡ c. Measured oliguria (<1 ml/kg/h)# or anuria over 6 h
Grade III	2.6 – 5.0 mg/dl (221 – 439µmol/l)	
Grade IV	5.1 – 10.0 mg/dl (440 – 880 µmol/l)	Moderate to Severe AKI: a. Documented AKI and increasing severities of azotemia and functional renal failure
Grade V	>10.0 mg/dl (>880 µmol/l)	

(‡Volume responsive is an increase in urine production to >1 ml/kg/h over 6 h; and/or decrease in serum creatinine to baseline over 48 h)

Table 2: IRIS AKI Subgrading

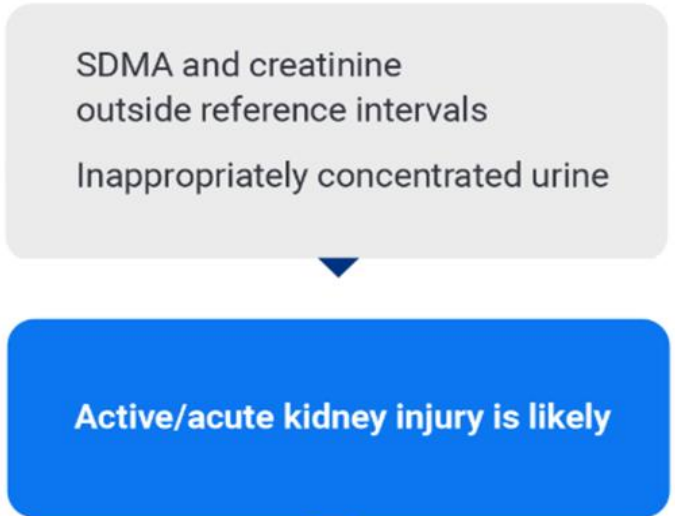
AKI Grade	Blood Creatinine	Subgrade
Grade I	<1.6 mg/dl (<140 µmol/l)	Each grade of AKI is further subgraded as: 1. Non oliguric (NO) or oligo-anuric (O) 2. Requiring renal replacement therapy (RRT)
Grade II	1.7 – 2.5 mg/dl (141 – 220 µmol/l)	
Grade III	2.6 – 5.0 mg/dl (221 – 439µmol/l)	
Grade IV	5.1 – 10.0 mg/dl (440 – 880 µmol/l)	
Grade V	>10.0 mg/dl (>880 µmol/l)	

Table 3: Illustration of IRIS AKI Grading During Hospitalization*

	Day 1	Day 2	Day 3	Day 4	Day 5
Patient 1	0.9	1.5	1.5	1.5	1.7
Patient 2	2.3 CKD	2.5 CKD	2.7	3.5	2.4
Patient 3	5.3	5.2	3.6	2.4	1.6
Patient 4	4.8	5.8	6.9	10.8	RRT
Patient 5	18.2	RRT	RRT	RRT	RRT

Non AKI · AKI Grade I · AKI Grade II · AKI Grade III · AKI Grade IV · AKI Grade V

Presents for non-wellness. Sick *or* nonclinical. Azotemic.



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  - CKD
  - AKI
  - Pyelo
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  - Pancreatitis
  - Trauma
  - …

Treat your patient:

Other diagnostics prn

If hospitalize

- Appropriate fluid tx
  (Avoid hypervolemia)
- SDMA, Creat q12-48h
- Lytes, PCV/TS min q24h
- Urine output q6-12h
- IRIS AKI grading q24h

- Weigh 2-4 x/d

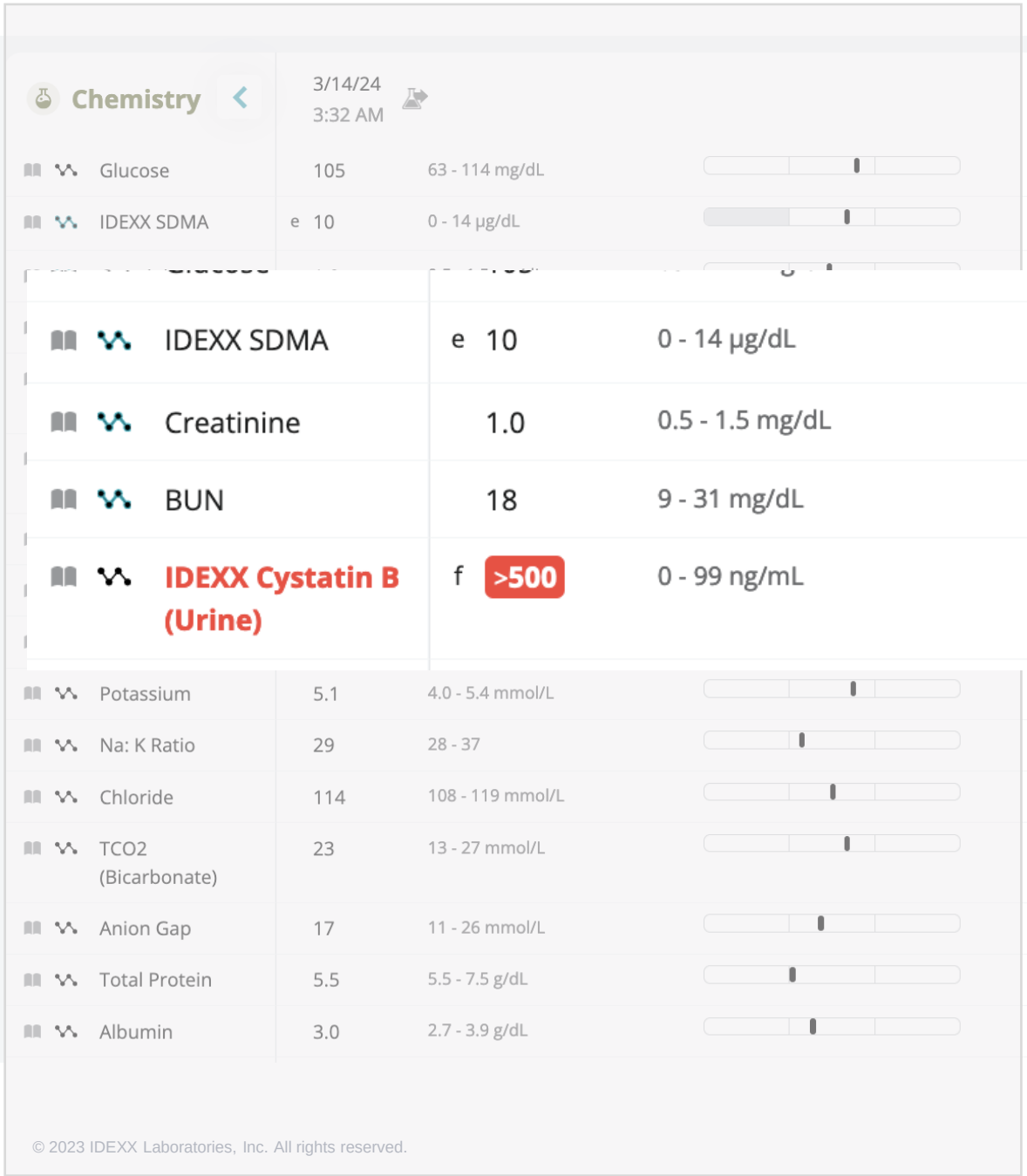
2-year-old male neutered Labrador

- Presenting complaint
  - Raisin ingestion sometime in past 8 hr (owner found empty box when returned from work)
  - No priors
  - Current on vaccination, parasite prophylaxis…
- PE
  - Vitals normal
  - No significant findings

Chemistry

	3/14/24 3:32 AM	
Glucose	105	63 - 114 mg/dL
IDEXX SDMA	e 10	0 - 14 µg/dL
Creatinine	1.0	0.5 - 1.5 mg/dL
BUN	18	9 - 31 mg/dL
BUN: Creatinine Ratio	18.0	
Phosphorus	3.9	2.5 - 6.1 mg/dL
Calcium	9.3	8.4 - 11.8 mg/dL
Sodium	149	142 - 152 mmol/L
Potassium	5.1	4.0 - 5.4 mmol/L
Na: K Ratio	29	28 - 37
Chloride	114	108 - 119 mmol/L
TCO2 (Bicarbonate)	23	13 - 27 mmol/L
Anion Gap	17	11 - 26 mmol/L
Total Protein	5.5	5.5 - 7.5 g/dL
Albumin	3.0	2.7 - 3.9 g/dL

3/14/24 3:32 AM		
FREECATCH		
DARK YELLOW		
TURBID		
1.049	>= 1.030	
5.5	6.0 - 7.5	pH
2+		PROT
NEGATIVE		
NEGATIVE		
3+		BLD
1+		
NORMAL		
0-2		
10-15		RBC
b RARE COCCI <9/HPF		
c RARE RODS <9/HPF		
d 4+ (>10)/HPF		CRYST



Treatment options for this dog

- Cystatin B increased = *active* tubular injury → must do *something*
- Not azotemic, USG normal
- Hydration normal

- **Induce vomiting and give 1 dose activated charcoal**
  - **Raisins in stomach up to 24h, not rapidly broken down or absorbed by GI tract**
- Send home and recheck renal values and cystatin B in 24-48h?
- SC fluids before sending home?
  - In case further vomiting, decreased appetite?
- Hospitalize for IV fluids at maintenance rate for 24-48 h?
  - Fluids not beneficial euhydrated patients, don’t hasten toxin excretion
- Hospitalize for IV fluids at 2-4x maintenance for 48 h?

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- ~~Hospitalize for IV fluids at 2-4x maintenance for 48 h?~~

3 d later: treatment for possible UTI and IV fluids x 48 h hours

Chemistry

3/17/24
1:07 AM

IDEXX SDMA	a 8	0 - 14 µg/dL	
Creatinine	1.2	0.5 - 1.5 mg/dL	
BUN	26	9 - 31 mg/dL	
IDEXX Cystatin B (Urine)	b <50	0 - 99 ng/mL	
Ratio			
Phosphorus	5.1	2.5 - 6.1 mg/dL	
Calcium	9.5	8.4 - 11.8 mg/dL	
Sodium	148	142 - 152 mmol/L	
Potassium	5.1	4.0 - 5.4 mmol/L	
Na: K Ratio	29	28 - 37	
Chloride	114	108 - 119 mmol/L	
TCO2 (Bicarbonate)	25	13 - 27 mmol/L	
Anion Gap	14	11 - 26 mmol/L	
Total Protein	**5.1**	5.5 - 7.5 g/dL	
Albumin	2.7	2.7 - 3.9 g/dL	
Globulin	2.4	2.4 - 4.0 g/dL	

Urinalysis

3/17/24
1:07 AM

Collection	FREECATCH	
Color	DARK YELLOW	
Clarity	CLOUDY	
Specific Gravity	1.061	>= 1.030
pH	**5.5**	6.0 - 7.5
Urine Protein	**1+**	
Glucose	NEGATIVE	
Ketones	a TRACE	
Blood / Hemoglobin	**3+**	
Bilirubin	1+	
Urobilinogen	NORMAL	
White Blood Cells	0-2	
Red Blood Cells	**30-50**	
Bacteria	NONE SEEN	
Additional Bacteria		
Epithelial Cells	1+ (1-2)/HPF	
Mucus	NONE SEEN	
Casts	NONE SEEN	
Crystals	NONE SEEN	

Some common questions:

- How soon does cystatin B increase?
  - 2 to a few hr post snake bite, 4 hr post cardiac bypass, at presentation in blocked cats…
- How long does it remain in urine?
  - Hours to days…
- How specific is it for tubular injury if it's present in all cells in the body?
  - Should not be present in urine of normal animals
  - Increase in sepsis, pancreatitis, etc due to AKI and/or damage to other tissues
  - Still useful marker – another monitoring tool for whatever is causing increase

Some cystatin B thoughts

- Prognostic – some evidence in cats with AKI?
- Predictive of azotemia in 48 hr after acute toxicity?
- Return to normal correlated with resolution of azotemia?
- Need more studies cats and dogs.
- Urothelial carcinoma in people – uCysB correlated with grade, stage, and recurrence progression in urothelial carcinoma in people…pets?

If Cystatin B increased:

Tubular epithelial cell damage is happening.

Do *something*.

Serial cystatin B to monitor.

Thank you!