



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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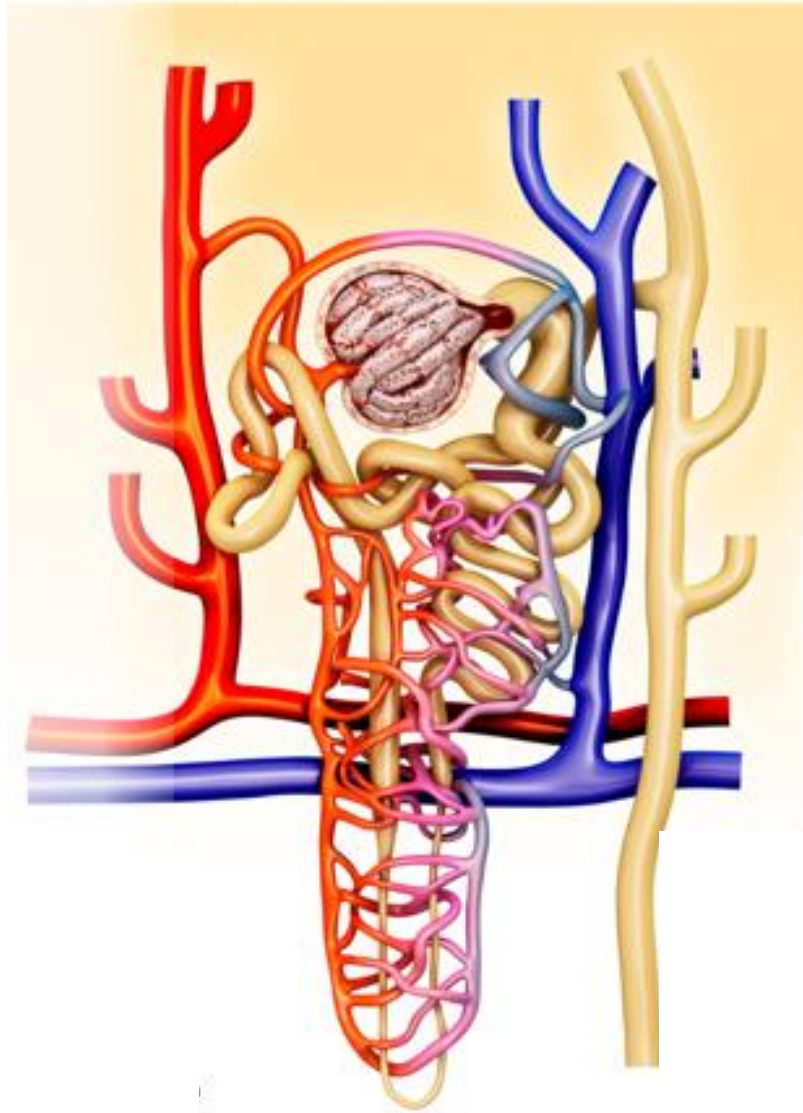
IDEXX

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 $\approx 16\%$
 - 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.

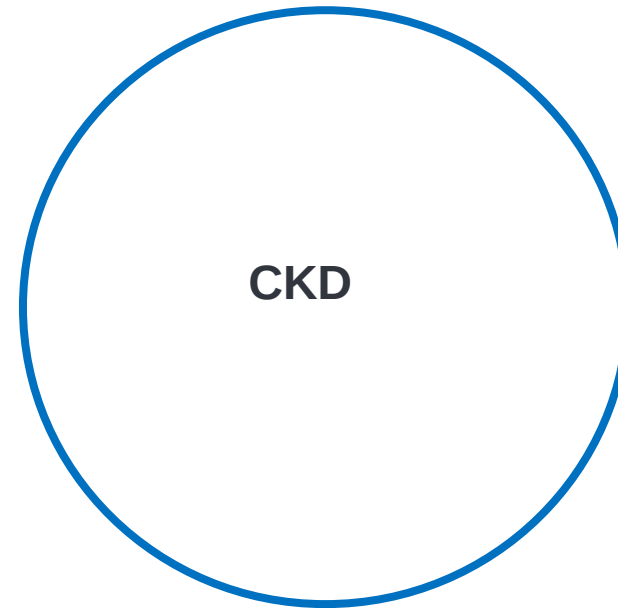
Functional markers in blood.

Need both to fully assess kidney.

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

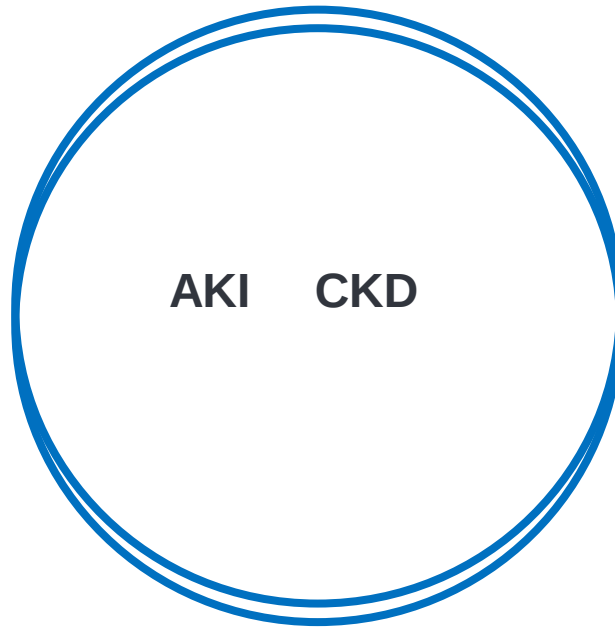
- AKI present or possible
 - Acutely ill with supportive lab results +/- non-physiologic oliguria/anuria
 - Known or possible exposure to nephrotoxin
 - Chronic NSAIDs
- Systemic disease present resulting in:
 - Renal hypoperfusion
 - Cytokine storm
- Early CKD to predict risk of progression
 - Is there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

It used to be...



Now it's...

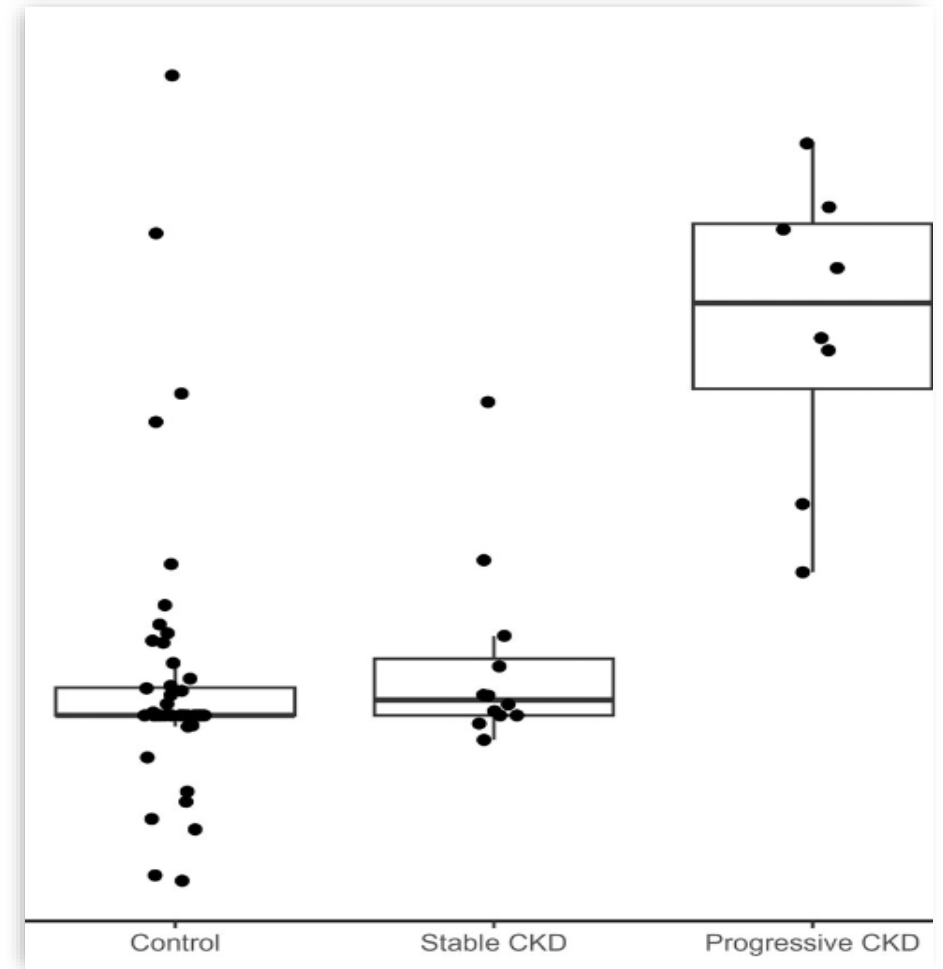
An AKI patient may have or develop CKD.



A CKD patient may have concurrent active kidney injury.

Cystatin B detects active ongoing injury with CKD

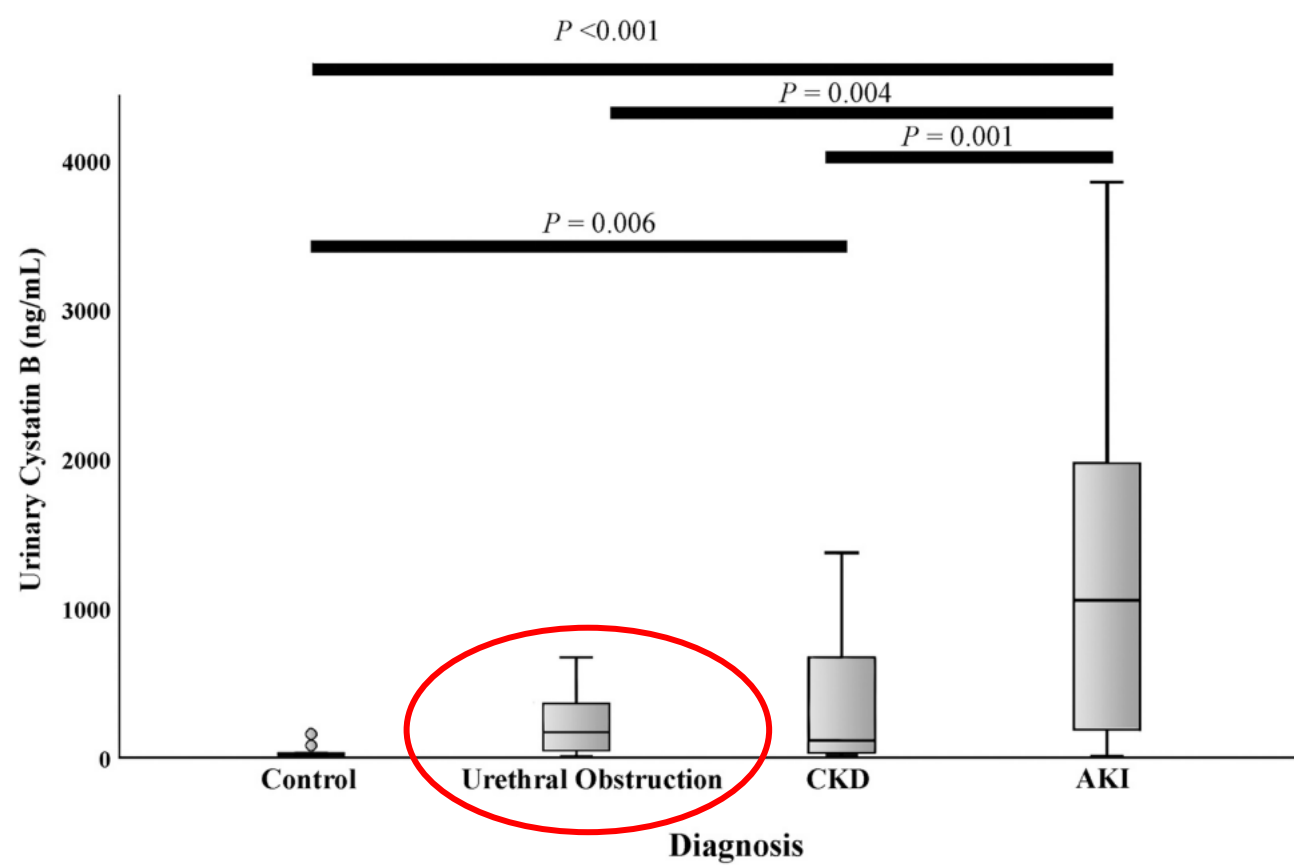
- CKD progressive and irreversible
- **Rate** of progression unpredictable
- Cystatin B identifies active ongoing injury in dogs and cats with CKD
- Increased Cys B in dogs with IRIS Stage 1 CKD predictive of more rapid progression
- Identifies which pets need more frequent monitoring



Segev, et al. J Vet Intern Med 2023

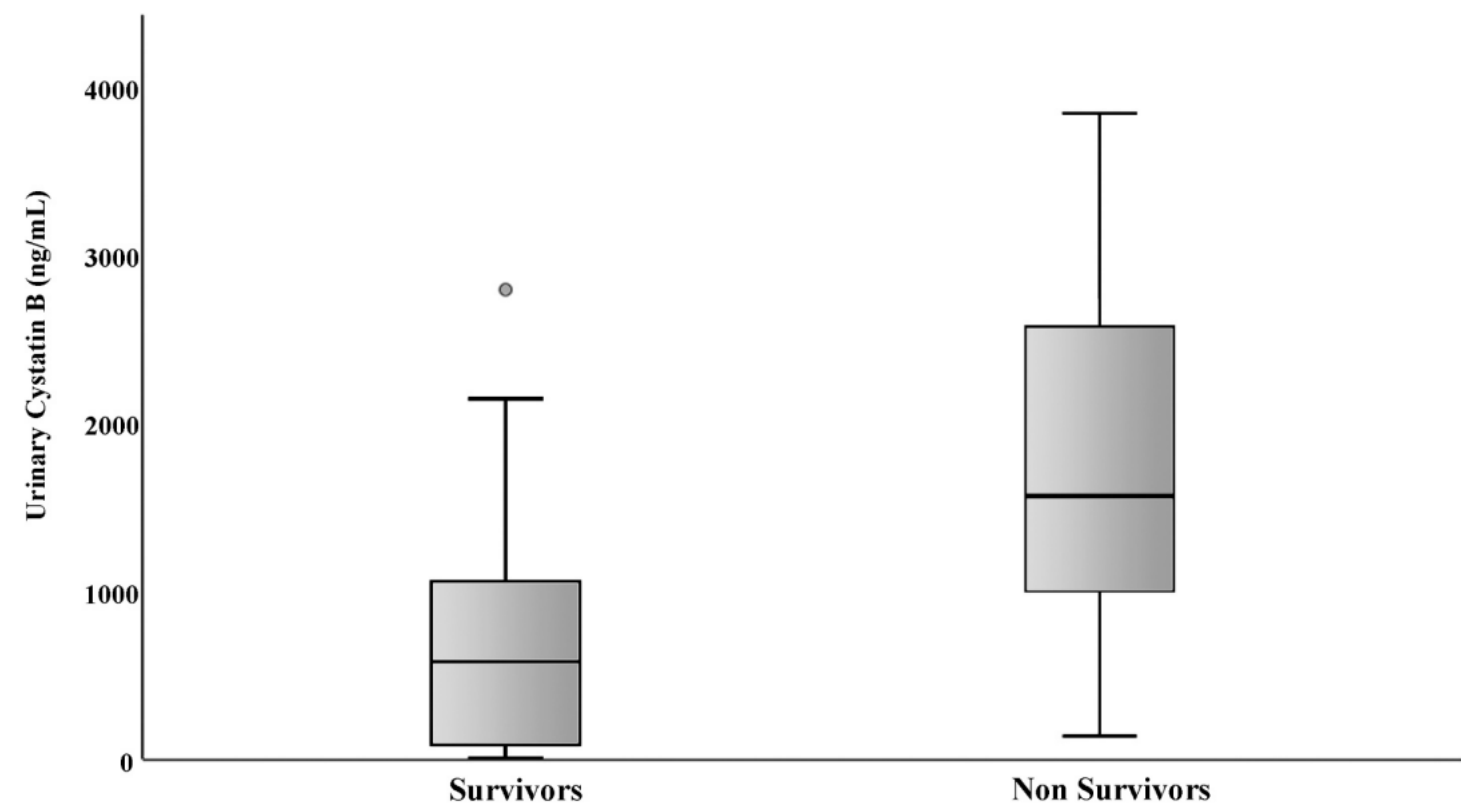
Chen, et al. Vet Journal 2024

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

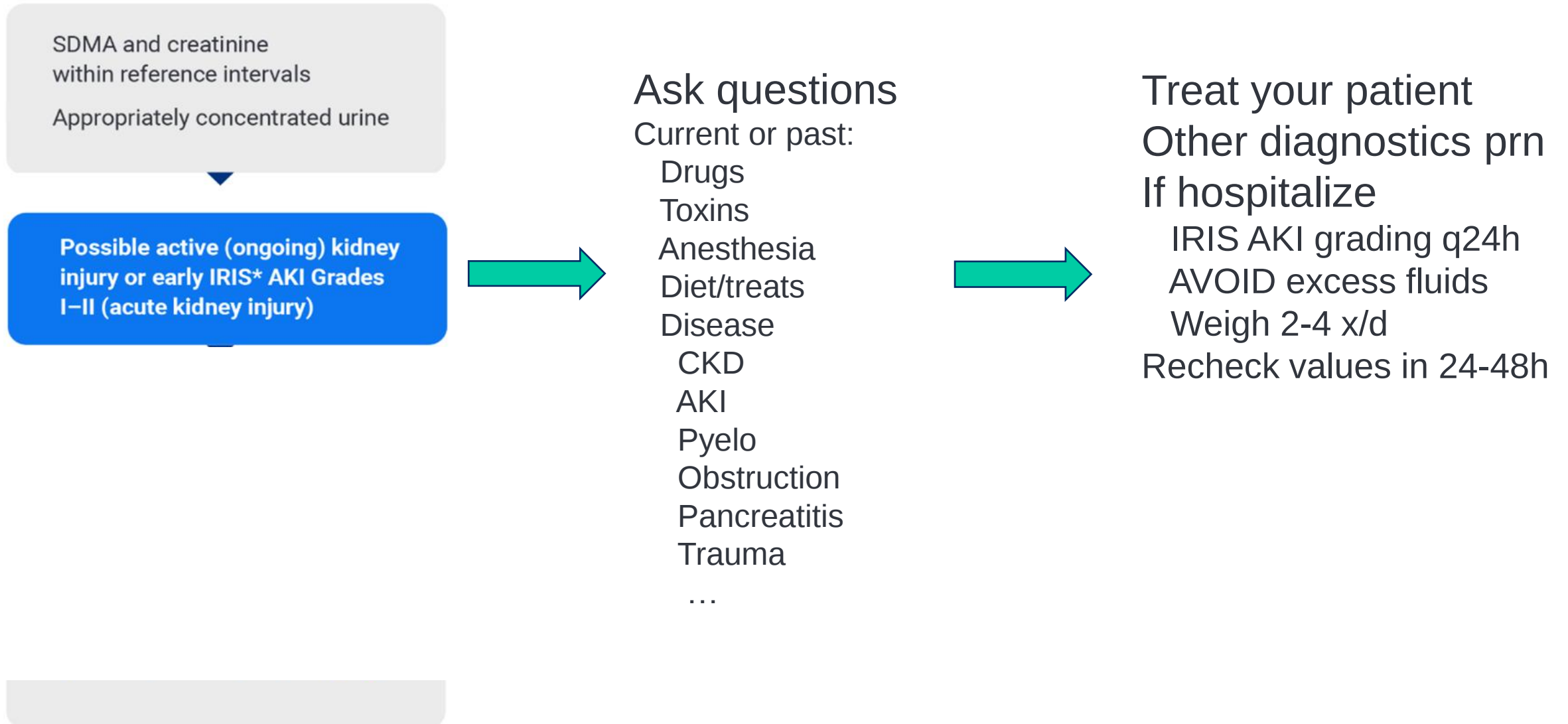
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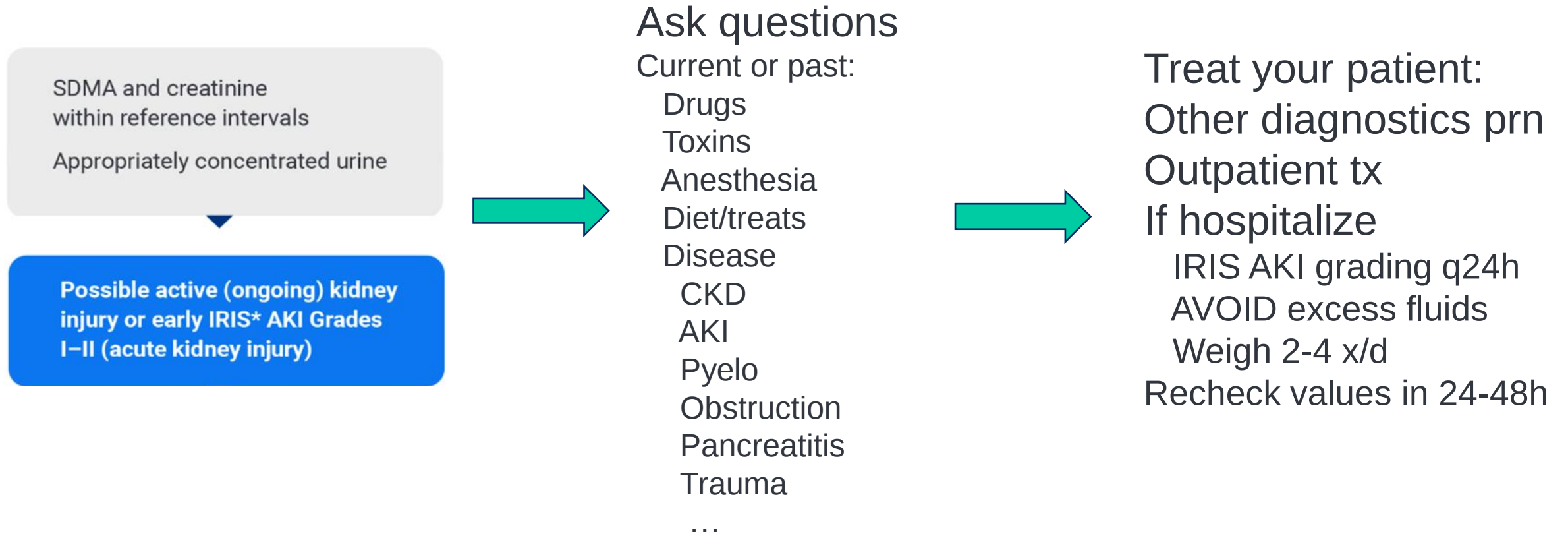
Recheck 1-2 weeks

Sooner if signs occur

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



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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 – 439 µmol/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

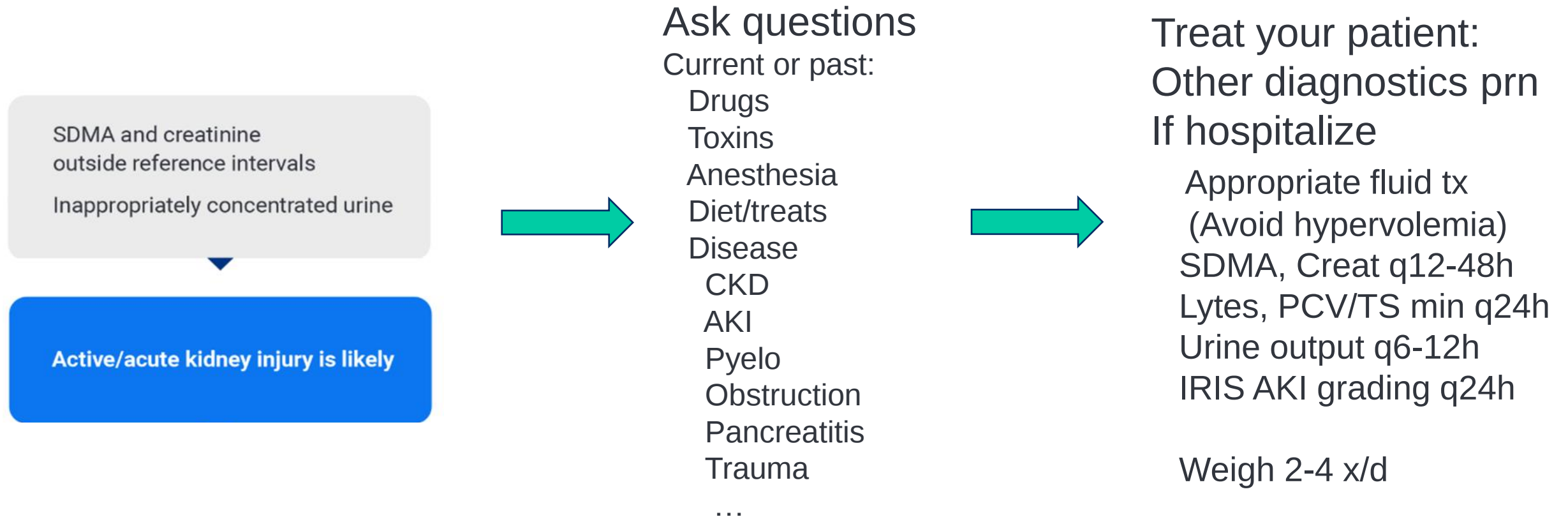
AKI Grade	Blood Creatinine	Subgrade
Grade I	<1.6 mg/dl (<140 µmol/l)	Each grade of AKI is further subgraded as: 1. Non oliguric (NO) or oligo-anuric (O) 2. Requiring renal replacement therapy (RRT)
Grade II	1.7 – 2.5 mg/dl (141 – 220 µmol/l)	
Grade III	2.6 – 5.0 mg/dl (221 – 439 µmol/l)	
Grade IV	5.1 – 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	3.5	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.



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

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Creatinine	1.0	0.5 - 1.5 mg/dL	
BUN	18	9 - 31 mg/dL	
IDEXX Cystatin B (Urine)	f >500	0 - 99 ng/mL	

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	

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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- Cystatin B increased = *active* tubular injury → must do *something*
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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 📄				📄 Urinalysis 3/17/24 1:07 AM 📄			
IDEXX SDMA		a 8	0 - 14 µg/dL	Collection		FREECATCH	
Creatinine		1.2	0.5 - 1.5 mg/dL	Color		DARK YELLOW	
BUN		26	9 - 31 mg/dL	Clarity		CLOUDY	
IDEXX Cystatin B (Urine)		b <50	0 - 99 ng/mL	Specific Gravity		1.061	>= 1.030
Ratio				pH		5.5	6.0 - 7.5
Phosphorus		5.1	2.5 - 6.1 mg/dL	Urine Protein		1+	
Calcium		9.5	8.4 - 11.8 mg/dL	Glucose		NEGATIVE	
Sodium		148	142 - 152 mmol/L	Ketones		a TRACE	
Potassium		5.1	4.0 - 5.4 mmol/L	Blood / Hemoglobin		3+	
Na: K Ratio		29	28 - 37	Bilirubin		1+	
Chloride		114	108 - 119 mmol/L	Urobilinogen		NORMAL	
TCO2 (Bicarbonate)		25	13 - 27 mmol/L	White Blood Cells		0-2	
Anion Gap		14	11 - 26 mmol/L	Red Blood Cells		30-50	
Total Protein		5.1	5.5 - 7.5 g/dL	Bacteria		NONE SEEN	
Albumin		2.7	2.7 - 3.9 g/dL	Additional Bacteria			
Globulin		2.4	2.4 - 4.0 g/dL	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!