
VMX
2025
VETERINARY MEETING & EXPO
Festival of the HeARTS
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JANUARY 25-29
ORLANDO, FLORIDA
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The AKI Patient:
All the Critical Details

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VMX 2025 VETERINARY MEETING & EXPO

Conflict of Interest Disclosure:

Nancy Sanders is a full-time IDEXX employee

The information contained herein is intended to provide general guidance only. Diagnosis, treatment, and monitoring should be patient specific and is the responsibility of the veterinarian providing primary care.

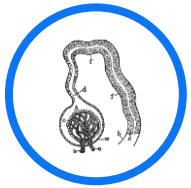
Learning Objectives

1. Compare and contrast the significance of acute and active kidney injury vs. chronic kidney disease
2. Review biomarkers of acute and active kidney injury, including urinary cystatin B
3. Explain the cellular sources for cystatin B and the significance of elevated urinary concentrations
4. Apply acute kidney injury concepts to clinical cases

Timeline of kidney biomarkers

Proteinuria

Described by Hippocrates 400 B.C.

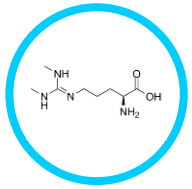


Creatinine

Jaffe reaction 1886

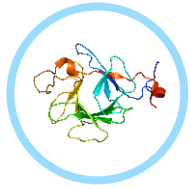
Glomerular filtration rate

Cockcroft-Gault equation for estimating GFR in 1973



SDMA

Validated in 2015



FGF-23

Launched for felines with chronic kidney disease 2022

Urinary cystatin B

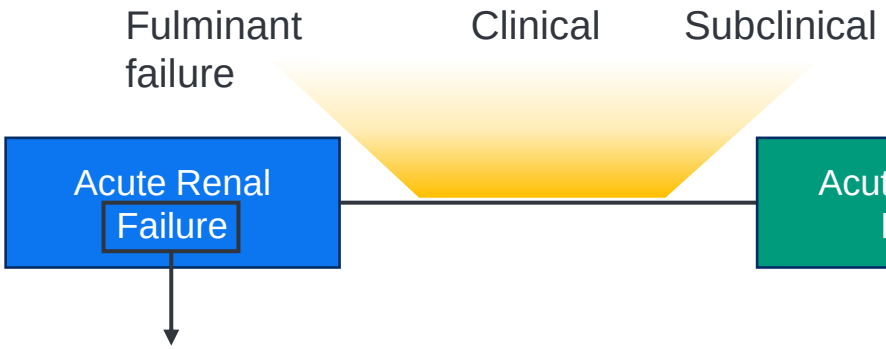
Detects both active and acute kidney injury

Launched December 2023

Acute kidney injury (AKI) vs. chronic kidney disease (CKD): Why do we care?

AKI	CKD
+ Early detection to prevent progression	+ Early detection/intervention in attempt to slow progression
+ Institute supportive care and specific therapy when possible	+ Institute dietary therapy, supportive care
+ Determine resolution or progression	+ Determine likelihood of rapid progression
+ Short-term financial and emotional investments are intense	+ Long-term financial, emotional, and time commitments
+ Prolonged hospitalization: associated with higher morbidity and mortality	+ Usually outpatient therapy; when hospitalization is required, usually associated with low morbidity and mortality

Terminology can be confusing; ARF, AKI, ATI, ATN



- Acute → short time span, generally ≤ 24-48 hours
- Impact disrupts renal cellular structure and function
- Injury does not necessarily = failure, or even azotemia
- Damage can be reversible

Acute tubular injury (ATI) or necrosis (ATN) is the most common cause of AKI in dogs and cats

- Failure has specific definition of > 90% loss of function with clinical effects
- Was a term often used to characterize significant loss of kidney function
  - Retention of uremic toxins
  - Dysregulation of fluid
  - Electrolyte and acid-base imbalance

Active Kidney Injury

- Often cannot characterize the timeline
- Inciting cause and time of onset are not always known
- Diagnostics indicate on-going and sustained injury
- Distinguish ***active kidney injury*** from ***kidney dysfunction***

J. Himmelfarb, T.A. Ikizler, Acute kidney injury: changing lexicography, definitions, and epidemiology, Kidney International,Volume 71, Issue 10,2007,Pages 971-976,ISSN 0085-2538, https://doi.org/10.1038/sj.ki.5002224.
Kellum, John A., Claudio Ronco, and Rinaldo Bellomo. "Conceptual advances and evolving terminology in acute kidney disease." *Nature Reviews Nephrology* 17.7 (2021): 493-502.

Veterinary criteria – IRIS AKI grading

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)	Moderate to Severe AKI: a. Documented AKI and increasing severities of azotemia and functional renal failure
Grade IV	5.1 – 10.0 mg/dl (440 – 880 µmol/l)	
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)

Risk
Nonazotemic

Injury
Mildly azotemic

Failure
Moderately to severely azotemic

International Renal Interest Society

http://www.iris-kidney.com/education/index.html

Subgrade

Each grade of AKI is further subgraded as:
1. Non oliguric (NO) or oligo-anuric (O)
2. Requiring renal replacement therapy (RRT)

http://www.iris-kidney.com/guidelines/grading.html

Soooo….
How do we *realistically* distinguish acute from chronic?

- Mostly by deductive reasoning and often after the fact
  - History
  - Current lab results and lab trends (historical)
  - Imaging
  - Response to therapy (future lab trends)
  - Intuition

Diagnosing kidney disease is more than documenting abnormal renal chemistries

Physical exam

Kidney palpation
Muscle mass
Cardiac auscultation

Medical history

Appetite/weight loss
Energy
Water consumption

Diagnostics: lab work

CBC, Chemistry
Urinalysis
Other

Imaging

Radiographs
Ultrasound
Other advanced

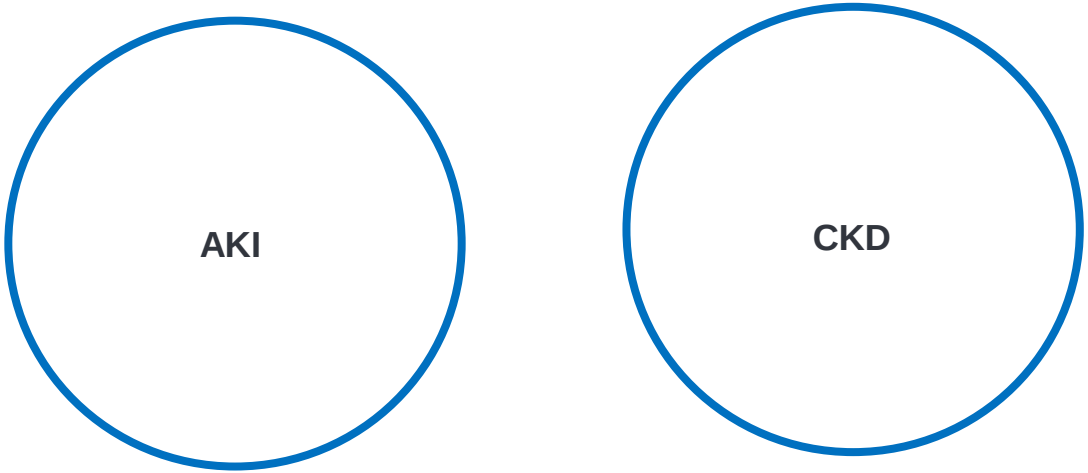
Clinical decision points

http://www.iris-kidney.com/education/education/differentiation_acute_kidney_injury_chronic_kidney_disease.html

Hallmarks of AKI (vs CKD)

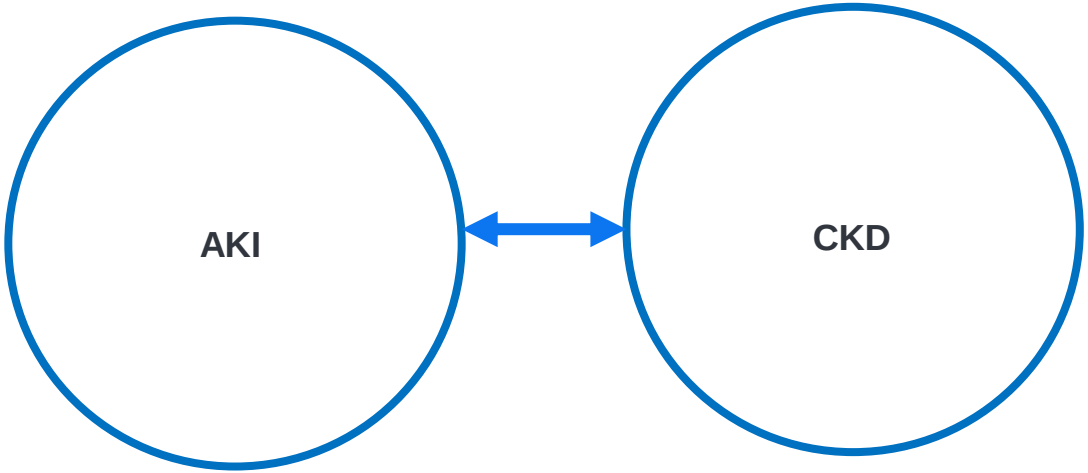
- History and physical exam
  - Acute onset – hours to days
  - Toxin exposure (lily, grapes, NSAIDs, anesthetics…)
  - Renomegaly, renal pain
  - Bradycardia/hypothermia (hyperkalemia) if severe hyperkalemia
- Lab findings
  - Hyperkalemia
  - Urinary granular casts, normoglycemic glucosuria…
- Imaging
  - Renomegaly in 70%
  - Hydroureter, pyelectasia, hydronephrosis
  - Ureteral calculi
  - Normal parathyroid gland

Back in the day…



More contemporary view…

Your AKI patient may have or develop CKD

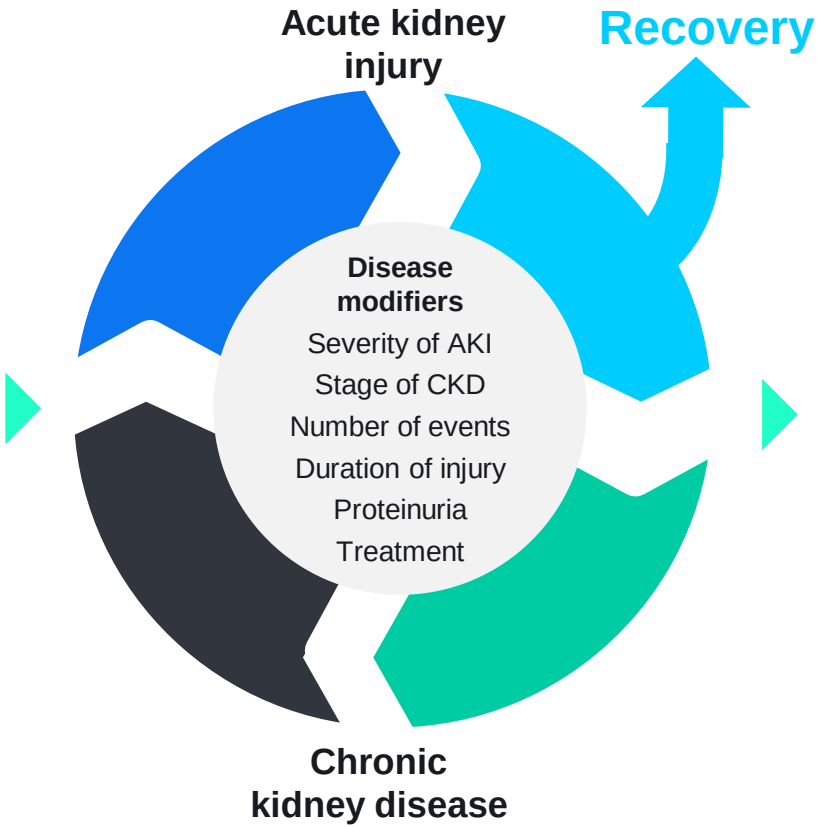


Your CKD patient may have concurrent active kidney injury

Kidney function in health and disease is impacted by risk factors, injury, and outcomes

Risk factors

- Breed
- Age
- Sex
- Diet
- Drugs
- Pre-existing disease
  - CKD
  - Hypertension
  - Metabolic disease
  - Cardiac disease



Outcomes

- Recovery
- Persistent damage
- Cardiovascular events
- Additional kidney events
- Diminished quality and quantity of life
- Cost events

Source: Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66. doi:10.1056/NEJMra1214243

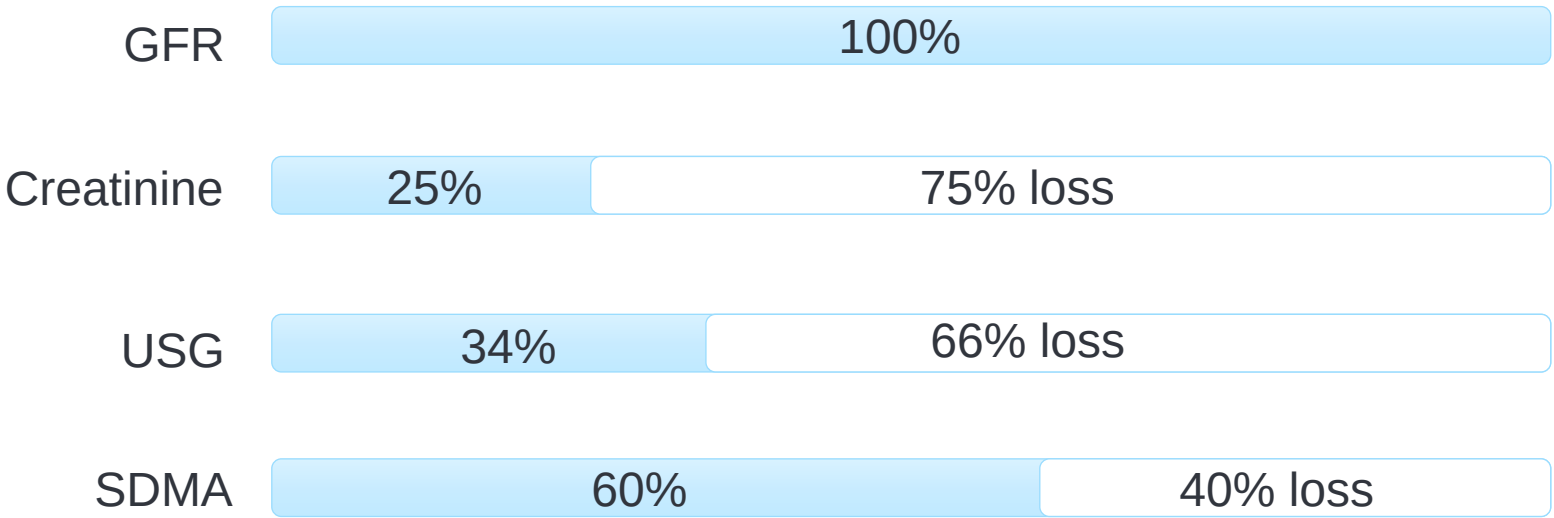
You suspect kidney disease: what next?

In the meantime:

Attempt to determine definitive diagnosis and disease-specific therapy

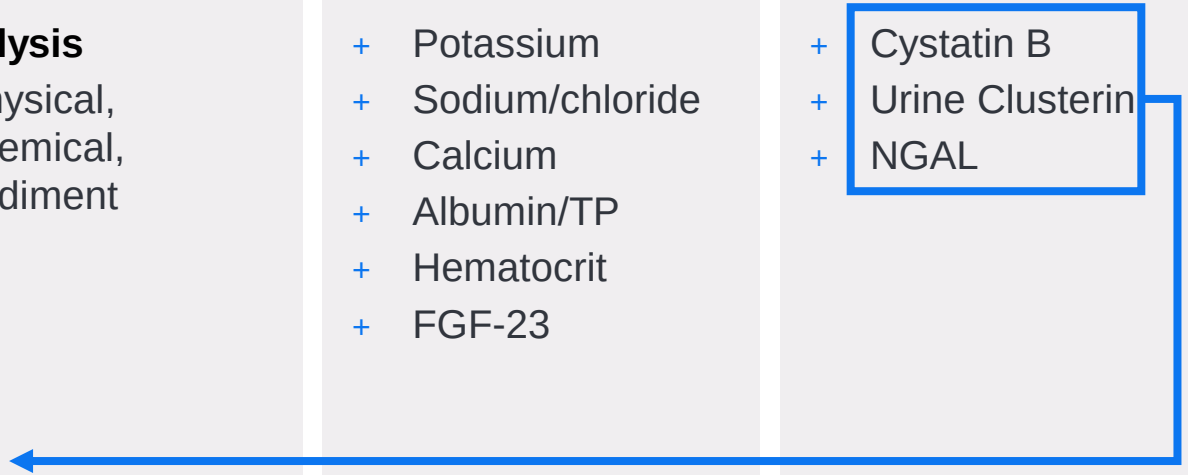
GFR biomarkers fall short as early detectors of kidney disease

Performance of current renal “functional” biomarkers (estimates of GFR)



Categories of biomarkers and analytes to evaluate kidney function and injury

Indirect markers of function	Urine-based markers	Other important analytes	Acute kidney injury markers
Most specific (i.e. limited extrarenal effects): + SDMA + Creatinine **Less Specific (i.e. more extrarenal effects):** + BUN + Phosphorus	**Urinalysis** + Physical, chemical, sediment **UPC**	+ Potassium + Sodium/chloride + Calcium + Albumin/TP + Hematocrit + FGF-23	+ Cystatin B + Urine Clusterin + NGAL



You need broad assessment to understand kidney health

What can we measure in clinical practice?

Functional Markers

How well are the kidneys clearing waste from the body (GFR)

Creatinine, SDMA, BUN

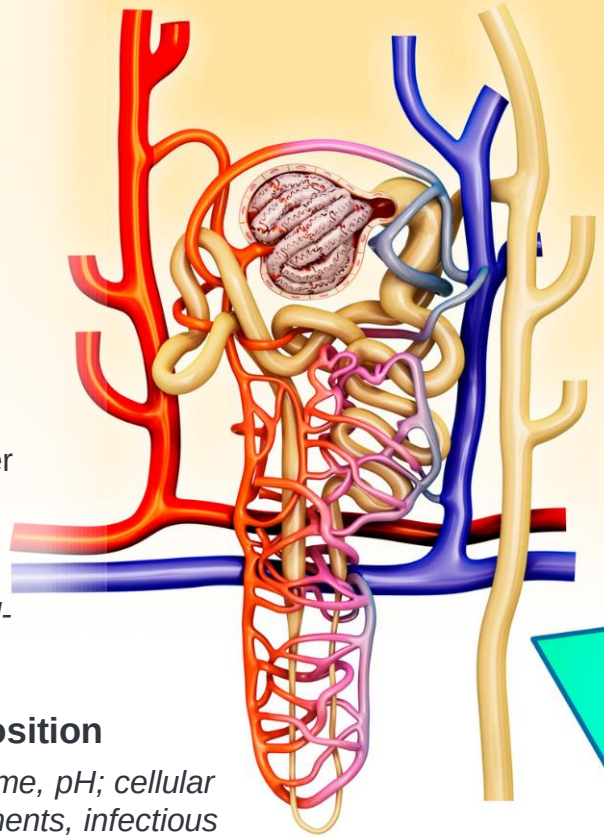
Tubular Function

Important in solute & water management;

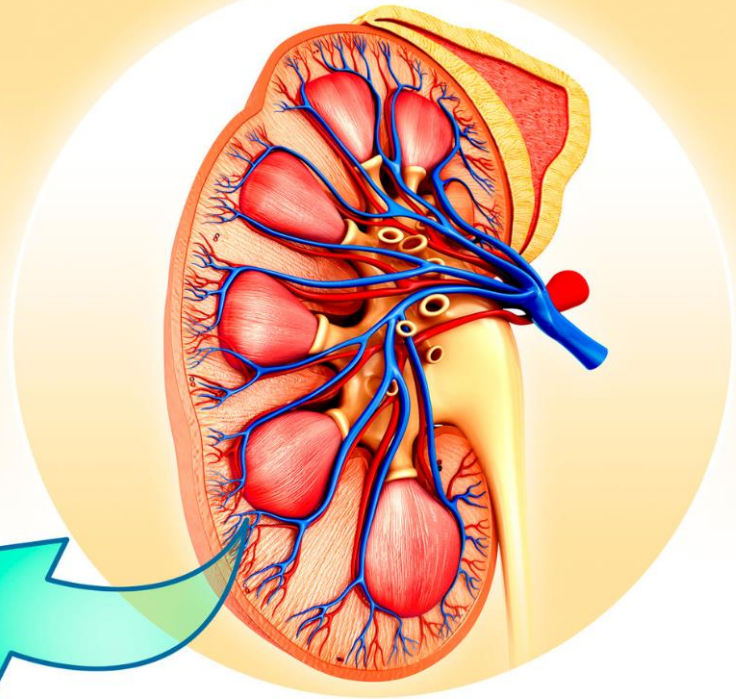
Urine concentration electrolytes, glucose, acid-base

Urine composition

Concentration/volume, pH; cellular and crystalline elements, infectious organisms, protein



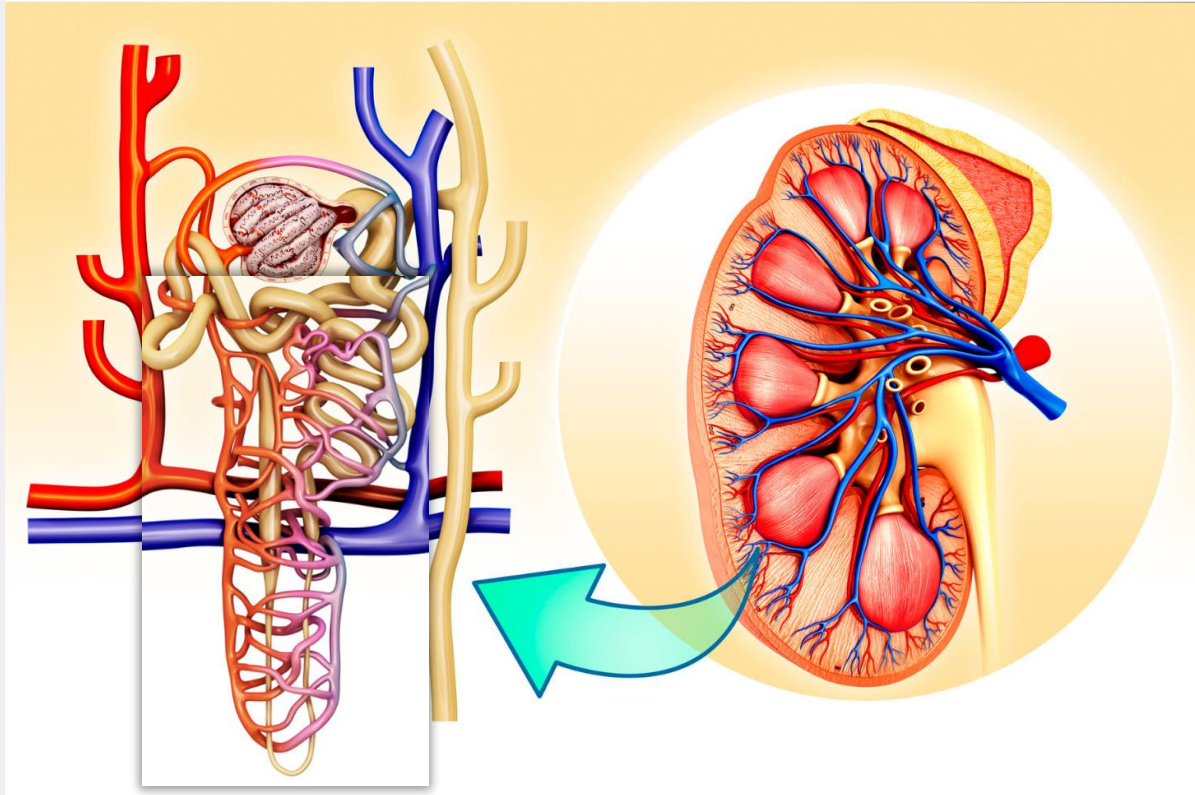
The functional nephron



Renal tubules are where the action *really* is

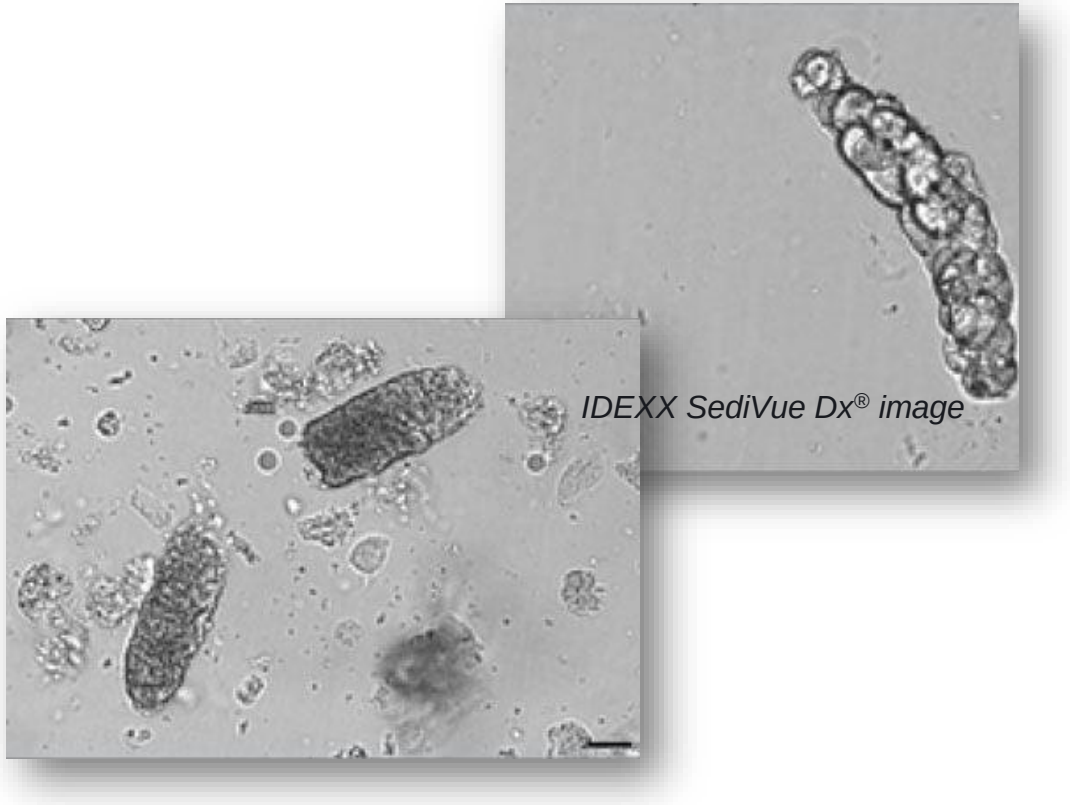
Tubular function

- The actual work of the kidney primarily takes place here. Filtering, reabsorbing, and secreting solutes and water
- Impact urine concentration and what is excreted
- Dysfunction can impact electrolytes, protein levels, glucose, acid-base balance
- Captured in chemistry panel and urinalysis



Traditional renal *injury* markers are good, not great

+ Proteinuria
+ Hematuria, pyuria
+ Bacteriuria, + urine culture
+ Renal epithelial cells
+ Glucosuria (normoglycemia)
+ Cylindruria (casts)
+ Decreased USG



IDEXX SediVue Dx® image

Injury markers are in urine

Functional markers are in blood

Take home message:
You can’t assess kidney health without urine

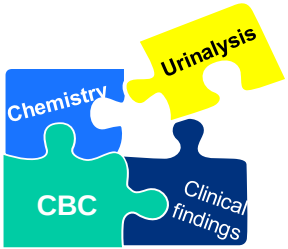
Designed by Freepik

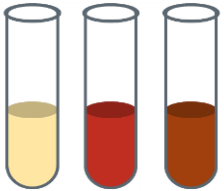
The complete urinalysis should be part of the minimum data base

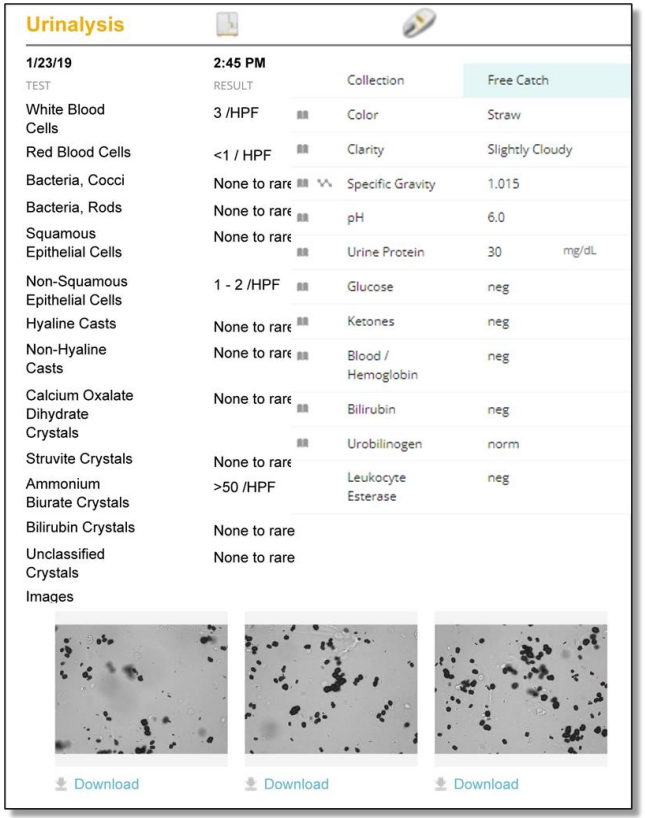
+ Three parts: physical, biochemical, and microscopic exam

+ Part of minimum data base for any patient, evaluation of PU/PD, diagnosis and follow-up if specific conditions

+ Urinalysis provides much more than an evaluation of the urinary system.



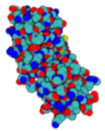




Cystatin B fills a gap in our abilities to detect early and active renal injury

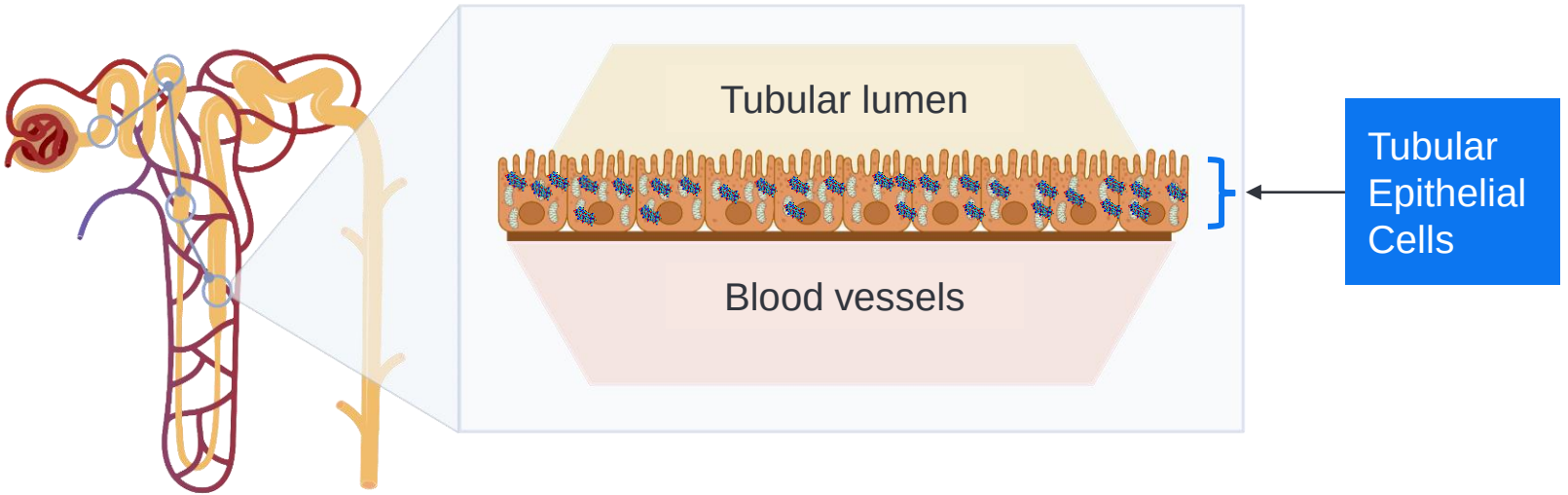
.

What is Cystatin B?

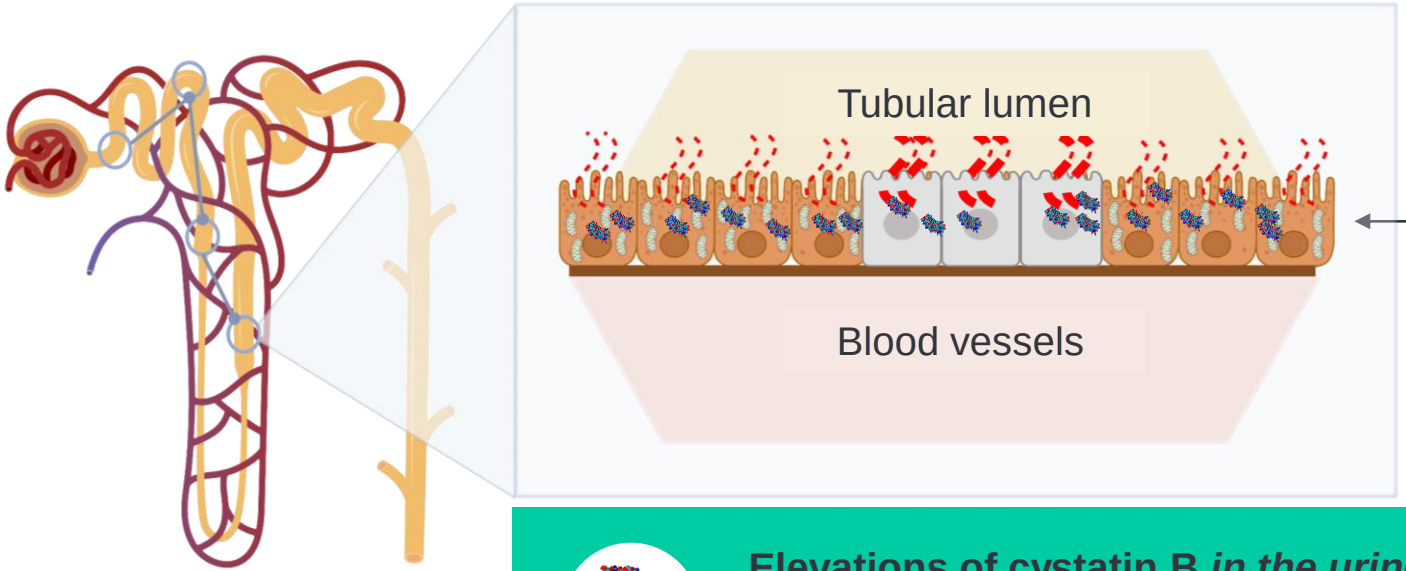


- Member of cystatin family
  - Protease inhibitors that help protect against leakage of proteolytic enzymes from lysosomes
  - Trace amounts in the serum of healthy subjects
- A small, intracellular protein
  - 11 kDa
  - Ubiquitous in many cells, including proximal renal tubular cells
- Freely filtered at the glomerulus
- Increased urinary [cystatin B] indicates active, ongoing tubular injury
  - Think of it as the ALT of the kidney

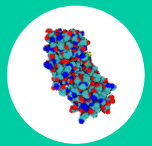
Cystatin B is a very small protein that is contained in the epithelial cells of the renal tubules



During **active or acute kidney injury**, renal tubular epithelial cells (responsible for secretion and reabsorption of solutes and water) can be damaged

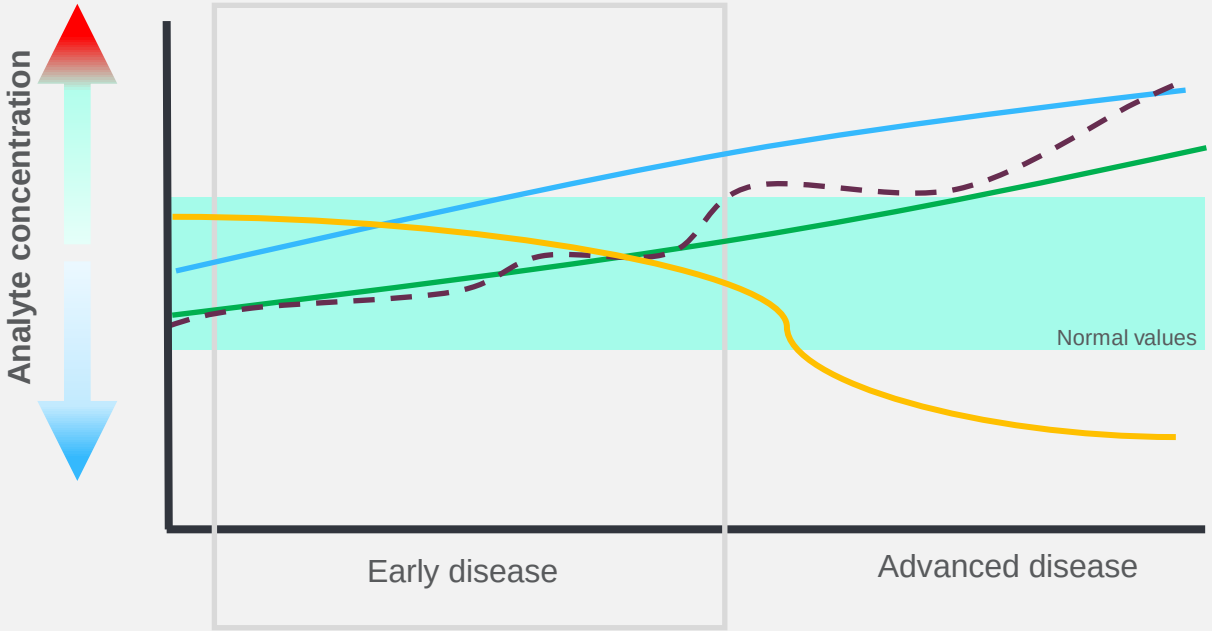


Cystatin B leakage from injured or necrosed tubular epithelial cells



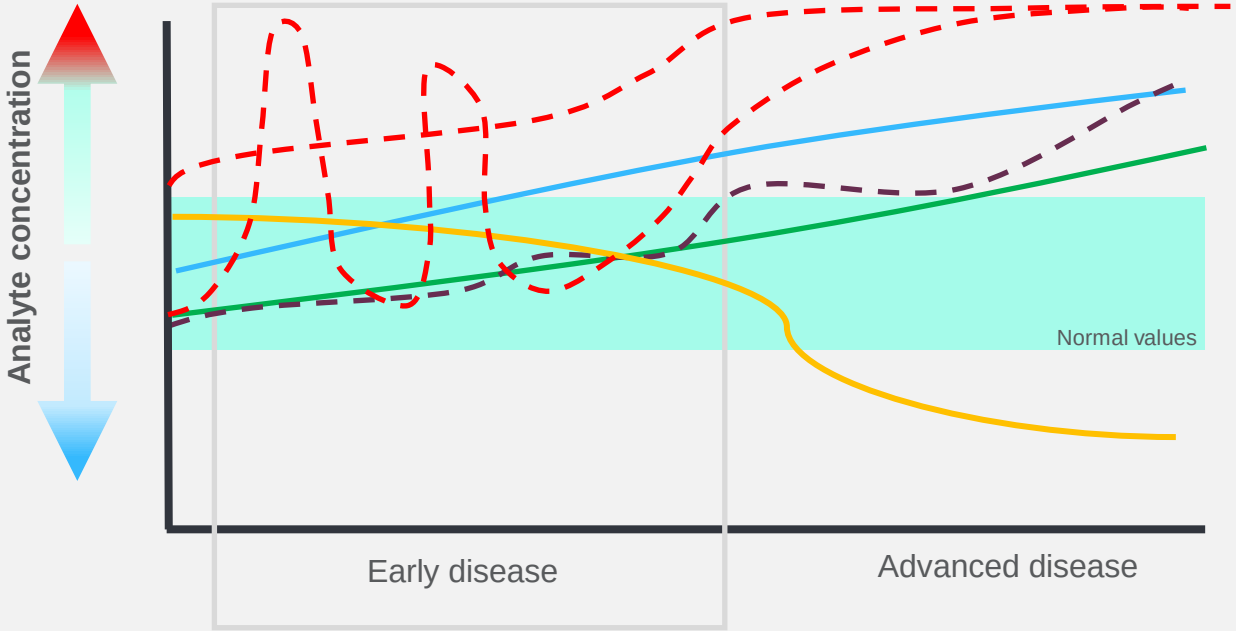
Elevations of cystatin B *in the urine* can occur with or without increases in functional markers, **alerting to earlier, ongoing, and unresolved** kidney injury.

Current indirect markers of renal function vs. disease stage



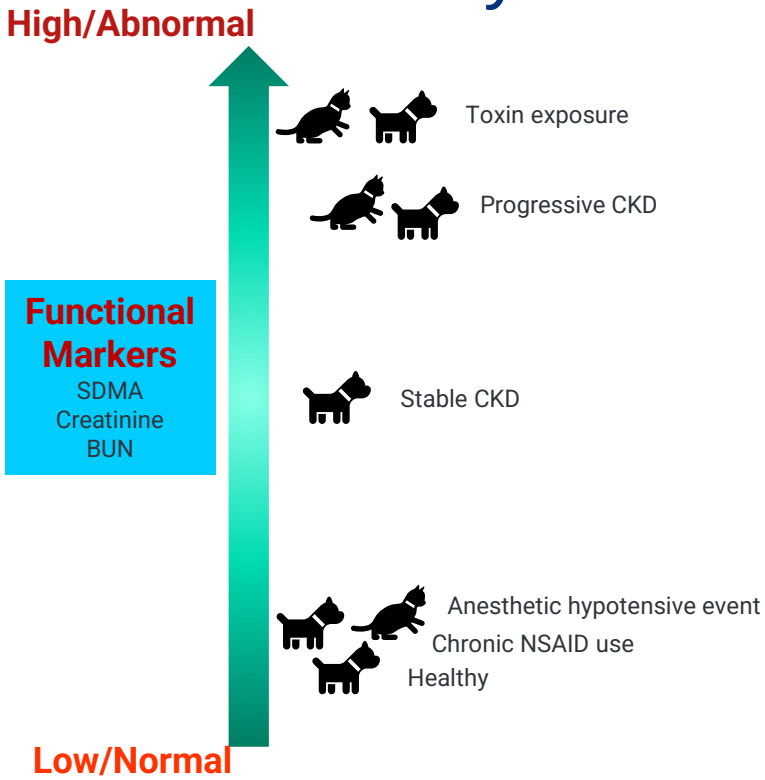
SDMA
Creatinine
BUN
USG

Kidney injury markers are additive to current indirect functional markers

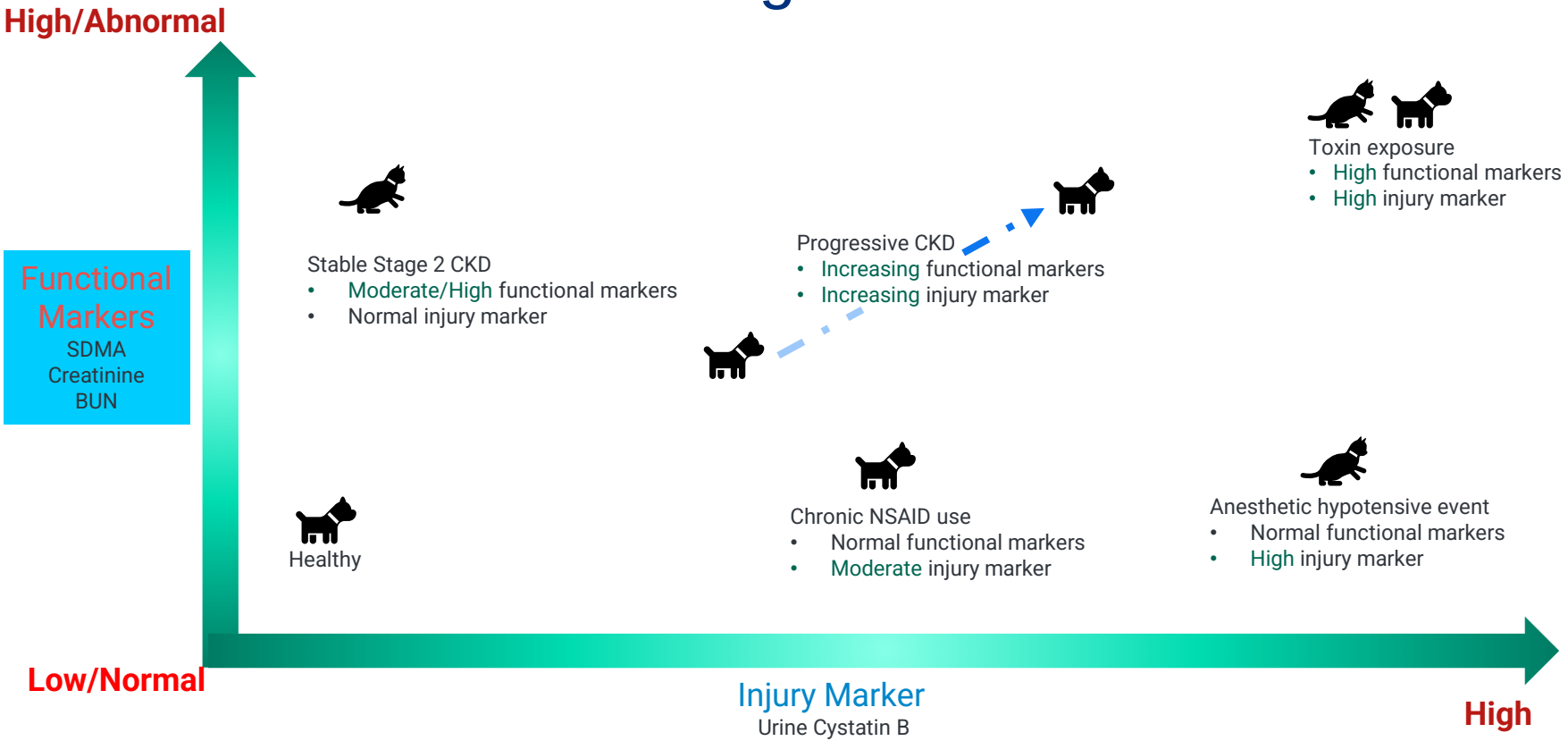


Renal tubular markers
SDMA
Creatinine
BUN
USG

Traditional diagnostics only allow for case evaluation by functional markers



Addition of an injury marker provides better case discrimination and management



Abnormal renal functional markers reflect progression of injury to dysfunction *after* the fact:
Early recognition of renal injury is an opportunity to *change course of disease*

Ingested grapes

SDMA	14	0 – 14 µg/dL	
Cystatin B	<15	<100 ng/dL	

Stable functional renal markers

24 hours Later

SDMA	11	0 – 14 µg/dL	
Cystatin B	<15	<100 ng/dL	

SDMA	14	0 – 14 µg/dL	
Cystatin B	324	<100 ng/dL	

Progressive functional renal markers

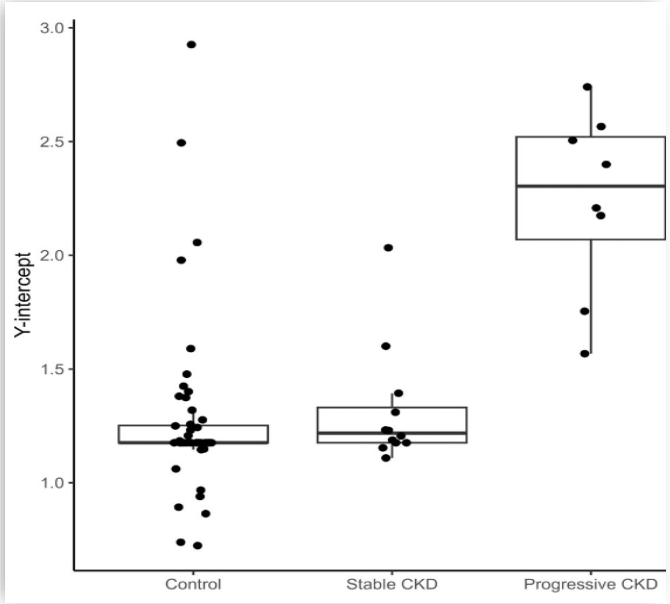
SDMA	23	0 – 14 µg/dL	
Cystatin B	604	<100 ng/dL	

Two dogs ingested grapes
Similar scenarios

Therefore, markers of tubular injury are earlier indicators of damage than functional markers

Cystatin B has value with evaluating patients with CKD as well!

- CKD progressive and irreversible
- ***Rate*** of progression unpredictable
- Cystatin B identifies active, progressive injury in dogs with CKD
- Increased uCysB in dogs with IRIS Stage 1 CKD predicts rapid progression
- Identifies which dogs need more frequent monitoring



y-intercepts calculated from inverse urinary cystatin B (uCysB) vs time

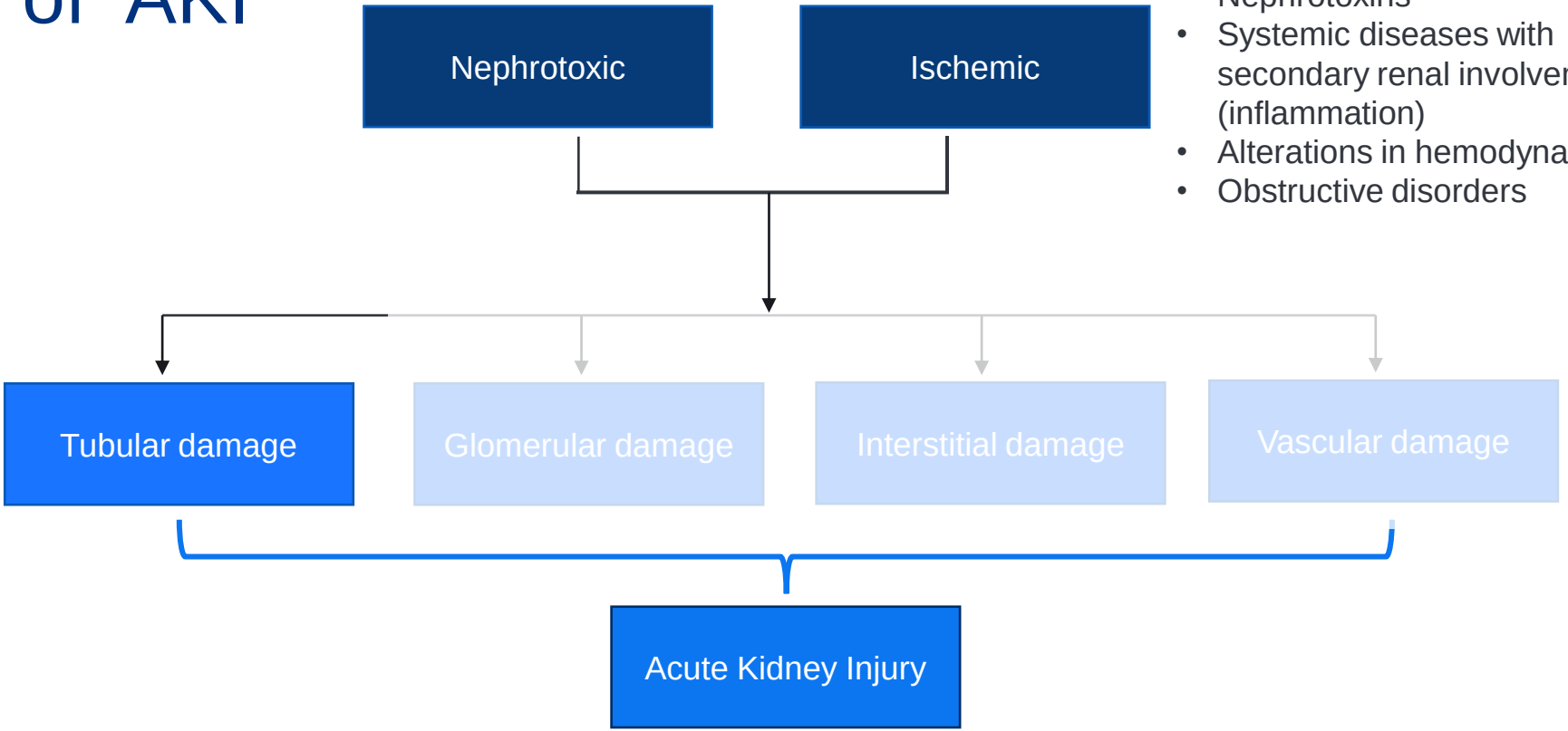
Segev, et al. J Vet Intern Med. 2023

Uses for the IDEXX Cystatin B Test

The IDEXX Cystatin B Test

1. Kidney *injury* marker
2. Urine-based test
3. Use in UNWELL dogs and cats
4. Available at IDEXX Reference Laboratories
5. Included in select panels

Pathophysiology of AKI



Common etiologies:

- Infectious diseases
- Nephrotoxins
- Systemic diseases with secondary renal involvement (inflammation)
- Alterations in hemodynamics
- Obstructive disorders

Causes of AKI include:

Cat	Dog
+ Toxins (plants, chemotherapeutics)	+ Toxins (plants, chemotherapeutics, foods)
+ Pyelonephritis	+ Pyelonephritis
+ Acute pancreatitis	+ Acute pancreatitis
+ Marked dehydration	+ Marked dehydration
+ Etiology unknown ≈30%	+ Leptospirosis
	+ Lyme nephritis
	+ Congestive heart failure

AKI can develop in hospital: monitor and grade daily

+ Dehydration
+ Age > very young or old
+ Diuretic or nephrotoxic drug therapy
+ Hypokalemia or hypercalcemia
+ Sepsis
+ Congestive heart failure
+ Acute pancreatitis
+ Systemic hypertension
+ CKD

Avoid iatrogenic AKI!
Nephrotoxic drugs
Hemodynamic instability
Fluid overload

Fluid therapy for kidney disease: less may be more

- Fluids are drugs – avoid overdose
- Fluids do not improve kidney function
- Hypervolemia causes AKI and kills patients that already have it
- Not every patient with kidney disease (acute or chronic) needs fluids!!!

Fluid therapy: keep it simple

- Type
  - Replacement fluid, e.g. LRS, to restore volume and hydration
  - Maintenance fluid, .e.g., 0.45% NaCl in 2.5% dextrose, for ongoing needs
  - Additives, e.g., KCl as needed
- Rate
  - Hypovolemia: 10-15 ml/kg dog, 5-10 ml/kg cat, over 15-30 min, x 2-3 (then natural colloid)
    - Never add KCl to resuscitation fluids
  - Dehydration: % dehydration as decimal x BW (kg) x 1000 = ml to administer over 4-24 hr

Assessment of fluid therapy success is essential

- Perfusion parameters – HR, CRT, mucous membranes, pulses, lactate, base excess
- Body weight 2-4x/day – >5-10% increase slow or stop fluids
- Lung auscultation ≥ q12 hrs, more frequently if any changes in RR/RE

Fluid tips for AKI and CKD

AKI

- Correct hypovolemia in <1hr
  - Correct dehydration 4-6 h4
- Fluid-responsive AKI improvement within hours
  - If creatinine not normal w/in ≈12 hr not fluid responsive
- Fluids not obligatory
- No forced diuresis

CKD

- Not in stable CKD patients
- SC fluids not standard care
- Correct hypovolemia
- Correct dehydration
- No forced diuresis
- Trial if inappetence (subclinical dehydration)

If azotemia worsens with IV fluid therapy,
consider *decreasing* fluid rate.

Especially if total daily volume exceeds maintenance or if weight gain.

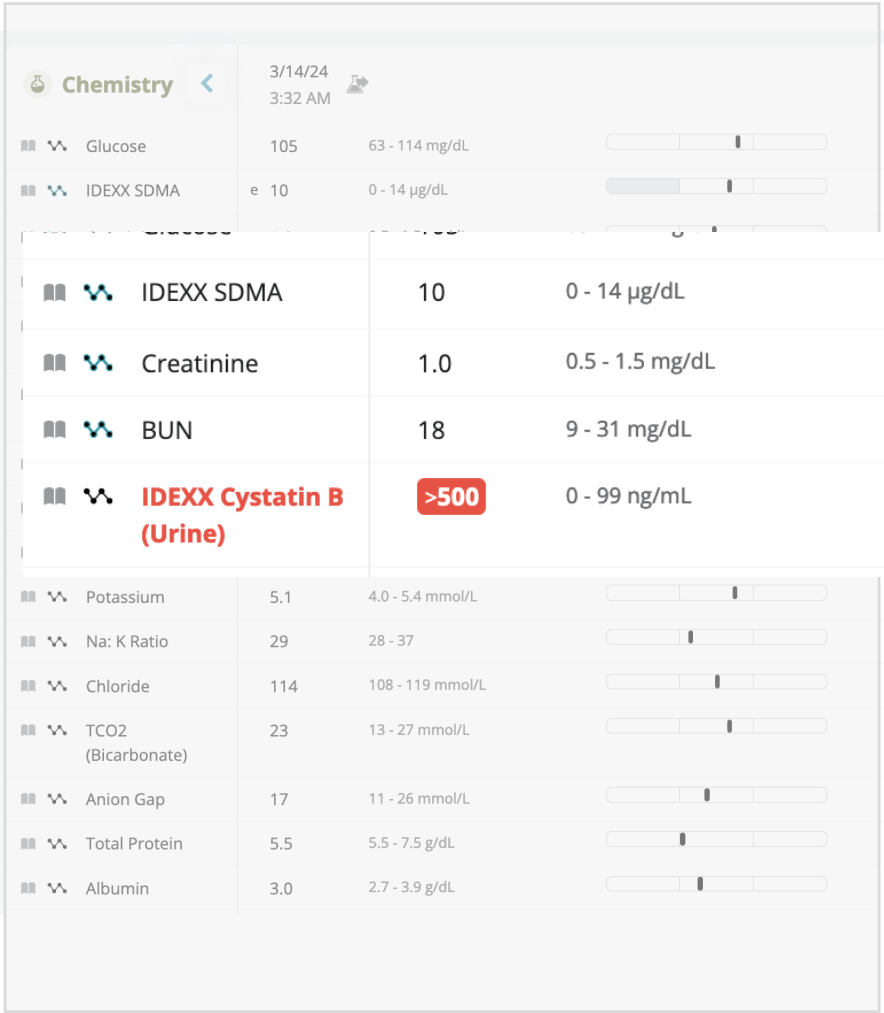
Oliguria & anuria complicate AKI treatment

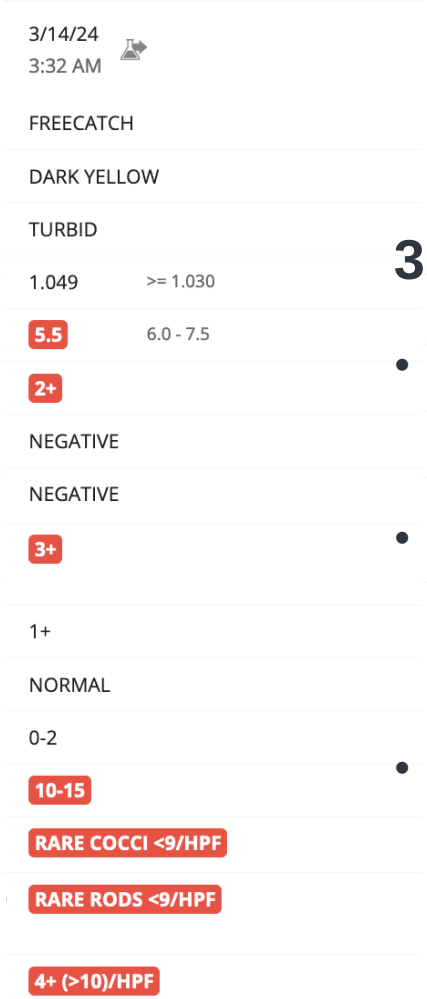
- ***Increased risk of volume overload***
- Pathologic oliguria equals <1 ml/kg/hr of urine when volume, hydration, & BP are normal
  - Expect physiologic oliguria with hypovolemia & dehydration
- Furosemide only effective drug
  - Loading dose 0.66 mg/kg IV then 0.66 mg/kg/hr by constant rate infusion (best)
  - 2 mg/kg IV, no urine 20-40 minutes give 4 then 6 mg/kg hourly, then effective dose q6-8h
- If urine production does not improve, strictly calculate patient ins and outs and closely monitor body weight

Cases!!!

We’re not done yet ?!

My dog ate some raisins.





3 y/o m/c Lab

- Confirmed raisin ingestion
- Amount/time prior to presentation uncertain
- Previously healthy

3 days later – treatment for possible UTI(?), and IV fluids for 48 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)	<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

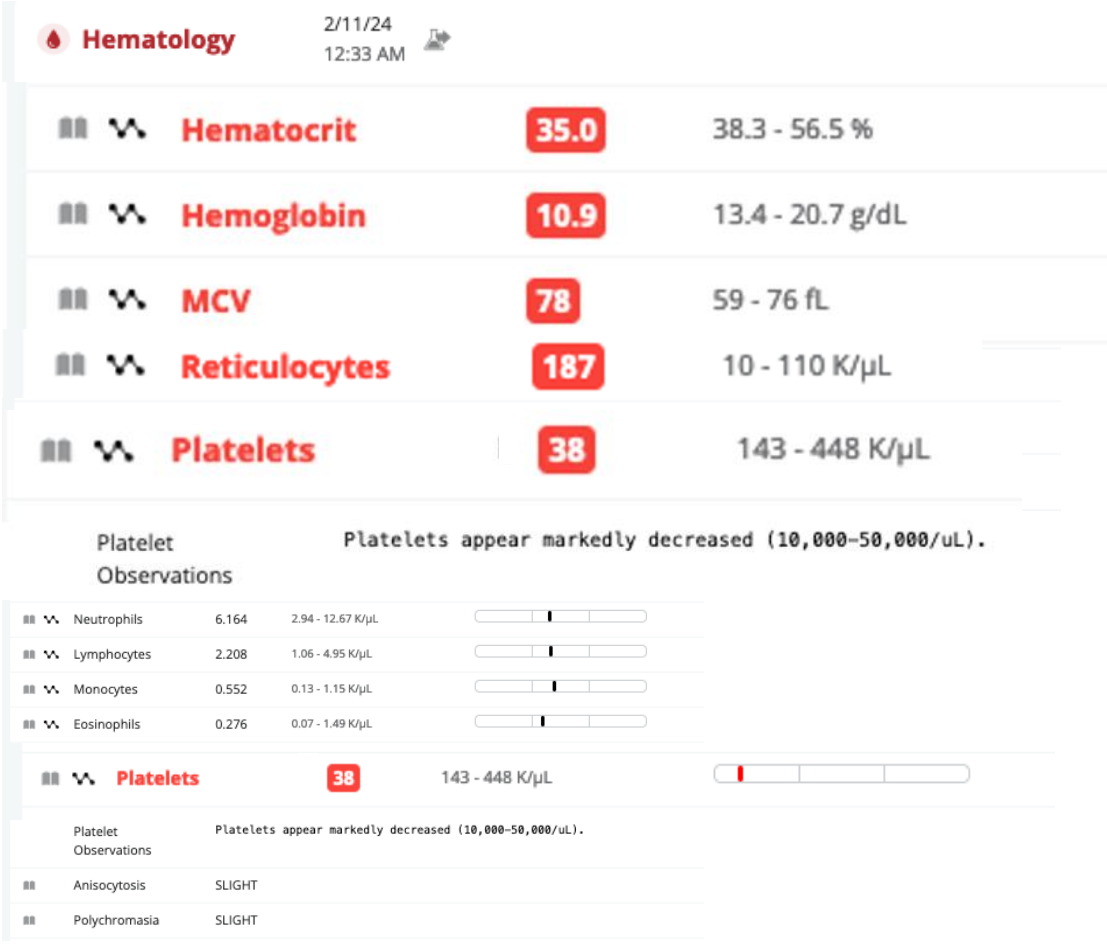
Collection	FREECATCH	
Color	DARK YELLOW	
Clarity	CLOUDY	
Specific Gravity	1.061	>= 1.030
pH	5.5	6.0 - 7.5
Urine Protein	1+	
Glucose	NEGATIVE	
Ketones	TRACE	
Blood / Hemoglobin	3+	
Bilirubin	1+	
Urobilinogen	NORMAL	
White Blood Cells	0-2	
Red Blood Cells	30-50	
Bacteria	NONE SEEN	
Additional Bacteria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

All dogs had degeneration or necrosis (or both) of proximal renal tubules with basement membranes remaining intact, and epithelial regeneration was observed in 5 out of 10 cases.

J Vet Diagn Invest 17:223–231 (2005)

Canine renal pathology associated with grape or raisin ingestion: 10 cases

My dog is a little off and she is drinking a lot.



Hematology 2/11/24 12:33 AM

Hematocrit	35.0	38.3 - 56.5 %
Hemoglobin	10.9	13.4 - 20.7 g/dL
MCV	78	59 - 76 fL
Reticulocytes	187	10 - 110 K/µL
Platelets	38	143 - 448 K/µL

Platelet Observations: Platelets appear markedly decreased (10,000-50,000/uL).

Neutrophils	6.164	2.94 - 12.67 K/µL
Lymphocytes	2.208	1.06 - 4.95 K/µL
Monocytes	0.552	0.13 - 1.15 K/µL
Eosinophils	0.276	0.07 - 1.49 K/µL

Platelets 38 143 - 448 K/µL

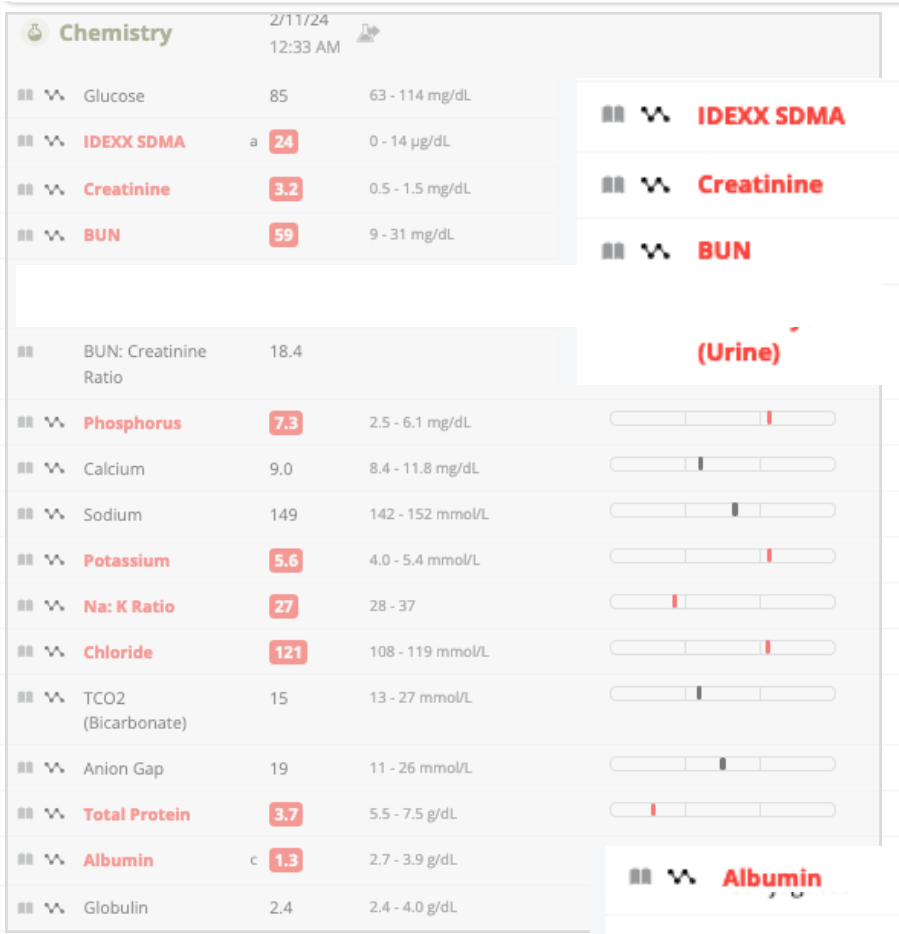
Platelet Observations: Platelets appear markedly decreased (10,000-50,000/uL).

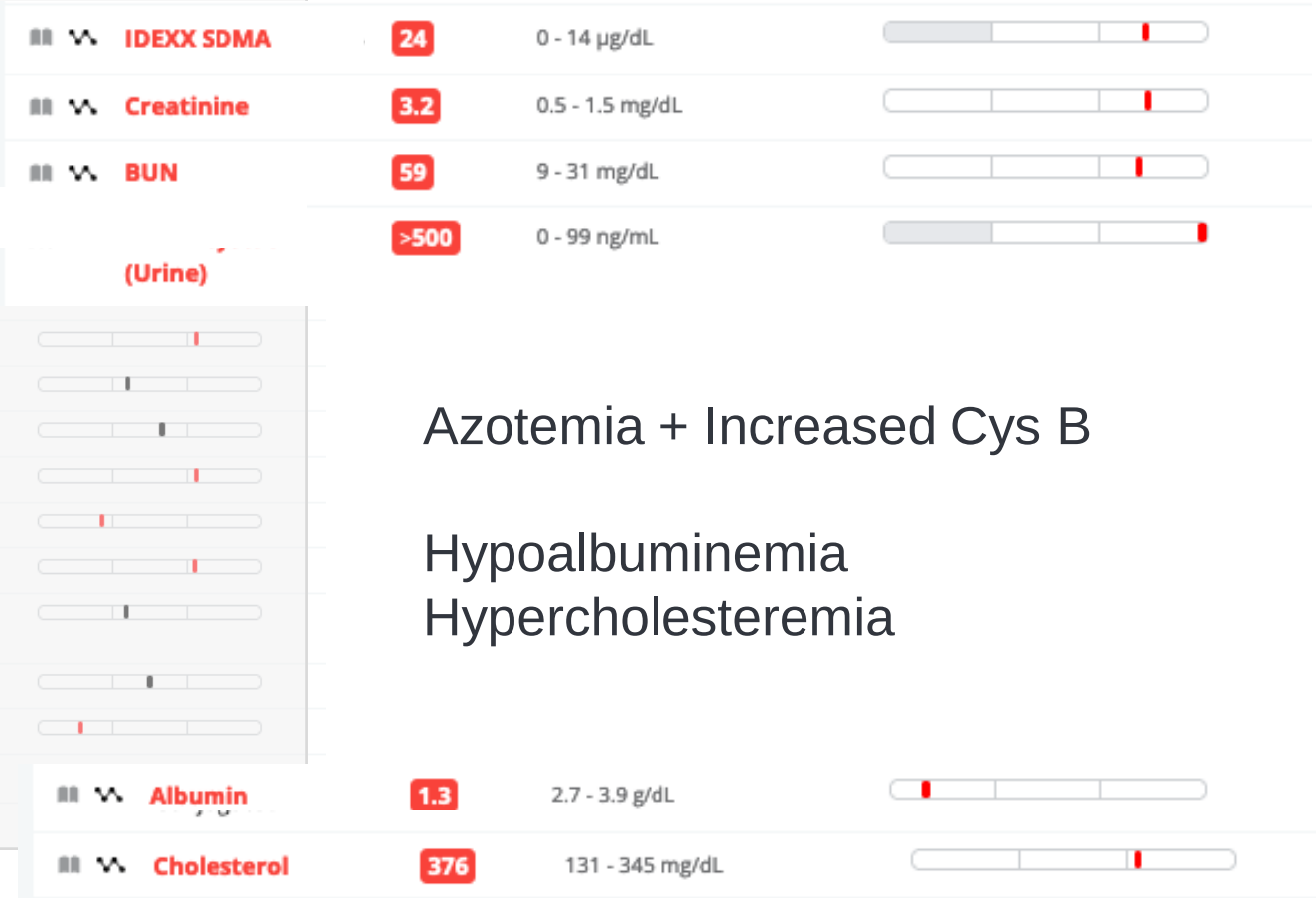
Anisocytosis	SLIGHT
Polychromasia	SLIGHT

Lady

- 3-year-old FS Lab X
- Lives upstate NY
- Recent onset PU/PD
- A little “off”

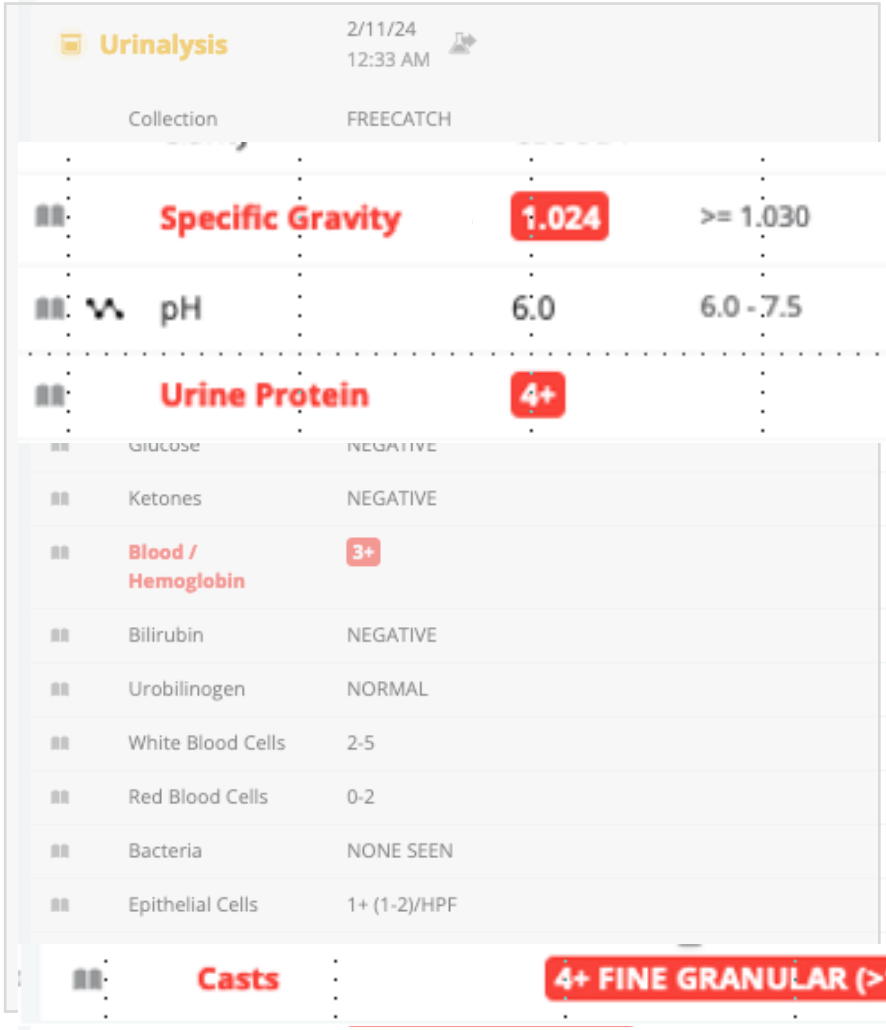
Regenerative Anemia
Marked Thrombocytopenia





Azotemia + Increased Cys B

Hypoalbuminemia
Hypercholesteremia



Inappropriate USG
Proteinuria

Granular Casts

Regenerative Anemia
Marked
Thrombocytopenia

+

Azotemia + Increased Cys B

Hypoalbuminemia
Hypercholesteremia

+

Inappropriate USG
Proteinuria

Granular Casts (> 0-10 per/LPF)

Next Diagnostics Steps?

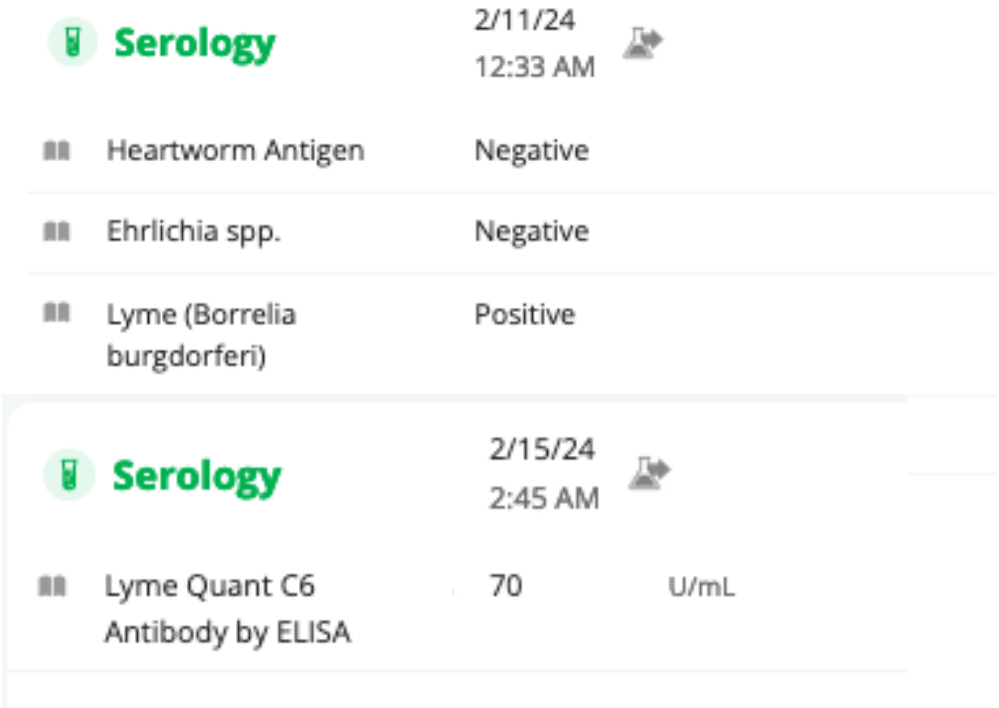
UPC
Infectious Screening
Systolic blood pressure

Marked proteinuria, negative leptospirosis titers

	Urine Creatinine	88.9	mg/dL
	Urine Protein	969.7	mg/dL
	Urine Protein: Creatinine Ratio	10.9	
	Color	Yellow	

L. autumnalis	NEG @ 1:100
L. bratislava	NEG @ 1:100
L. canicola	NEG @ 1:100
L. gryppotyphosa	NEG @ 1:100
L. icterohaem-orrhagiae	NEG @ 1:100
L. pomona	NEG @ 1:100

Acute/active tubular disease, significant glomerular component
Lyme Nephritis possible diagnosis

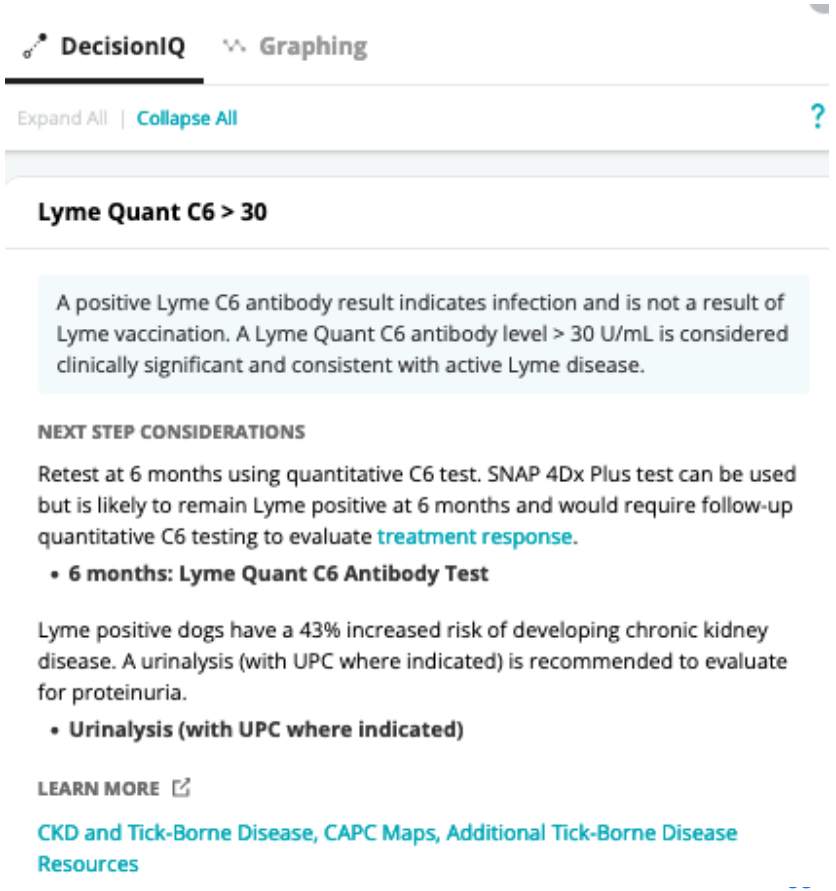


Serology 2/11/24 12:33 AM

Heartworm Antigen	Negative
Ehrlichia spp.	Negative
Lyme (Borrelia burgdorferi)	Positive

Serology 2/15/24 2:45 AM

Lyme Quant C6 Antibody by ELISA	70	U/mL



DecisionIQ Graphing

Expand All | Collapse All ?

Lyme Quant C6 > 30

A positive Lyme C6 antibody result indicates infection and is not a result of Lyme vaccination. A Lyme Quant C6 antibody level > 30 U/mL is considered clinically significant and consistent with active Lyme disease.

NEXT STEP CONSIDERATIONS

Retest at 6 months using quantitative C6 test. SNAP 4Dx Plus test can be used but is likely to remain Lyme positive at 6 months and would require follow-up quantitative C6 testing to evaluate treatment response.

- **6 months: Lyme Quant C6 Antibody Test**

Lyme positive dogs have a 43% increased risk of developing chronic kidney disease. A urinalysis (with UPC where indicated) is recommended to evaluate for proteinuria.

- **Urinalysis (with UPC where indicated)**

LEARN MORE

CKD and Tick-Borne Disease, CAPC Maps, Additional Tick-Borne Disease Resources

IRIS Grading Criteria

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, or imaging evidence of AKI, oliguria/anuria, volume respor b. Progressive nonazotemic incr creatinine: ≥ 0.3 mg/dl (≥ 26.4 c. Measured oliguria (<1 ml/kg/h 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)	Moderate to Severe AKI: a. Documented AKI and increasing severities of azotemia and functional renal failure
Grade IV	5.1 – 10.0 mg/dl (440 – 880 µmol/l)	
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)

IDEXX SDMA	24	0 - 14 µg/dL	
Creatinine	3.2	0.5 - 1.5 mg/dL	
BUN	59	9 - 31 mg/dL	
IDEXX Cystatin B (Urine)	>500	0 - 99 ng/mL	

Injury
Azotemic

Failure
Azotemic

IRIS AKI grade III
(Not enough info for sub-grading)

Take Home

- Acute kidney injury and chronic kidney disease are a continuum
- A COMPLETE urinalysis is of UTMOST importance when evaluating kidney and systemic disorders
- Become familiar with renal biomarkers and their indications as well as their limitations
- IDEALLY, patients at risk for renal injury (stage I AKI) are identified and managed BEFORE azotemia develops
- Fluid therapy paradigms have changed…dramatically
- Newer kidney biomarkers
  - SDMA is an earlier and more accurate measure of GFR
  - Urine cystatin B, a *urine* biomarker, is a marker specifically of ACTIVE renal tubular injury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