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5 biochemical abnormalities you should never ignore in your healthy patients.

Bill Saxon, DVM, ACVIM, ACVECC
IDEXX Medical Education Specialist

Financial Disclosure

OR

I have a direct or indirect relationship with IDEXX. Because of the nature of the relationship, it **will not** influence my presentation.

5 things to never ignore

- Trends in values that are withing reference interval
- Increased or discordant GFR biomarkers
- Increased ALT (especially if higher than ALP)
- Decreased or decreasing albumin
- The importance of urinalysis in interpreting results and providing early clues

Creatinine and SDMA normal but trending up.

What would you do?

Na is decreasing and potassium is increasing, both normal?

Next step(s)?

ALT is within normal range but increasing?

This could be bad, more later…

Assess *all* main kidney functions with appropriate marker

Filter waste from blood

- GFR biomarkers
  - SDMA
  - Creatinine
  - BUN
  - (FGF-23)
  - Others someday

Functional markers - insensitive at early detection of AKI.

Assess *all* main kidney functions with appropriate marker

2 of the 3 primary kidney functions are assessed in ***urine***.

Control body fluid	Maintain plasma proteins
▪ Complete urinalysis ▪ Urine specific gravity ▪ Urine chemistries ▪ Sediment examination ▪ Tubular injury markers ▪ Cystatin B	▪ Glomerular integrity ▪ Urine protein ▪ Urine protein-to-creatinine ratio (UPC)

What if GFR biomarkers are increased or discordant?

Assess all potential causes of decreased GFR.

1

Prerenal

- **Dehydration**
- **Trauma/shock—hypotension**
- **Anesthesia**
- **Cardiac disease**
- Sepsis
- Thrombosis, infarct
- Burn injury, heat stroke
- Transfusion reaction
- Hyperviscosity, polycythemia

2

Renal

- Kidney disease: CKD, acute kidney injury, kidney stones
- Infection/infectious: **Pyelonephritis**, FIP, sepsis, heartworm
- Immune mediated: **Lyme nephritis**, vasculitis
- Metabolic: **Pancreatitis**, hypercalcemia
- Neoplasia: **Lymphoma**
- Toxin: **Lily, NSAID**, ethylene glycol (antifreeze), aminoglycoside antibiotics

3

Postrenal

- **Urethral obstruction**
- **Ureteral obstruction**
- Urinary tract trauma/disruption: Tear, rupture, blood clot

One of these dogs has a kidney problem…

SDMA 19 ug/dL, Creat 159 umol/L

USG 1.055

SDMA 19 ug/dL, Creat 159 umol/L

USG 1.010

A word about urine specific gravity…

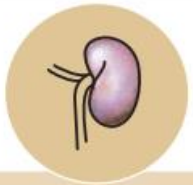
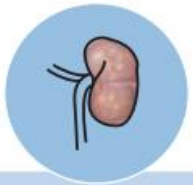
No such thing as ‘normal’ USG: context is critical.

- *Any* USG possible depending on hydration status and other factors
  - Dog 1.001 to >1.075 and Cat 1.001 to >1.085
- Healthy pet with no clinical signs (e.g., PU/PD)
  - Dilute urine not a problem, monitor
- CKD
  - IRIS CKD normals: >1.030 dog, >1.035 cat
- All
  - Steadily decreasing USG over time early indicator of kidney disease.

GFR biomarker ideally:	BUN (early 1900s)	Creatinine (1926)	SDMA (2015)	?
Produced at constant rate			X	X
Freely filtered at glomerulus	X	X	X	X
No tubular secretion/reabsorption			X	X
No nonrenal elimination		X	X	X
Physiologically inert		X	X	X

- BUN > creatinine = dehydration, upper GI bleed, high protein diet, glomerular
- ↑ Creatinine only = increased muscle mass, recent high protein meal…
- ↑ SDMA = decreased GFR

Discordant SDMA and creatinine in CKD patient?

	Stage 1 No azotemia (Normal creatinine)	Stage 2 Mild azotemia (Normal or mildly elevated creatinine)	Stage 3 Moderate azotemia	Stage 4 Severe azotemia
Creatinine in mg/dL Stage based on stable creatinine — Canine	Less than 1.4 (125 µmol/L)	1.4–2.8 (125–250 µmol/L)	2.9–5.0 (251–440 µmol/L)	Greater than 5.0 (440 µmol/L)
Creatinine in mg/dL Stage based on stable creatinine — Feline	Less than 1.6 (140 µmol/L)	1.6–2.8 (140–250 µmol/L)	2.9–5.0 (251–440 µmol/L)	Greater than 5.0 (440 µmol/L)
SDMA* in µg/dL Stage based on stable SDMA — Canine	Less than 18	18–35	36–54	Greater than 54
SDMA* in µg/dL Stage based on stable SDMA — Feline	Less than 18	18–25	26–38	Greater than 38
UPC ratio Substage based on proteinuria — Canine	Nonproteinuric **<0.2**	Borderline proteinuric **0.2–0.5**	Proteinuric **>0.5**	
UPC ratio Substage based on proteinuria — Feline	Nonproteinuric **<0.2**	Borderline proteinuric **0.2–0.4**	Proteinuric **>0.4**	
Systolic blood pressure in mm Hg Substage based on blood pressure	Normotensive **<140**	Prehypertensive **140–159**	Hypertensive **160–179**	Severely hypertensive **≥180**

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

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

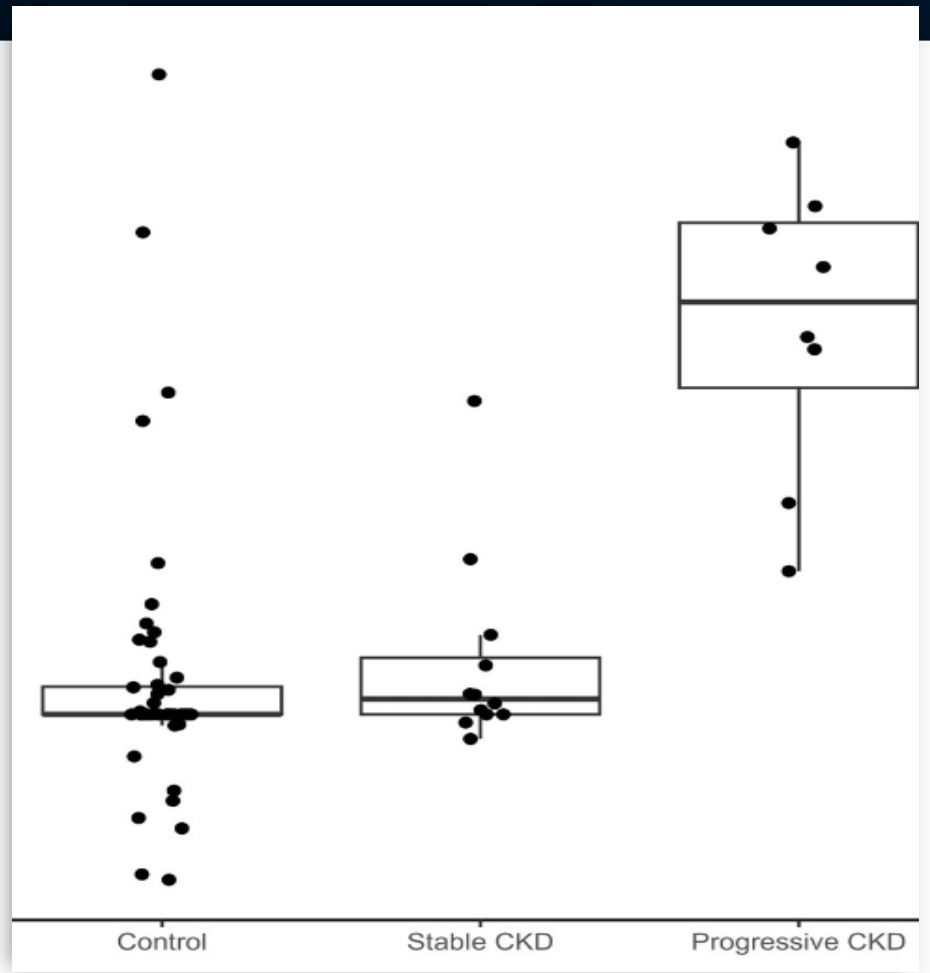
Does your CKD patient have ongoing active kidney injury?

Why does this matter?

Is there a way to know?

Cystatin B detects active ongoing injury with CKD

- CKD progressive and irreversible
- ***Rate*** of progression unpredictable
- Cys B identifies active ongoing injury in dogs (likely cats) with CKD
- Increased Cys B in dogs with IRIS Stage 1 CKD predictive of rapid progression
- Helps identify which dogs need more frequent monitoring

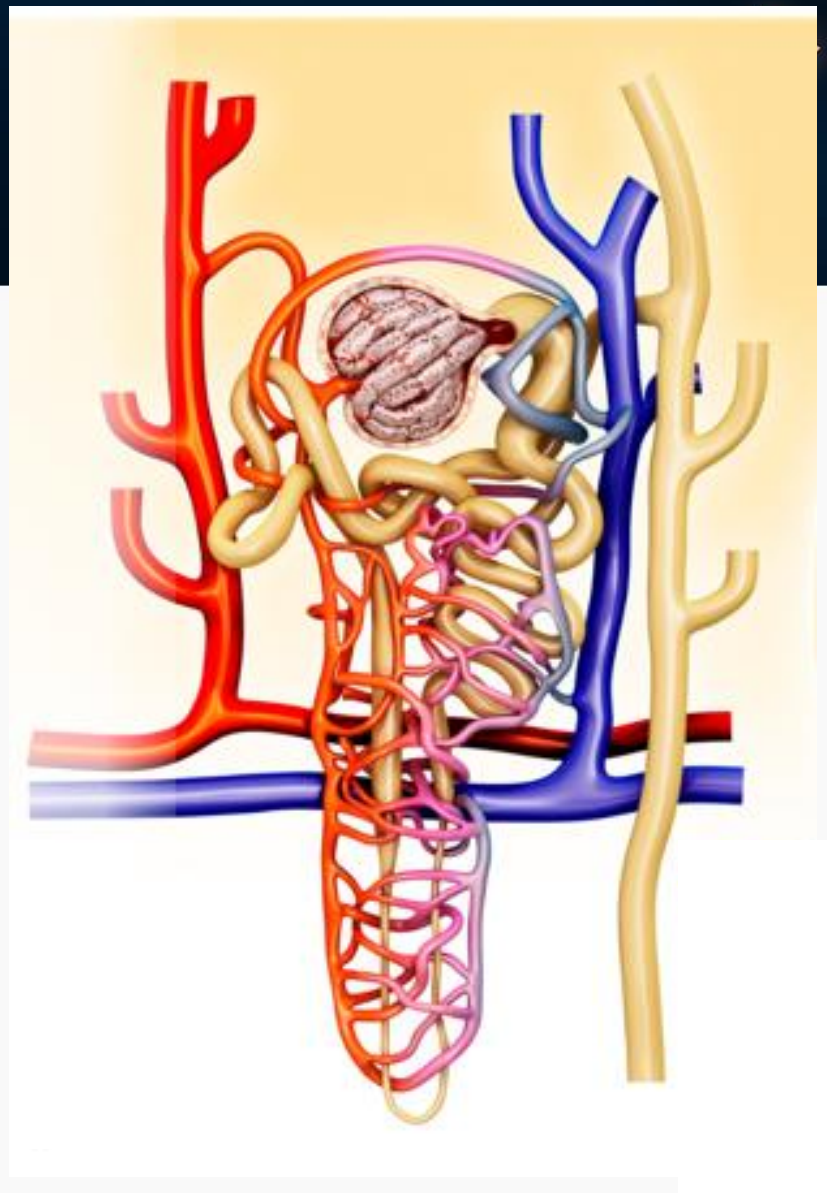


Segev, et al. J Vet Intern Med. 2023

Cystatin B (urine)

- Tubules most vulnerable part of nephron
- Impacted first
- Functional markers lag by 2 days

- Cys B allows EARLY detection of:
  - Tubular damage – primary or secondary
  - Toxin exposure
  - Severe systemic disease, e.g., pancreatitis
  - **Active inflammation in CKD**



ALT is increased (or increasing):

- Increased ALT = **active** hepatocellular damage/leakage
- Consider magnitude and breed
  - Labrador, Doberman, Bedlington, Westies, Dalmatian
- Most common abnormality with chronic hepatitis
- May be early and only indication of copper associated hepatopathy
  - Clinical signs may be absent
- If both ALT and ALP increased and ALT > ALP, work up sooner…

Copper-associated hepatopathy

- Incidence increasing in past decade

Situation	Liver copper concentration (dogs) ug/g dry weight
Normal pre commercial dog food (1930s)	50-75
Normal today	120-400
Toxic	>1000

- Euglycemic glucosuria clue
- Cu quantification on formalin tissue (or deparaffinized tissue from block)

Copper-associated liver disease: treatment

- Low copper diet for life when hepatic copper >600 ug/g dry wt
  - Royal Canin Hepatic®, Hill's l/d®
  - Supplemental protein - cottage cheese, boiled chicken, egg whites (no organ meats, nuts, grains, shellfish)
  - No Cu-containing mineral supplements, treats
- Penicillamine chelation when hepatic copper >1000 ug/g dry wt (+/- >600)
  - Compounded formulation effective
  - 7.5-10 mg/kg q12h 1 hr before or 2 hr after meal, 1 hr apart from other drugs
  - GI side effects in ≈30% at 15 mg/kg q12h (decrease dose, divide in 3-4 smaller doses, with small amount of food)

Hepatic Cu concentration	**Treatment duration (mo)**	**Normalization**
1000-1500	3-4	Within 6 mo
1500-3000	4-6	Within 9 mo
>3000	6-8	>9 mo

Albumin is decreased (or decreasing)

Consider	Look at globulins
Renal	Normal
Liver	Normal or high
GI	Normal or low

- Hypoalbuminemia negative prognosis regardless of cause
- <2.0 mg/dL increased thromboembolism risk (?)
- UPC if persistent proteinuria or immediately if hypoalbuminemia

Updated IRIS proteinuria treatment recommendations

- Renal diet
- Telmisartan 1.0 mg/kg/day
- Clopidogrel 1.1-3 mg/kg/day (dogs), 18.75 mg/cat/day if albumin <2.0 mg/dL
- If poor response consider:
  - Increasing telmisartan by 1 mg/kg/d up to 3 mg/kg/d
  - Adding amlodipine if hypertension does not resolve with telmisartan
  - Omega-3 fatty acids, 70-80 mg/kg of sum of EPA and DHA
- Monitor:
  - SDMA/creatinine, K, blood pressure 5-7 d after start and dose change of RAAS inhibitor
  - UPC (pooled), albumin + above 3-4 wk after start and dose change
  - CBC, panel, UA, UP/C (pooled), blood pressure q4-6 mo

Announcement of changes to IRIS Guidelines: (Board met July 26, 2022)

- Treatment recommendations for dogs:
  - ARBs should be first line of treatment together with a clinical renal diet.
  - Reduction of UPC below 0.5 not possible in many with primary glomerular disease and more realistic goal is 50% reduction in UPC and lowest UPC possible without causing harm.
  - No reliable predictor of thromboembolic complications and antithrombotic therapy cannot be guided by serum albumin concentration. Clopidogrel is first line drug.

IRIS cautions with renal vasoactive drugs:

- ACEI or ARB use is contraindicated in any dog that is clinically dehydrated and/or is showing signs of hypovolemia.
- Correct dehydration before using these drugs otherwise glomerular filtration rate may drop precipitously.
- The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected.

Urinalysis your best friend when interpreting biochemistries.

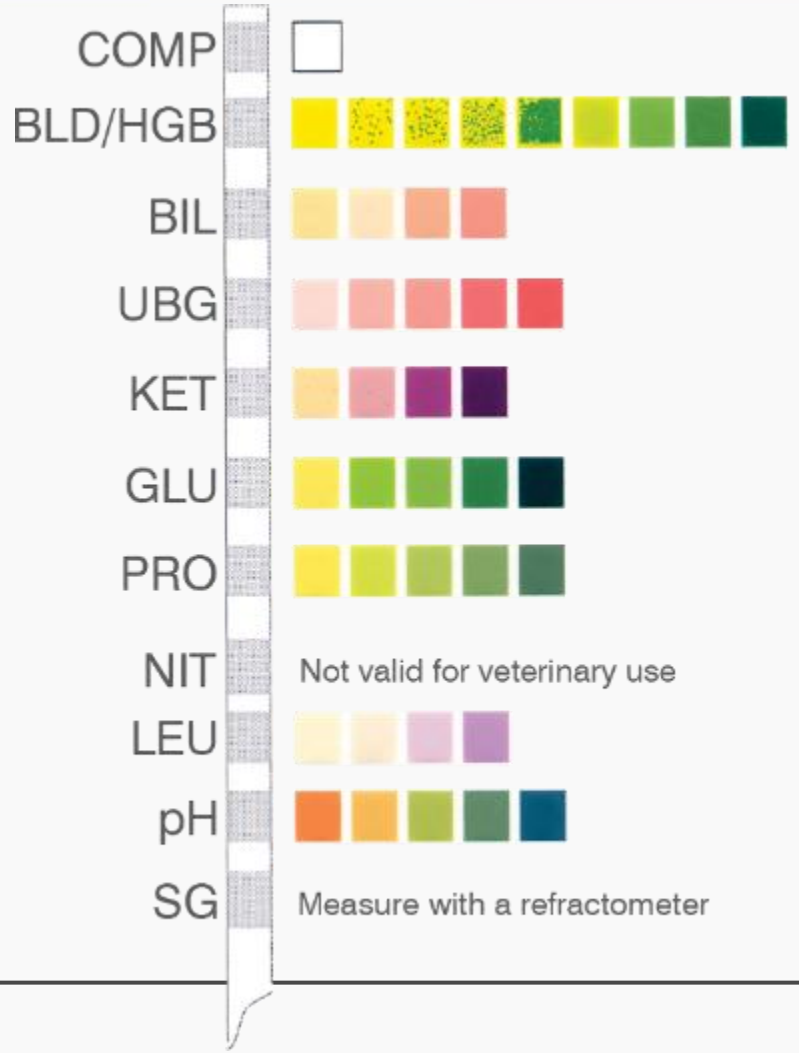
Complete urinalysis includes:

1
Physical analysis

2
Chemical analysis

3
Sediment analysis

Urine chemistries with dipstick



We've already seen:

- USG essential for interpreting increased BUN, Creat, SDMA
- Euglycemia glucosuria clue for copper-associated hepatopathy

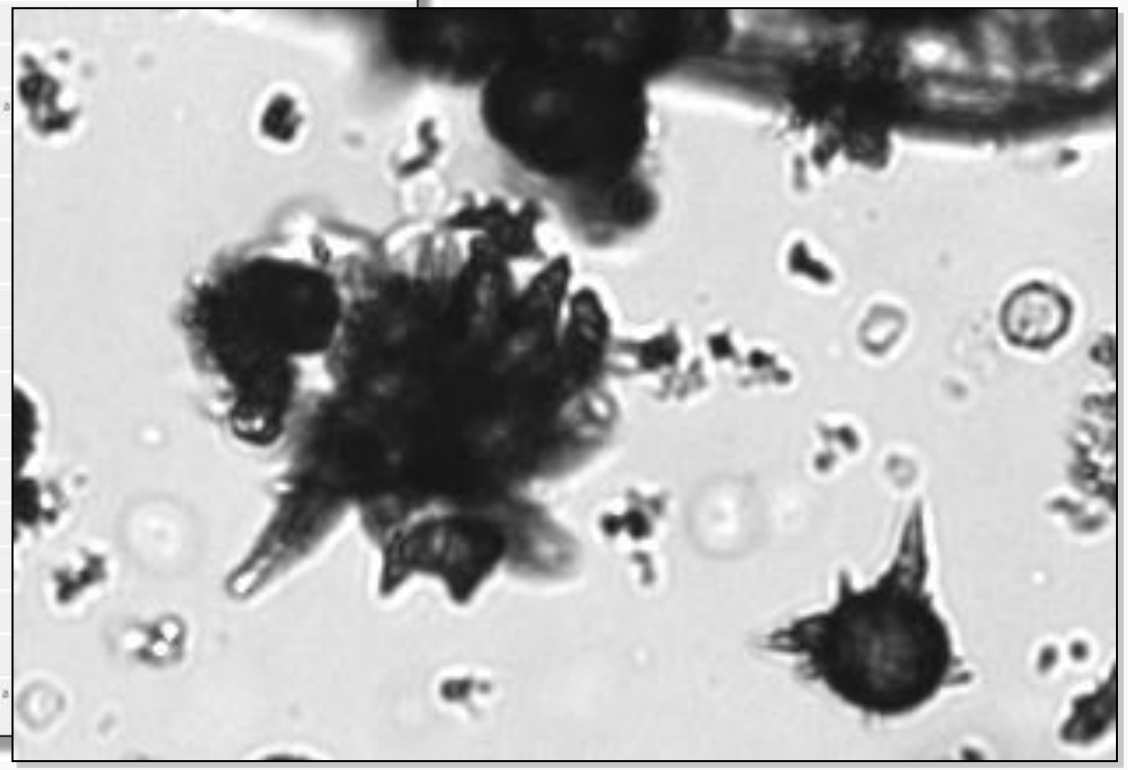
1.5-year-old female spayed Boxer

- Presenting complaint
  - Decreased activity
  - No pertinent prior medical history
  - Current on vax, parasite prophylaxis
- PE
  - Vitals normal
  - Slightly quiet
  - Otherwise unremarkable
- CBC, biochemistries normal

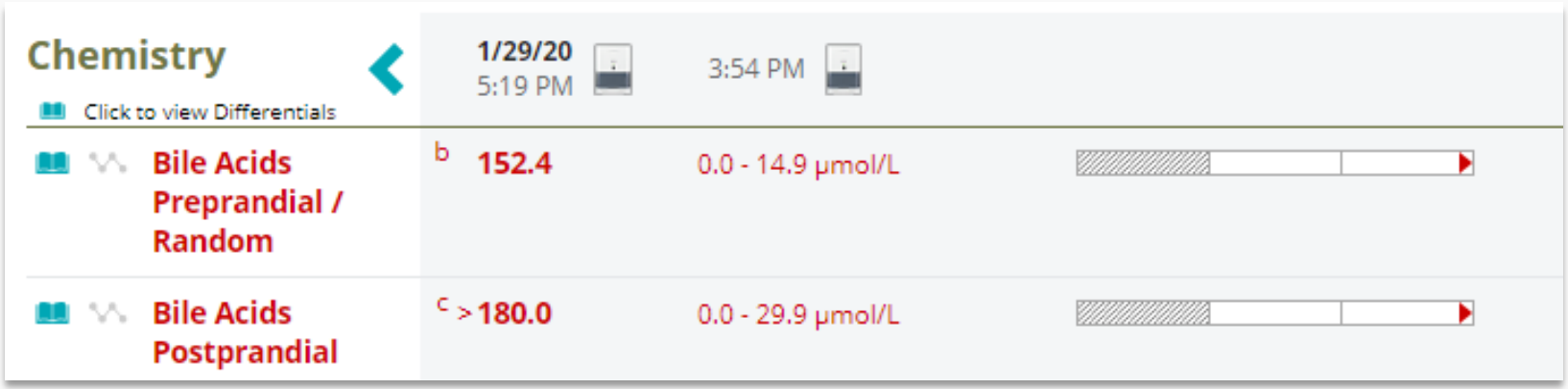
Next steps?

Collection	FREE-CATCH
Color	YELLOW
Clarity	CLOUDY
Specific Gravity	
pH	
Protein	
Glucose	
Ketones	
Blood / Hemoglobin	
Bilirubin	
Urobilinogen	
White Blood Cells	
Red Blood Cells	
Bacteria	
Epithelial Cells	
Mucus	
Casts	
Crystals	

Crystals	3* AMM Biurate (6-10/LPF)



IDEXX SediVue Dx™ Urine Sediment Analyzer image



Chemistry	1/29/20 5:19 PM	3:54 PM	
Click to view Differentials			
Bile Acids Preprandial / Random	[b] 152.4	0.0 - 14.9 µmol/L	
Bile Acids Postprandial	[c] > 180.0	0.0 - 29.9 µmol/L	

Differentiating portosystemic shunt from portal vein hypoplasia

	Portosystemic Shunt	Portal Vein Hypoplasia
Clinical signs	+/-	No
Urate crystals	+/-	No
Increased bile acids	Yes	Yes
Shunt vessel on AUS	+/-	No
Protein C	<70%	≥70%

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	
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	

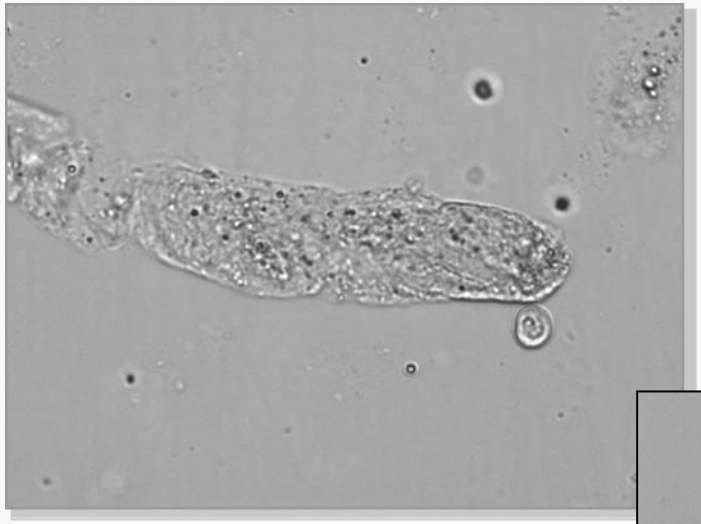
3/14/24 3:32 AM		
FREECATCH		
DARK YELLOW		
TURBID		
1.049	>= 1.030	
5.5	6.0 - 7.5	
2+		
NEGATIVE		
NEGATIVE		
3+		
1+		
NORMAL		
0-2		
10-15		
b RARE COCCI <9/HPF		
c RARE RODS <9/HPF		
d 4+ (>10)/HPF		

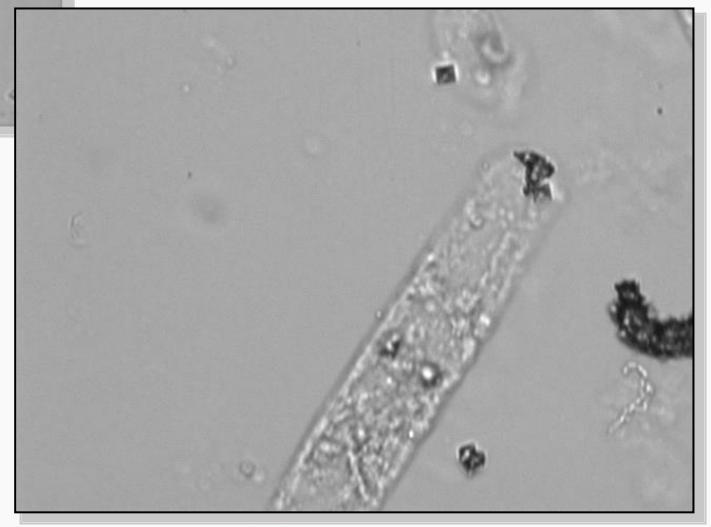
Tubular injury are earlier indicators of damage than functional markers – by 2 days.

.

Current injury markers good not great

- Proteinuria
- Hematuria
- Pyuria
- Bacteriuria
- Renal epithelial cells
- Glucosuria (normoglycemia)
- + Urine culture
- Granular casts ≈16%
- Decreased urine production
- Decreased USG



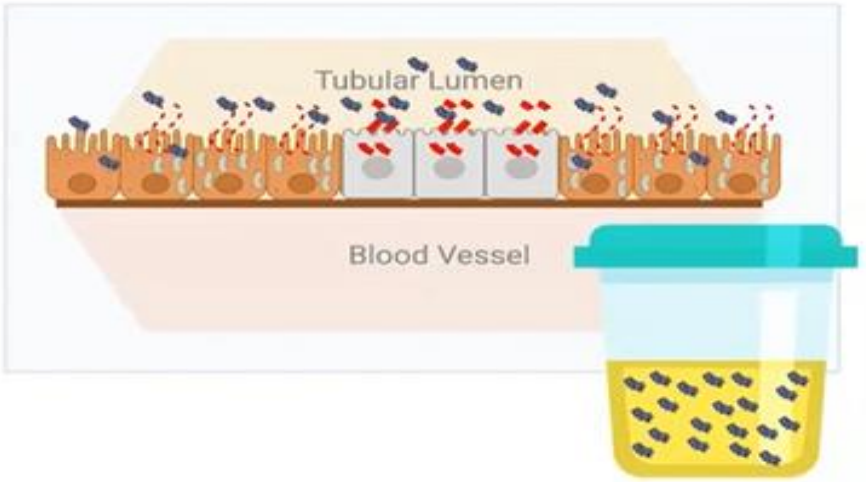


Urine Cystatin B

- 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
- Increased urine concentration indicates active ongoing tubular damage

- Urine test recommended in sick patients to identify early kidney damage

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



1

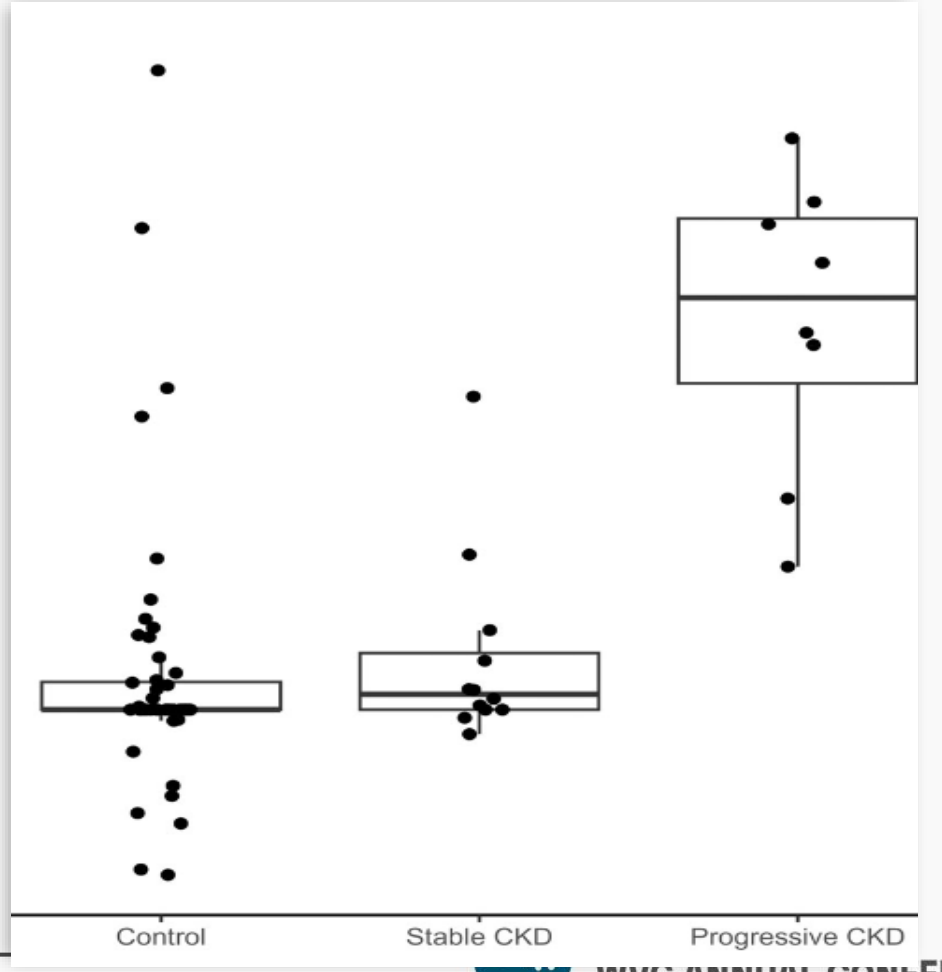
- Primary Renal Injury
  - "Acute on Chronic" Crisis
  - Toxin (grapes/raisins, lilies, ethylene glycol)

2

- Secondary Renal Injury
  - Infectious
    - Pyelonephritis
    - VBD
  - Systemic Disease (pancreatitis, vasculitis)
  - Hypo-/hypertension
  - Blood loss
  - Trauma

Cystatin B detects active ongoing injury with CKD

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



Segev, et al. J Vet Intern Med. 2023

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	
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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	

How big of a deal is eating grapes or raisins?

Tartaric acid toxic principle.

- Grapes, raisins, currants, tamarinds/tamarind paste, cream of tartar (homemade playdough)
  - Baked goods safe
- Idiosyncratic, not dose-dependent – consider treating all
  - Anecdotally 1-2 raisins, grapes treated more conservatively
- Vomiting most common sign as early as 4 hr post ingestion
  - Neurologic signs in some
  - Lack of signs does not mean AKI won't develop
- Induce vomiting, give 1 dose activated charcoal
  - Remain in stomach up to 24 hours so induce vomiting in all
- Fluids IF indicated, SC or IV
  - Monitor cystatin B, GFR biomarkers 24-48 h if not azotemic on presentation

Thank you.