Fluids do’s and don’ts for managing AKI.

Is diuresis over?

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Disclosure:

Bill Saxon is a full-time employee of IDEXX.

VETERINARY PRACTICE GUIDELINES

2024 AAHA Fluid Therapy Guidelines for Dogs and Cats

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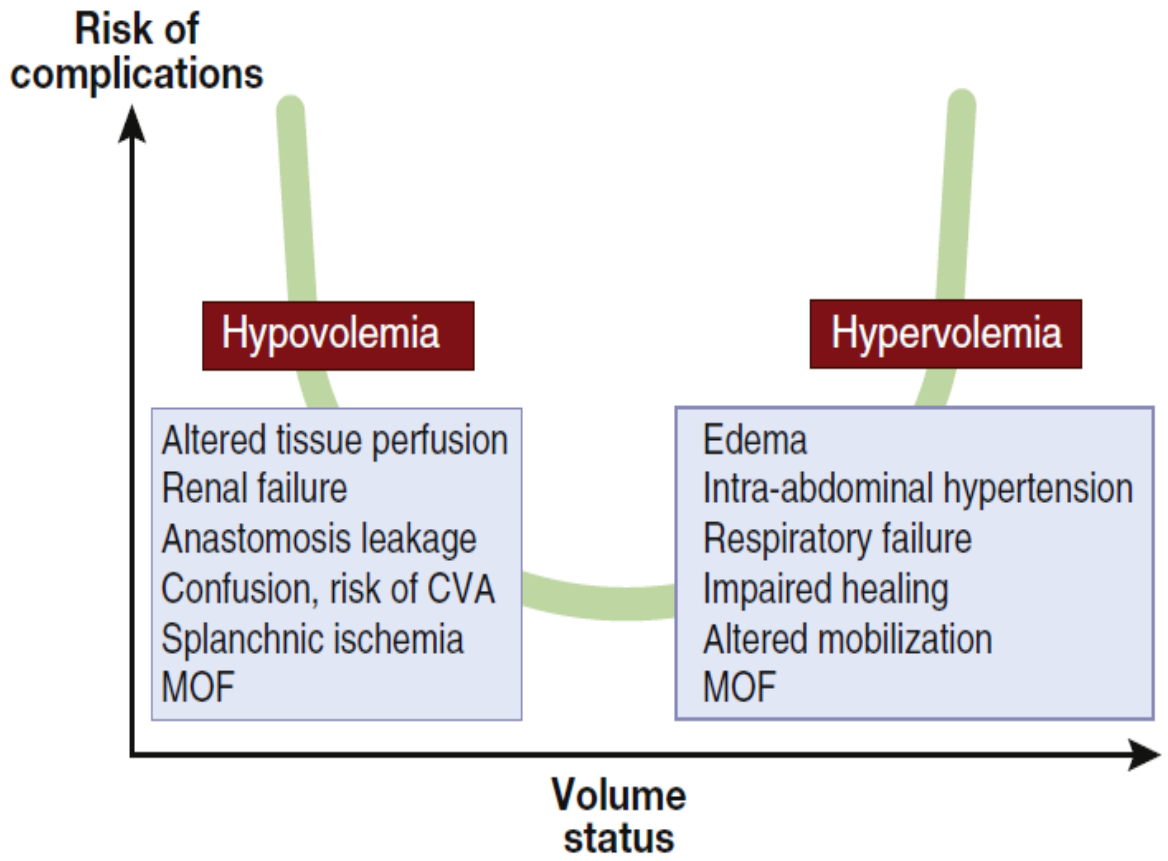
Why are we rethinking fluid therapy with kidney disease?
And in general?

- Recognition that hypervolemia is as dangerous as hypovolemia
- Causes increased venous pressure = impaired perfusion gradient
- Causes interstitial edema = impaired oxygen delivery
- Interstitial edema in kidney increases intrarenal pressure (rigid capsule)
- Leads to decreased renal perfusion and decreased GFR (tubules compressed)
- Causes AKI and kills pets that have it (worse than sepsis and AKI in people)
- Not all acute or chronic kidney disease is fluid responsive
  - Not all with AKI or CKD or fluid tolerant
- If azotemia doesn't improve within 12-24 hr (max) of appropriate fluids, back off



If diuresis is over…

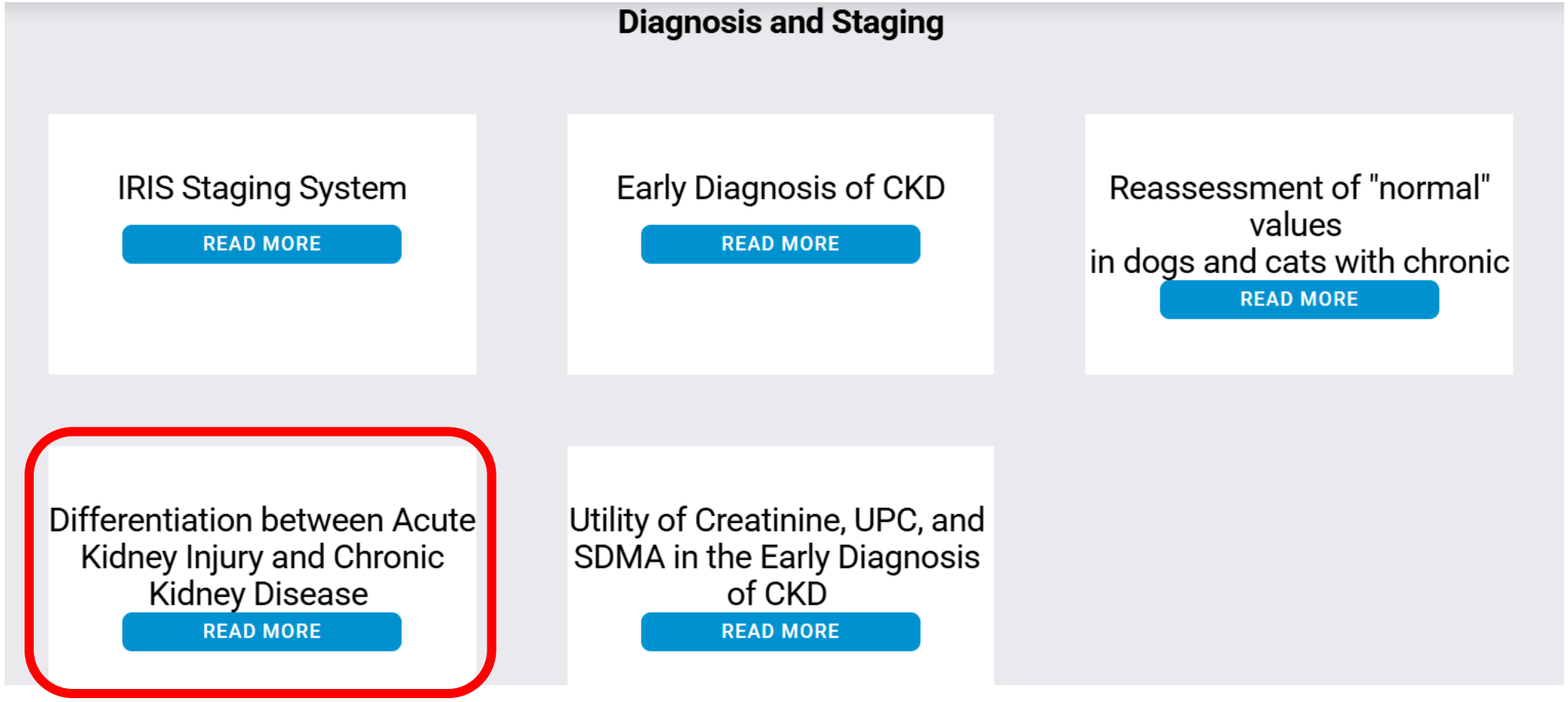
Fluid responsiveness. Fluid tolerance. Can we determine?

- Responsiveness
  - Assess volume and hydration
  - POCUS – LA:Ao, caudal vena cava
  - Correct deficits
  - If azotemia / urine production not improved within 12-24 hr NOT fluid responsive
- Tolerance
  - Renal resistance index, lung B lines, gallbladder edema, weight gain
  - Cautious fluid trial (?), no fluids (?)
  - Lasix, vasopressors…

- Practically speaking – pick initial fluid and rate, monitor for signs of volume overload
- It is okay to not give fluids to kidney patients

AKI diagnosis update…

https://www.iris-kidney.com



Hallmarks of AKI (v CKD)

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

AKI can develop in hospital: monitor and grade daily.

Prerenal, renal, postrenal causes.

- 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

Earliest evidence of AKI in URINE.

Tubular injury markers in urine up to 2 days before functional markers (SDMA, creat) increased.

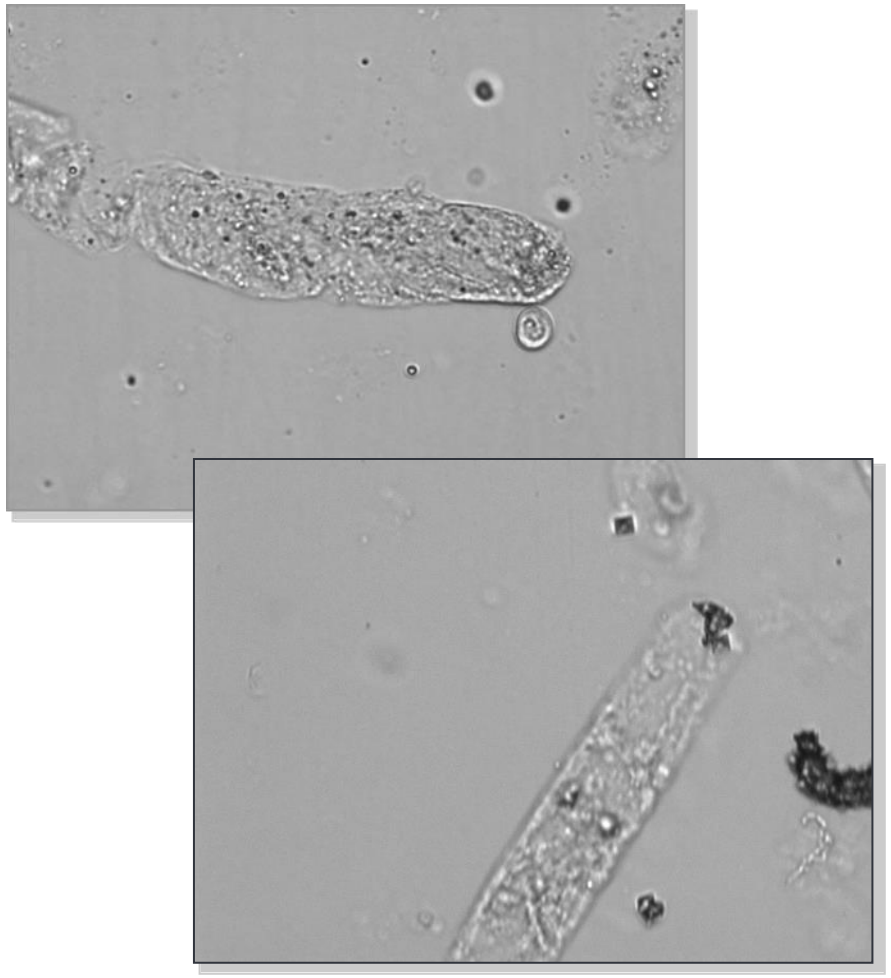
.

Traditional injury markers lack sensitivity and specificity…

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

} **30%**

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



Cystatin B in urine indicates *active* tubular damage

- 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

AKI treatment:

- Stabilize
- Correct life-threatening hyperkalemia
- Treat underlying cause if found, e.g., lepto
- Manage oliguria/anuria
- Monitor for development of CKD
  - 40% humans with AKI develop CKD

Fluid therapy for AKI.

Me: How do you guys treat oliguric AKI?

Brilliant pediatric nephrologist at CHUP: Fluid restriction.

Me: But what about that human paper showing Lasix + dopamine is the way to go!?

Brilliant pediatric nephrologist at CHUP: Severely flawed study…

Me: How do you guys treat oliguric AKI?

Brilliant pediatric nephrologist at CHUP: Fluid restriction.

Me: But what about that human paper showing Lasix + dopamine is the way to go!?

Her again: Severely flawed study…

If you have AKI you'd rather have sepsis than hypervolemia.

“Fluid therapy is not the mainstay of treating azotemic patients.”

“..it is to support kidneys by correcting treatable abnormalities…so that kidneys can heal themselves.”

2024 AAHA Fluid Therapy Guidelines

What are those treatable abnormalities?

- CKD
  - Dehydration
  - Hypokalemia
  - Severe metabolic acidemia
  - Anemia

- AKI
  - Hypovolemia
  - Hyperkalemia
  - Hypoglycemia
  - Hypercalcemia

No evidence of benefit of fluids in euhydrated (and euvolemic) patients.

Isotonic crystalloid with buffer go-to first choice

- Lactate ringers if I had to pick one
  - Contains buffer (lactate) → non-acidifying, non-vasodilating
  - Contains Ca
  - Lactate per se is anti-inflammatory (pancreatitis)
- Plasma-Lyte A/148, Normosol R
  - Acetate (vasodilating?), gluconate buffer
  - Mg, no Ca
- Safe in hyperkalemic patients
  - Trivial K content will not raise serum potassium

Is 0.9% NaCl over?

- Acidifying
  - No buffer
  - Chloride is a metabolic acid
  - Longer time to correction of acidemia with DKA, urethral obstruction
- High Na content may raise Na too fast in adrenal crisis – osmotic demyelination
- High chloride → renal vasoconstriction
- Amount of K in LRs, Plasma-Lyte, Normosol R trivial
- Indicated with hypochloremic metabolic alkalosis
  - GI obstruction

How much fluid and how fast

- If lose fluid fast replace fast – 1-2 hr with hypovolemia
  - 10-20 ml/kg dog, 5-10 ml/kg cat over 15-30 minutes, repeat x2-3
  - Mucous membranes, capillary refill time, HR, pulse strength, lactate, urine production
  - FFP 15-20 ml/kg over 4-6 hr (will raise albumin by 0.5 g/dl)

- If lose fluid slowly replace slowly – 6-24 hr with dehydration
  - BW (kg) x % dehydration as decimal x 1000 = mls to deliver

- Keep up with ongoing losses and provide maintenance

- Frequent body weight, accurate gram scale
  - 5% increase → consider adjusting
  - 10% increase → volume overload
  - Gut and kidneys affected early

If azotemia worsens on IV fluids consider *decreasing* fluid rate.

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

STOP fluids, +/- Lasix 1-4 mg/kg IV

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

2-year-old male neutered Labrador

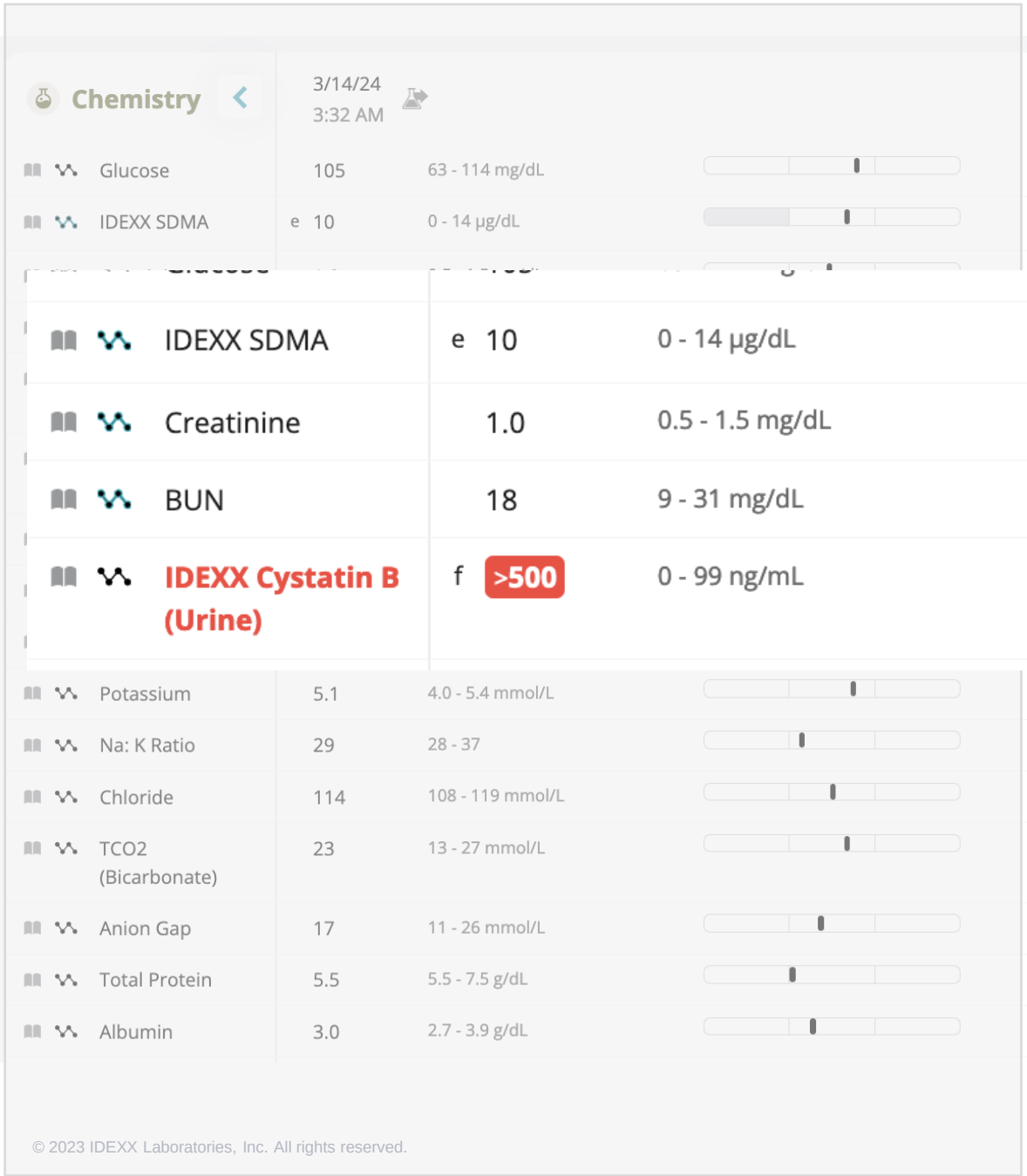
- Presenting complaint
  - Raisin ingestion sometime in past 8 hr (owner found empty box when returned from work)
  - No priors
  - Current on vaccination, parasite prophylaxis

- 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
- 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 48 h?
  - Fluids not beneficial euhydrated patients, don't hasten toxin excretion
- ~~Hospitalize for IV fluids at 2-4x maintenance for 48 h?~~

Detect non-physiologic oliguria / anuria

- Measuring urine output **important** yet often neglected
- Indwelling urinary catheter and closed aseptic collection system optimal
  - Collection bag below patient
  - Daily disinfection of ports, visible portion of catheter, prepuce, etc.
  - Change q2-3 days
- Estimate using absorbent pads when catheterization not possible
  - Weigh before and after use
  - 1 gm = 1 ml
- Oliguria <0.5-1.0 ml/kg/hr
  - AFTER hydration and volume restored (physiologic oliguria)
  - Consider if urine production does not increase to 2-5 ml/kg/h after rehydration
  - Ensure collection system connected, patent

Treating oliguria/anuria has gotten easier.

- Furosemide - most effective
  - Loading dose 0.66 mg/kg IV then CRI at 0.66 mg/kg/h (0.5-1.0 mg/kg/h)

- Furosemide - simplest
  - 2 mg/kg IV initially
    - If no urine production within 20-40 minutes
  - 4 then 6 mg/kg IV hourly
  - Effective dose q6-8 h

- Mannitol, dopamine, fenoldopam no

- If no increase in urine production ins and outs or renal replacement therapy

Ins and outs for oliguria/anuria

- Match fluids exactly with urine produced to avoid fluid overload

- Total fluids to administer (and not a drop more) =
  Insensible loss (respiration, feces) 22 ml/kg/d +
  Sensible loss (urine) +
  Ongoing loss (vomiting, diarrhea)

- Given in 4 or 6 hr intervals

In and outs for 4 kg cat, normal hydration, no v/d

- Fluids in 6 h increments
- Insensible loss 20 ml/kg/d ÷ 4 = 5 ml/kg x 4 kg = 20 ml
- Urine production = 0 ml
- No v/d = 0 ml
- 20 ml total volume to administer over next 6 h = 3-4 ml/h

6 hours later…

Urine produced in preceding 6 h = 20 ml

Vomitus = 10 ml

Insensible loss in 6 h = 25 ml

55 ml total volume to administer over next 6 h = 9-10 ml/h

Repeat calculation every 6 hours until urine production > 1 ml/kg/h

Fluid therapy during recovery phase

- Polyuria may be profound
  - Especially with obstructive disease (or lepto in dogs)
- Higher fluid rates than any other disease
- Hypokalemia may result – spike fluids
- Monitor urine volume, body weight, perfusion and hydration parameters and keep up!
- Taper 10-25% per day once stable and continue reassessing

Adjusting drug dosages and/or frequency with AKI

- Important if excreted by kidneys
- Patient interval (hr) = normal interval (h) x serum creatinine (fluoroquinolones)
- Patient dose = normal dose / serum creatinine (penicillins)
- Creatinine serves as estimated of GFR
  - Nonlinear with creatinine > 4 mg/dL

Prognosis

- Mortality 58-73%
- Better outcomes with infectious causes
- Degree of azotemia not associated with outcome
- Poor prognostic indicators
  - Decreased urine production
  - Hypothermia
  - Hyperkalemia
  - Hypoalbuminemia
  - Decreased HCO_3 at admission
- Kidney dysfunction that lasts >3 months after AKI = CKD

Thank you!

AKI on the human side

- Prerenal azotemia leading to ischemic tubular necrosis in 75% cases
- Hospital acquired due to multiple insults
  - **Hypotension, sepsis, nephrotoxic drugs, radiocontrast agents**
  - **Chronic liver disease, cardiovascular, respiratory, prior kidney disease**
  - Mortality rate higher with AKI and sepsis (70%) than AKI alone (45%)
  - AKI up to 23% ICU patients
- **40% go on to develop CKD**

- Early recognition of risk factors important in improving outcomes
  - More intensive monitoring and early specific treatment in unstable patients

Dehara, EF, et al., SWISS Med Weekly. 2008;138:128-133

Treating oliguria/anuria simplified

- Furosemide - most effective route
  - Loading dose 0.66 mg/kg IV then CRI at 0.66 mg/kg/h (0.5-1.0 mg/kg/h)

- Furosemide - simplest route
  - 2 mg/kg IV initially
    - If no urine production within 20-40 minutes
  - 4 then 6 mg/kg IV hourly
  - Effective dose q6-8 h

- Mannitol, dopamine, fenoldopam no

- If no increase in urine production ins and outs +/- renal replacement therapy

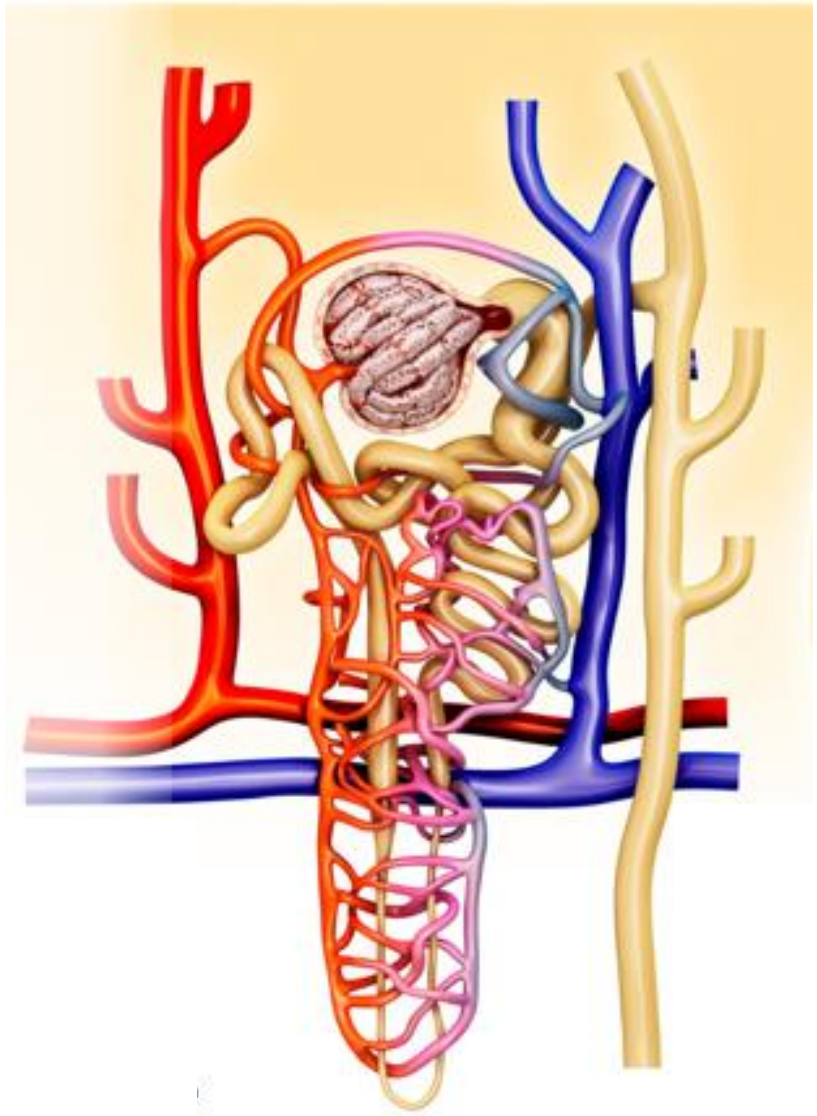
Fluid responsive azotemia should improve within hours.

If not, decrease or stop fluids.

We should probably be thinking about *fluid responsiveness* and *fluid tolerance*…

Tubules are the most vulnerable part of the nephron

Dogs
400K/kidney



Cats
200K/kidney

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

By up to 2 days…

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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.”

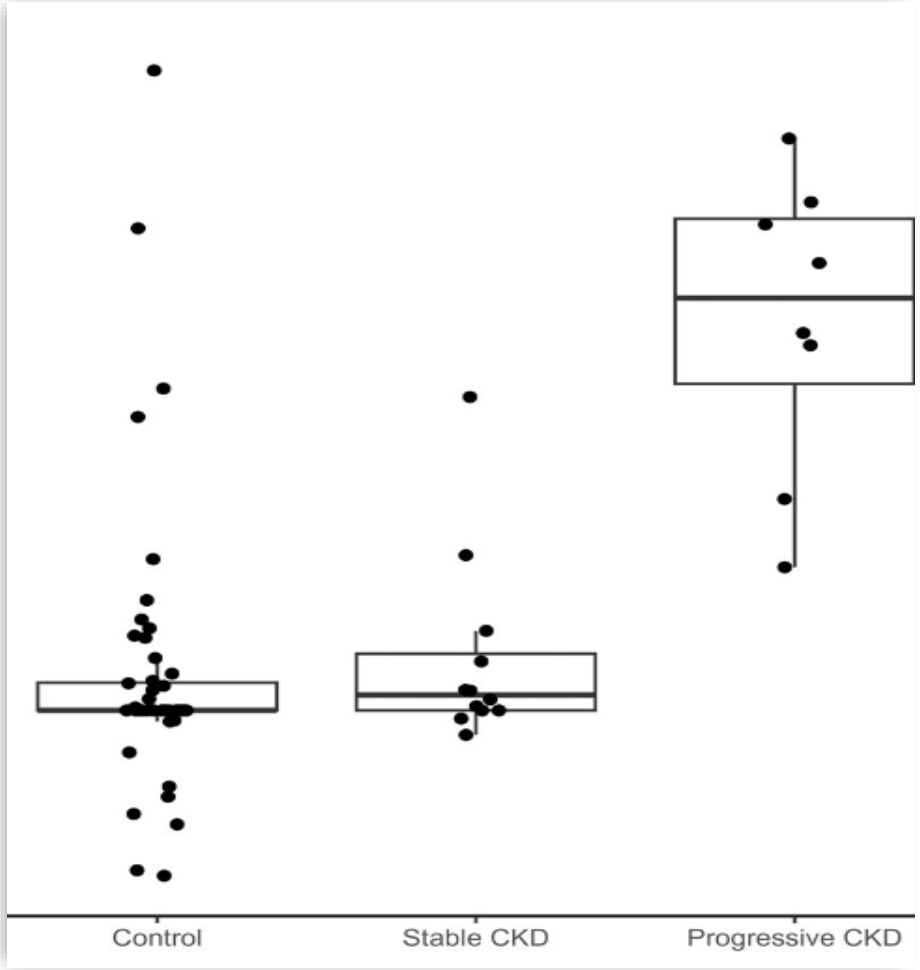
*Segev, Vaden, Cowgill (IRIS board members)

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
  - Concurrent active injury component

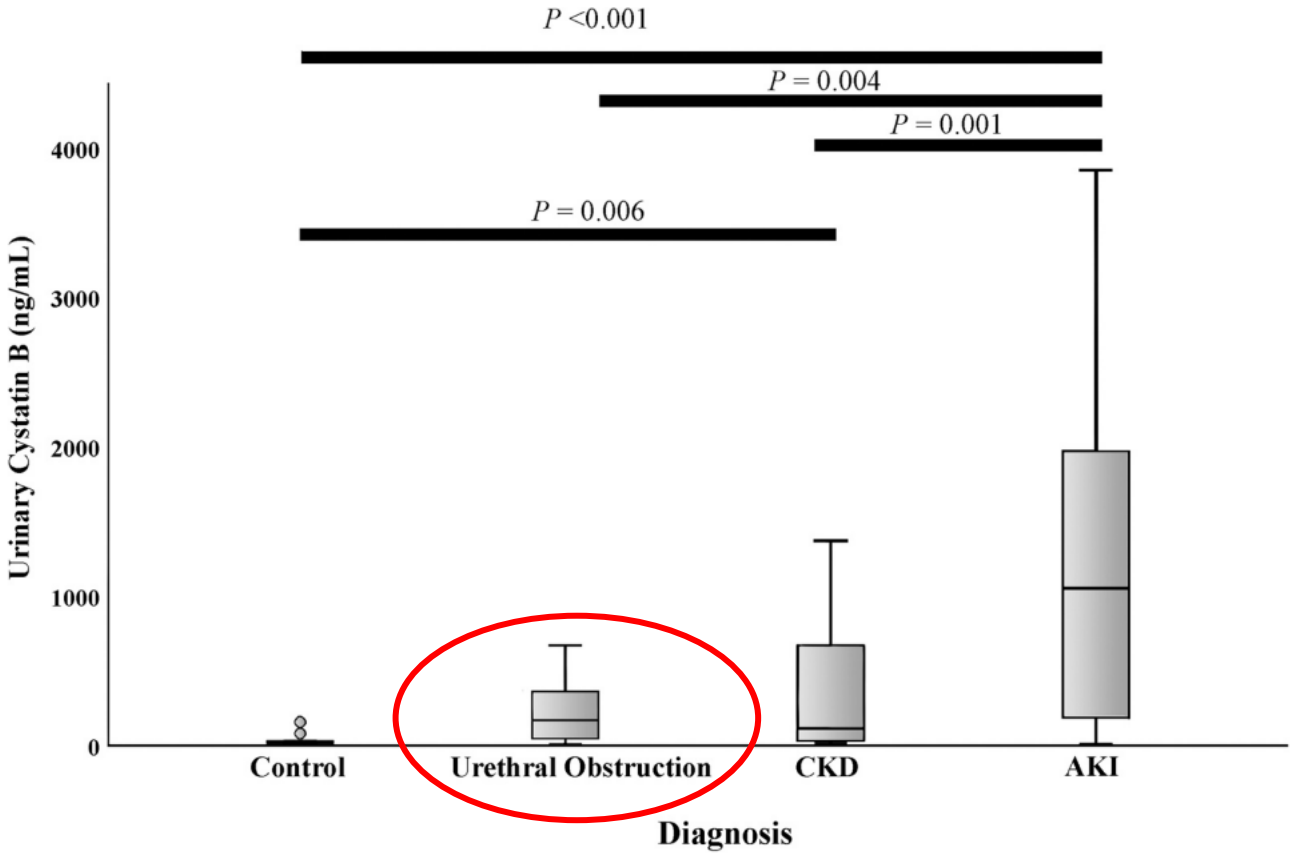
Cystatin B detects active ongoing injury with CKD

- 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 identify which dogs need more frequent monitoring



Segev, et al. J Vet Intern Med. 2023

Starting to see cat studies...



Chen et al. Vet Journal 2024

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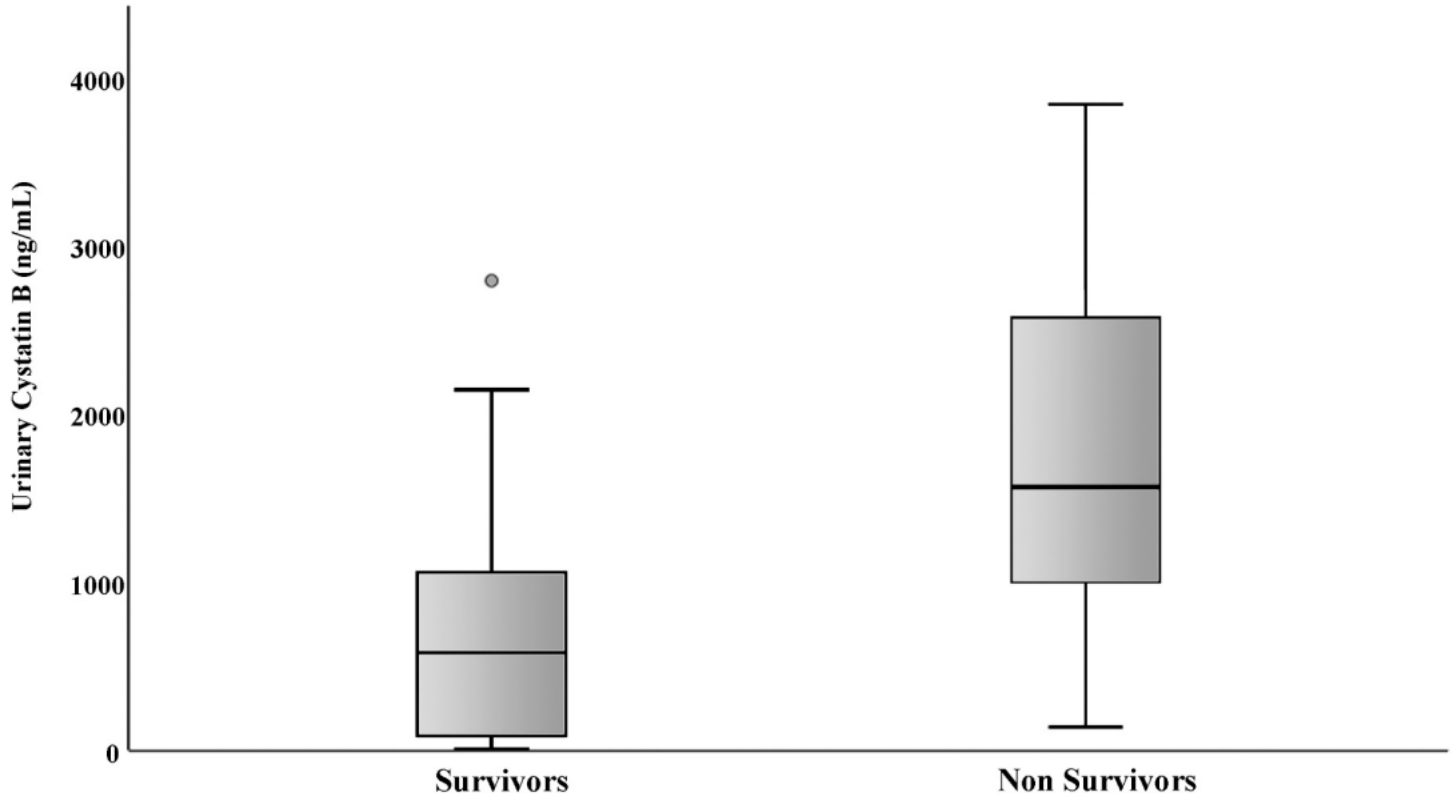


Chen et al. Vet Journal 2024

24 AAHA Fluid Tx Guide

Box 5: Common Fluid Overload Case Scenarios

1. ***Continued IV fluid therapy in a feline patient with renal disease.*** A cat is dehydrated, uremic, and anuric on presentation. Although IV fluid administration improves hydration status, uremia persists. IV fluids are continued with the misguided goal of improving GFR. However, no effective increase in GFR will occur no matter how much fluid this patient receives.
2. ***IV fluid therapy in a patient anesthetized for a lengthy procedure.*** A dog receives 10 mL/kg of fluids throughout a 6 hr procedure and develops respiratory distress during anesthetic recovery.
3. ***SC fluid therapy in a cat with occult or fulminant heart disease.*** A cat presents for evaluation of vomiting associated with malaise of congestive heart failure and is given SC fluids despite no evidence of dehydration.

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	

We’ve probably all done this…

- Cat with CKD presents dehydrated, not eating, oliguric, azotemic
- We start IV fluids at 2-4 times maintenance
- After 24 hours hydration normal, urinating, still azotemic, not eating
- We continue and maybe increase IV fluids to drive SDMA and creatinine down (increase GFR) and improve appetite

- Now we know better
  - Once hydrated, if still inappetent no more than maintenance fluids (+ ongoing losses), with potassium prn
  - Mirtazapine or capromorelin (Elura®) only when hydration normal
  - Ideally NE or NG tube for hydration, nutrition

IV fluids after nephrotoxin exposure: harmful or helpful?

- NSAIDs, lily (cat), grapes (dog)
- Fluids at 2-3x maintenance 2-3 d to induce diuresis standard recommendation
  - Diuresis may not increase toxin excretion or prevent tubular damage
  - Increases ANP which can degrade EG
  - Kidney interstitial edema → ↑ intraparenchymal pressure (rigid capsule) – ↓ perfusion/GFR
- Excessive fluid may *contribute* to AKI rather than prevent it.
- No mandatory hospitalization for IV fluids
- Use basic principles
  - Correct dehydration/hypovolemia, replace losses from V/D, maintenance if inappetence
  - Discharge when eating and drinking normally w/o excessive losses

If azotemia worsens on IV fluids consider *decreasing* fluid rate.

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

STOP fluids, +/- Lasix 1-4 mg/kg IV

Oliguria/anuria complicates AKI treatment

- Increases risk of volume overload
- Physiologic oliguria with hypovolemia, dehydration is normal
- Pathologic oliguria = <1 ml/kg/hr of urine when volume, hydration, BP normal
- 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 strict ins and outs

Thank you!

Ins and outs for oliguria/anuria

- Never in dehydrated or hypovolemic pets
- Match fluids exactly with urine produced to avoid fluid overload

- Total fluids to administer (and not a drop more) =
  Insensible loss (respiration, feces) 22 ml/kg/d +
  Sensible loss (urine) +
  Ongoing loss (vomiting, diarrhea)

- Given in 4 or 6 hr intervals

In and outs for 5 kg cat, normal hydration, no v/d

Fluids are given in 6 h increments

Insensible loss 20 ml/kg/d ÷ 4 = 5 ml/kg x 5 kg = 25 ml

Urine production = 0 ml

No v/d = 0 ml

25 ml total volume to administer over next 6 h = 4-5 ml/h

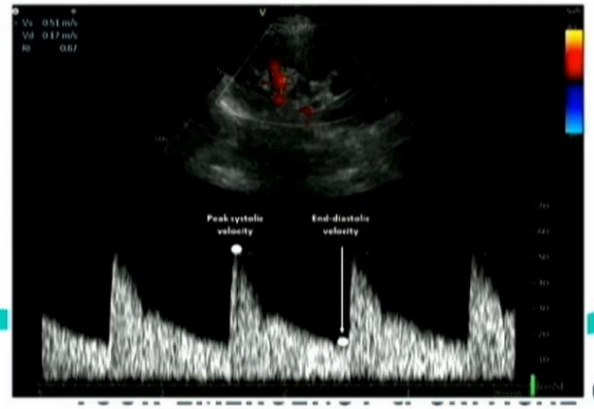
Heart Kidney – IVECCS 2025

Fluid Tolerance?

Renal Resistive Index | Intra-abdominal Pressure | Lung Ultrasound

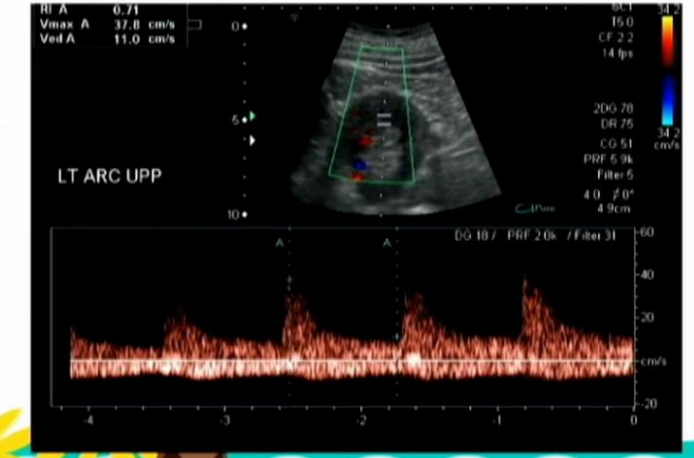
Reflects increased **intrarenal vascular resistance**.

$$\mathrm{RRI} = \frac{PSV - EDV}{PSV}$$



- No true validated measurements
- Presence of fluid
- GB Edema

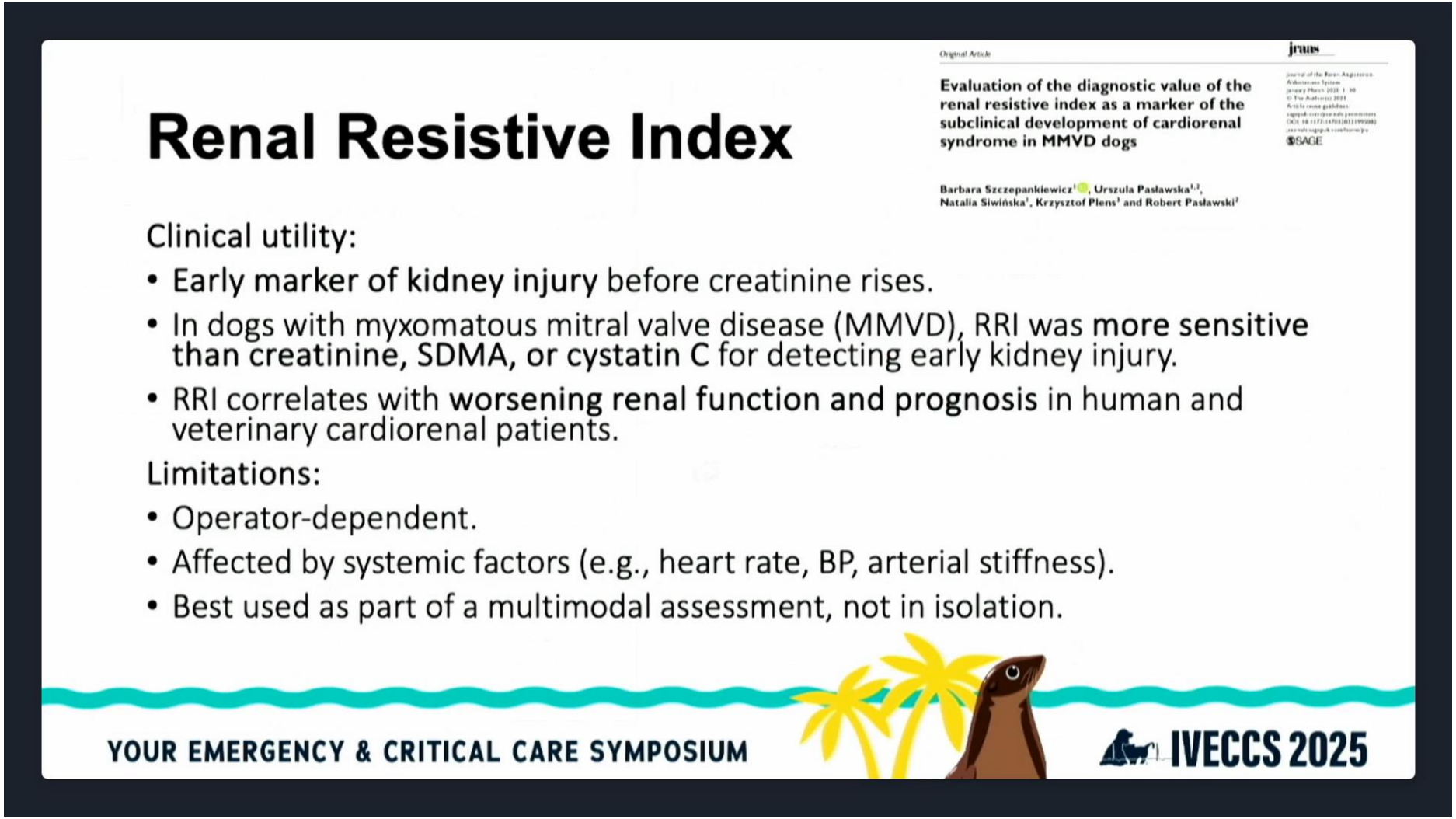
- B-lines
- Pleural effusion



CARE SYMPOSIUM

IVECCS 2025

Heart Kidney – IVECCS 2025



This is a problem because early detection is the key to good outcomes regardless of type of kidney disease.

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Injury markers in urine.

Functional markers in blood.

Take home message: can’t assess kidneys without urine.

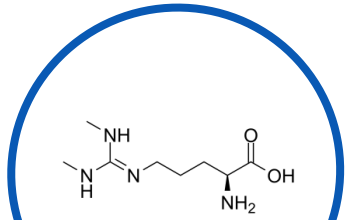
What hasn’t changed with fluid therapy.

- Initial fluid choice almost always LRs or similar
  - Isotonic, buffer, Ca or Mg, trivial K
  - 0.9% NaCl if hypochloremia
- If lose fluid fast replace fast – 30-60 min with hypovolemia
  - 10-20 ml/kg dog, 5-10 ml/kg cat over 15-30 minutes, repeat x2-3
  - Mucous membranes, capillary refill time, HR, pulse strength, lactate, urine production
  - FFP 10-20 ml/kg after 3 or so crystalloid boluses
- If lose fluid slowly replace slowly – 6-24 hr with dehydration
  - BW (kg) x % dehydration as decimal x 1000 = mls to deliver
- Keep up with ongoing losses and provide maintenance
  - Maintenance fluids, e.g., 0.45% NaCl in 2.5% dextrose or dilute LRs 1:1 w D5W
- Frequent body weight, accurate gram scale
  - 5% increase → consider adjusting
  - 10% increase → volume overload

Evolution in assessing kidneys…

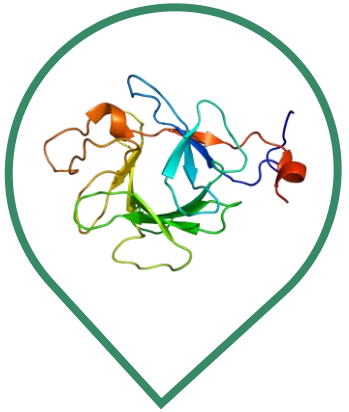
BUN early 1900s, **creatinine** 1920s, **Urinalysis** forever**.**

Yawn…
For almost 100 years!



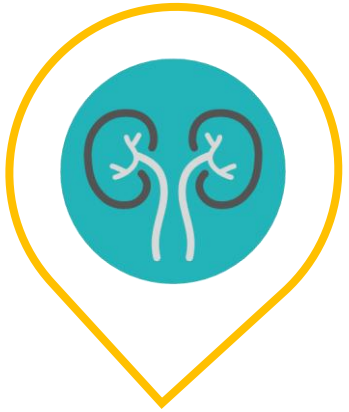
SDMA

Validated for use in dogs
2015



FGF-23

Launched for felines with chronic kidney disease
2022



Urinary Cystatin B

Detects both active and acute kidney damage

When to run FGF-23:

CKD diagnosed

Phosphate <1.5 mmol/L (<4.6 mg/dL)

No hypercalcemia, anemia, marked inflammation

Guide to instituting and monitoring dietary therapy

Lyme follow-up (Sykes Inf Dz text, Consensus Statement)

- There is no evidence that treatment of healthy seropositive dogs is beneficial and it may lead to drug adverse effects and contribute to antimicrobial resistance in other bacteria and antimicrobial shortages.
- Whether there are any advantages or disadvantages of vaccinating dogs that are already seropositive as a result of natural infection remains to be elucidated.
- The recent identification of reinfection (as opposed to relapse) as a cause of recurrent clinical signs of borreliosis in human patients suggests that vaccination of previously exposed individuals may offer some benefit, because the protection induced by vaccination (anti-OspA antibodies) differs from that induced by natural infection (no anti-OspA antibodies). However, whether recurrent Lyme disease occurs in dogs as a result of reinfection is not known.

More Lyme follow-up

- The routine use of Bb vaccinations in Bb-endemic areas in North America was recommended by 3/6 panelists, for seronegative as well as healthy nonclinical, nonproteinuric seropositive dogs, because no natural immunity occurs from previous infection…
- The 3/6 panelists who dissented cited inconsistent efficacy and duration of immunity (see above), cost, need for proper tick control, lack of controlled studies with respect to tick control when assessing vaccines in the field, theoretical concerns for immune-mediated sequelae,1, 153 and because most Bb-seropositive dogs remain nonclinical, nonproteinuric carriers.
- The evidence for a negative impact of vaccination remains anecdotal at best (wrt increased risk of immune-complex GN).
- Neither source mentioned using QuantC6 level to guide vaccination or not.

“*What the hell am I supposed to do with Cystatin B results?*”

“What the hell am I supposed to do with SDMA results?”

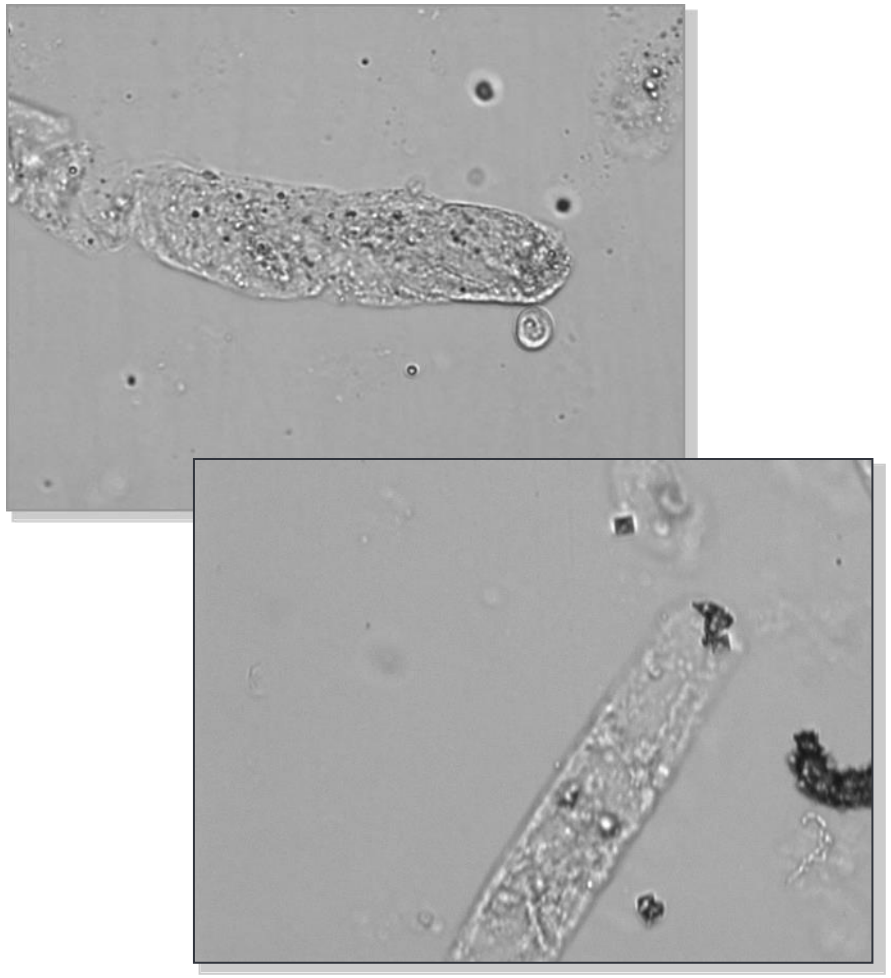
“Why is there even a cystatin B to begin with?”

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



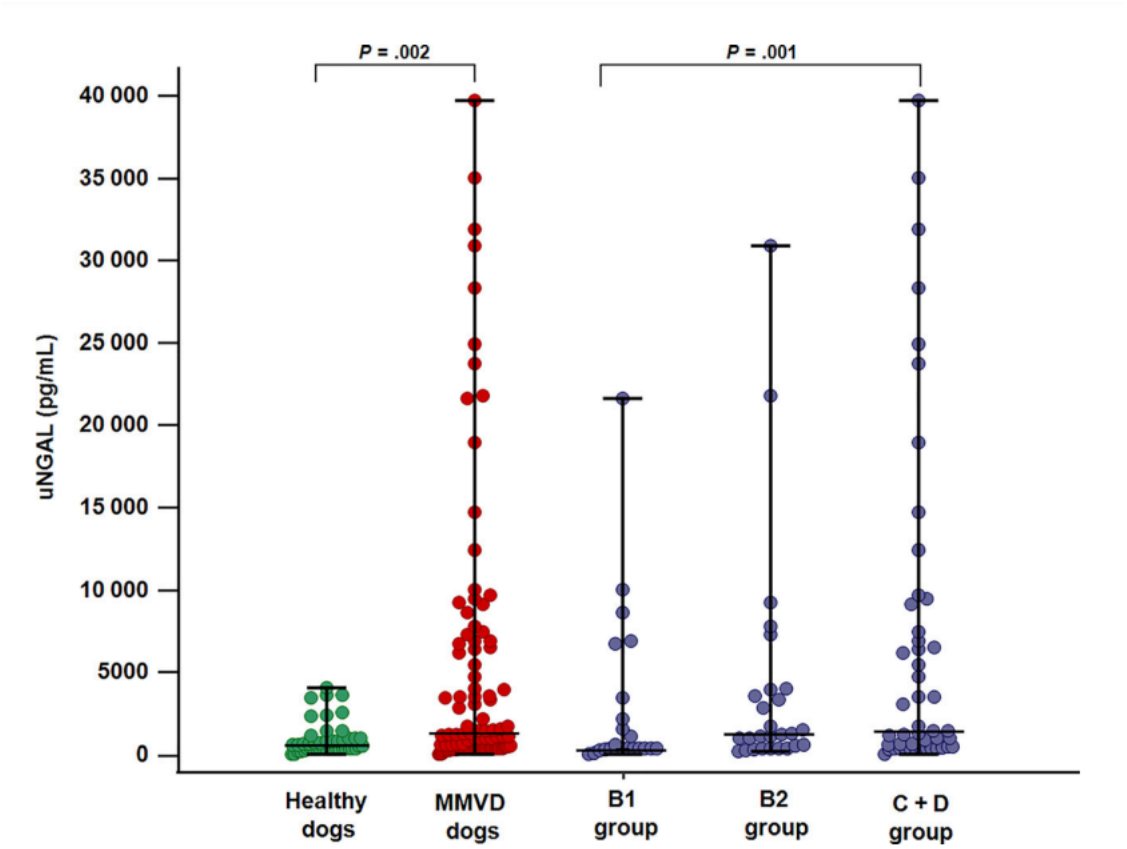
Cystatin B = ALT

SDMA, creat = bile acids

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
  - CKD can have active injury component

Subclinical *tubular* damage in all MMVD stages



Troia, et al. JVIM 2022

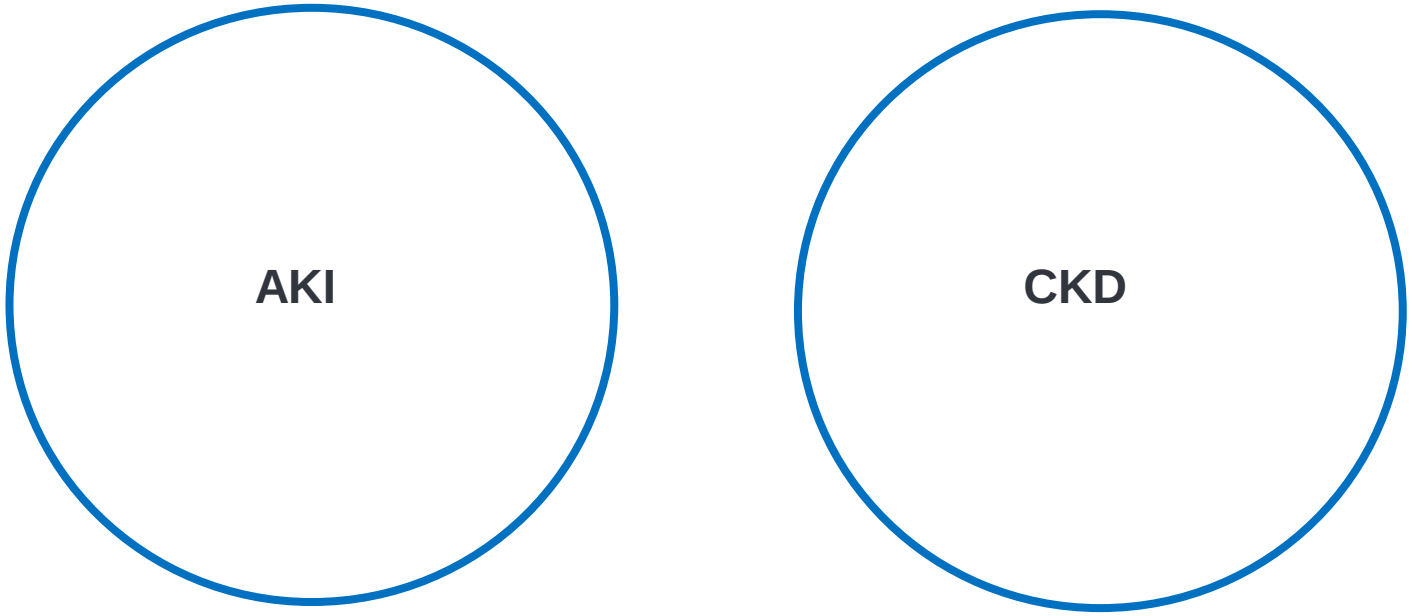
The ideal pet to run a cystatin B on…

- AKI present or possible
  - Acutely ill with supportive lab results +/- oliguria/anuria
  - Known or possible exposure to nephrotoxin
  - Chronic NSAIDs

- Systemic disease present resulting in:
  - Decreased renal perfusion
  - Cytokine bombardment

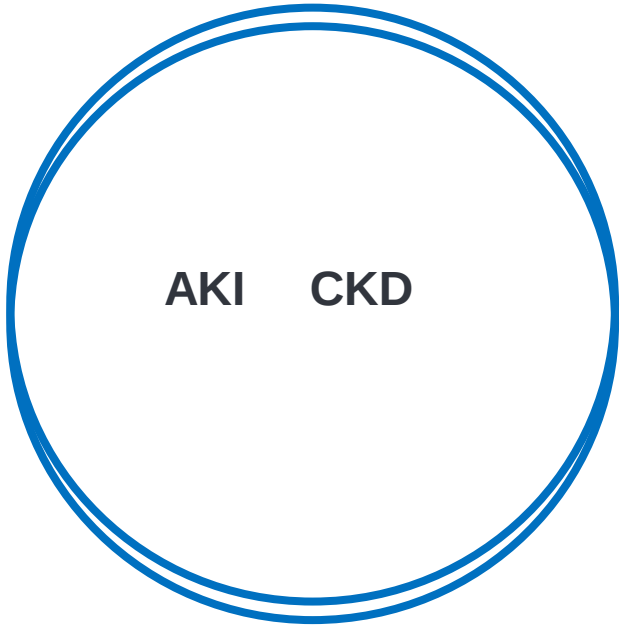
- CKD present
  - Is there an active injury component?

It used to be…



Now it’s…

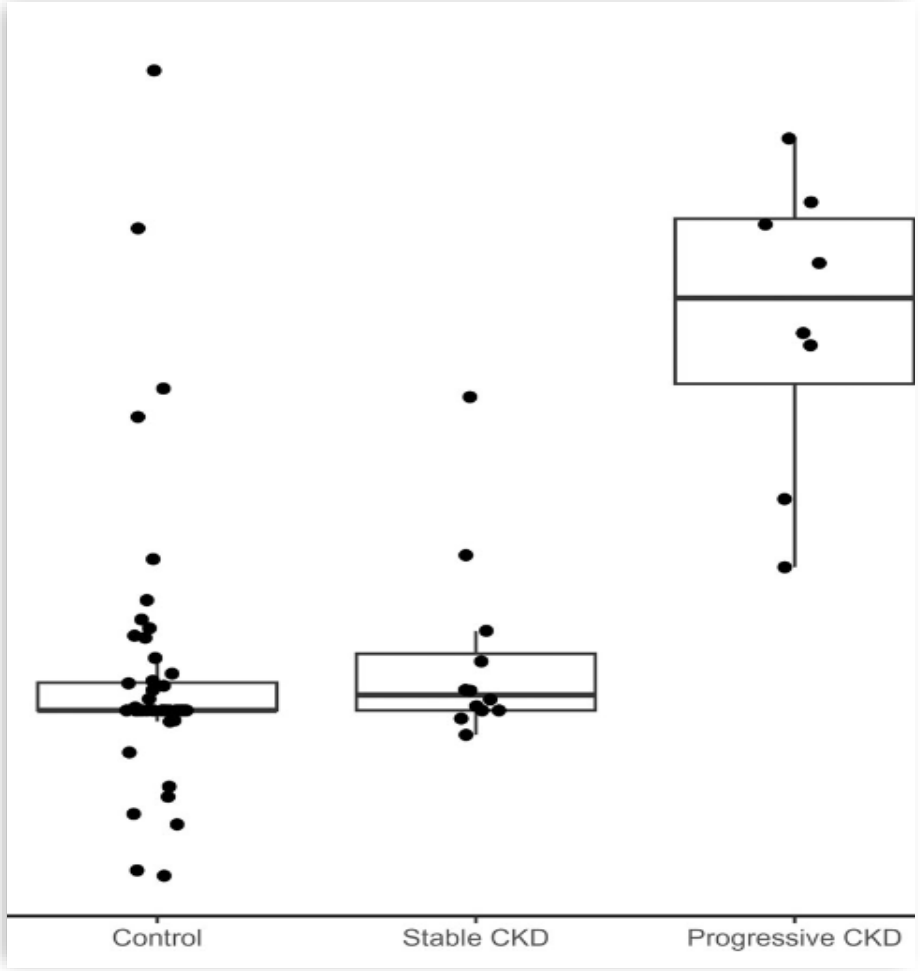
An AKI patient may have or develop CKD.



A CKD patient may have concurrent active kidney injury.

Cystatin B detects active ongoing injury with CKD

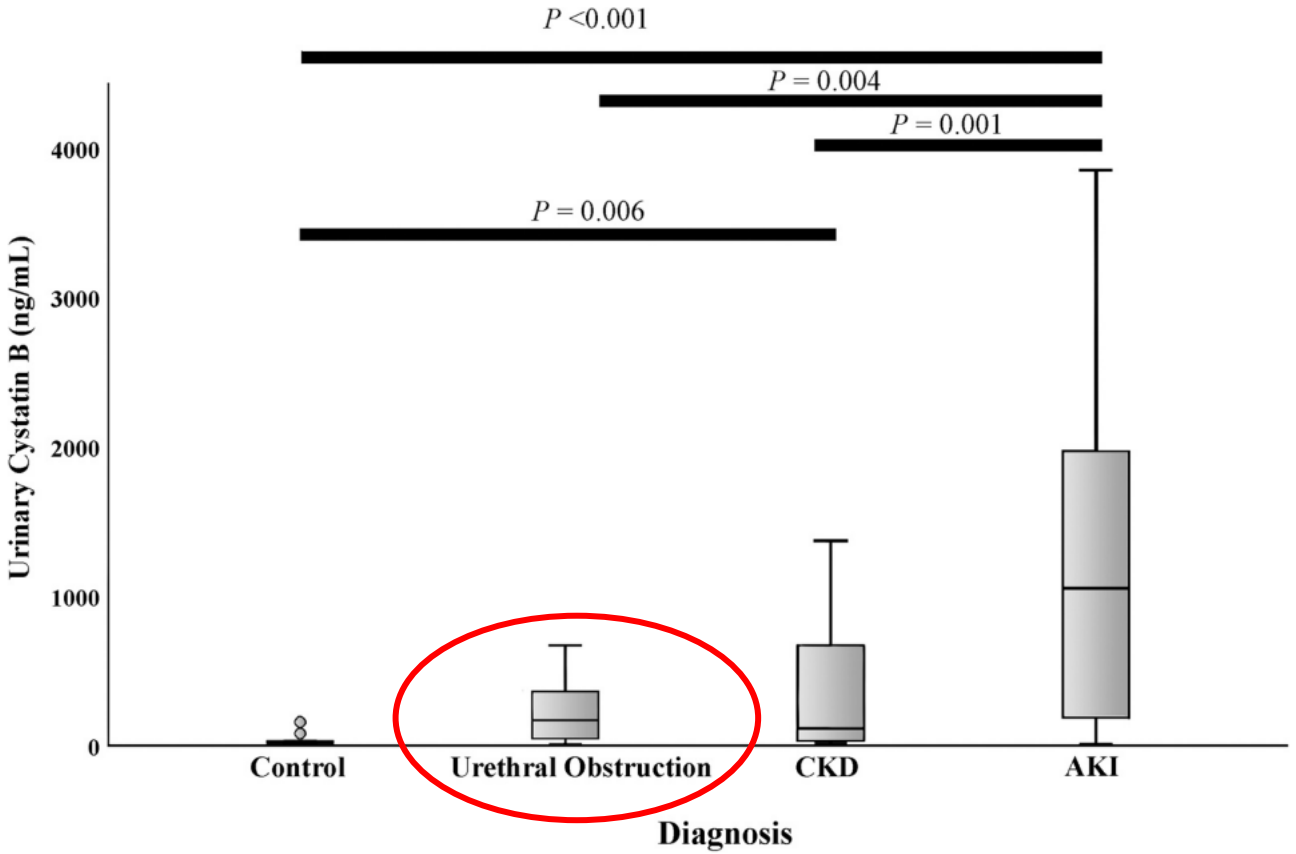
- CKD progressive and irreversible
- ***Rate*** of progression unpredictable
- Cystatin B identifies active ongoing injury in dogs and cats with CKD
- Increased Cys B in dogs with IRIS Stage 1 CKD predictive of more rapid progression
- Identifies which pets need more frequent monitoring



Segev, et al. J Vet Intern Med 2023

Chen, et al. Vet Journal 2024

Starting to see cat studies…(more please).



Chen et al. Vet Journal 2024

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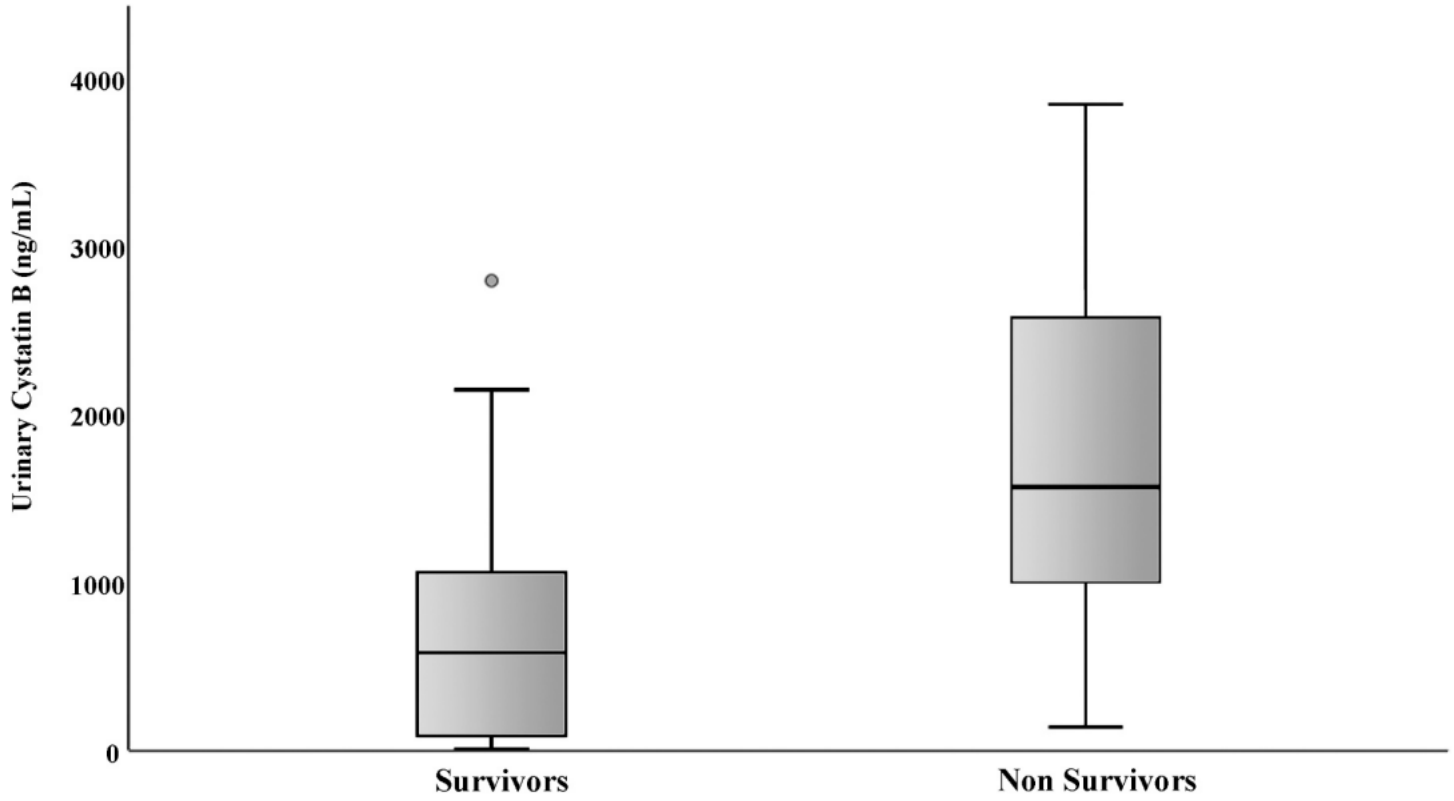


Chen et al. Vet Journal 2024

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, UcysB 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

A comprehensive history, such as diet, medications, supplements, preventives, travel, and other information, should be obtained

Consider rechecking cystatin B and other kidney markers, including SDMA, in 1–2 weeks or sooner if clinical signs become apparent

Ask questions!

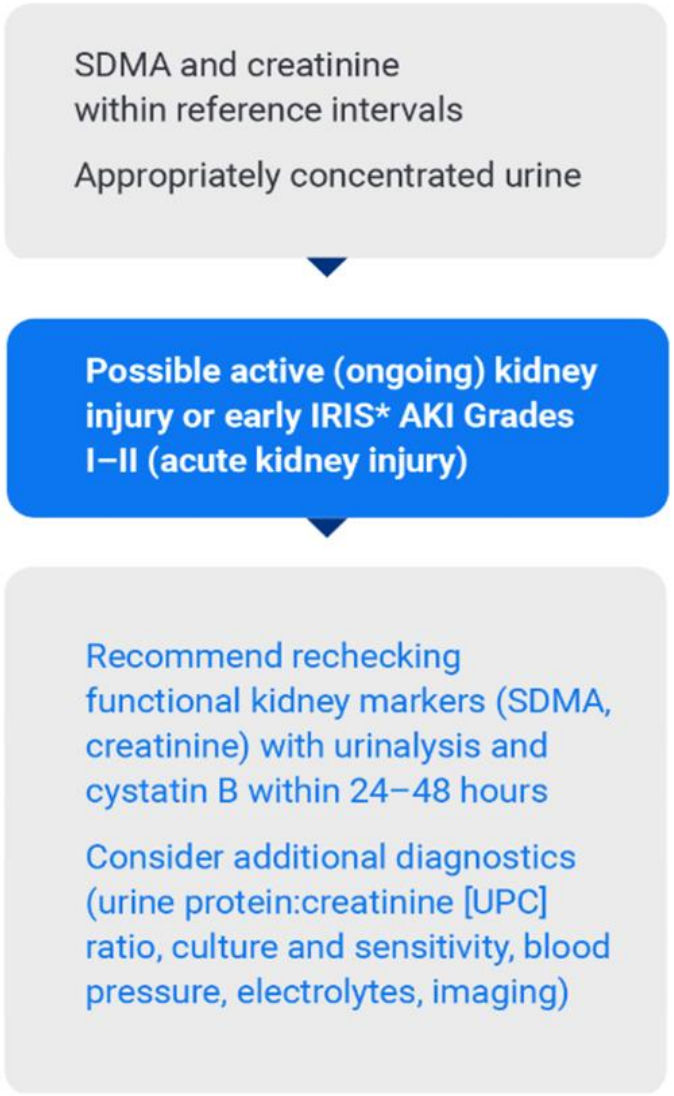
Current or past:

- 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. Labs normal.



Ask questions

Current or past:

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

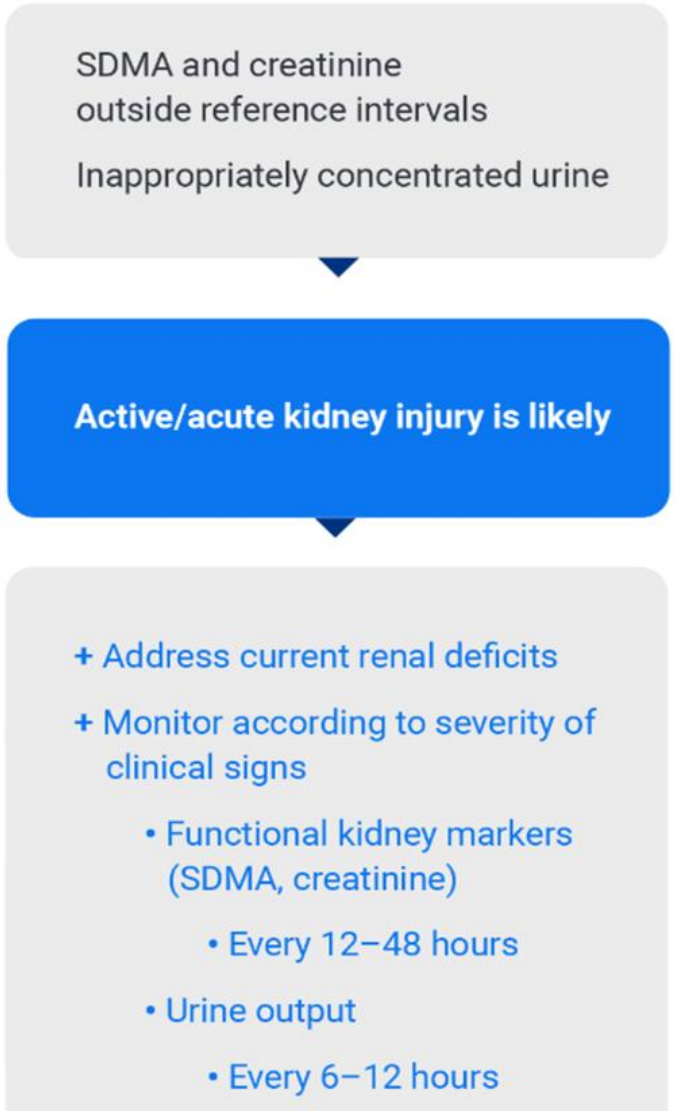
Treat your patient

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. Labs abnormal.



Ask questions

Current or past:

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

Treat your patient

If hospitalize

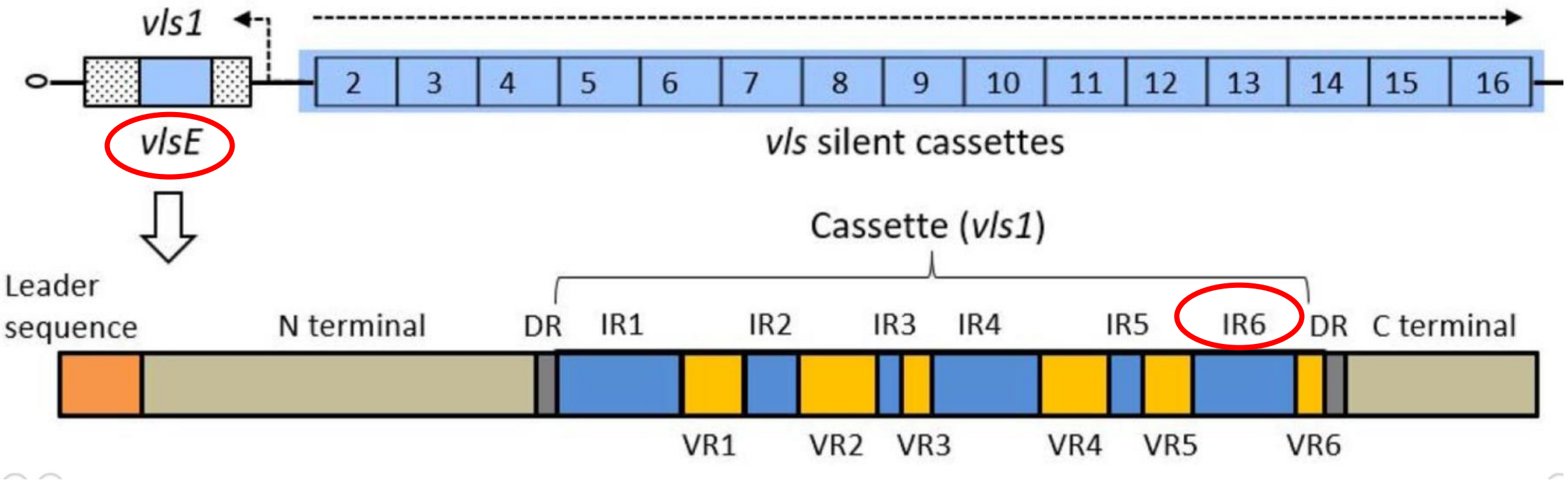
- SDMA, Creat q12-48h
- Lytes, PCV/TS min q24h
- Urine output q6-12h
- IRIS AKI grading q24h
- AVOID excess fluids
- Weigh 2-4 x/d

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?
- Cystatin B in every cell, freely filtered, increased w systemic disease
  - If SIRS, sepsis still useful monitoring tool.

“Why is the Lyme C6 considered a marker of acute infection when these titers can stay elevated for months to years?”

C6: constant region of variable surface protein



- VlsE = variable major protein-like sequence, expressed
- IR6 = invariant region 6
- C6 = Constant IR 6

Making sense out of C6 antibody

- Antibodies to C6 indicate organism is or was living in the dog (or human)

Duration of anti-C6 antibody

- Continual VlsE turnover prevents C6 accumulation
- Lower concentration of Ag-Ab complexes in follicular dendritic cells
- Less stimulation of memory B-cells
- Limited B-cell memory leads to quick *decline* in anti-C6 titer

- Titer may persist for ‘a long time’ (Consensus Statement), ‘months to years’ (human paper) due to:
  - High titer (robust immune response) in majority of nonclinical dogs
  - Organism may never be cleared
    - Enters ‘protected’ collagen tissue
    - Develops into latent cyst or L-form (may recrudesce)
  - Re-exposure (endemic areas)

SNAP 4Dx Plus: positive >10 U/ml

Quant C6: significant >30 U/ml

High initial Quant C6 may never decrease below these levels.

Making sense out of C6 antibody

- Antibodies to C6 indicates organism is or was living in the dog (or human)

- Duration of titer depends on antigen load, length of infection before diagnosis, organism clearance (or not), re-exposure

Magnitude of anti-C6 antibody

- Correlated with:
  - Antigen (organism) load
  - Circulating immune-complex concentration
- Not correlated with or predictive of:
  - Clinical disease (most not clinical)
  - Disease severity
- Pre- and post-treatment titer (4/6 Consensus Statement panelists) to:
  - Monitor tx
    - >50% decrease 3-6 months post tx = effective therapy
    - ≥4-fold decrease in titer = effective therapy (humans)

    } Without re-exposure!
  - Use post-tx titer as baseline for future comparison
    - Subsequent increase = re-exposure

Making sense out of C6 antibody

- Antibodies to C6 indicates organism is or was living in the dog (or human)
- Duration of titer depends on antigen load, length of infection before diagnosis, organism clearance (or not)
- Decrease in Quant C6 of >50% from baseline 3-6 months post tx = effective tx

Stuff you know for review

- Qualitative C6 annually as wellness/preventive care in dogs in endemic areas
- Positive SNAP 4Dx Plus → CBC, chem, UA
  - Nonclinical:
    - Proteinuria, ↓ plt, azotemia, ↑ CRP → treat
    - Labs normal → don't treat, monitor for proteinuria minimum 2-3 x/yr (5/5 N American panelists)
    - Baseline and 3-6 mo post tx Quant C6
  - Sick:
    - Treat plus labs to determine severity and rule out other causes of signs
    - VBD PCR panel for co-infection
    - Baseline and 3-6 mo post tx Quant C6
- 2/6 panelists treat nonclinical, nonproteinuric dogs if Quant C6 is high
  - Concern over immune complexes causing future problems
  - 4/6 that don't treat don't see problems and cite Quant C6 concentration not predictive

Standard proteinuria treatment – updated IRIS recommendations

- Renal diet
- Telmisartan 1.0 mg/kg/day
- Clopidogrel 1-4 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
  - q4-6 mo, CBC, panel, UA, UP/C (pooled), blood pressure

“Why is the Lyme C6 considered a marker of acute infection when these titers can stay elevated for months to years?”

*If a dog has not been treated for Lyme disease increased anti-C6 antibody means active infection (clinical or **subclinical**, acute or chronic), or prior infection cleared by effective immune response.*

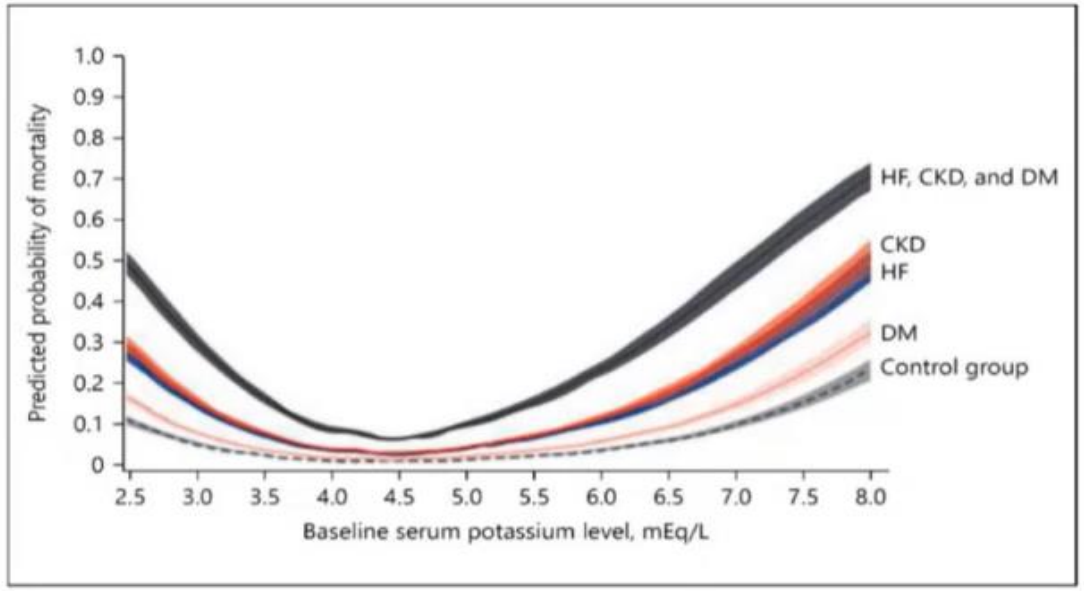
In a treated dog increased anti-C6 means effective treatment if >50% decrease from pre-tx level, ineffective treatment if not, or re-exposure if increased from 3-6 month post-tx level.

Use CBC, panel, UA to determine whether or not to treat.
Use QuantC6 to determine response to tx or recurrence.

Some C6 antibody thoughts

- Outer surface C6 antigen only expressed when bug in dog and dividing
- C6 antibody therefore = bug in dog and dividing (most aren't clinical, but may be proteinuric)
- More bug, higher the C6 titer
- With successful tx titer should decrease by half or to normal w/in 3-6 mo
- Persistent high titer post treatment may be re-exposure in highly endemic area
- As long as the dog is not clinical, not proteinuric, (and has normal CRP?) just monitor yearly and focus on tick prevention
- No consensus on using magnitude of Quant C6 to determine tx or no
- I personally wouldn't tx if clinically normal, not proteinuric, normal CRP, and client not flight risk

Mortality increased with hyper- and HYPOkalemia
(with every 0.1 mEq/L change <4 and ≥5 mEq/L)



Collins et al Am J Nephrol 2017

Hyperkalemia

- Absolute K value not predictive of arrhythmia
- Rate and magnitude of increase important
- Ca, Na, Mg, acid-base involved

- Bradycardia (rarely tachycardia) and hypothermia specific for K >8

- Sinoventricular rhythm
  - SA node fires, impulses transmitted to AV node and ventricles by internodal pathways
  - P waves absent because atrial myocytes not activated

Rule out pseudohyperkalemia

- Thrombocytosis

- Hemolysis in Japanese breed
  - High potassium mutation first in Korean dogs, in 10/13 Japanese breeds
  - Intracellular K concentration 35x higher

- EDTA contamination of serum sample
  - Hyperkalemia with hypocalcemia

Treat life-threatening hyperkalemia

- IV isotonic crystalloid (ok if contains K)
- 10% calcium gluconate
  - Cardioprotective, buys time
  - 0.5-1.5 ml/kg over 10-15 minutes
- Regular insulin and 50% dextrose
  - ¼ U/kg with 2 gm 50% dextrose/U of insulin
- HCO3 rarely necessary
  - Consider if pH<7.1, HCO3<12 mmol/L
  - BW (kg) x 0.3 x (24 – HCO3) = mEq HCO3 deficit
  - Give ½ deficit IV over 30 minutes
  - If pH not >7.2 remainder in IV fluids over 2-4 hr

Hypokalemia causes and exacerbates arrhythmias

- Renal loss
  - Concurrent kidney, thyroid, adrenal (hyperaldosteronism)
- GI loss
  - Vomiting presenting sign in 30% cats in heart failure
- Inappetence
  - Dehydration especially cats on diuretics
  - Mirtazipine early once hydrated
- Diuretics

Hypokalemia w heart disease: prevent and manage

- K supplementation in 1/3-1/2 cats and 1/3 dogs in heart failure (referral)
- K <4 prior to diuretics → supplement
- K normal prior to diuretics → recheck lytes 7 days
  - ≥4 no supplementation
  - <3.7 supplement
- K at 4 week recheck
  - ≥4.5 on supplementation stop
  - <3.7 start or increase supplement

Potassium gluconate:
Cats 2-6 mEq/d divided q8-12
Dogs 2.2 mEq/10 kg

Chloride

- Cl usually just does what Na does and mainly indicates hydration status
- Cl is also a METABOLIC ACID (strong ion) so if it changes more than Na there is an acid-base problem
  - If Na is normal and Na-Cl >40 hypochloremic metabolic alkalosis
  - If Na is normal and Na-Cl <32 hyperchloremic metabolic acidosis

  } Or use 36 cutoff

  - If both are low and Cl is further from low end of RI than Na – hypochloremic metabolic alkalosis
- Or you can determine corrected Cl with formula
  - Corrected Cl = (Normal Na/Measured Na) x Measured Cl
- Hypochloremic metabolic alkalosis is common and in vomiting patients should prompt investigating for upper (really any) GI obstruction
- This is the only instance when 0.9% NaCl is initial fluid of choice (has most Cl by far of any other crystalloid)

Chloride low: hydration or acid-base abnormality?

- Na 139 mEq/L (142-150 mmol/L)
- Cl 80 mEq/L (105-118 mmol/L)

- Difference from reference interval
  - Na 3 below lower limit
  - Cl 25 below lower limit

- Corrected Cl = (Normal Na/Measured Na) x Measured Cl
  - 146 (142+150/2)/139 x 80 = 84

What fluid do you use to treat adrenal crisis?

Adrenal crisis: rethinking fluid choice

- LRs advantages
  - Contains buffer
  - Na concentration lower than 0.9% NaCl
  - Trivial K concentration
- 0.9% NaCl concerns
  - Acidifying
  - Higher Na concentration may raise serum Na too fast
    - Osmotic demyelination syndrome
  - Renal vasoconstriction due to high Cl concentration

Hyponatremia: hydration status impacts treatment

- Dehydrated patient
  - Addison's, vomiting and diarrhea, excess diuretic, kidney disease
  - LRs lowest [Na] of replacement fluids – probably safest to restore volume/hydration
- Overhydrated patient
  - Congestive heart failure, hepatic fibrosis, nephrotic syndrome, primary polydipsia, renal failure (oliguric)
- Euhydrated patient – artifact
  - Marked lipemia
  - Possibly marked hyperproteinemia, e.g., multiple myeloma
  - Hyperglycemia

- Complications of raising Na unlikely if acute drop and Na >110 mEq/L
  - Shoot for max increase 10-12 mEq/L/day
  - Initial fluid choice Na within 10 mEq/L of pet Na

Suspect EEH when:

- Gastrointestinal signs
  - Megaesophagus?
- Albumin: globulin <1.08
  - Over 1/3 hyperglobulinemic
  - Hypoalbuminemia more common w EEH
- Low cholesterol (<133 mg/dL)
- Lack of stress leukogram in sick animal
  - Lymphocyte count >1500–1750cells/µL
  - Eosinophil count >500 cells/µL
- Reticulocytosis without anemia
- Increasing Ca, decreasing BG, regurgitation…

EEH in 30-40% of Addisonians.

Reagan KL, McLarty E, Marks SL, et.. al. Characterization of clinicopathologic and abdominal ultrasound findings in dogs with glucocorticoid deficient hypoadrenocorticism. J Vet Intern Med. 2022;36(6):1947-1957. doi:10.1111/jvim.16564

Pretend cystatin B is ALT.

Use labwork to decide what to do with C6 titer.

Don’t over do it (or under do it) with IV fluids.

Phosphorous is enemy no.1 w CKD. FGF23 helps.

Thank you.

Assess *all* main kidney functions with appropriate marker

Filter waste from blood

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

Run on blood.
Only part of the picture.

Assess *all* main kidney functions with appropriate marker

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

Control body fluid

- Complete urinalysis
  - Urine specific gravity
  - Urine chemistries
  - Sediment examination
  - Tubular injury markers
    - Cystatin B

Maintain plasma proteins

- Glomerular integrity
  - Urine protein
  - Urine protein-to-creatinine ratio (UPC)

Blood and urine are required to assess kidney function.

Current GFR (functional) biomarkers:
BUN
Creatinine
SDMA

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

Investigate all 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

Cannot interpret SDMA, Creat without USG

One of these dogs has a kidney problem…

(Normal USG >1.030 *when azotemic*)

SDMA 19 ug/dL, Creat 159 umol/L

USG 1.055

SDMA 19 ug/dL, Creat 159 umol/L

USG 1.010

CKD: progressive, irreversible

Rate of progression variable

- Persistent (≈ >3 month) abnormality in 1 or more kidney function or structure
  - Azotemia (overt or progressive increase in creat or SDMA within ref interval)
  - Persistently SDMA >14 ug/dL precedes increase in creatinine
  - Persistent renal proteinuria
  - Persistent USG <1.030 dog, <1.035 cat with nonrenal cause excluded
  - Tubular dysfunction, e.g., normoglycemic glucosuria, granular casts, cystatin B
  - Structural abnormality, e.g., small, irregular kidneys, cysts…
- Single abnormality common
  - Proteinuria without azotemia or decreased USG
  - Decreased USG without increased creatinine
- **Prerenal or postrenal factors excluded**

Euvolemic cat with stable renal function:

- Creat 2.3 mg/dl
- SDMA 22 ug/dl
- UP/C 0.32
- Systolic BP 200 mm Hg

IRIS CKD Stage 2
Borderline proteinuria
Severely hypertensive

If SDMA 32 ug/dl?

IRIS CKD Stage 3
Borderline proteinuria
Severely hypertensive




	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)
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
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**	
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**

After treating hypertension:

- Creat 2.5 mg/dl
- SDMA 24 ug/dl
- UP/C 0.12
- Systolic BP 155 mm Hg

IRIS CKD Stage 2
Non-proteinuric
Prehypertensive (treating)




	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**

AKI: potentially reversible, kidney function *may* return to normal

- Abrupt decline in kidney function
- Toxin, ischemia, infection…
- Tubules impacted first
- GFR may be normal, i.e., no azotemia up to 2 days post insult
- May be present on presentation or develop in hospital (unstable patients)

IRIS AKI grading system

Creatinine increase ≥ 27 mg/dl in 48 h

(Or increase 1.5x baseline in 7 d)

Urine production <1 ml/kg/h over 6 hr

Laboratory evidence of *nonazotemic* AKI

- SDMA increased
- Urinary casts, glucosuria with normoglycemia

AKI dynamic

- Improve, worsen, progress to CKD
- Apply grading scheme daily or more often

Table 1: IRIS AKI Grading Criteria

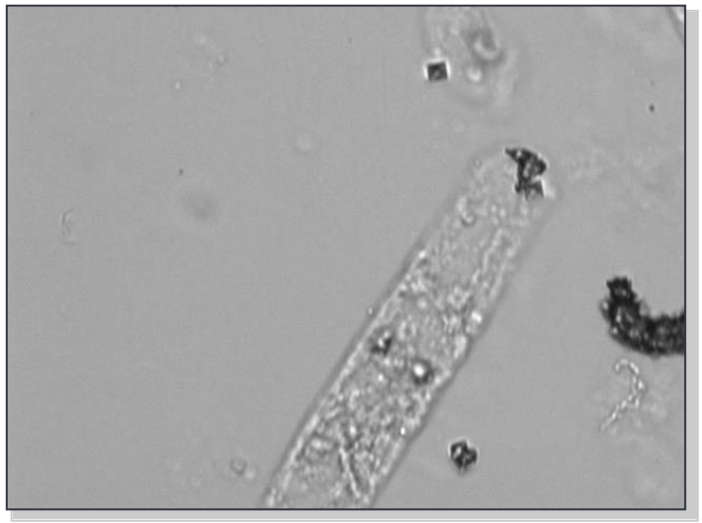
AKI Grade	Blood Creatinine	Clinical Description
Grade I	<1.6 mg/dl (<140 µmol/l)	Nonazotemic AKI: a. Documented AKI: (historical, clinical, laboratory, or imaging evidence of AKI, clinical oliguria/anuria, volume responsiveness‡) and/or b. Progressive nonazotemic increase in blood creatinine: ≥ 0.3 mg/dl (≥ 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)	

Injury markers = Urine

Take home: can’t assess kidneys without urine.

Current urine markers good not great.

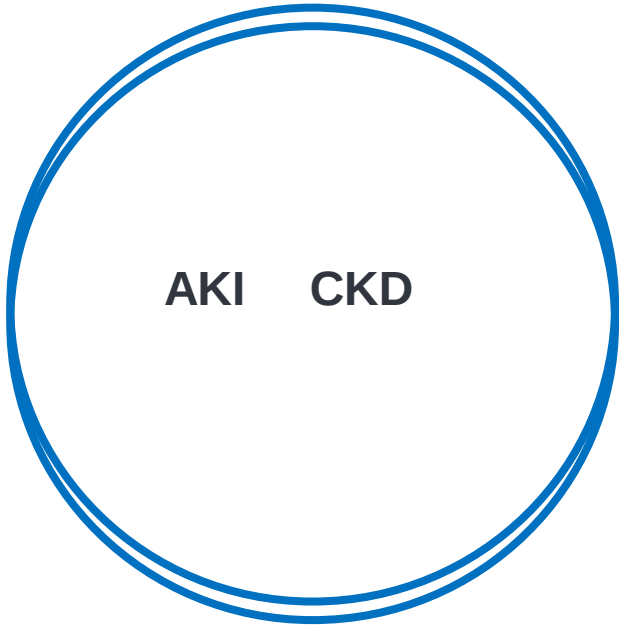
- Proteinuria
- Hematuria
- Pyuria
- Bacteriuria
- Renal epithelial cells
- Glucosuria (normoglycemia)
- + Urine culture
- Granular casts ≈16%
- Decreased urine production
- Decreased USG



What’s new:

Diagnostics
Treatment

Your AKI patient may have or develop CKD.



Your CKD patient may have concurrent active kidney injury.

Traditional and newer markers to assess kidneys

Functional markers (serum)

BUN

CREA (70-75% function loss before increase)

SDMA (30-40% function loss before increase)

FGF-23 maybe someday

Often normal w/in 1st 48 h of acute injury

Injury markers (urine)

Granular casts

Renal epithelial cells

Proteinuria

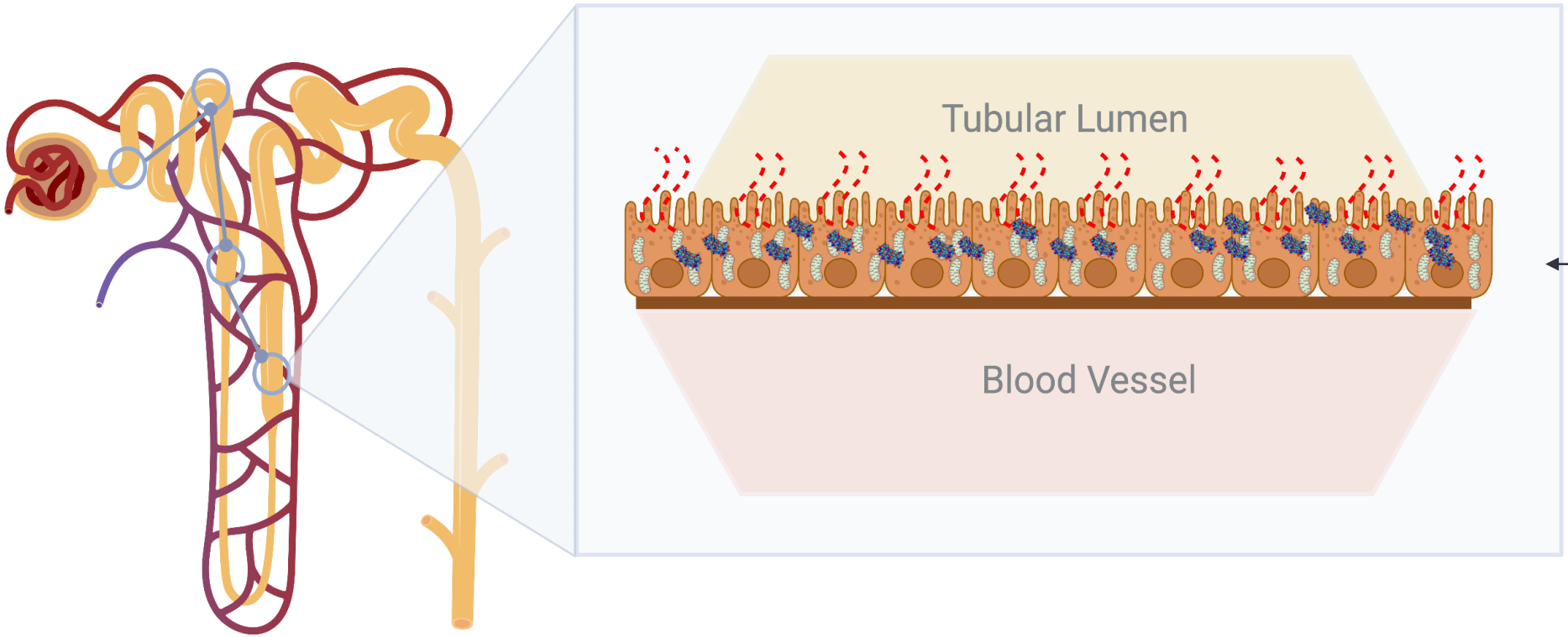
Normoglycemic glucosuria

Cystatin B now

Detect subclinical kidney injury before ↓ GFR

Urine Cystatin B detects *active* kidney tubular damage

(ALT of the kidney)

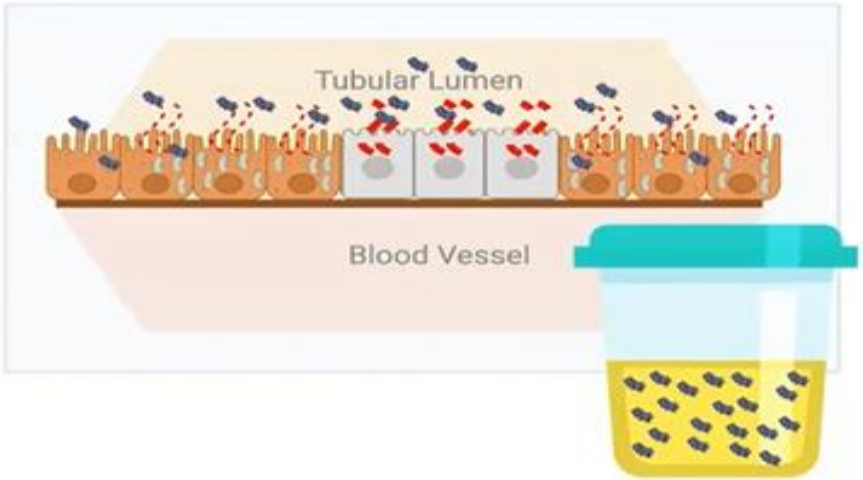


Cystatin B leakage from injured or necrosed tubular epithelial cells

Harjen HJ, Anfinsen KP, Hultman J, et al. Evaluation of urinary clusterin and cystatin B as biomarkers for renal injury in dogs envenomated by the European adder (Vipera berus). Top Companion Anim Med. 2022;46:100586. doi:10.1016/J.TCAM.2021. 100586

Starybrat D, Jepson R, Bristow P, et al. Prospective evaluation of novel biomarkers of acute kidney injury in dogs following cardiac surgery under cardiopulmonary bypass. J Vet Emerg Crit Care. 2022; 32(6):733-742. doi:10.1111/VEC.13250

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)

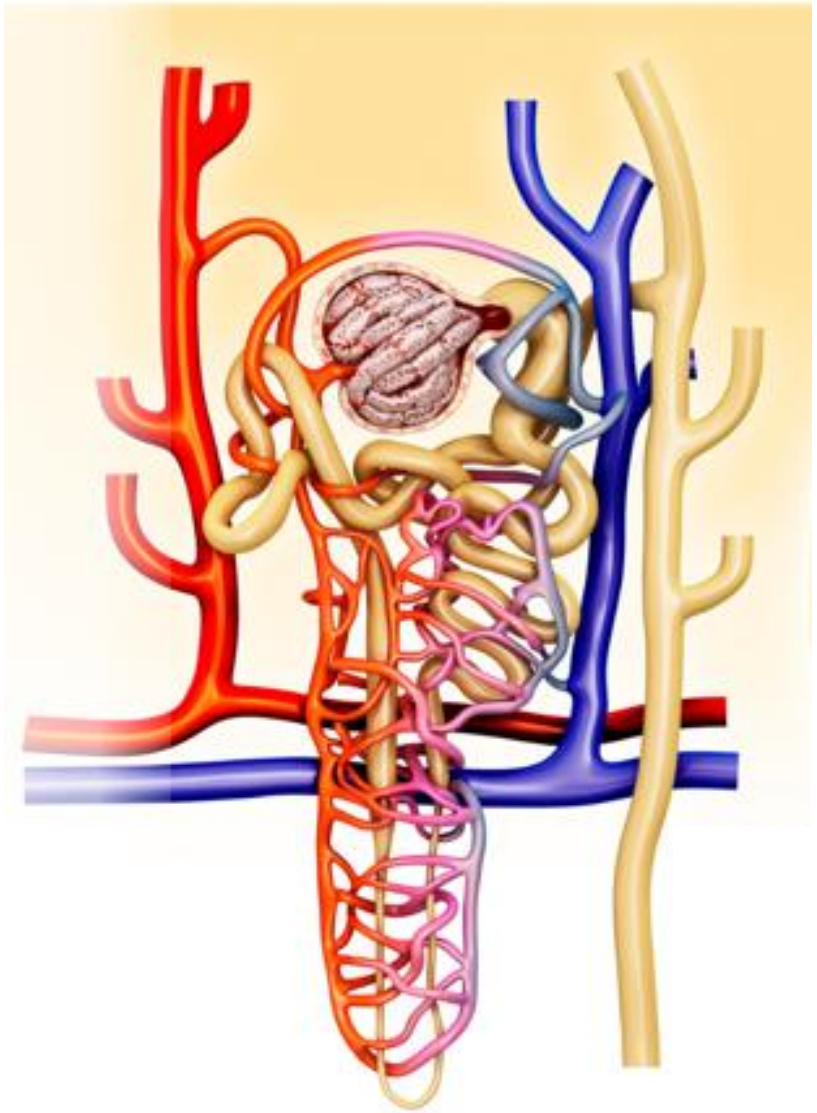
2

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

Cystatin B (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**



Consider uCystatin B with:

- AKI
  - Confirm active injury following toxin exposure
  - Monitor treatment and recovery from acute injury event
  - Monitor high risk patient on NSAIDs
  - Monitor kidneys during shock, heat stroke, pancreatitis, envenomation…
- CKD
  - Predict progression of Stage 1 CKD in dogs
  - Identify early CKD (?)
- Others…??

All cats with CKD should be fed a renal diet.
True or false?

FALSE!

Phosphorous is enemy number one.

Decreased phosphorous excretion happens early in kidney disease.

Speeds disease progression and ↑ morbidity and mortality.

Controlling phosphorous is the whole point of kidney diets.

FGF23 is the earliest marker of phosphate retention.
Increases *before* serum phosphate.

FGF-23 guide to starting early renal diet in cats

Earliest indicator of phosphate retention.

- Phosphaturic hormone produced by osteoblasts and osteoclasts
- Secreted in response to increased phosphate and calcitriol
- Acts on kidneys and parathyroid glands to decrease phosphate, calcitriol, PTH
- Early marker of altered phosphate homeostasis / CKD-MBD
- Increases *before* plasma phosphate increased

Renal diet is **Medicine** (only with CKD)

(**Double life expectancy**, decrease uremic episodes)

↓ **phosphorus**

↓ **protein**

↓ **sodium**

↑ **omega-3 fatty acids**

↑ potassium (cat)

Alkalinizing

↑ caloric density

↑ B vitamins

↑ antioxidants

Quality of evidence as an intervention	
Increased longevity:	GOOD
Improved QoL:	GOOD

Two types of diets for CKD:

- Renal diet
  - IRIS CKD Stages 2, 3, and 4
  - IRIS proteinuric CKD Stage 1, 2, 3, and 4
  - Phosphate- and protein-restricted

- Early renal diet
  - IRIS CKD Stage 1
  - *When appropriate*
  - Phosphate-restricted

When to run FGF-23:

CKD diagnosed

Phosphate <1.5 mmol/L (<4.6 mg/dL)

No hypercalcemia, anemia, marked inflammation

Guide to instituting and monitoring dietary therapy

Why not feed an early renal diet to all cats with CKD and normal phosphate.

- Not safe
- Some may develop hypercalcemia
- Some may develop hypophosphatemia
- Best not to change a cat’s diet if you don’t have to
- Cost…

Standard proteinuria treatment – new IRIS recommendations

Renal diet

Telmisartan 1.0 mg/kg/day

Clopidogrel 1-4 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
- q4-6 mo, CBC, panel, UA, UP/C (pooled), blood pressure

Hypertension: secondary ≥80%, idiopathic 13-20%.

- Cat
  CKD, hyperthyroidism, primary hyperaldosteronism, glomerulopathy, pheochromocytoma

- Dog
  CKD, AKI, Cushing's, diabetes mellitus, glomerulopathy, pheochromocytoma, hypothyroidism (rare)

Cats:
Amlodipine:
<200 mm Hg 0.625 mg SID
≥200 mm Hg 1.25 mg SID

Telmisartan:
2 mg/kg once daily

Dogs:
Benazepril:
0.25-0.5 mg/kg SID
Amlodipine:
0.125-0.25 mg/kg SID
Telmisartan:
1-2 mg/kg SID

Varenzin™-CA1 (molidustat oral suspension)

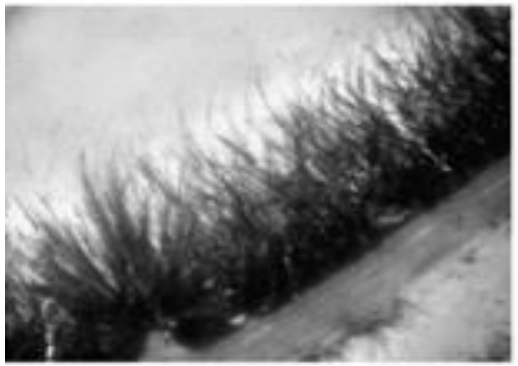
- Exogenous EPO in cats - 30% develop anti-EPO antibodies
- Darbepoetin – less antigenic but still risk so not until PCV <20 (IRIS guidelines)
- Varenzin increases EPO production by:
  - Inhibits prolyl hydroxylase → prevents degradation of HIF-α
  - HIF-α can dimerize with HIF-β and turn on EPO genes
- Varenzin use:
  - PCV ≤27
  - Stage 2+ CKD
  - 5 mg/kg PO SID (round to nearest 0.1 mL) x 28 d, off 7 d, repeat
  - Target PCV 30-40%
  - Stagger with phosphate binder
  - Iron dextran, monitor blood pressure (as with darbepoetin)
  - GI side effects

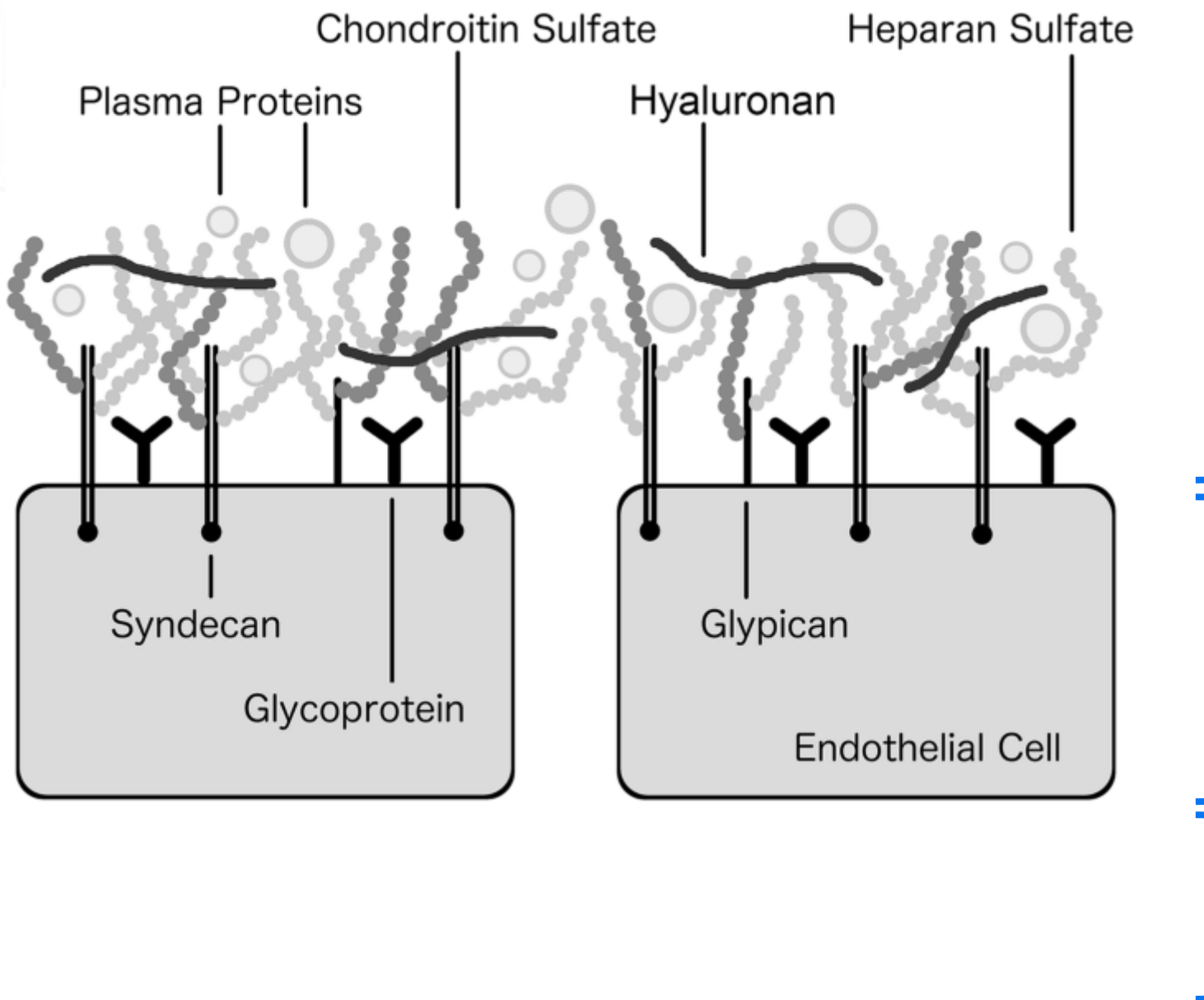
All cats with CKD benefit from fluid therapy.
True or false?

FALSE!

Fluids are a drug.

Overdosing fluids is as harmful as underdosing.




Chondroitin Sulfate
Heparan Sulfate
Plasma Proteins
Hyaluronan
Syndecan
Glycoprotein
Glypican
Endothelial Cell
Lumen
Endothelium
Interstitium

Fluid therapy for kidney disease

- Does not improve kidney function
  - May increase urine *volume*
  - Forced diuresis is *over*
- Excess can *cause or exacerbate* kidney damage
  - Endothelial glycocalyx degradation
  - Interstitial edema

- Apply basic principles
  - Correct dehydration
  - Restore volume
  - Replace losses from V/D
  - Provide maintenance if inappetence

Assume all inappetent cats are 5% dehydrated…and correct

Estimated dehydration	Physical examination reveals:
<5%	Not detectable
5-6%	Dry, ‘tacky’ mucous membranes
6-8%	Mild decrease skin turgor
8-10%	Obvious decrease skin turgor, retracted globes
10-12%	Persistent skin tenting, dull corneas, hypovolemia
>12%	Death due to hypovolemic shock

Formula: % dehydration as decimal x BW (kg) x 1000 = ml to administer over 4-24 hr

e.g., 5% dehydrated, 5 kg cat

0.05 x 5 = 0.25 L x 1000 = 250 ml.

If azotemia worsens on IV fluids consider *decreasing* fluid rate.

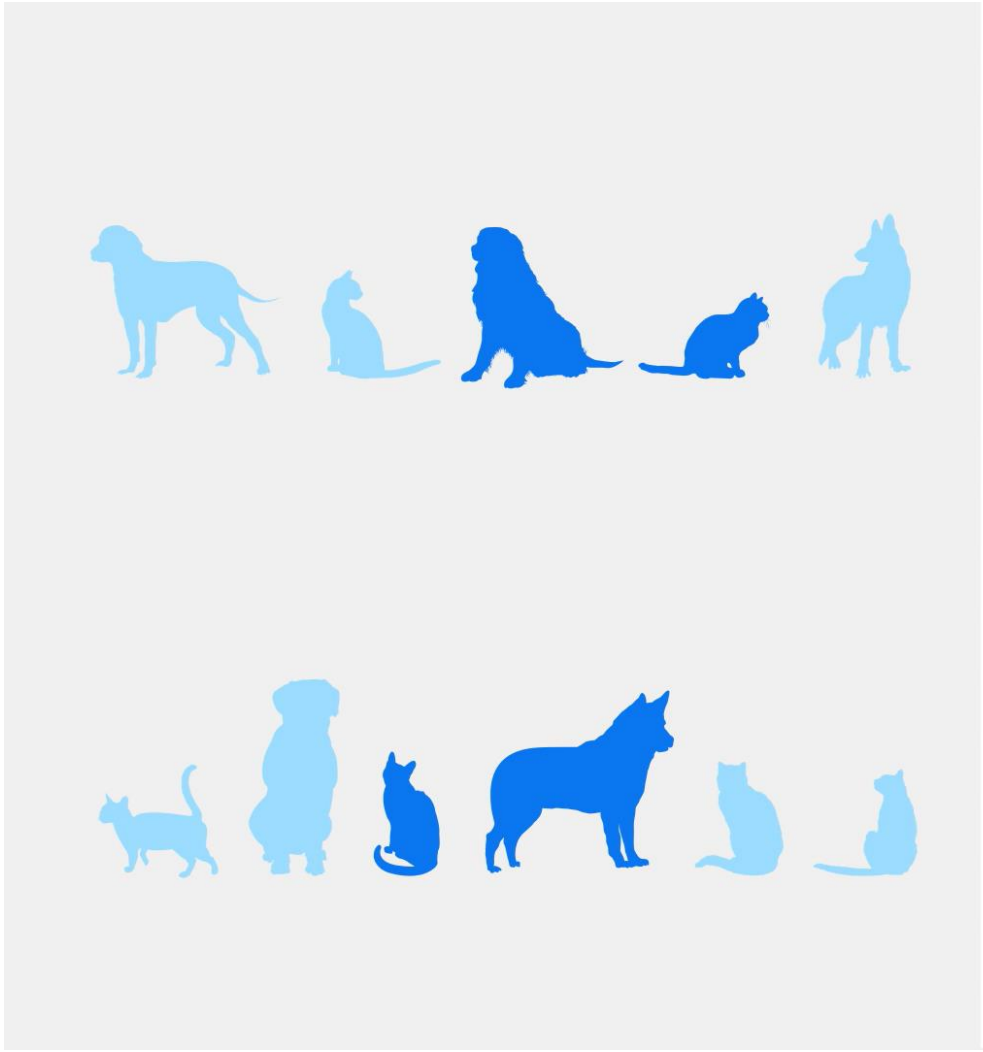
Especially if total daily volume exceeds maintenance or if weight gain.

STOP fluids, +/- Lasix 1-4 mg/kg IV

Thank you!

GFR biomarkers fall short at detecting early kidney damage/disease…

By up to 2 days



Current functional markers

SDMA 25%–40% decline in GFR[1–3]

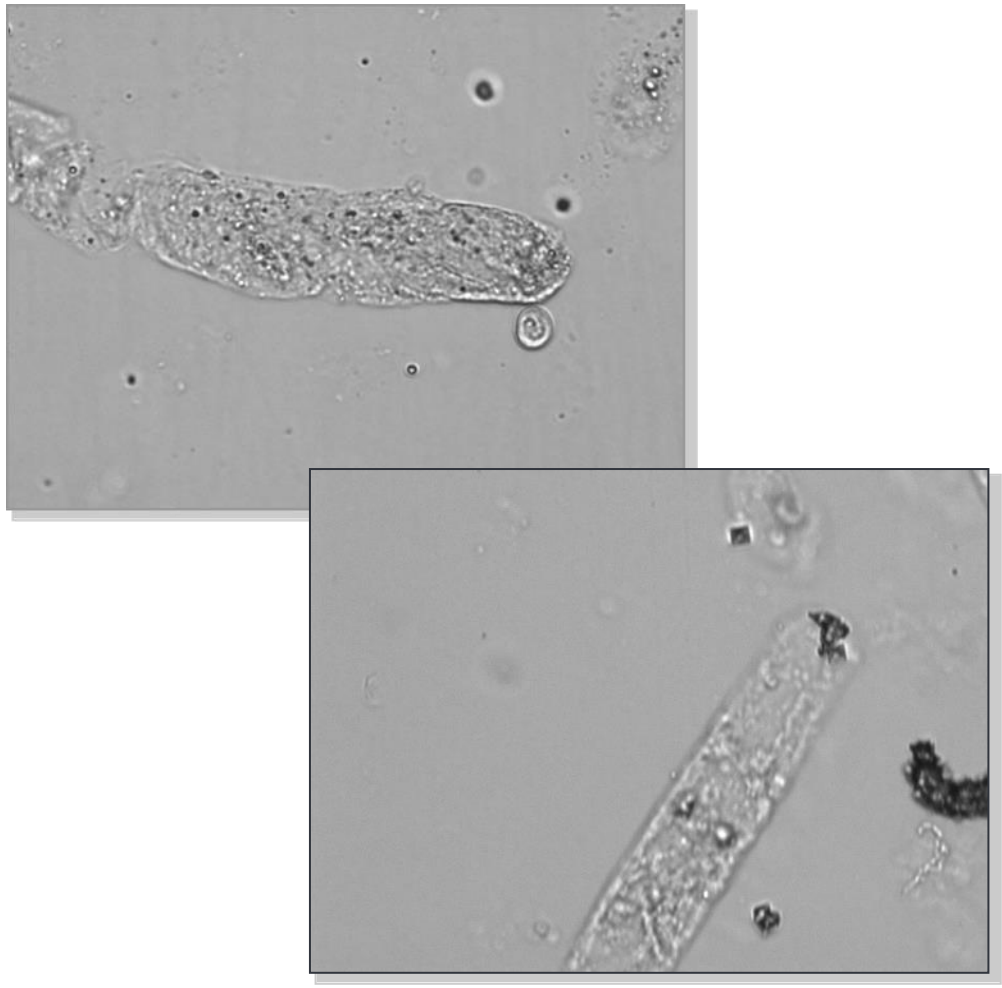
Creatinine 75% decline in GFR[1,3,4]

Tubular injury markers detect kidney damage earlier.

Traditional injury markers good but…

Lack sensitivity e/o specificity.

- **Granular casts ≈16%**
- **Euglycemic glucosuria**
- Proteinuria
- Hematuria
- Pyuria
- Bacteriuria
- Renal epithelial cells
- + Urine culture
- Decreased urine production
- Decreased USG

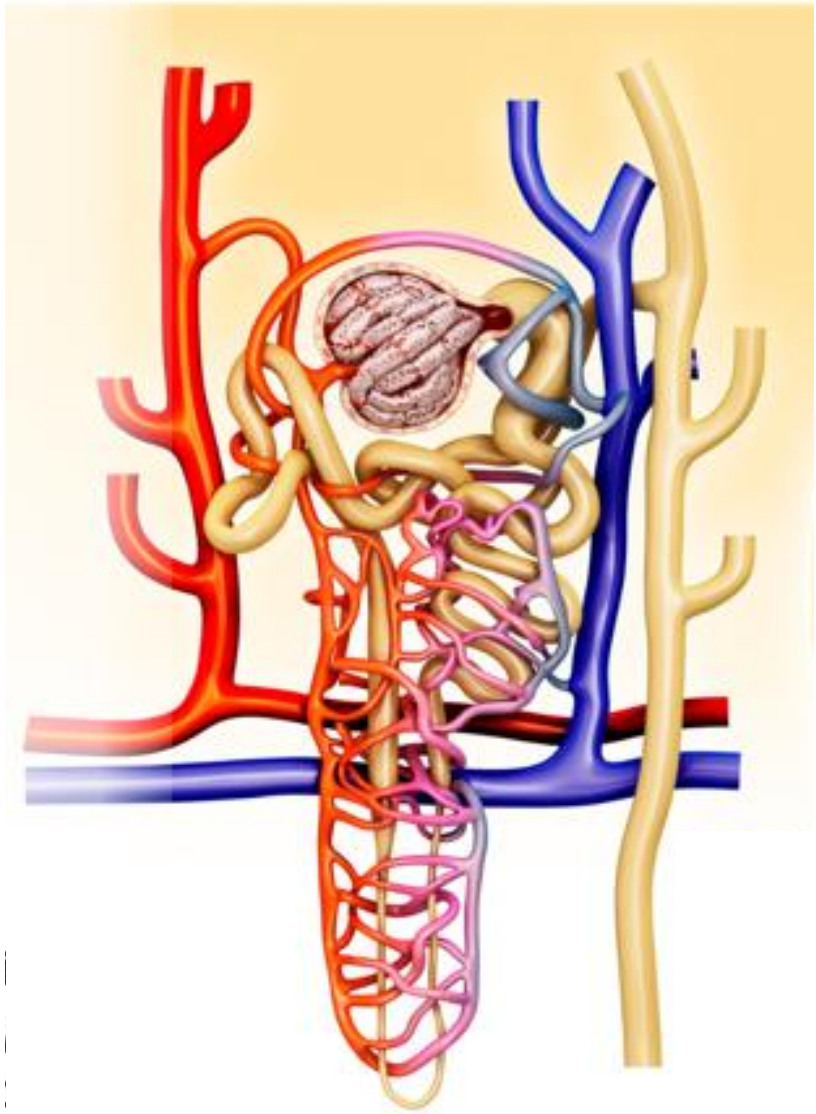


Cystatin B is a urine test of acute and active tubular injury.

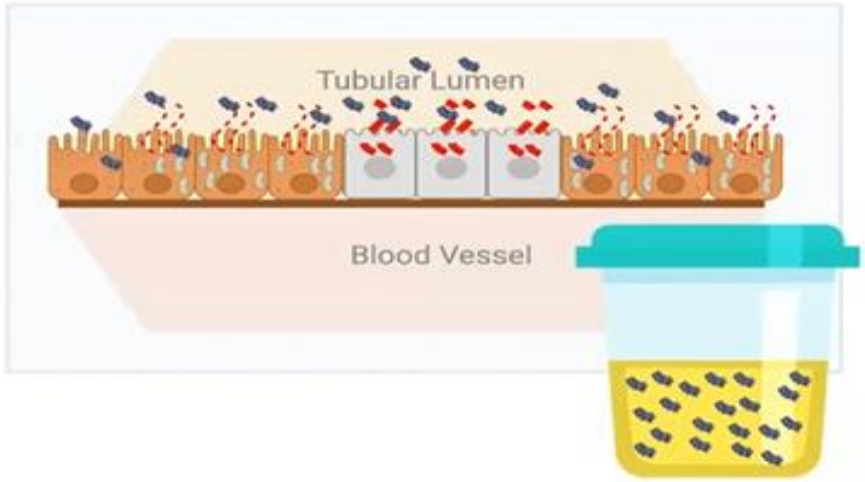
Importance of Cystatin B

- 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



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)

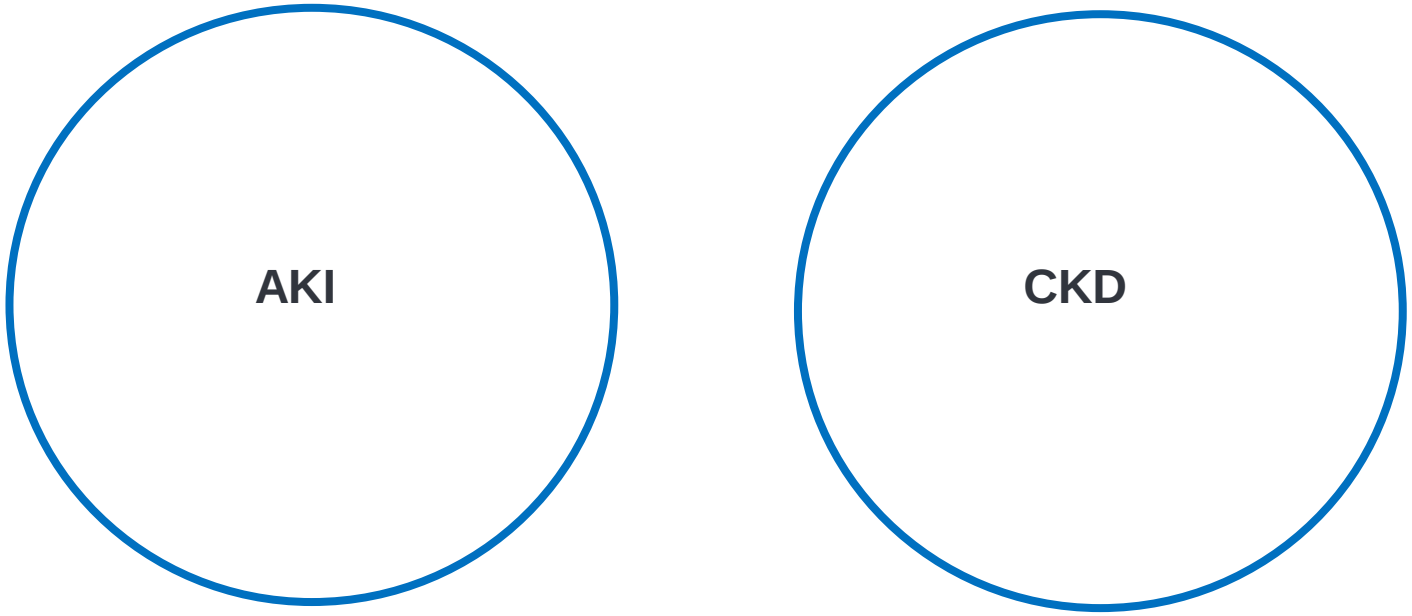
2

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

But wait. There’s more…

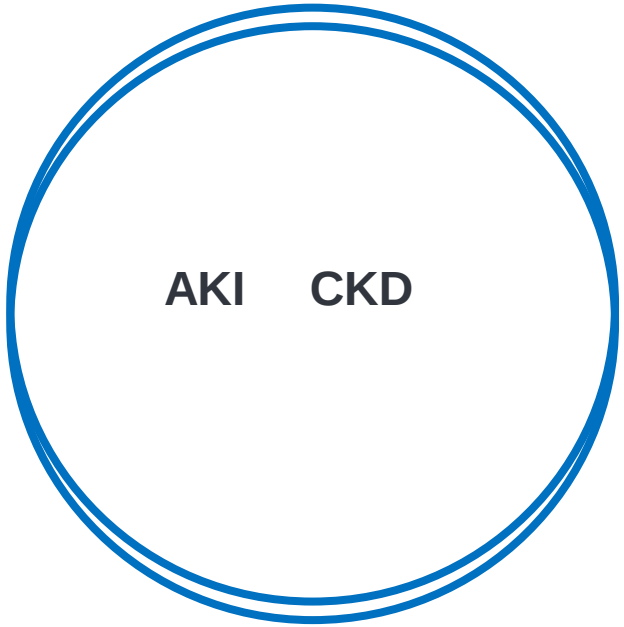
.

Back in the day…



Today…

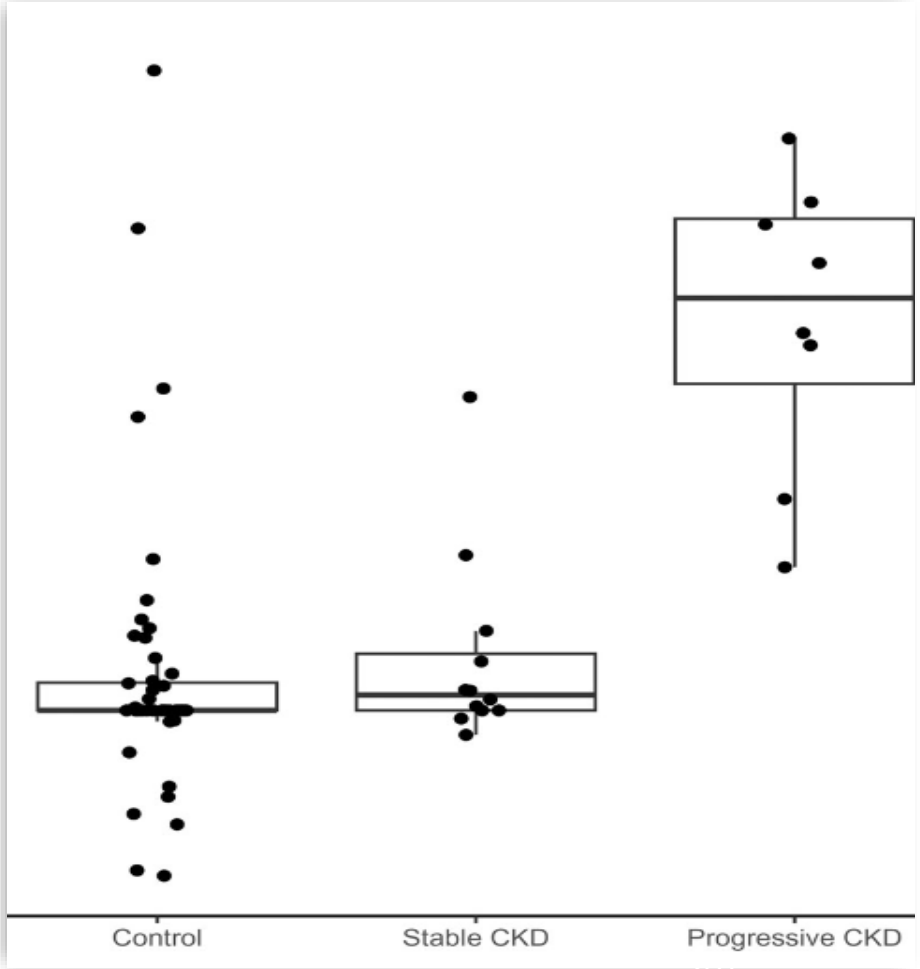
An AKI patient may have or develop CKD.



A CKD patient may have concurrent active kidney injury.

Cystatin B detects active ongoing injury with CKD

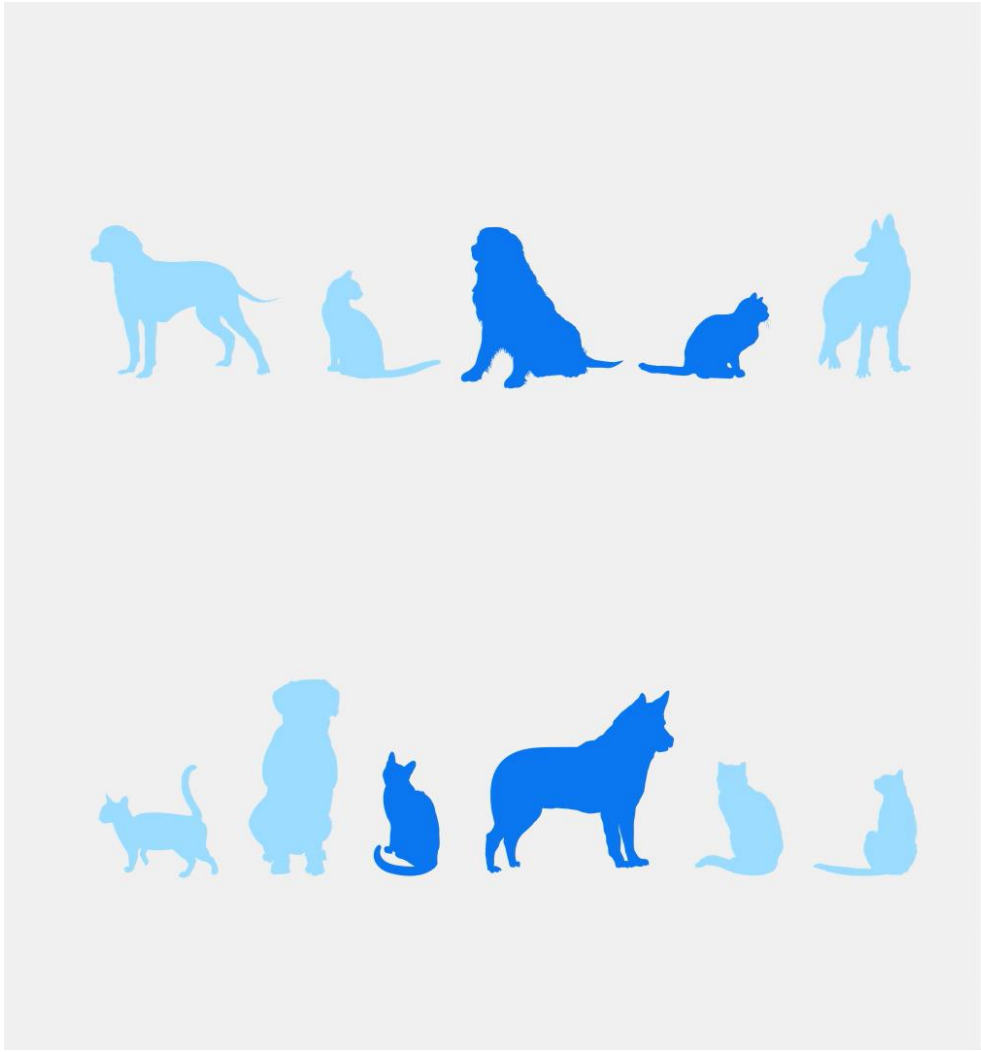
- CKD progressive and irreversible
- ***Rate*** of progression unpredictable
- Cys B identifies active ongoing injury in dogs (likely cats) with CKD
- Increased Cys B in dogs with IRIS Stage 1 CKD predictive of rapid progression
- Helps vets identify which dogs need more frequent monitoring



Segev, et al. J Vet Intern Med. 2023

When to run Cystatin B

- AKI
  - Confirm active injury following toxin exposure
  - Monitor treatment and recovery from acute injury event
  - Monitor high risk patient on NSAIDs
  - Monitor kidneys during shock, heat stroke, pancreatitis, envenomation…
- CKD
  - Predict progression of Stage 1 CKD in dogs
  - Identify early CKD (?)
- Others…??



Current functional markers

SDMA 25%–40% decline in GFR[1–3]

Creatinine 75% decline in GFR[1,3,4]

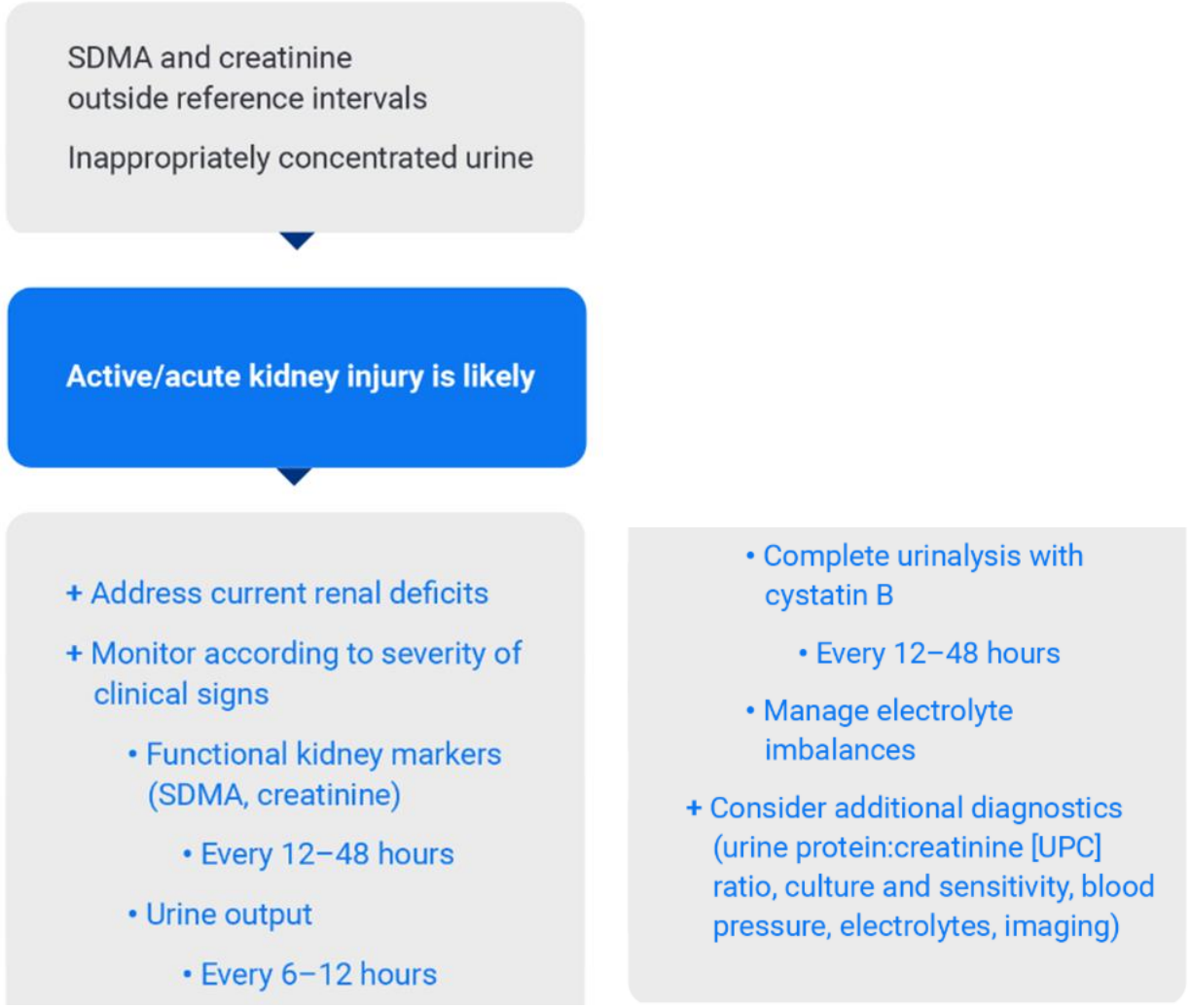
Cystatin B (active and/or acute injury)

recommended for use in dogs and cats presenting for non-wellness or emergency visits.

Cystatin B is a sick animal test.

.

Next steps when cystatin B is increased



Notes for cyst b

- cystatin B is not recommended for use in healthy animals where no concern for kidney injury exists.
- Increased cystatin B concentration absent changes in kidney function or indication of potential kidney injury should be interpreted in the context of the clinical presentation
- Increased cystatin B concentration in appropriately concentrated urine with serum SDMA and creatinine within reference intervals suggests possible active (ongoing) kidney injury. Similarly, patients with early IRIS* AKI Grade I or II may not exhibit clinical signs or changes in functional markers while still experiencing subclinical kidney injury. Patients with increased cystatin B concentrations (≥ 100 ng/mL) should have a complete urinalysis and cystatin B along with functional kidney markers rechecked within 24–48 hours.

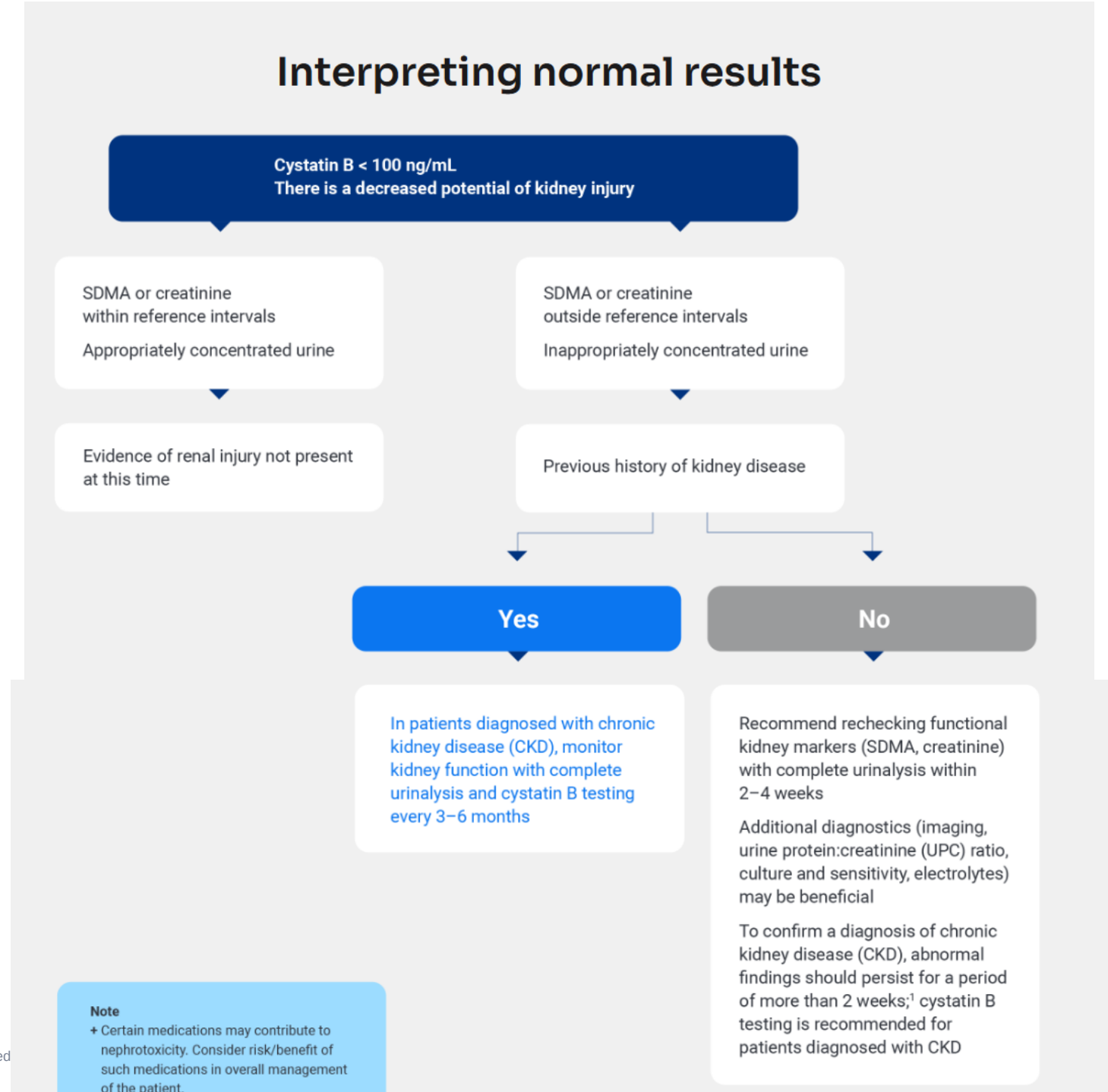
Cys B notes

- Increased cystatin B concentration in urine that is inappropriately concentrated with serum SDMA and creatinine outside of reference intervals suggests that active/acute kidney injury is likely. Address current renal deficits and monitor patients closely for biochemical disturbances and urine output, and consider additional diagnostics, such as imaging, urine protein:creatinine ratio, and urine culture and MIC susceptibility. Cystatin B concentration < 100 ng/mL indicates that kidney injury is not present at the time of testing. If you suspect kidney injury despite results within the expected range, you may wish to recheck urinalysis with cystatin B within 5–7 days.

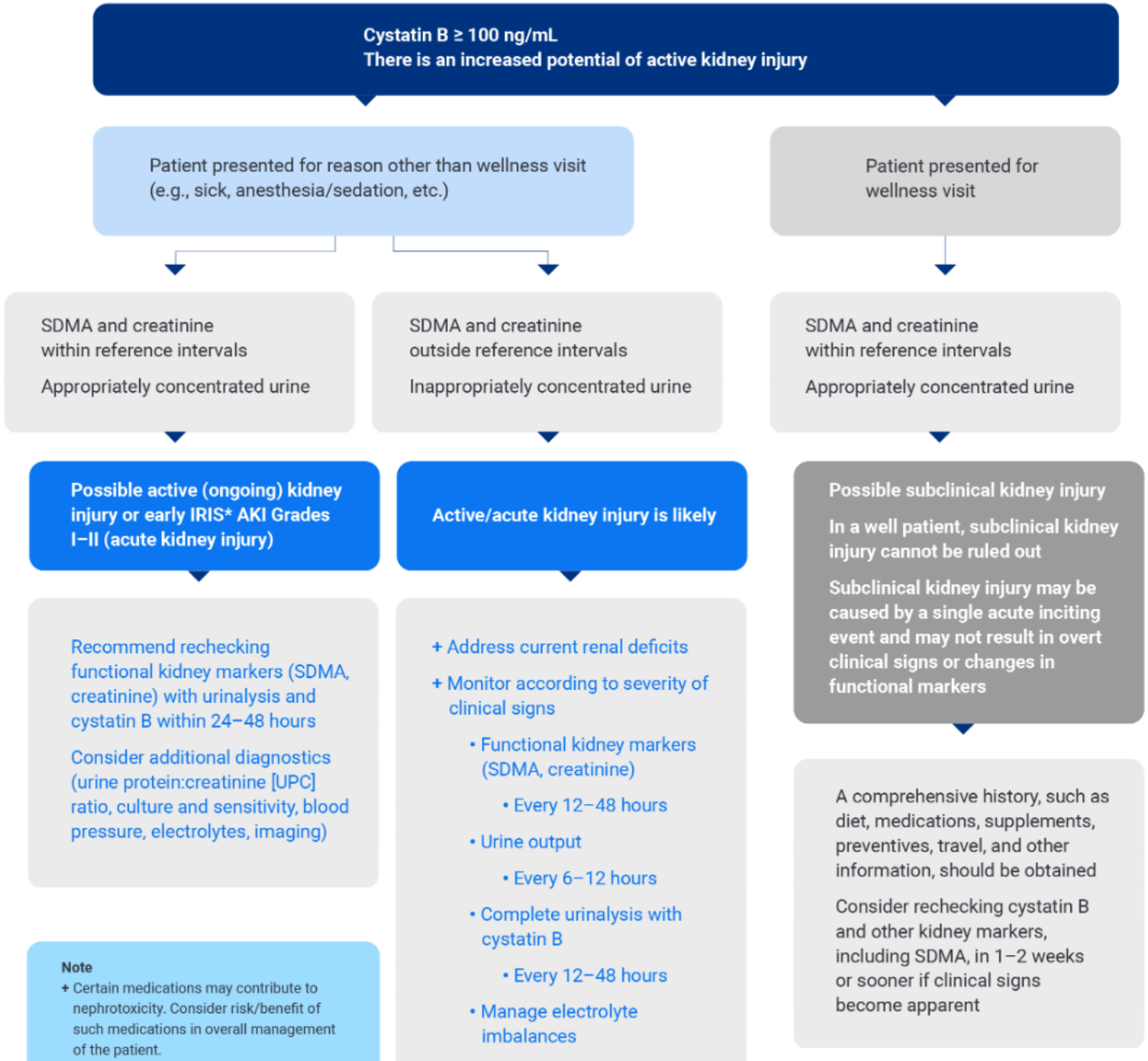
How should I interpret Cys B

- For a patient that is presenting unwell, a cystatin B result < 100 ng/mL suggests kidney injury is unlikely. In an unwell patient with a cystatin B result ≥ 100 ng/mL, active/acute kidney injury is suspected and should be considered along with a complete history and full chemistry profile that includes SDMA. Additional diagnostics may be warranted.

Interpreting normal results



Interpreting increased results



Some cystatin B thoughts

- Normal animals should have none/very low levels in urine
- Presence in urine = *active* tubular epithelial cell damage (leakage)
- How high is it?
- Patient clinical or not?
- At least recheck it in 1-4 wk (base on how concerned you are)
- Run it in IRIS Stage I CKD
- Use it to monitor NSAID use?
- Predictive of azotemia in 48 hr (say after acute toxicity?)
- Return to normal correlated with resolution of azotemia?
- If SIRS, sepsis? Still useful monitoring tool…

Magnitude of anti-C6 antibody

- Correlated with antigen (organism) load
- Correlated with circulating immune-complex concentration
- Not correlated with/predictive of clinical disease (most not clinical)
- Not correlated with disease severity
- Pre- and post-treatment titer (4/6 Consensus Statement panelists)
  - Monitor tx
    - >50% decrease 3-6 months post tx = effective therapy
    - ≥4-fold decrease in titer = effective therapy (humans)
  - Use post-tx as baseline for future comparison
    - Subsequent increase = re-exposure

Duration of anti-C6 antibody?

- VlsE constantly turning over → antigen doesn't accumulate
- Lower concentration of ag-ab complexes in follicular dendritic cells
- Decreased stimulation of memory B-cells
- Limited B-cell memory leads to quick decline in anti-C6 antibody titer
- Human: ≥4-fold decrease 6 months post treatment = effective tx
- Dogs: >50% decrease 3-6 months post treatment = effective tx

Features of C6 antibody

- Correlates with antigen load (quantitative)
- Correlates with circulating immune-complex concentration
- Not correlated with clinical disease (most are not clinical)
- Magnitude is not correlated with disease severity
- Serial titers can be used to monitor treatment efficacy

Will a high anti-C6 titer ever become negative?

- Depends on how high
- SNAP positive at >10 U/mL
- Quant C6 >30 U/mL considered significant
- Qualitative SNAP may remain positive for ‘a long time’ after treatment (Consensus Statement)

Rational use of SNAP: clinically normal dogs

- Annual wellness/preventive care in healthy dogs in endemic areas
- All positives followed by CBC, chem, UA
- Labs normal → no treatment
  - Monitor for proteinuria min 2-3 x/yr (5/5 N American panelists)
- Proteinuria, thrombocytopenia, azotemia →
  - Treat
  - Quant C6 (baseline to monitor treatment response, future comparison)
  - VBD PCR panel (co-infection)

Where is there consensus?

SNAP

Rational use of Quant C6

- Healthy dog with positive SNAP →
  - First time positive SNAP → to establish pre-treatment baseline (4/6 panelists)
  - Prior positive SNAP → determine residual vs re-exposure

- Sick dog →
  - Establish baseline for monitoring response to treatment and re-exposure (4/6 panelists)

Quant C6 for monitoring treatment

Seropositive nonclinical, nonproteinuric dogs

- Consensus Panel:
  - No treatment (4/6 panelists)
  - Reevaluate for proteinuria at least 2-3 x/yr (5/5 N American panelists)

- Sykes: No evidence that treating ‘healthy’ seropositive dogs beneficial

Interpreting persistent titers

- 4/6 panelists recommend pre- and 6 mo post-tx Quant C6
- Check for decrease as indicator of decreased antigenic load
- Establish new baseline for future comparison (SNAP may be positive for ‘long time’)

Positive C6 antibody:

- *Borrelia burgdorferi* is or was living in the dog
- With clinical signs → current infection
- With no clinical signs → current subclinical infection or prior exposure

Serop

“Why is the Lyme C6 considered a marker of acute infection when these titers can stay elevated for months to years?”

Any clearer now?

Some C6 antibody thoughts

- Outer surface C6 antigen only expressed when bug in dog and dividing
- C6 antibody therefore = bug in dog and dividing (most aren't clinical, but may be proteinuric)
- More bug, higher the C6 titer
- With successful tx titer should decrease by half or to normal w/in 3-6 mo
- Persistent high titer post treatment maybe re-exposure in highly endemic area
- As long as the dog is not clinical, not proteinuric, (and has normal CRP?) just monitor yearly and focus on tick prevention
- No consensus on using magnitude of Quant C6 to determine tx or no
- I personally wouldn't tx if clinically normal, not proteinuric, normal CRP, and client not flight risk

C6 people

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C_6 Test as an Indicator of Therapy Outcome for Patients with Localized or Disseminated Lyme Borreliosis

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Management of Lyme disease would benefit from a test to assess therapy outcome. Such a test could be employed to ascertain if treatment of early Lyme disease was successful and would be helpful to clinicians assessing patients with lingering posttreatment symptoms. We reported recently that levels of the antibody to C_6, a *Borrelia burgdorferi*-derived peptide that is used as an antigen in the C_6-Lyme diagnostic test, declined after successful antibiotic treatment of Lyme borreliosis patients. We assessed retrospectively the change in anti-C_6 antibody titers in 131 patients with either early localized disease (erythema migrans) or disseminated disease. All of these patients were treated with antibiotics and were free of the clinical signs shown at presentation within 12 weeks after the initiation of treatment. Decreases in reciprocal geometric mean titers (rGMT) of the anti-C_6 antibody were quantified for the subpopulation of 45 patients whose baseline rGMT were ≥80 and whose second serum specimens were obtained at least 6 months after the baseline specimen. Eighty percent of this patient group (36 of 45) experienced a ≥4-fold decrease in their rGMT ($P < 0.0003$). These results suggest that a change in the anti-C_6 antibody titer may serve as an indicator of therapy outcome for patients with localized or disseminated Lyme borreliosis.

C6 people

- Detection of the antibody to the C6 peptide, which reproduces the IR6 sequence (an immunodominant, conserved region of VlsE, the antigenic variation protein of *B. burgdorferi*), is currently used for serologic diagnosis of Lyme disease in humans (2, 12, 14; http://www.immunetics.com/c6/) and in canines (13).
- It has been reported recently that levels of the antibody to C6 declined after successful antibiotic treatment of either Lyme borreliosis patients or animals that had been experimentally infected with *B. burgdorferi* (19). In humans, the anti-C6 antibody titer diminished by a factor of 4 for successfully treated patients (*n* 30) and by a factor of 4 for treatment-resistant patients (*n* 4) (19).
- These preliminary results indicated that quantification of the anti-C6 antibody titer as a function of time should be investigated as a test to assess the response to Lyme disease treatment (19).
- 6 month post treatment titer
- On another issue, the authors point out that the “persistence of the anti-VlsE antibody response for months or years after antibiotic treatment cannot be equated with spirochetal persistence in Lyme disease” (18).
- We never equated the persistence of the anti-C6 antibody with the persistence of infection.
- In our initial study (19), as well as in the study we report on here, we refer only to the magnitude of the anti-C6 antibody titer change as having potential diagnostic value as a predictor of treatment outcome.

C6 people

- VIsE constantly turned over – doesn't accumulate – antigen thus not avail in lg amounts at any time v other outer surface components.
- Thus B-cell memory short-lived – b-cell pool maintained by stim w ag's stored as immune complexes on follicular dendritic cells
- After ab's scant reserve of VIsE ag to complex and be stored in FDC thus limiting B-cell memory – leading to quick decline in anti-C6 ab level
- for patients with localized and perhaps also disseminated Lyme borreliosis, anti-C6 antibody titers decrease fourfold within 6 months posttreatment in a significant majority, but not all, of the patients for whom antibiotic treatment for Lyme disease is efficacious.
- Conversely, a fourfold decrease in the anti-C6 antibody titer within 6 months posttreatment may be interpreted as an indication of successful treatment, but a lesser decline is uninterpretable and may be due either to treatment failure or to persistence of the antibody for reasons other than persistence of infection.
- In conclusion, as shown by our results thus far, the C6 test may serve as an indicator of therapy outcome in patients with localized or disseminated Lyme borreliosis, but further studies with larger patient populations are needed to clarify whether it is best suited for patients with early disease or whether it may also be used to predict the outcome of therapy of late Lyme borreliosis.

Lyme dogs Sykes Ch 51

- Lyme nephritis – membranoproliferative glomerulonephritis
- Goldens, labs, Shetland sheepdogs, Berners
- The advantages of the C6 ELISA assay are that (1) it detects IgG antibodies 3 to 5 weeks after the time of infection, so by the time dogs develop clinical signs they are virtually always seropositive,41 and (2) it is negative in dogs that have been vaccinated for Lyme disease, because the antigen is not expressed by organisms used in Lyme vaccines.
- No correlation of C6 and disease severity
- Positive results do not correlate w disease (Europe)

Lyme dog Sykes Ch 51

- A multiplex fluorescent bead assay has been marketed in North America for detection of antibodies to three antigens of B. burgdorferi: OspA, OspC, and OspF.43 The assay uses tiny beads to which OspA, OspC, and OspF are coupled. Dog serum is added to the beads, and if present, antibodies in the serum bind to the antigens and can be detected using a fluorescent conjugate. The pattern of reactivity to each antigen can be used to differentiate among the response to vaccination, early infection, and chronic infection. The presence of anti-OspA antibodies suggests previous vaccination, because vaccines contain OspA, and the spirochete rarely expresses OspA within the host. OspC is expressed as the spirochete moves to the tick salivary glands and shortly after it enters the host. Thus an antibody response to OspC may suggest recent infection; titers decline and become undetectable beyond 3 months after infection.44 Antibodies to OspC appear as early as 3 weeks after experimental infection of dogs, and OspF as early as 5 weeks.44 OspF is expressed in more chronic infections, and can be detected together with the C6 antibody response in naturally exposed dogs

Lyme dog Sykes Ch 51

- There is no evidence that treatment of healthy seropositive dogs is beneficial and it may lead to drug adverse effects and contribute to antimicrobial resistance in other bacteria and antimicrobial shortages.
- Recommended doses have included 5 mg/kg PO q12h and 10 mg/kg PO q12h or 10 mg/kg PO q24h, 4 wk (30 d)

2018 Lyme consensus statement

- Antibodies against C_6, VlsE (variable major protein-like sequence, expressed), and OspF indicate natural exposure because these antigens are not present in any Bb vaccines.
- After experimental natural exposure, OspC antibodies increase by 2–3 weeks, and wane in 3–5 months (without re-exposure), whereas OspF antibodies increase by 6–8 weeks and remain increased in untreated carriers
- Determination of quantitative titers to C_6 (or potentially OspF), pre- and 3[94] to 6 months post-treatment, were recommended by 4/6 panelists to check for a decrease after treatment as an indicator of decreased antigenic load, and to establish a new baseline for future comparison, because qualitative tests may stay positive a long time after treatment.[96]
- An increased result over baseline may indicate re-exposure or relapse.

2018 Lyme consensus statement

- The dissenting panelists state there is no published evidence that quantitative test results predict current illness, the potential for development of chronic disease, or differentiate reinfection from reactivation of a chronic infection.
- Panelists (5/5) recommended that a qualitative Bb antibody assay be included with annual wellness and preventive care for healthy dogs living in or near endemic areas in North America (there is no evidence to support screening healthy cats for Bb antibodies). Screening for Bb antibodies allows: (1) follow-up proteinuria screening for all seropositive dogs and early intervention for possible Lyme nephritis (see treatment), (2) follow-up minimal data base including CBC and serum biochemistry to identify cytopenias and kidney disease associated with tick and wildlife exposure, (3) identification of seropositive dogs (sentinels) that may indicate risk of exposure of humans, horses, cats or other dogs in the area and the need for modification of preventive protocols; and, (4) recognition of successful preventive strategies in high risk areas. Panelists identified potential pitfalls when screening healthy dogs, including the potential for overuse of antibiotics in rare dogs with false positive assay results, overuse of antibiotics in healthy dogs that would never develop LB, assay expense, induction of anxiety in the owner, and the additional time necessary for owner education

2018 Lyme consensus statement

- 4/6 panelists do not routinely recommend treatment for nonclinical, nonproteinuric, seropositive dogs. stating that: (1) this practice potentially promotes overuse of antibiotics; (2) no data exists proving treatment of healthy dogs is associated with decreased risk of illness; (3) Bb may not be cleared from all tissues with treatment; and, (4) reinfection may commonly occur in dogs in endemic areas. Seropositivity indicates tick and wildlife exposure and possible coinfection(s). Tick control and possible vaccination should be readdressed (see below). Panelists in North America (5/5) recommend reevaluation for proteinuria at least 2–3 times per year, even if the dog is treated with antibiotics, because clearance may not occur, and because the pathogenesis of Lyme nephritis is unknown.

2018 Lyme consensus statement

- If a seropositive dog is nonclinical and nonproteinuric, there is no current evidence-based data that a quantitative C_6 antibody test (Lyme Quant C6 [IDEXX Laboratories, Westbrook, Maine]) result helps decision-making regarding whether antimicrobial treatment is warranted.
- The magnitude of Quant C_6 is not predictive of illness.
- A majority of untreated nonclinical nonproteinuric seropositive dogs probably have high concentrations, as do experimentally infected dogs, which all remain nonclinical.
- In the absence of clinical signs increased Quant C_6 may indicate exposure and a robust immune response to the organism.[96], [124]
- Some dogs may eventually either clear the organism or remain nonclinical carriers, as did experimental dogs.

2018 Lyme consensus statement

- There is correlation between C6 and circulating immune-complex concentration
- Hence some rec tx pos clin normal nonproteinuric dogs to prevent GN
- 3-6 month repeat titer, want to see >50% drop – org may never be cleared, enters ‘protected’ collagen tissue or develop into a latent cyst or L-form (hence recrudescence).
- 3/6 panelists recommend vax, 3/6 didn’t – see notes
- Consensus was not reached on whether to treat all Bb-seropositive dogs and cats, whether to use quantitative C_6 antibody test results to guide treatment recommendations or to follow treatment responses, how long to use antibiotics for Lyme nephritis cases, and whether or not to use Bb vaccines, even in Bb-endemic areas.