CREATING CLARITY

AKI in dogs and cats:
Update on diagnosis and treatment.

Bill Saxon, DVM, DACVIM, DACVECC

IDEXX Medical Education Specialist

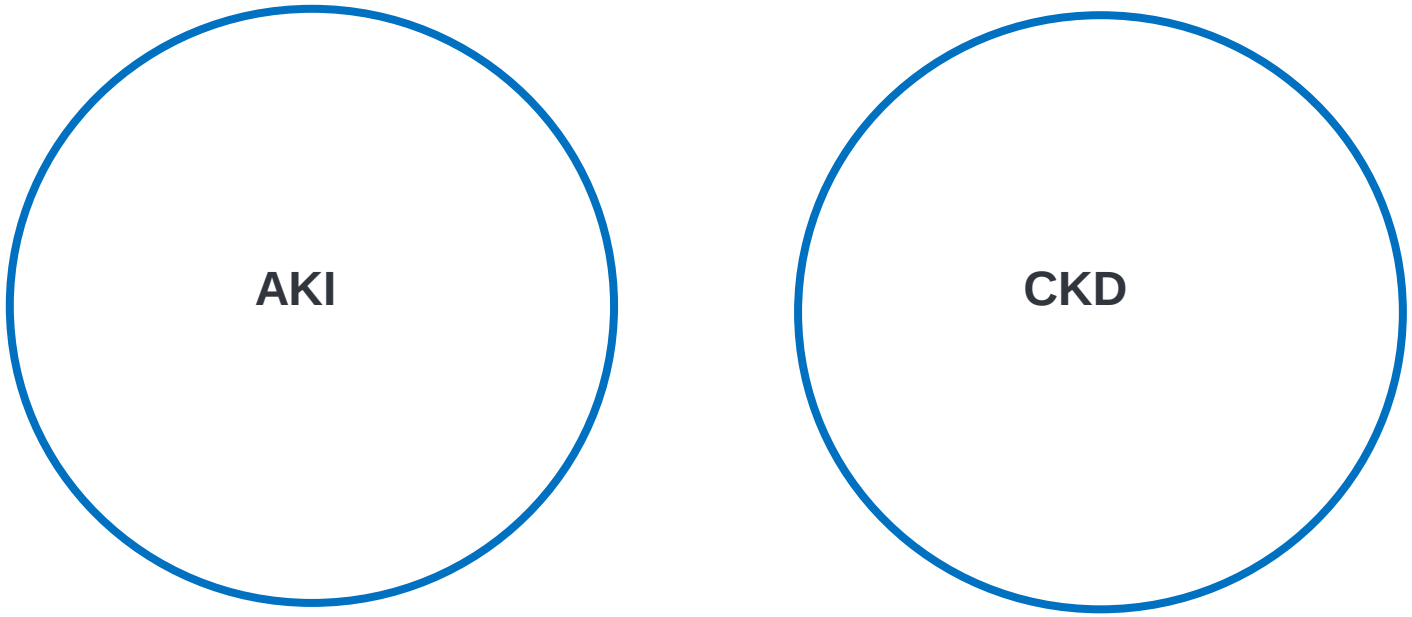
CKD: progressive, irreversible, no return to normal function

- Persistent (≈ >3 month) abnormality in 1 or more kidney function or structure
  - Azotemia (overt or progressive increase in creat or SDMA within ref interval)
  - Persistent 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**
- **Rate of progression variable and hard to predict**

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

- Abrupt decline in kidney function
- Prerenal, renal, postrenal causes
- Earliest evidence found in urine
- Azotemia not always present initially
- AKI may be present on presentation or develop in hospital (unstable patients)
- May lead to CKD

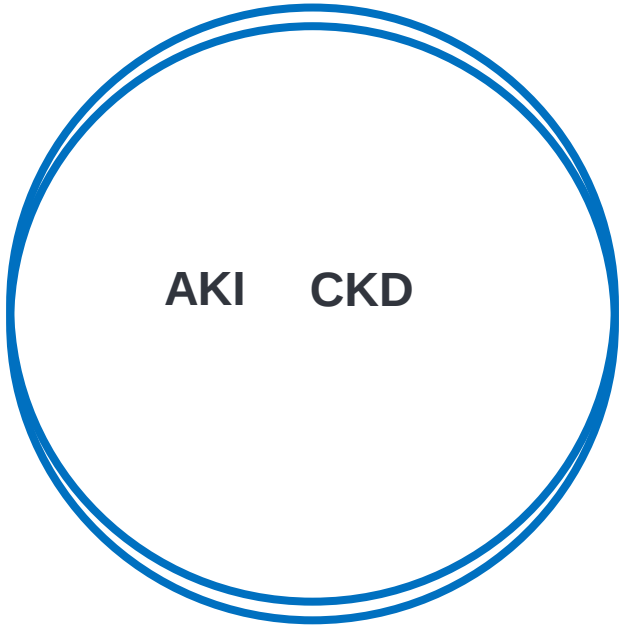
Back in the day…



Today…

Today…

Your AKI patient may have or develop CKD.



Your CKD patient may have concurrent active kidney injury.

Practically speaking:

- AKI and CKD might not be separate processes
- One may be predominant at presentation
  - Stable CKD patient on treatment in for monitoring visit…
  - Crashing emergency patient with marked azotemia…
- Important to remember
  - Both may be present on presentation
  - One may lead to the other
- Key to new understanding
  - CKD can have active injury component which may lead to faster progression
  - AKI – severe, sustained, intermittent – can lead to CKD
  - Inflammation is likely unifying abnormality…

Causes of AKI: may develop in hospital

Cat	Dog
▪ Obstruction (ureteral, urethral) ▪ *Lilium spp*. ingestion ▪ Diuretics (congestive heart failure) ▪ NSAIDs ▪ Chemotherapeutics ▪ Pyelonephritis ▪ Acute pancreatitis ▪ Etiology unknown 30%	▪ Leptospirosis ▪ NSAIDs ▪ Sepsis ▪ Lyme nephritis ▪ Grapes/raisin ingestion ▪ Chemotherapeutics/antifungals ▪ Aminoglycosides ▪ Acute pancreatitis ▪ Congestive heart failure

Rule out ureteral obstruction in cats with AKI

Renal pelvic dilation >13 mm rules in obstruction
No or minimal dilation does not rule out obstruction
<3.4 mm on IV fluids acceptable
Serial ultrasound

AKI risk factors: monitor these patients closely.

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

IRIS AKI grading system

Creatinine increase ≥ 0.3 mg/dl in 48h

(Or increase 1.5x baseline in 7d)

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

Laboratory evidence of *nonazotemic* AKI

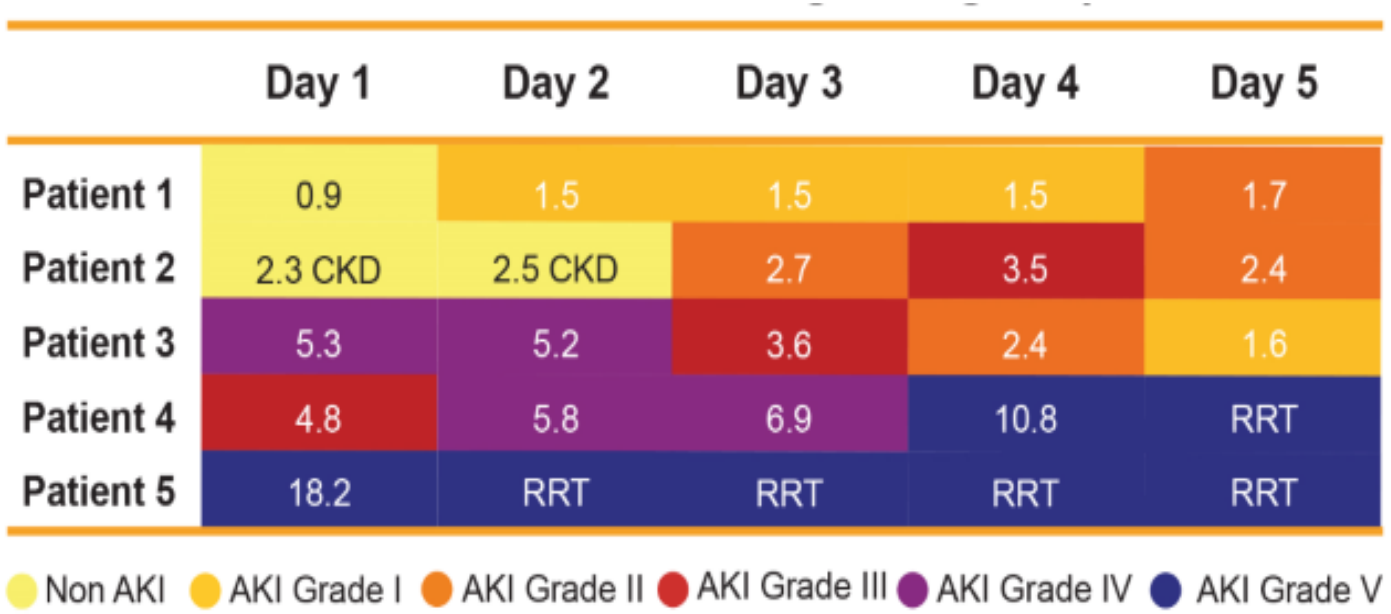
- SDMA increased
- Urinary casts, glucosuria with normoglycemia
- Urine cystatin B

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)	



IRIS
International
Renal Interest Society

Guidelines | Education | Emerging Themes | About IRIS | Related sites | Renal Week | Hemodialysis Academy

Education

- IRIS Staging System
- Risk Factors for CKD

Differentiation between Acute kidney injury and chronic kidney disease (updated 2022)

Gilad Segev, Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Israel

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Hallmarks of AKI (vs CKD)

- History and physical exam
  - Acute onset – hours to days
  - Toxin exposure (lily, NSAIDs, anesthetics…)
  - Renomegaly, renal pain
  - Bradycardia/hypothermia (hyperkalemia)
- Lab findings
  - Hyperkalemia
  - Urinalysis abnormalities differ
- Imaging
  - Renomegaly in 70%
  - Hydroureter, pyelectasia, hydronephrosis
  - Ureteral calculi
  - Normal parathyroid gland

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

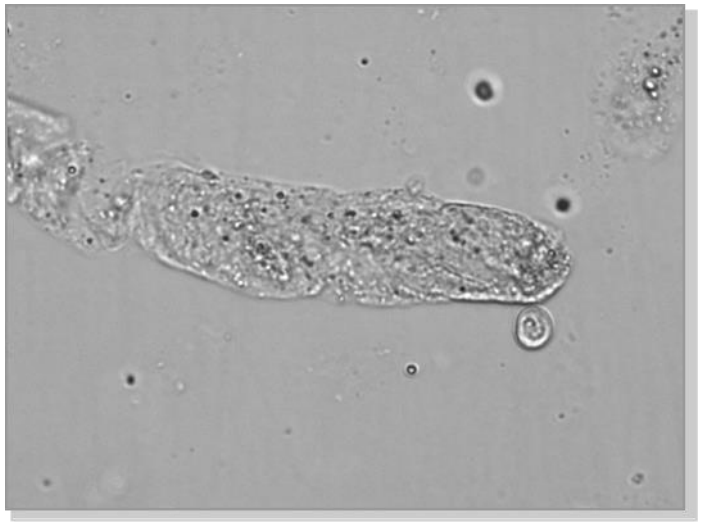
Hot Topic: active injury biomarkers.

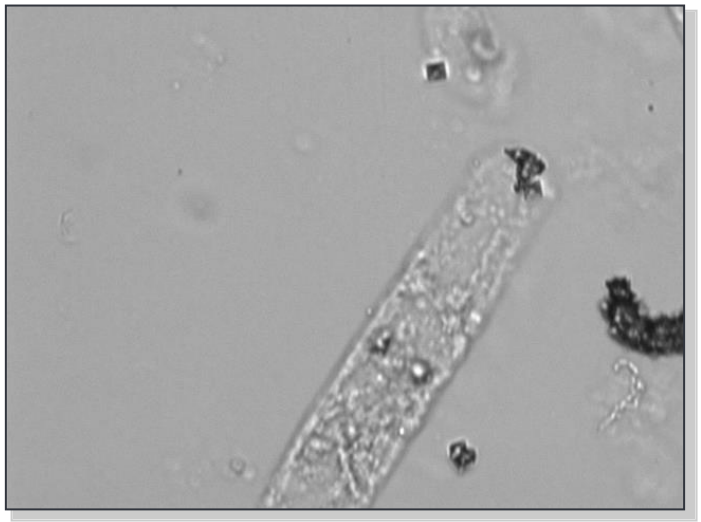
- Presence in URINE sensitive predictor of acute or sustained renal tubular cell injury
- Released from stressed, damaged, ruptured kidney cells
- Epithelial damage present in AKI precedes increase in functional markers
  - SDMA, creatinine often normal first 48 hr
- Degree of epithelial damage associated with disease progression and survival

"…IRIS encourages more studies to be initiated and ultimately published in peer-reviewed journals to provide the evidence for their use in clinical practice."

AKI: earliest evidence in URINE.

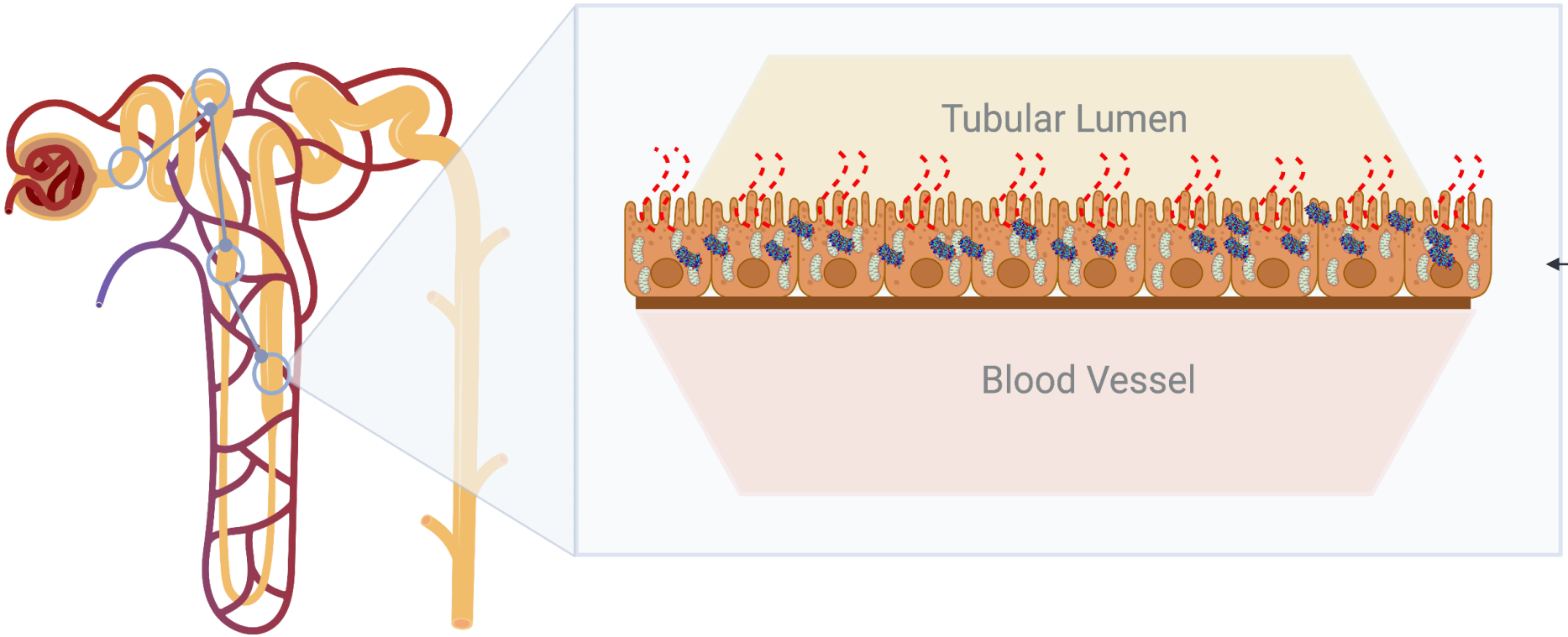
- Proteinuria
- Hematuria
- Pyuria
- Bacteriuria
- Renal epithelial cells
- Glucosuria (normoglycemia)
- + Urine culture
- Granular casts ≈16%
- Decreased urine production
- Decreased USG





Urine Cystatin B detects *active* kidney tubular damage

(ALT of the kidney)



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

Consider Cystatin 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…??

AKI treatment:

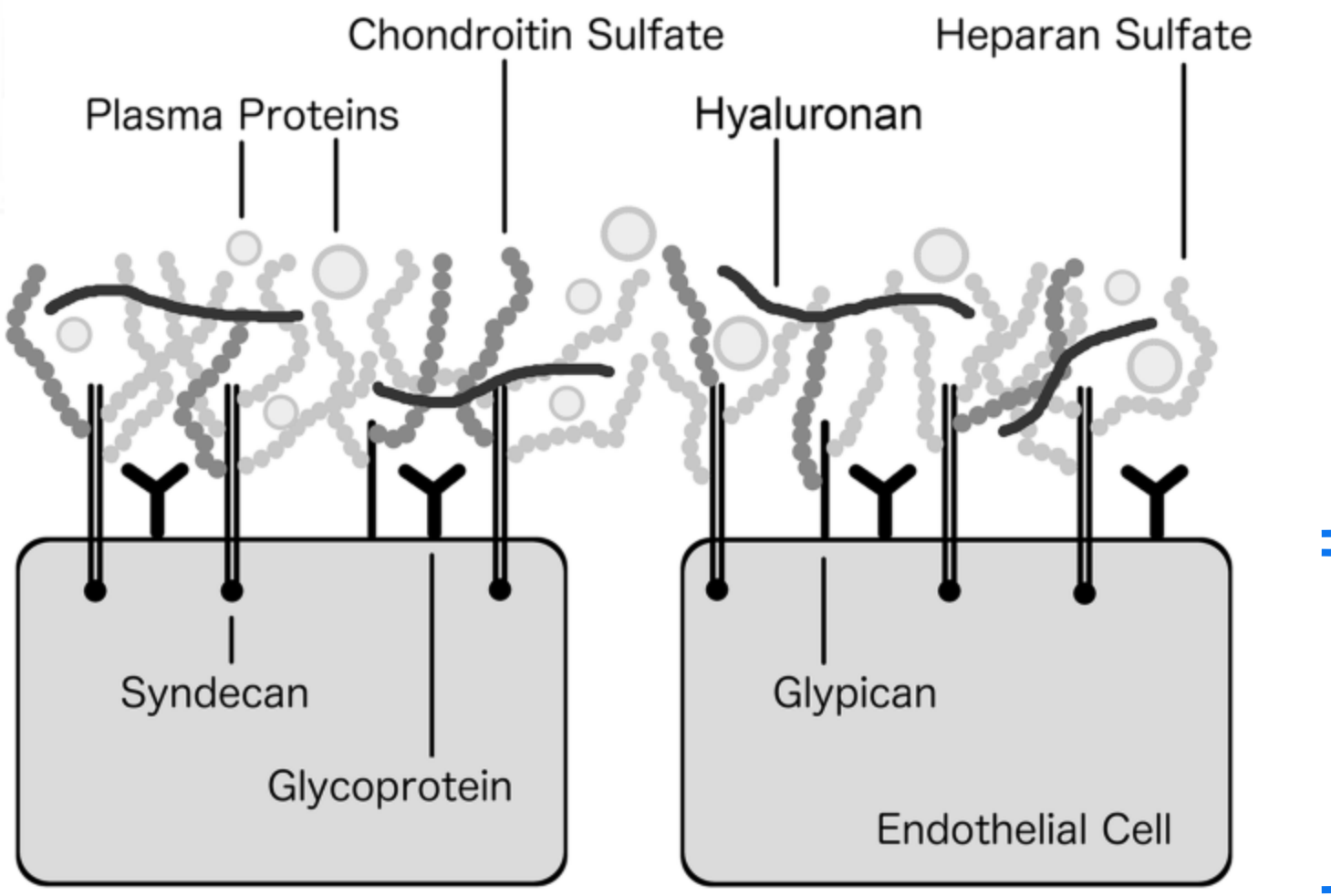
- Stabilize
- Correct life-threatening hyperkalemia
- Specific treatment if cause identified
- Manage oliguria/anuria
- Monitor for development of CKD

Fluids are a drug – avoid overdose.

Rethinking fluid therapy for kidney disease

- Fluids do not improve kidney function
  - May increase urine *volume*
- Excess more likely to cause harm than improve kidney function
  - Endothelial glycocalyx degradation
  - Interstitial edema
- Forced diuresis is over

- Apply basic principles
  - Correct dehydration
  - Restore volume
  - Replace ongoing losses, e.g., vomiting, diarrhea…
  - Provide maintenance until eating and drinking normally


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

IV fluids for AKI

- Avoid excess fluid
  - Decreased GFR and RBF due to increased renal interstitial pressure
  - Tissue hypoxia due to impaired O2 diffusion
- Aim for euvolemia and euhydration
  - CRT, membranes, HR, pulses, mentation, lactate, base excess = perfusion parameters
- Balanced crystalloid with calcium
  - LRs, Hartmann’s
  - Normosol-R, Plasma-Lyte 148 no Ca, acetate vasodilatory (?)
- Not 0.9% NaCl even if hyperkalemia
  - Acidifying
  - Afferent arteriolar constriction

IV fluids for AKI, cont'd.

- Correct dehydration in 4-6 hr
  - Body weight (kg) x estimated % dehydration x 1000 = fluid deficit in milliliters
- Provide maintenance and keep up with ongoing losses
  - 44-66 ml/kg/d
- Switch to lower sodium fluid for longer maintenance therapy
  - LRs half-strength with 2.5% dextrose, 0.45% NaCl in 2.5% dextrose
  - Home made: 1:1 dilution of LRs and 0.5% dextrose
- Monitor body weight
  - Know baseline, precise scale, take into account IV catheters, bandages, e collars, etc.
  - 5% BW gain minimum threshold for clinical signs (chemosis, mild interstitial edema, regurgitation)
  - 10% BW gain pulmonary edema, body cavity effusion

IV fluids after nephrotoxin exposure: help or hurt?

- NSAIDs, lily (cat), grapes (dog)
- Fluids at 2-3x maintenance 2-3 d to induce diuresis standard recommendation
  - No evidence that increases toxin excretion or prevents 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

Treat life-threatening hyperkalemia

- Hypothermia *and* bradycardia indications to treat
- 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

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

Detect oliguria and 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 after rehydration to 2-5 ml/kg/h
  - Ensure collection system connected, patent

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

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

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 (dogs)
- Higher fluid rates than any other disease
- Hypokalemia may result – add KCl to fluids
- Monitor urine volume, BW, perfusion, 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 drug excreted by kidneys
- Interval (hr) = normal interval (h) x serum creatinine
- Dose = normal dose / serum creatinine

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 HCO3 at admission
- Kidney dysfunction that lasts >3 months after AKI = CKD

Key Takeways

- AKI can be present on admission or develop in the hospital
- AKI predisposes to CKD and vice versa
- Daily grading using IRIS AKI guidelines is indicated in unstable patients
- Earliest indicators of AKI are in urine
- Azotemia not always present with AKI
- Urine cystatin B is a sensitive marker of kidney tubule damage
- Monitoring body weight and urine output is critical
- Hypervolemia can cause or exacerbate AKI
- Prognosis is generally guarded but better with infectious causes and early appropriate therapy

Thank you!