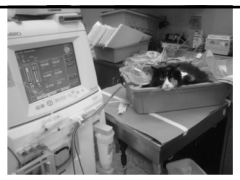

Acute Kidney Injury and Acute Azotemia

It's Not Always the Kidneys' Fault!

UNIVERSITY OF CALGARY VETERINARY MEDICINE
Serge Chalhoub, DVM, DACVIM
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Veterinary Clinical and Diagnostic Sciences

1

On the Menu

1. What is acute kidney injury and acute azotemia
2. Diagnosis of AKI
3. AKI prognosis
4. Ureteral obstruction and acute azotemia in cats, treatments

TRUE NORTH VETERINARY DIAGNOSTICS

Thank you!!!

2

Punch

- **6 year-old FS DSH presents to you after 3 days of hiding, anorexia**
  - No previous medical history
  - PE: Lethargic, 7% dehydration, pale pink MM CRT <2 sec, small bladder
    - Quick assessment tests: PCV 34%, TS 76g/L, lactate 5mmol/, Azostix highest reading for BUN

Poll: What is going on with Punch? What should we do next?

3

What We Traditionally Do…

Well ☺

- IRIS Stage Feline CKD
- Improve quality of life
- Diagnose once a patient is symptomatic
- Diet as therapy
- Proteinuria and hypertension

Not Well ☹

- Early diagnosis and treatment, acute kidney injury (AKI)
- We forget about post renal causes of azotemia
- Understanding the pathophysiology
- Still lots of grade 4 evidence-based treatments

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1. Acute Kidney Injury (AKI)

- **AKI is an insult/damage to the kidneys**
  - Think of it as a "punch" to the kidneys
    - There is a decrease in renal function: glomerular filtration rate (GFR) decreases from the damage
  - The kidneys have less ability to do their job, which is to eliminate waste
    - So waste products (azotemia) can accumulate in the bloodstream when GFR drops
  - If the AKI is severe or prolonged, it will lead a significant drop in GFR (severe AKI), previously called ARF
    - Severe state of renal dysfunction and low GFR

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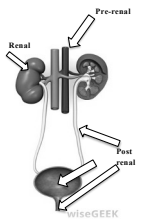
AKI: General Causes

- **Kidneys very susceptible to damage**
  - Receive 20% of cardiac blood output, multiple meds/ toxins concentrate in kidneys

➢ **AKI can result from causes affecting the kidneys directly**
  ➢ Which means it can lead to renal azotemia (ex. lilies or grapes, pyelonephritis)

➢ **Or causes that come before the kidneys**
  ➢ Which means it can lead to pre-renal azotemia (ex. dehydration, hypovolemia, hypotension, hypoperfusion, Addison's in dogs)

➢ **Or causes from after the kidneys**
  ➢ Which means it can lead to post renal azotemia (ex. Ureterolith, urethral obstruction)



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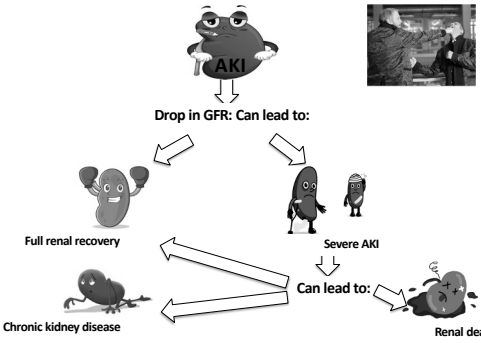

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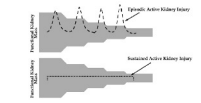
What's the AKI/CKD Theory?

- **AKI can initiate CKD in people and dogs, and now known in cats**
  - Ischemia model: AKI cause maladaptive repair mechanisms which initiate CKD
- **Causes of tubular hypoxia:**
  - Age, sympathetic activity, toxins, anemia, stress, dehydration, BP changes, tubular hypermetabolism of age, inflammation, infections



Cowgill et al. Is progressive chronic kidney disease a slow acute kidney injury? Vet Clin Small Anim 46 (2016)

Even if AKI episode returns values to "normal", chance of maladaptive repair and mini AKI's until future CKD

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2. Wait… How Do We Diagnose AKI?

- **AKI can be difficult to detect**
  - May be mild damage, may not see acute azotemia (traditional definition)
    - Poor traditional biomarker sensitivity
- **But when we are "azotemic", that means GFR has significantly and severely decreased**
  - This means there is a significant accumulation of nitrogenous waste products (acute azotemia)
    - Azotemia is what we can measure in the bloodstream
    - Detectable when kidneys are >75% damaged and then BUN/creatinine above reference range
  - If the waste products (azotemia) are substantial, they can lead to uremia
    - The clinical signs of azotemia

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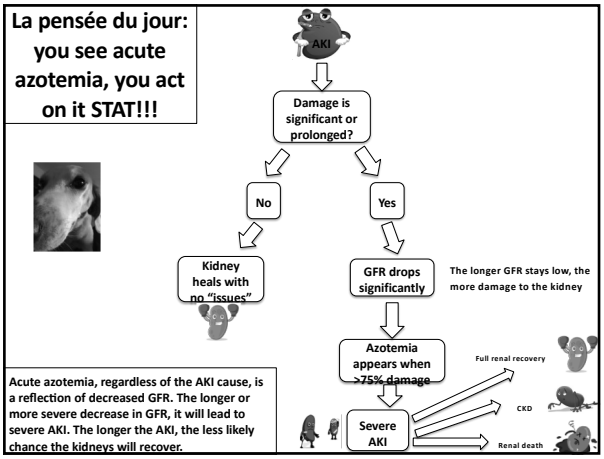
La pensée du jour: you see acute azotemia, you act on it STAT!!!



Acute azotemia, regardless of the AKI cause, is a reflection of decreased GFR. The longer or more severe decrease in GFR, it will lead to severe AKI. The longer the AKI, the less likely chance the kidneys will recover.

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AKI Diagnosis

- **AKI can be difficult to diagnose**
  - Urine specific gravity (USG) decreases with 67-70% of renal damage
    - So not much better… ☹
- **So what can we say when we have a patient suspected of having AKI?**
  1. Acute azotemia present?: means decreased GFR, and now must go find the cause now and/or act on it
     - Pre-renal, renal, post renal

     OR…
  2. Any changes to the patient's creatinine? (even if still in normal range)
     - Can be considered a significant indicator of GFR changes

     OR…
  3. Any changes in SDMA?

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IRIS AKI Staging

- **Stable grade I-II**
  - More likely to survive
  - 3-5d hospitalization
- **Progressive grade or higher grade**
  - Longer hospitalization or worse outcome
  - May need renal replacement therapies
- **Grade IV-V**
  - Often poor prognosis

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)	

http://www.iris-kidney.com/pdf/4_Idc-revised-grading-of-acute-kidney-injury.pdf

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Acute Azotemia

J Vet Intern Med 2012;26:1093–1098

Acute Azotemia as a Predictor of Mortality in Dogs and Cats

E. Harison, C. Langston, D. Palma, and K. Lamb

- **Dogs and cats with initial creatinine <1.6mg/dL, had > 1 measurement within 2, 3, 7 days; AKI defined as increase in creatinine by >0.3mg/dL**
  - Placed into levels 0-2; mortality assessed at 30 and 90 days
  - Cats placed in level 2 within 3 or 7 days were 3X more likely to die at 30 days and 4X more likely to die at 90 days
- **Detecting increasing azotemia predicts mortality**

Table 2. Acute kidney injury staging criteria.

Level	Highest Additional Creatinine (mg/dL)
Level 0	≤ 1.6 and change of <0.3
Level 1	≤ 1.6 and change of ≥ 0.3
Level 2	>1.6 and change of ≥ 0.3

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Kidney Injury Molecule-1

Original Article

jfms Journal of Feline Medicine and Surgery

A specific immunoassay for detection of feline kidney injury molecule 1

S Karlyn Bland[1], Mary Ellen Clark[1], Olivier Côté[2] and Dorothee Bienzle[1]

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DOI: 10.1177/1098612X18810494
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SAGE

- **Point-of-care urine assay that shows marked (but transient) increases in cats with sepsis, urethral obstruction even with normal or normalizing creatinine; serial samples useful**

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SDMA for AKI

Journal of Veterinary Internal Medicine ACVIM Open Access

Standard Article

J Vet Intern Med 2017;31:799–804

Plasma Symmetric Dimethylarginine Concentration in Dogs with Acute Kidney Injury and Chronic Kidney Disease

D.P. Dahlem, R. Neiger, A. Schweighauser, T. Francey, M. Yerramilli, E. Obare, and S.M.L. Steinbach

- **SDMA elevated in both AKI and CKD dogs**
- **Study not designed to test SDMA as marker of early kidney disease**

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Early Diagnosis

- **More sensitive tests of GFR**
  - **Geriatric patients**
    - **Yearly screening, prediction and earlier detection of kidney disease**
    - **Better preparation for anesthesia (dentals, mass removals etc.)**
  - **Any patient**
    - **More sensitive for AKI, congenital disorders, non renal azotemia**
  - **CKD patients**
    - **Monitoring of treatment outcomes, earlier detection of changes**

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AKI Diagnosis

- **Consider all the facts**
  - History, physical exam, lab analysis, previous labs, etc.
  - Investigate causes
    - Lab work, infectious diseases, drug testing, medical imaging
    - ALL azotemic patients (acute or chronic) should have labwork, urinalysis, urine culture, and medical imaging to determine the type of azotemia

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AKI

- **Pre-Renal Azotemia**
  - **Decreased renal blood flow**
- **Renal Azotemia**
  - **Direct AKI**
- **Post Renal Azotemia**
  - **Ureter/urethra obstruction**

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Pre-Renal Azotemia

- **Decreased renal blood flow**
- **Consider cat vs. dog**
  - Addison's disease
  - Severe (?) dehydration, hypovolemia
    - Dehydration by itself should not cause moderate to severe azotemia
  - Congestive heart failure
  - 3rd space loss, hemorrhage
  - Medications: ACEi, ARBS, diuretics

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Renal Azotemia

- **Intoxication**
  - Grapes, lilies
- **Infectious**
  - Pyelonephritis
  - Leptospirosis
  - Tick-borne diseases
- **Ischemia, hypoxemia**
- **Acute on chronic kidney disease**

- **History**
- **Urinalysis, urine culture**
- **Tick-borne disease and other infectious disease testing**
- **Leptospirosis testing**

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Post Renal Azotemia

- **Ureteral obstructions**
  - CaOx stones
  - Strictures
  - DSB
  - Neoplasia
- **Urethral obstructions**

- **Medical imaging**
  - Ultrasound
    - VPOCUS!
  - Radiographs
  - CT
  - Contrast studies

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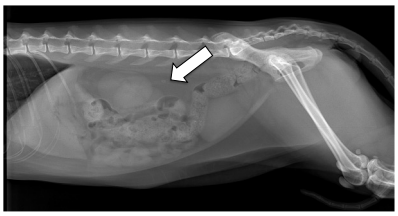
Medical Imaging



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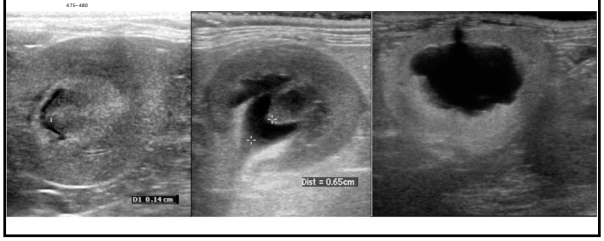
POCUS Short Axis Renal Pelvic Dilation

- **> 13 mm consistent with obstruction**
- **➢ 7 mm likely obstructive**
- **➢ Pyelonephritis vs. obstruction**
- **➢ Absence of significant dilation with obstruction?**

Renal pelvis normally not dilated but may be 1-3 mm



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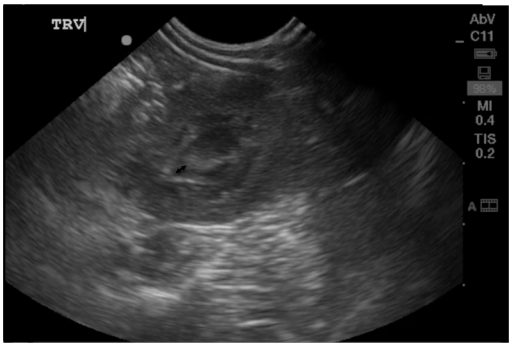

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Poll: What is the prognosis for AKI/ARF?

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3. AKI Prognosis

Acute intrinsic renal failure in cats: 32 cases (1997–2004)

Stefanie Worwag, VMD, and Cathy E. Langston, DVM, DACVIM

Conclusions and Clinical Relevance—Results suggested that survival rates of cats with ARF were similar to survival rates in dogs and that residual renal damage persisted in approximately half of cats surviving the initial hospitalization. (*J Am Vet Med Assoc* 2008;232:728–732)

- **Diagnosis based on acute clinical signs, creatinine >2.5mg/dL**
  - Excluded renal/ureteral calculi or neoplasia
  - Causes: nephrotoxins, ischemia, other
- **50% died; 50% made it**
  - Of those that made it, ½ left with CKD

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AKI Prognosis

Prognosis of acute kidney injury in dogs using RIFLE (Risk, Injury, Failure, Loss and End-stage renal failure)-like criteria

March 12, 2011 | Veterinary Record

Y-J. Lee, C-C. Chang, J. P-W. Chan, W-L. Hsu, K-W. Lin, M-L. Wong

- **30-day mortality index in "injury": 41%; in "failure": 78.5%**
- **Very similar to cats: 50% died; 50% made it**
  - Cats: of those that made it, ½ left with CKD

TABLE 1: Acute Dialysis Quality Initiative criteria for the definition and classification of acute kidney injury and the RIFLE (Risk, Injury, Failure, Loss and End-stage renal failure) criteria used in the present study

RIFLE category	Serum creatinine criteria	Urine output criteria	Modified criteria
Risk	×1.5-fold from serum creatinine baseline or 50% to 25% decrease in GFR	<0.5 ml/kg/h for >6 hours	Creatinine 116-174 μmol/l
Injury	×2.0-fold from serum creatinine baseline or 75% to 50% decrease in GFR	<0.5 ml/kg/h for >12 hours	Creatinine 175-347.9 μmol/l
Failure	×3.0-fold from serum creatinine baseline or decrease in GFR >75%, or an absolute serum creatinine >354 μmol/l or with an acute rise of at least 44.2 μmol/l	<0.3 ml/kg/h for >24 hours or anuria ×12 hours	Creatinine >347.9 μmol/l

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AKI Prognosis

J Vet Intern Med 2012;26:1093–1098

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E. Harison, C. Langston, D. Palma, and K. Lamb

- **Dogs and cats with initial creatinine <1.6mg/dL, had < 1 measurement within 2, 3, 7 days; AKI defined as increase in creatinine by >0.3mg/dL**
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  - Cats placed in level 2 within 3 or 7 days were 3X more likely to die at 30 days and 4X more likely to die at 90 days
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Table 2. Acute kidney injury staging criteria.

Level	Highest Additional Creatinine (mg/dL)
Level 0	≤ 1.6 and change of <0.3
Level 1	≤ 1.6 and change of ≥0.3
Level 2	>1.6 and change of ≥0.3

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The longer or more severe decrease in GFR, it will lead to severe AKI. The longer the AKI, the less likely chance the kidneys will recover.

Can lead to:

Depends on severity or prolongation of damage

"Full" renal recovery

Severe AKI

25%

25%

50%

Can lead to:

50%

Chronic kidney disease

Renal death

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4. Treatment Goals

- **Limiting further renal damage**
  - Ex.: treating hypotension
- **Treating initial cause, antidotes if available**
  - Ex. Ethylene glycol
- **Improving renal oxygen delivery**
  - Ex. IV fluids

- **Supporting entire body**
  - Ex. Nutrition
- **Treat consequences of azotemia, uremia**
  - Ex. Nausea, vomiting
- **Maintaining adequate urine output (1-2ml/Kg/hr)**

General rule: if your azotemia improves by 40-50% within 48-72h then better prognosis

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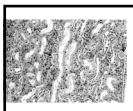

Phases of AKI

- **Phase 1*****
  - **Induction phase**, non clinical; AKI until definable change in renal function; length of time variable
- **Phase 2*****
  - **Extension phase**, continued hypoxia and inflammation
- **Phase 3**
  - **Maintenance phase** 1-3 weeks; irreversible damage has occurred; increased or decreased UOP
- **Phase 4**
  - **Recovery phase** if occurs, usually increased UOP and decreased sodium; medullary washout and post obstructive diuresis

*****Highest chance of returning renal function**

- **If not: fibrosis**

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Treatment: IV Fluids

- **Initial stabilization:**
  - Correction of dehydration, shock
  - Important not to drown them…
  - IVF will help with correction of deficits
    - But it will not "fix" azotemia
    - Cats and their hearts…
  - **Maintenance + losses**
    - 50ml/kg/day

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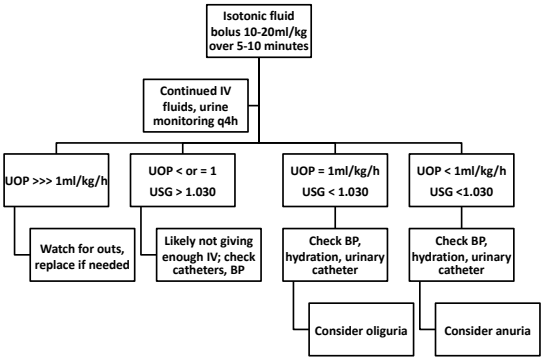
IV Fluids



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Monitoring Therapy

- **Urine output q4h**
  - Ins (IVF, medications, food)
  - Outs (sensible vs. insensible (22ml/kg/d)
- **Body weight q4-8h**
- **Hydration q4h**
- **PCV q12h**
- **Electrolytes q12h**
- **Blood pressure q8h**

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Medical Management

- **NG tube, feedings**
- **GI protectants**
  - Pantoprazole, omeprazole, metoclopramide
- **Antiemetics**
  - Ondansetron, maripotant, metoclopramide
- **Emergency drugs, antidotes**
  - Antibiotics
  - 2-MP, ethanol
  - Dexamethasone
- **Dialysis?**

- **Diuretics**
  - Furosemide, mannitol
  - Only if oliguria, anuria

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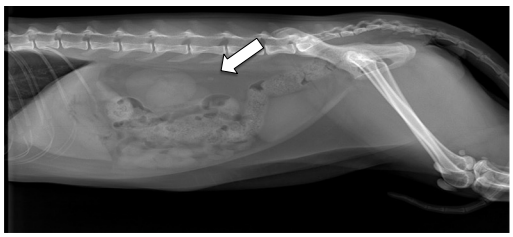
Coming Back to Punch



Poll: What do we do for Punch?

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Intravenous Pyelogram

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Nephrolith Significance?

- **Non obstructing renal calculi**
  - Pelvis vs. parenchyma
  - Obstructive vs. non obstructive
  - Cats vs. dogs

A case-control study of the effects of nephrolithiasis in cats with chronic kidney disease

Sheri J. Ross, DVM, PhD, DACVIM; Carl A. Osborne, DVM, PhD, DACVIM; Chalermpol Lekcharoensuk, DVM, MPH, PhD; Lori A. Koehler; David J. Polzin, DVM, PhD, DACVIM

Objective—To determine whether nephrolithiasis was associated with an increase in mortality rate or in the rate of disease progression in cats with naturally occurring stage 2 (mild) or stage 3 (moderate) chronic kidney disease.

Nephroliths do not seem to increase mortality or progression in cats with mild to moderate CKD

24 months of monitoring. No associations were detected between nephrolithiasis and rate of disease progression, incidence of uremic crises, or death.

Conclusions and Clinical Relevance—Results suggested that in cats with mild or moderate chronic kidney disease, nephrolithiasis was not associated with an increase in mortality rate or in the rate of disease progression. Findings support recommendations that cats with severe kidney disease and nephrolithiasis be managed without surgery. *J Am Vet Med Assoc* 2007;230:1854–1858

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Earlier Detection of Nephroliths?

PLOS ONE

RESEARCH ARTICLE

Serum concentrations of symmetric dimethylarginine and creatinine in cats with kidney stones

Jean A. Hall[1]*, Maha Yerramilli[2], Edward Obare[2], Jun Li[2], Murthy Yerramilli[2], Dennis E. Jewell[3]

1 Department of Biomedical Sciences, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon, United States of America, 2 IDEXX Laboratories, Inc., One IDEXX Drive, Westbrook, Maine, United States of America, 3 Pet Nutrition Center, Hill's Pet Nutrition, Inc., Topeka, Kansas, United States of America

43 cats with kidney stones vs. 21 healthy geriatric cats

- **39/43 had increased SDMA (92% vs. 17% azotemic)**
  - **Only 18/43 had elevated creatinine at some point (42%)**
  - **USG > 1.035 in 15/39*******
  - **SDMA elevated 27 months before creatinine increased**

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Cats and Ureteral Stones

- **Should you go to surgery?**
  - Obstruction
  - Pelvic dilation (>5mm)
  - Progressive azotemia
  - Pain, decreased appetite
  - Acute azotemia

- **Consensus: the quicker the better if the stone is obstructive**
  - But, what about if there is existing CKD?
    - Studies show that intervention can still be of benefit

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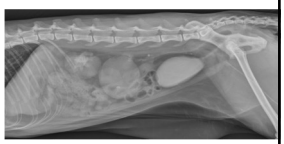
When To Go To Surgery for Ureteral Obstruction?

- **No consensus on what time frame for cats**



- **Dogs:**
  - 4d of complete obstruction + correction: near-complete return of GFR
  - 14d: 46% recovery
  - 40d: little recovery

Fink RL et al. Renal impairment and its reversibility following variable periods of complete ureteral obstruction. Aust NZ J Surg 1980;50:77-83

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Cats and Traditional Ureteral Surgery

- **Better outcome with surgery?**
  - 101 cats; median intervention time 3d
    - 31% had major complications, 18% died
      - Slightly less complications if sx sooner
      - 24-month survival rate 88% for survivors vs. 66% for medical management alone

Management and outcome of cats with ureteral calculi: 153 cases (1984–2002)

Andrew E. Kyles, DVM, PhD, DACVS; Elizabeth M. Hardie, DVM, PhD, DACVS; Brent G. Wooden, DVM; Christopher A. Adin, DVM, DACVS; Elizabeth A. Stone, DVM, MS, DACVS; Clare R. Gregory, DVM, DACVS; Kyle G. Mathews, DVM, MS, DACVS; Larry D. Cowgill, DVM, PhD, DACVIM; Steffi Vaden, DVM, PhD, DACVIM; Thomas G. Nyland, DVM, DACVR; Gerald V. Ling, DVM

- **But… this was prior to current techniques**

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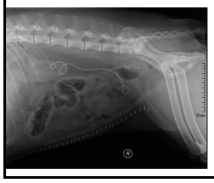
Ureteral Stents

- **Permanent: double pigtail ureteral stents**
  - Placement: endoscopy (dogs) or laparotomy (dogs, cats)
  - Fluoroscopic guidance useful
  - Guidewire, ureteral dilator, pigtail catheter
  - Ureterolith NOT removed!



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Ureteral Stents

Feline double pigtail ureteric stents for management of ureteric obstruction: short- and long-term follow-up of 26 cats

Journal of Feline Medicine and Surgery
1–7
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DOI: 10.1177/1098612X14531763
jfms.com
SAGE

Nicola Jayne Kulendra, Hattie Syme, Livia Benigni and Zoe Halfacree

- **Survival to discharge 85%**
- **Post-op mortality 15%, median survival 419 days (44-994 days)**
  - Survivors vs. non survivors: no significant difference in creatinine
- **Quality of life good in most cats**
  - Chronic recurrent cystitis 35%

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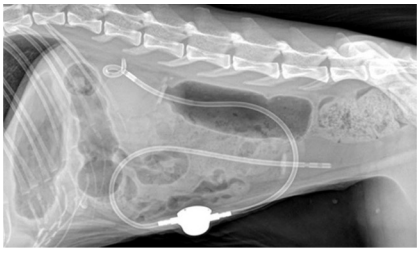
Subcutaneous Ureteral Bypass (SUB)



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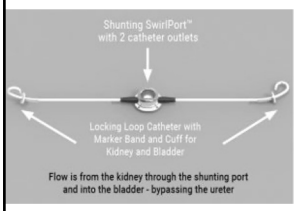
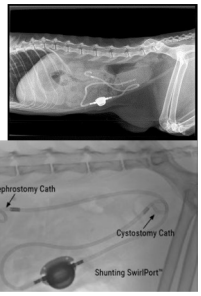
SUBs

- **Locking loop nephrostomy tube, Huber port, cystostomy catheter**
  - Long term, indwelling device





https://norfolkvetproducts.com/products/sub-2/

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SUB Outcomes

Predictors of outcome for cats with ureteral obstructions after interventional management using ureteral stents or a subcutaneous ureteral bypass device

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- **No clinical or biochemical parameter was associated with survival to discharge**
  - Therefore, hard to predict prior to surgery which cats will do better
- **Shorter long-term survival with higher BUN/creatinine at discharge**
- **Cats in IRIS Stage 1-2 post procedure lived longer than cats with IRIS stage 3-4 post procedure**

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SUB Outcomes

Use of a subcutaneous ureteral bypass device for treatment of benign ureteral obstruction in cats: 174 ureters in 134 cats (2009–2015)

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- **94% survival to discharge**
- **Factors associated with survival to discharge: anuria/oliguria, fluid overload**
- **Survival: overall 827d; if at stage 1 or 2 three months later, MST >2000d**
- **Factors associated with survival: history of CKD, fluid overload, weight loss**
  - MST 1072d without fluid overload vs. 70-80d with fluid overload
  - MST 1007d without CKD vs. 815d with CKD
  - IRIS staging at 3 months determined survival
    - Pre-operative creatinine not a factor
- **Mineralization and blood clots most common complications; 14% chronic hematuria**

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Care of SUBs

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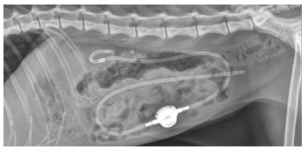
Back to Punch

- **Unilateral SUB placement**
- **Creatinine stabilized at 182umol/L**
  - Comes in every 3-4 months for flush



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What if no Surgery?

- **Supportive care**
  - Azotemia may improve to a range that is compatible with QOL
  - Depends on how much adaptation
  - Migration?
  - Unknown prognosis

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Final Words

- **Azotemia or any changes in creatinine should not be ignored**
- **Determine cause with history, medical imaging, labwork**
  - **Not assuming "Chronic" "Kidney" Disease"**
- **The sooner you act on it the better**
- **Don't forget about ureteroliths in cats**
- **Cats and urethral obstructions…**

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THANK YOU!

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