The Mysterious Case of the Halloween Cat

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Noir

CKD: Definitions

- Kidney disease: structural or functional lesions that affect one or both kidneys
- Chronic kidney disease: > 2 - 4 months
- CKD can lead to renal failure: Persistent azotemia and inability to form hypersthenuric urine
  - USG < 1.035 is inappropriate in the face of dehydration or azotemia
  - USG between 1.035 and 1.040 = grey zone in cats
Advantages of CKD Staging

- Uniform terminology and better comparison between studies e.g., terms like end-stage renal failure and renal insufficiency are often poorly defined
- Diagnostic and therapeutic efforts can be better tailored to the patient
- More accurate prognosis

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**IRIS* Classification of Feline Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Creatinine*</th>
<th>Stage I Non-azotemic CKD</th>
<th>Stage II Mild renal azotemia</th>
<th>Stage III Moderate renal azotemia</th>
<th>Stage IV Severe renal azotemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>µMol/L</td>
<td>&lt;140</td>
<td>140-250</td>
<td>251-440</td>
<td>&gt;440</td>
</tr>
<tr>
<td>mg/dL</td>
<td>&lt;1.6</td>
<td>1.6-2.8</td>
<td>2.9-5.0</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>Prevalence %</td>
<td>33.3%</td>
<td>37.2%</td>
<td>15.4%</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

Further classify based on the presence or absence of proteinuria and systemic hypertension

*IRIS: INTERNATIONAL RENAL INTEREST SOCIETY  www.iris-kidney.com
Whistler et al. (75 Selected Cases of Chronic Kidney Disease  Elliott et al, ACVIM, 2004)

*Stable serum creatinine in a well hydrated patient

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**Classification of Renal Proteinuria* in Cats:**

<table>
<thead>
<tr>
<th>UP/C</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.2</td>
<td>Normal</td>
</tr>
<tr>
<td>&gt;0.2</td>
<td>&lt;0.4 Borderline</td>
</tr>
<tr>
<td>&gt;0.4</td>
<td>Abnormal (Renal; either glomerular or tubular)</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>Abnormal (Glomerular range proteinuria)</td>
</tr>
</tbody>
</table>

* Persistent and associated with a normal urine sediment

Risk Assessment
Classification of Blood Pressure:

<table>
<thead>
<tr>
<th>Systolic</th>
<th>Diastolic</th>
<th>Risk of future target-organ damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>&lt;95</td>
<td>Minimal</td>
</tr>
<tr>
<td>150-159</td>
<td>95-99</td>
<td>Mild</td>
</tr>
<tr>
<td>160-179</td>
<td>100-119</td>
<td>Moderate</td>
</tr>
<tr>
<td>≥180</td>
<td>≥120</td>
<td>Severe</td>
</tr>
</tbody>
</table>


Diagnosis of Stage I CKD
(Normally hydrated and muscled cats should have a serum creatinine < 1.6 mg/dl)

- Kidney palpation or imaging abnormalities
- Persistent urine concentrating deficits of renal origin (rule out extra-renal causes)
- Persistent renal proteinuria
- Increases in serum creatinine within the reference range that are not associated with changes in muscle mass or hydration status
  - e.g., an increase in Sr Cr from 0.7 to 1.4 mg/dl over time could indicate ≥ 50% nephron loss
Staging: Diagnostic Approach

<table>
<thead>
<tr>
<th>SrCr (mg/dl)</th>
<th>Willie</th>
<th>Sarah</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stage I:** Nonazotemic CKD

**Stage II:** Mild azotemia

**Stage III:** Moderate azotemia

**Stage IV:** Severe azotemia

Characterize renal disease ("Renal Evaluation" - e.g., serum chemistry, UA, urine culture, assessment of proteinuria, U/S, biopsy?)

Characterize stability of renal function ("Evaluate Progression" - interval based on species, individual patient, severity of dysfunction; e.g., serum creatinine, urine protein)

Characterize patient’s problems ("Patient Evaluation" - e.g., potassium, phosphorus, and calcium imbalances, acidosis, hypertension, gastrointestinal abnormalities)

Staging: Therapeutic Approach

<table>
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<tr>
<th>SrCr (mg/dl)</th>
<th>Willie</th>
<th>Sarah</th>
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<tr>
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**Stage I:** Nonazotemic CKD

**Stage II:** Mild azotemia

**Stage III:** Moderate azotemia

**Stage IV:** Severe azotemia

**Disease-specific therapy**
(“Specific Therapy” – e.g., renoliths, pyelonephritis, LSA)

**Therapy to slow progression**
(“Renoprotective Therapy” – e.g., ACE inhibitors, diet)

**Patient-specific therapy**
(“Symptomatic Therapy” – e.g., anorexia, vomiting, acidosis)
UTI and CKD in Cats

- Prospective study at the RVC in London involving 51 cats with CKD, bacterial UTI was identified in 15 cases (29%)
  - Majority of cats with UTI were female
  - None showed typical lower urinary tract signs
  - Infections may have ascended and contributed to the renal damage


USG and Urine Sediment as Risk Factors for UTI in Cats

- 614 cats studied: Positive urine cultures found in 17% of cats with CKD, 13% of cats with DM, 22% of cats HT, and 5% of cats with FLUTD
- Decreasing USG was not associated with positive urine culture
- Pyuria and hematuria were associated with positive urine cultures
- Persians, females, increasing age, and decreasing body weight were also associated with positive cultures


Effects of Nephroliths in Cats with CKD

- Retrospective study of 14 cats with Stage II/III CKD; 7 with nephroliths and 7 without
- Cats were followed q 3 months for up to 24 months
- No differences between groups in lab data; no associations between nephroliths and rate of disease progression, incidence of uremic crises, or death
- Recommendation: Cats with CKD and nephroliths be managed without surgery

Ross, et al. JAVMA 2007;230:1854-1859
Progression of CKD

- Loss of nephrons
- AA dilation
- RAAS activation
- EA constriction
- Elevated intraglomerular pressure
- Proteinuria
- Progressive glomerular and tubulointerstitial damage

Systemic Hypertension in Cats with CKD

- 17 of 28 (61%) average BP = 147/97 mmHg
  Kobayashi, JVIM 4:58, 1990
- 15 of 23 (65%) BP >160/100 mm Hg
  Stiles, JAAMA 50:564, 1994
- 20 of 103 (19%) systolic BP > 175 mm Hg
  Syme, JAVMA 220:1799, 2002

Glomerulosclerosis – Feline CKD Models

- Normal Cats
- Moderately Hypertensive
- Severely Hypertensive

Cats: Proteinuria and CKD Progression

- Relatively mild proteinuria in cats with spontaneous CKD appears to be a negative predictor of survival
  - Hazard ratio (risk of death or euthanasia) of 2.9 for cats with UP/C’s between 0.2 and 0.4
  - Hazard ratio of 4.0 for cats with UP/C’s > 0.4

Syme, J Vet Intern Med 2006; 20:528

Effect of Proteinuria on Survival in Cats with Systolic Hypertension

<table>
<thead>
<tr>
<th>Magnitude of Proteinuria (UP/C)</th>
<th>Survival days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2</td>
<td>490</td>
</tr>
<tr>
<td>0.2 - 0.4</td>
<td>313</td>
</tr>
<tr>
<td>&gt; 0.4</td>
<td>162</td>
</tr>
</tbody>
</table>


Predictors of the Development of Azotemia in Cats

- Prospective, longitudinal cohort study of non-azotemic cats ≥ 9 years
- 95 cats (median age = 13) were followed for 12 months or until death or azotemia developed
- 29/95 (30.5%) developed azotemia (Sr Cr > 2.0 mg/dl)
- Proteinuria at presentation (median UP/C of 0.19 vs. 0.14) was significantly associated with development of azotemia

**Feline Glomerular Capillary Pressure**

*P<0.05: significant effect of ACEI in remnant kidney model

![Bar chart showing the effect of Placebo and Benazepril on PGC (mmHg)](Brown, AJVR 2001; 62:375-383)

**Effects of ACEI vs. CCA on Systolic Blood Pressure in Feline CKD Models**

*P<0.05: significant effect of treatment

![Bar chart showing 24-hour Average Systolic Blood Pressure by Radiotelemetry (mmHg)](Brown, et al: 2001)

Placebo vs. Benazepril (0.75 mg/kg/day)

Amlodipine (0.25 mg/kg/day)


Down 10.5 mmHg


Down 29.5 mmHg

**Effect of Proteinuria on Survival in Cats with Systolic Hypertension**

- 141 client-owned cats with SBP > 170 mmHg
- Treated with Amlodipine and followed until death or study endpoint
  - Initial dose of 0.625 mg/cat was increased to 1.25 mg/cat in 50% in order to decrease SBP < 160 mmHg
- Amlodipine resulted in a significant decline in both SBP and proteinuria
- Proteinuria (UP/C) (before and after Rx and Δ UP/C) were the only variables related to survival in these cats

Is attenuated proteinuria associated with decreased disease progression in cats?

- 61 cats with naturally-occurring CKD were studied in a prospective, randomized, double-blinded, placebo controlled study
  - Cats received benazepril (or placebo) at a dosage of 0.5-1.0mg/kg once daily for up to 6 months
  - UP/C’s were significantly lower in cats receiving benazepril at 120 and 180 days
  - Incidence rates of cats with stage 2 or 3 disease that did not progress was higher in the benazepril group (93±5%) vs. the placebo group (73±13%)

Mizutani, et al. JVIM 20:1074, 2006

Calcium, Vitamin D, and PTH Concentrations in Feline CKD

- 80 cats with spontaneous CKD
  - 84% had hyperparathyroidism; the magnitude of HPTH correlated with the severity of the CKD
  - Compared with age-matched controls, CKD cats had increased serum phosphorus and PTH and decreased Vitamin D$_3$
  - Ionized calcium was decreased only in cats with Stage IV CKD

Barber and Elliott, JSAP 1998;39:108-116

Renal Mineralization

Ross, et al. AJVR 1982;43:1023-1026

Failure to control dietary phosphorus in cats with CRF can result in renal mineralization and fibrosis and further loss of nephrons
Dietary Phosphorus Restriction in Cats with CKD

Ross, et al. AJVR 1982;43:1023-1026

Dietary Management and CKD in Cats

Barber, et al. JSAP 1999; 40:62
Elliott, et al. JSAP 2000; 41:235

Feeding a specifically formulated feline CKD diet, alone or in combination with an enteric phosphate binder, to cats with stable, spontaneous CKD (n = 50):
- Reduced PTH concentrations
- Controlled hyperphosphatemia
- Increased median survival time (633 vs. 264 days)
Therapeutic Targets for Management of Hyperphosphatemia in CKD

<table>
<thead>
<tr>
<th>IRIS Stage</th>
<th>Target Serum Phosphorus (mg/dl)</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.5-4.5</td>
<td>Normal ration + binder or renal diet</td>
</tr>
<tr>
<td>II</td>
<td>2.5-4.5</td>
<td>Renal diet ± binder</td>
</tr>
<tr>
<td>III</td>
<td>2.5-5.0</td>
<td>Renal diet + binder ± calcitriol</td>
</tr>
<tr>
<td>IV</td>
<td>2.5-6.0</td>
<td>Renal diet + binder ± calcitriol</td>
</tr>
</tbody>
</table>

Use of Calcitriol in Cats with CKD: Guidelines

- Cats should be eating well
- Serum phosphorus should be maintained < 4-6 mg/dl
- Hyperparathyroidism should be confirmed prior to Rx
- Serum ionized Ca and Phos should be monitored weekly for several weeks after initiation of Rx
- Monitoring of serum Ca++/Phos can decrease to monthly when stable
- Dose: 2.5-3.5 ng/kg/day

Hypokalemia in Feline CKD

- Occurs when urinary losses exceed oral intake
- Cardinal sign is muscle weakness
- Normokalemic cats with CRF may have low muscle potassium content
Anorexia/Calorie malnutrition

- Metabolic deficits and excesses (e.g., dehydration, acidosis, anemia, hypertension)
- Gastrointestinal tract dysfunction (e.g., motility, acidity, constipation, oral disease)
- Feeding management problems
- Increased diet palatability
- Appetite stimulants

Decreased GFR

Mucosal irritation, ulceration, and hemorrhage

Decreased gastrin clearance

Increased HCl secretion

Hypergastrinemia

Increased H2 – Receptor Stimulation (Parietal Cells)

Plasma Gastrin Concentrations in Cats with CKD

- Plasma gastrin levels in 30 cats with CKD were increased (median of 45 pg/ml) compared with 12 normal cats (< 18 pg/ml)
- Gastrin levels correlated with serum creatinine levels
- Confirms the use of H2-receptor blockers and proton pump blockers in cats as a means to treat uremic gastritis

Goldstein, et al. JAVMA 1998;213:826-828
Solve It! Series: The Mysterious Case of the Halloween Cat

Anorexia/Calorie malnutrition

- Feeding management problems:
  - Force feeding
  - Sudden dietary change
  - Social/antisocial eaters
  - Pilling and injections associated with feeding

- Increasing dietary palatability:
  - Warm the food
  - Moisten dry diets
  - Small amounts frequently
  - Meat and fat flavored diets
  - Provide variety
  - Hand feed while petting
  - Use flavoring agents

Use of feeding tubes
Survival in Cats with CKD

<table>
<thead>
<tr>
<th>Stage at Baseline (SrCr)</th>
<th># (%)</th>
<th>Median Survival (Days)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb (2.3-2.8)</td>
<td>82 (39.4)</td>
<td>1,151</td>
<td>(1,014, 1,565)</td>
</tr>
<tr>
<td>III (2.9-5.0)</td>
<td>84 (40.3)</td>
<td>679</td>
<td>(445, 910)</td>
</tr>
<tr>
<td>IV (&gt; 5.0)</td>
<td>42 (20.2)</td>
<td>35</td>
<td>(21, 99)</td>
</tr>
</tbody>
</table>

Survival time from onset of criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th># of Cats</th>
<th>Median Survival (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>211</td>
<td>771</td>
</tr>
<tr>
<td>Weight loss</td>
<td>142</td>
<td>401</td>
</tr>
<tr>
<td>Start of SQ fluids</td>
<td>142</td>
<td>273</td>
</tr>
<tr>
<td>Creatinine &gt; 4.0 mg/dl</td>
<td>115</td>
<td>123</td>
</tr>
<tr>
<td>Anemia (PCV &lt; 25%)</td>
<td>121</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 25% Weight loss</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>Creatinine &gt; 5.0 mg/dl</td>
<td>98</td>
<td>44</td>
</tr>
<tr>
<td>Clinical decompensation</td>
<td>135</td>
<td>40</td>
</tr>
<tr>
<td>Anemia intervention</td>
<td>42</td>
<td>25</td>
</tr>
</tbody>
</table>

Monitoring Feline CKD Patients
(Use of flow charts is ideal)

- **History and physical examination:** Appetite, body weight, hydration, blood pressure
- **Complete blood count:** Packed cell volume
- **Biochemistry profile:** BUN, creatinine, Ca/Phos, albumin, electrolytes
- **Urinalysis:** USG, proteinuria, bacteriuria
- **Ultrasound:** Pyelectasia, renoliths
Reciprocal of the serum creatinine vs. age for estimating progression of disease

Allen, et al. JAMVA 1987;190:866-868

1/Sr Creat

0.75

0.5

0.25

Patient’s Age

8.5 9.5 10.5 11.5 12.5

Noir:

- IRIS Stage II CKD (proteinuric, non-hypertensive)
- Treatment
  - Feed low protein diet
  - Gradual introduction
  - +/- enteric phosphate binder (depends on response to diet)
  - ACE Inhibitor (for proteinuria)
    - Benazepril 2.5 mg/cat/day
- Rechecks every 30 days

6 Month Recheck:

- Acute onset anorexia, lethargy, depression
- Physical exam
  - QAR
  - Vitals WNL
  - Heart and lungs auscultated normal
  - No pulse deficits
  - BCS 2.5/5; BW = 3.63 kg (stable)
**Diagnostics:**

- PCV/TP = 34% / 7.8 gm/dl (stable)
- BP = 165 mmHg (mild increase)
- BUN 62 mg/dl (increased from 54)
- Serum Creatinine 6.4 mg/dl
  - (increased from 2.7)
- Urine culture - negative
- UP/C 0.3 (stable)

**Treatment:**

- 1.5 x maintenance fluids overnight
- 24 hours later
  - BUN 72 mg/dl
  - Serum Creatinine 6.5 mg/dl

**Assessment:**

- Lack of response to fluid therapy
- Negative urine culture
- Increased blood pressure
  - Stress associated with declining renal function
- No change in UP/C
- No evidence of renal infiltrative disease on U/S
- Ultrasound changes suggestive of obstructive uropathy
“Acute on Chronic” Decompensation:

- Pre-renal causes
  - dehydration
- Renal causes
  - precipitous progression of renal disease
  - ascending urinary tract infection
  - renal neoplasia
  - nephroliths?
- Post-renal causes
  - obstructive uropathy
Antegrade Pyelography for Suspected Ureteral Obstruction: 11 cases (1995-2001)
Adin, et al. JAVMA 2003;222:1576-1581

- 100% sensitivity and specificity for the contrast procedure compared with surgery/necropsy findings (better than plain films and U/S)
- Correct identification of the site of obstruction 100% of the time
- Leakage of contrast material may prevent interpretation of the study (2 of 13 cases)
Outcome:

- Right sided ureterotomy & cystotomy
  - Several stones/blood clots removed from the ureter
- Post Operative
  - Uneventful
  - Eating well
  - Discharged 4 days later
  - BUN 49 mg/dl
  - Serum creatinine 3.2 mg/dl

Conclusions:

- IRIS CKD Staging
- Most common causes of acute uremic crisis with previously stable CKD:
  - Pre-renal dehydration (response to fluid Rx)
  - Ascending infection (urine cultures, pyelocentesis)
  - Renal neoplasia (US +/- FNA)
  - Obstructive uropathy (imaging +/- contrast)
  - Hypertensive crisis (Doppler BP was only mildly increased compared with baseline)
  - Primary disease progression (Dx of exclusion)
Questions to the Specialist

Please email your questions to solveit@aahanet.org by Sunday, December 18, 2011.

Dr. Grauer will provide written responses to all of the questions and answers will be posted on the Solve It! web pages by Friday, December 30, 2011.

To complete the evaluation, please go to the following website:

http://www.keysurvey.com/survey/392882/129c/

Thank you for your participation!