Management of chronic kidney disease in dogs and cats

Lunch and Learn
Fresno Veterinary Specialty and Emergency Center
March 19, 2013
Outline

- Diagnosis of chronic kidney disease (CKD)
  - Acute kidney injury (AKI) vs. CKD
  - International Renal interest Society (IRIS) staging
  - Evidence-based medicine

- Conservative management
  - Dietary therapy
  - Managing GI signs of uremia
  - Hyperphosphatemia
  - Metabolic acidosis
  - Hypokalemia
  - Hydration
  - Anemia
  - Calcitriol therapy
  - Proteinuria
  - Hypertension
  - Enteric dialysis
  - Renal transplantation

- Prognosis

- Follow-up monitoring
### Definition of CKD
- Presence of structural or functional abnormalities of one or both kidneys for 3 months or longer

### Markers of kidney damage

<table>
<thead>
<tr>
<th>Blood markers</th>
<th>Urine markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated BUN</td>
<td>Impaired urine concentrating ability</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Cylindruria</td>
</tr>
<tr>
<td>Hyperkalemia or hypokalemia</td>
<td>Renal hematuria</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Inappropriate urine pH level</td>
</tr>
<tr>
<td>Renal hypoalbuminemia</td>
<td>Inappropriate glucosuria</td>
</tr>
<tr>
<td>Imaging markers (e.g., size, shape, number)</td>
<td>Cystinuria</td>
</tr>
</tbody>
</table>
Diagnostic investigation

Initial diagnostic investigation:

- History
- Complete physical examination
- Systolic blood pressure measurement
- Body weight and body condition score (BCS)
- Complete blood count
- Serum chemistry
- T4
- Urinalysis
- Urine protein/creatinine ratio (UPC)
- Urine culture and sensitivity
- Imaging studies (radiographs and ultrasound)
## AKI vs. CKD

<table>
<thead>
<tr>
<th>Characteristics of CKD</th>
<th>Characteristics of AKI</th>
<th>Reliability for differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss &gt; 3 mo.</td>
<td>Normal BCS</td>
<td>++</td>
</tr>
<tr>
<td>Reduced appetite &gt; 3 mo.</td>
<td>Recent reduction of appetite</td>
<td>++</td>
</tr>
<tr>
<td>Poor hair coat</td>
<td>Healthy hair coat</td>
<td>+</td>
</tr>
<tr>
<td>PU/PD &gt; 3 mo.</td>
<td>Recent change in urine volume</td>
<td>++</td>
</tr>
<tr>
<td>Uremic breath &gt; 3 mo.</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Small kidney size</td>
<td>Normal/large kidneys</td>
<td>+++</td>
</tr>
<tr>
<td>Renal osteodystrophy</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Clinical signs mild despite marked azotemia</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Hypoproliferative anemia</td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

Reliability: + = weak; ++ = moderate; +++ = strong.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine (mg/dL) Dogs</th>
<th>Serum creatinine (mg/dL) Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>&lt; 1.4</td>
<td>&lt; 1.6</td>
</tr>
<tr>
<td>Stage 2</td>
<td>1.4 – 2.0</td>
<td>1.6 – 2.8</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2.1 – 5.0</td>
<td>2.9 – 5.0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>&gt; 5.0</td>
<td>&gt; 5.0</td>
</tr>
</tbody>
</table>
### IRIS stages of CKD in dogs and cats

<table>
<thead>
<tr>
<th>Classification</th>
<th>UPC Dogs</th>
<th>UPC Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuric (P)</td>
<td>&gt; 0.5</td>
<td>&gt; 0.4</td>
</tr>
<tr>
<td>Borderline proteinuric (BP)</td>
<td>0.2 – 0.5</td>
<td>0.2 – 0.4</td>
</tr>
<tr>
<td>Nonproteinuric (NP)</td>
<td>&lt; 0.2</td>
<td>&gt; 0.2</td>
</tr>
</tbody>
</table>

UPC = Urine Protein/Creatinine Ratio
IRIS stages of CKD in dogs and cats

<table>
<thead>
<tr>
<th>Arterial Pressure Stage</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>&lt; 150 mmHg</td>
<td>&lt; 95 mmHg</td>
</tr>
<tr>
<td>Stage I</td>
<td>150 to 159 mmHg</td>
<td>95 to 99 mmHg</td>
</tr>
<tr>
<td>Stage II</td>
<td>160 to 179 mmHg</td>
<td>100 to 119 mmHg</td>
</tr>
<tr>
<td>Stage III</td>
<td>&gt; or = 180 mmHg</td>
<td>&gt; or = 120 mmHg</td>
</tr>
</tbody>
</table>
Evidence-based medicine

- **Grade 1:**
  - One or more prospective, randomized, controlled clinical trials
  - Client-owned dogs or cats with naturally occurring disease

- **Grade 2:**
  - Prospective, randomized, controlled clinical trials
  - Laboratory/research colony dogs or cats with naturally occurring disease

- **Grade 3:**
  - Controlled, non-randomized studies
  - Cohort or case-controlled
  - Models of disease
  - Dramatic results from uncontrolled studies

- **Grade 4:**
  - Studies in other species
  - Case reports
  - Pathophysiological justification
  - Expert consensus or opinions
Dietary therapy

- Standard of care is to recommend feeding a renal diet to:
  - Grade 1 evidence for dogs with CKD stages 2-4
  - Grade 1 evidence for cats with CKD stages 2 and 3
  - Grade 3 evidence for cats with CKD stage 4

- Not just restricting protein intake:
  - Reduced phosphorus and sodium
  - Increased B vitamin, soluble fiber, and caloric density
  - Neutral effect on acid-base balance
  - Supplementation of omega-3 polyunsaturated fatty acids
  - Addition of antioxidants
  - Feline renal diets are supplemented with potassium

- Monitor BW, BCS, food intake, serum albumin, PCV/TS, quality of life

- Grade IV evidence for assisted feeding in cats with CKD
Encourage acceptance of therapeutic renal diet:

- Provide owner education
- Implement early
- Transition gradually (3-4 weeks)
- Provide old and new
- Use a suitable food dish
- Avoid stressful periods (food aversion)
- Temperature (fresh at room temp.)
- Texture and formulation (e.g., minced formula or dry vs. moist)
- Add flavor enhancers (e.g., low-sodium chicken broth, tuna juice, oregano, brewer’s yeast, small amount of regular food)
- If all else fails, try a different brand
Gastrointestinal signs of uremia

- **H2 blockers:**
  - Famotidine
  - Ranitidine

- **Antiemetics:**
  - metoclopramide
  - 5-HT3 receptor antagonists
  - NK1 receptor antagonist

- Sucralfate
Hyperphosphatemia

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Target serum Serum Phosphorus Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>3.5-4.5 mg/dL</td>
</tr>
<tr>
<td>Stage 3</td>
<td>3.5-5.0 mg/dL</td>
</tr>
<tr>
<td>Stage 4</td>
<td>3.5-6.0 mg/dL</td>
</tr>
</tbody>
</table>

Aluminum-containing intestinal phosphorus-binding agents: 30-90 mg/kg/d. Calcium acetate: 60-90 mg/kg/d; calcium carbonate: 90-150 mg/kg/d. Lanthanum carbonate: 30 mg/kg/d.

Grade IV evidence for dogs and cats with CKD beyond renal diet, but for each 1U increase in the phosphorus level at the time of diagnosis, there is an 11.8% increase in the risk of death.

Metabolic acidosis

- Metabolic acidosis based on blood gas analysis:
  - < 10% of cats with CKD stages 2 and 3
  - 50% of cats with overt signs of uremia
  - Grade IV evidence for dogs and cats with CKD beyond renal diet

- Alkalization therapy:
  - Indicated in dogs and cats with CKD stages 1 to 4
  - Blood pH < 7.3 and bicarbonate < 12
  - Potassium citrate, 40-60 mg/kg BID-TID
  - Sodium bicarbonate, 20-30 mg/kg PO BID-TID

- Repeat blood gas analysis in 10-14 days
Hypokalemia

- 20-30% of cats with CKD stages 2 and 3
- Up to 30 mEq/L of KCl in SC fluids
- Potassium gluconate (Tumil-K): 2-6 mEq per cat per day
- K citrate sol. (polycitra-K syrup): 40-60 mg/kg/day divided in 2-3 doses
- Recheck serum K concentration in 7-14 days
- Grade III evidence for dogs and cats with CKD, hypokalemia, and no overt clinical signs
- Grade IV evidence for or against for dogs and cats with CKD and normokalemia
- Lack of access to water, vomiting, diarrhea, pyrexia

- Cats seem more likely to benefit from SC fluids than dogs

- Balanced electrolyte solution (e.g., LRS) SC every 1 to 3 days

- 75-100 ml per dose

- Fluid overload; water via a feeding tube

- Grade IV evidence in cats with CKD stage 3 and 4
Anemia

- Common in dogs and cats with CKD stages 3 and 4
  - Insufficient renal erythropoietin
  - Chronic, low-grade gastrointestinal hemorrhage
  - Grade III evidence for rHuEPO in dogs and cats with CKD

- Erythropoietin therapy:
  - Darbepoetin alfa (DPO)
  - DPO is effective in 2 to 8 weeks in 14/25 cats
  - 1 µg/kg/wk or higher
  - Indicated in advanced CKD, symptomatic, and hematocrit < 22%
  - DPO (Aranesp), long-acting erythropoietin, 3 times longer than EPO
  - Substantially less likely to induce antierythropoietin antibodies
  - 1 µ of DPO = 200 U of EPO
  - Side effects: vomiting, hypertension, seizures, and fever

Erythropoietin therapy

- **Induction phase:**
  - DPO 1.5 µg/kg SC weekly
  - Recheck hematocrit weekly (target: lower end of the normal range)
  - Reduce frequency of administration to every other week
  - Polycythemia and death

- **Maintenance phase:**
  - Recheck hematocrit monthly (target: lower end of the normal range)
  - Recheck every 3 months

- **Iron supplementation:**
  - Iron dextran IM (50-300 mg) at the time of starting EPO or DPO
  - Anaphylactic reaction

- **Complications:**
  - Refractory anemia and erythroid hypoplasia
  - Hypertension
Calcitriol therapy

- **Indications:**
  - Grade I evidence in dogs with CKD stages 3 and 4 (possibly stage 2)
  - Grade I and III evidence failed to recommend either for or against use in cats with CKD

- **Preparation:**
  - Manage serum phosphorus first to achieve treatment targets
  - Absence of ionized hypercalcemia

- **Dosage:**
  - 2.0-2.5 ng/kg every 24 hours
  - Administration in the evening on an empty stomach
  - If hypercalcemia occurs, double the daily dose and give every other day
  - Should not exceed about 5.0 ng/kg/d

- **Monitoring:**
  - Ideally obtain baseline ionized calcium and PTH
  - Repeat serum phosphorus, ionized calcium and PTH
Proteinuria

Indications:
- Dogs and cats with CKD stages 2, 3 and 4 when UPC > 0.5 and 0.4
- Dogs and cats with CKD stage 1 when UPC > 2.0
- Grade I evidence to reduce proteinuria in cats with CKD
- Grade I and grade III evidence for or against to prolong survival in cats with CKD
- Grade I evidence for increasing appetite in cats with UPC > 1.0
- Grade II evidence to reduce proteinuria and prolong survival in dogs with PLN

Angiotensin-converting enzyme inhibitors:
- In combination with renal diet
- Enalapril or benazapril 0.25-0.5 mg/kg PO q12-24hrs
- Enalapril up to 2.0 mg/kg/d

Adverse effects:
- Decline in kidney function
- Hyperkalemia

Monitoring:
- Serum creatinine and potassium before and 1 to 2 weeks after initiating therapy
**Indications:**
- Ocular lesions or neurologic signs or systolic BP > 200 mmHg
- At least 3 independent measurements over several days to weeks
- Dogs and cats with CKD stages 2 to 4 and systolic BP > 160 mmHg
- Dogs and cats with CKD stage 1 and systolic BP > 180 mmHg

**Calcium channel blockers:**
- Amlodipine (Grade III evidence in cats with CKD)
- Few side effects and relatively rapid onset of action
- In cats, it may reduce proteinuria
- Cats: 0.625 mg/cat if < 5 kg; 1.25 mg/cat if > 5 kg
- Dogs: 0.1-0.5 mg/kg every 24 hours
Enteric dialysis:

- Recruiting the gastrointestinal tract as a means of excreting wastes normally eliminated by the kidneys;
- Polymers designed for oral administration adsorb uremic toxins and excess fluid in the gastrointestinal tract for excretion in the feces.


Azodyl:

- Synbiotic (probiotic-prebiotic combination), containing strains of 3 naturally occurring bacteria and psyllium husk in an enteric-coated capsule that releases the contents in the ileo-colic region;
- designed for oral administration to enhance gastrointestinal excretion of nitrogenous waste products and ameliorate clinical signs of uremia;
- one case series suggested that this synbiotic, administered by sprinkling onto food, reduced azotemia in cats with CKD, but a recent double-masked, controlled clinical trial failed to demonstrate improvement of azotemia.

Injected mesenchymal stem cells:

- paracrine effects;
- unilateral intrarenal injection;
- large number of sedations;
- unlikely clinical application;
- intravenous administration;
- allogeneic instead of autologous.
Prognosis

- **Dogs:**
  - Poorer with CKD stages 3 and 4
  - Months to a year or two
  - Die or are euthanized because of CKD
  - Proteinuria and hypertension are negative prognostic indicators

- **Cats:**
  - Variable clinical course, but progresses slower than dogs
  - Months to years
  - Die or euthanized for causes unrelated to CKD
  - Proteinuria is a negative prognostic indicator (cats with UPC>0.4 have a 4 times higher risk of death compared to cats with UPC<0.2)

Prognosis

- Median survival for cats with CKD:
  - Stage IIb (crea. > 2.3 - 2.8 mg/dL): 1,151 days (range, 2 - 3,107)
  - Stage III (crea. 2.9 - 5.0 mg/dL): 778 days (range, 22 - 2,100)
  - Stage IV (crea. > 5.0 mg/dL): 103 days (range, 1 – 1,920)


- Median survival for cats with CKD:
  - Stage IIb: normotensive, 504 days; hypertensive, 187 days.
  - Stage III: normotensive, 154 days; hypertensive, 281 days.
  - Stage IV: normotensive, 57 days; hypertensive, 21 days.

Follow-up monitoring

- **When stable:**
  - Dogs and cats with CKD stages 3 and 4, every 1-2 months
  - Dogs and cats with CKD stages 1 and 2, every 4-6 months

- **Recheck:**
  - History
  - Blood pressure
  - Physical examination
  - Body weight and BCS
  - Hematocrit
  - Serum chemistry
  - Urinalysis
  - UPC
  - Urine culture
• Median survival time and renal transplantation:
  
  • Baseline creatinine > 4.0 mg/dL: 123 days
  
  • Baseline creatinine > 5.0 mg/dL: 44 days


• Median survival time and renal transplantation:

  • Serum creatinine > 4.5 mg/dL: 21 days (range, 5 – 63 days).

  Elliot et al., *J Small Anim Pract* 2003; 44: 261-268
Renal transplantation

- Recommended criteria:
  - early decompensated CKD;
  - weight loss of no greater than 20% of healthy body weight;
  - no recent urinary tract infection;
  - no concurrent serious medical conditions;
  - no evidence of cardiac dysfunction;
  - negative tests for chronic systemic viral infections;
  - emotional and financial commitment by the owner.
<table>
<thead>
<tr>
<th>Evidence grade</th>
<th>Therapeutic recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Renal diets in dogs (CKD stage 2-4) and cats (CKD stage 2 and 3)</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors (reduce proteinuria and increase appetite in cats with CKD and UPC &gt; 1.0)</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>ACE inhibitors in dogs with PLN</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Renal diets in cats with CKD stage IV</td>
</tr>
<tr>
<td></td>
<td>Amlodipine in cats with CKD and proven hypertension</td>
</tr>
<tr>
<td></td>
<td>Recombinant human erythropoietin in cats and dogs with CKD</td>
</tr>
<tr>
<td></td>
<td>Potassium supplementation in dogs and cats with CKD and hypokalemia</td>
</tr>
<tr>
<td></td>
<td>Dietary phosphorus restriction in dogs and cats with CKD stage 3 and 4</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Long-term administration of SC fluids in cats with CKD</td>
</tr>
<tr>
<td></td>
<td>Potassium supplementation in dogs and cats with CKD and normokalemia</td>
</tr>
<tr>
<td></td>
<td>Intestinal phosphate binders in dogs and cats with CKD</td>
</tr>
<tr>
<td></td>
<td>Alkalinizing therapy in dogs and cats with CKD</td>
</tr>
<tr>
<td></td>
<td>Assisted feeding in cats with CKD</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors in non-proteinuric cats with CKD</td>
</tr>
</tbody>
</table>