CKD: Updates on Diagnosis, Treatment, and How to Delay Progression

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Specialized Veterinary Services

IRIS Staging of Chronic Kidney Disease (Dogs)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine (mg/dl)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>&lt;1.4</td>
<td>Animal at increased risk.</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>Nonazotemic. Some other renal abnormality present.</td>
</tr>
<tr>
<td>2</td>
<td>1.4-2.0</td>
<td>Mild renal azotemia. Clinical signs usually mild or absent.</td>
</tr>
<tr>
<td>3</td>
<td>2.0-5.0</td>
<td>Moderate renal azotemia. Extrarenal clinical signs may be present.</td>
</tr>
<tr>
<td>4</td>
<td>&gt;5.0</td>
<td>Increasing risk of severe crisis.</td>
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IRIS Staging of Chronic Kidney Disease (Cats)

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<tr>
<th>Stage</th>
<th>Creatinine (mg/dl)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>At Risk</td>
<td>&lt;1.6</td>
<td>Animal at increased risk.</td>
</tr>
<tr>
<td>1</td>
<td>&lt;1.6</td>
<td>Nonazotemic. Some other extrarenal abnormality present.</td>
</tr>
<tr>
<td>2</td>
<td>1.6-2.8</td>
<td>Mild renal azotemia. Clinical signs usually mild or absent.</td>
</tr>
<tr>
<td>3</td>
<td>2.8-5.0</td>
<td>Moderate renal azotemia. Extrarenal clinical signs may be present.</td>
</tr>
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<td>4</td>
<td>&gt;5.0</td>
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Symmetric dimethylarginine (SDMA)

- Creatinine is most commonly used to estimate GFR
- SDMA also used to evaluate GFR
  - Occurs from methylation of arginine (all nucleated cells)
  - Excreted exclusively in the urine
  - Increases when GFR increases
  - Not influenced by lean muscle mass
  - SDMA can increase with 25-40% loss of renal mass

Substaging by Proteinuria

- Rule out pre-renal
  - Hemoglobin
  - Myoglobin
  - Immunoglobulins
- Rule out post-renal
- Goal is to identify renal proteinuria
  - Tubular
  - Glomerular (>2.0)

Substaging by Proteinuria

- UPC should be measured in all cases
  - Rule out hemorrhage and UTI
  - If azotemic and UPC>1.0 (greater risk)
  - Need at least 2 urine samples 2 weeks apart
  - If borderline re-evaluate in 2 months
  - Proteinuria may decline as renal function worsens
Response to Persistent Proteinuria

- Monitor
  - Detect worrisome trends
  - Stable patients “at risk”
- Investigate
  - Treatable infections
  - Inflammation
  - Neoplasia

Response to Persistent Proteinuria

- Intervene
  - Slow the rate of progression
  - Diet
    - Omega-3 fatty acids
      - Evaluate Omega 6:3 ratio (5:1)
      - Dosage 0.25-0.5 g/kg (DHA & EPA)
      - Safe upper limit 140 mg/kg
      - 1.1 IU of Vit E/kg of fish oil
      - Nordic Naturals, Welactin, Nature’s logic
    - RAAS Inhibition

Nonazotemic Dogs and Cats

<table>
<thead>
<tr>
<th>Level of Response</th>
<th>Magnitude of Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor</td>
<td>MA, UPC ≤ 0.5</td>
</tr>
<tr>
<td>Investigate</td>
<td>UPC &gt; 1.5</td>
</tr>
<tr>
<td>Intervene</td>
<td>UPC &gt; 2.0</td>
</tr>
</tbody>
</table>

- RAAS Inhibition
Substaging by Blood Pressure

<table>
<thead>
<tr>
<th>Blood Pressure Intervals</th>
<th>Blood Pressure Stage</th>
<th>Risk of Organ Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>Normotensive</td>
<td>Minimal</td>
</tr>
<tr>
<td>150-159</td>
<td>Borderline Hypertensive</td>
<td>Low</td>
</tr>
<tr>
<td>160-179</td>
<td>Hypertensive</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;180</td>
<td>Severely Hypertensive</td>
<td>High</td>
</tr>
</tbody>
</table>

- Take multiple blood pressure measurements
- Use breed specific reference ranges
- Sighthounds tend to have higher blood pressure

- Target organ damage
  - Eyes
  - Brain
  - Kidneys
  - Cardiovascular system

Inhibition of Renin-Angiotensin-Aldosterone System (RAAS)

- RAAS= major target system to reduce proteinuria
- Angiotensin-converting enzyme inhibitor (ACEI)
  - Enalapril and Ramipril
  - Proven to reduce proteinuria (Grauer et al, 2000)
- Angiotensin-receptor blocker (ARB)
  - Losartan and Telmisartan
- Aldosterone-receptor blocker
  - Spironolactone
- Renin Inhibitors
  - Aliskirine
Doses of Common Inhibitors of RAAS

<table>
<thead>
<tr>
<th>Dose</th>
<th>Brand Name</th>
<th>Schedule</th>
<th>Target Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125 mg/kg PO q24h</td>
<td>Benazepril</td>
<td>Definite</td>
<td>12.5 mg PO once daily</td>
</tr>
<tr>
<td>0.25 mg/kg PO q24h</td>
<td>Lisinopril</td>
<td>Definite</td>
<td>25 mg PO once daily</td>
</tr>
<tr>
<td>5 mg PO q24h</td>
<td>Enalapril</td>
<td>Definite</td>
<td>5 mg PO once daily</td>
</tr>
<tr>
<td>10 mg PO q24h</td>
<td>Captopril</td>
<td>Definite</td>
<td>10 mg PO once daily</td>
</tr>
</tbody>
</table>

Inhibition of RAAS

• Angiotensin-converting enzyme inhibitors (ACEis)
  • Decrease efferent arteriolar resistance
  • Serum Creatinine should be monitored
  • Creatinine (>30% from baseline)
  • Increased risk with dehydration
  • Caution with Stage 4 CKD
  • Hyperkalemia
  • Enalapril
    • Primarily excreted by kidney
  • Benazepril
    • Mostly eliminated through liver
    • Not affected by renal function

Inhibition of RAAS

• Angiotensin-receptor blockers (ARBs)
  • Block Angiotensin II receptor
  • Reduce proteinuria
  • Combined therapy (ACEi & ARB)
    • Blockade of AII receptor-increased renin
    • ACEi incompletely block formation of Angiotensin II
    • Monotherapy-incomplete block of RAAS
  • Aldosterone-receptor blockers
    • Adverse effects from hyperaldosteronism
    • Useful if persistent proteinuria with ACEi & ARB
Monitoring RAAS Inhibition

- When adjusting therapy (dose or drug)
  - 1-2 weeks
  - Creat, K, BP, UPC
  - Day-to-day variation in UPC
    - Greater when UPC>4.0 (Nabity MB. et al, 2007)
  - Use 2-3 collections
  - Target UPC <0.5

- Hyperkalemia
  - Common in dogs with renal disease
  - Potassium >6.0 (monitor)
    - Evaluate ECG
  - Potassium >6.5 (modify)

- Treatment
  - Reduce ACEi or ARB
  - Stop Spironolactone
  - Potassium-reduced home cook diet (Segovis C. et al, 2010)
  - Potassium binder (Kayexalate)

Antithrombotic Therapy

- Thromboembolism=complication of proteinuria
  - Reported rate up to 25% (Cook AK. et al, 1996)
  - Reduced level of Antithrombin III
    - Correlate with albumin
    - Increased risk of thromboembolism

- Heparin and Warfarin
  - Current recommendations (Consensus Statement)
    - Low dose aspirin (0.5-5.0 mg/kg daily)
    - <1 mg/kg/day may not be effective (Hoh CM. et al, 2011)
    - Clopidogrel 1.1 mg/kg q24
Hypertension

- Often silent and slowly progressive
- Be certain of diagnosis
  - White-coat effect
  - Evaluate
    - Cuff size
    - Site
    - Position
- When to treat
  - Systolic > 160 mmHg
  - Diastolic > 100 mmHg
- Goals of treatment
  - Systolic < 150 mmHg
  - Diastolic < 95 mmHg

Management of Hypertension

- RAAS Inhibitors
  - Reduce BP 10-15%
  - Antiproteinuric
  - ACE is appropriate 1st step
  - ARB if needed
  - Calcium channel blocker (Amlodipine)
    - 0.1-0.75 mg/kg PO q24
- Beta Blocker (Atenolol)
  - 0.25-1.0 mg/kg PO q12
  - Direct Vasodilator (Hydralazine)
    - 0.5-2mg/kg PO q12

Renal Secondary Hyperparathyroidism

- Reduced GFR
  - Promotes phosphorus retention
  - Inhibition of 1a-hydroxylase
  - Decrease calcium
- Increased PTH production
  - Increase phosphaturia
  - Maintain normal phosphate (initially)
- Calcitriol deficiency
  - Parathyroid gland hyperplasia=PTH
  - Want to minimize Ca & P disturbances
Dietary Intervention

• Feed a Renal Diet
  • 1st step in treatment of CKD
  • IRIS Stage 2-4
  • Recent studies show benefit: IRIS Stage 1
  • Geriatric dogs (Hall JA et al, 2016)
  • Geriatric cats (Hall JA et al, 2016)
  • Controversial in cats
  • Modest protein restriction

• Diet modifications
  • Reduced protein, phosphorus
  • Increased B vitamins, caloric density and soluble fiber
  • Supplemented omega 3 and antioxidants
  • Major benefit
  • Decrease progression of CKD
  • Increase survival

Phosphorus

• Negative effects of phosphorus
  • Renal secondary hyperparathyroidism
  • Increased levels of FGF-23 (Finch NC et al, 2013)
  • Reduced levels of calcitriol
  • Increased Ca x P product=mineralization
  • Risk of death 4.2x higher when Ca x P product>70 (Braff J et al, 2014)
  • Progression of CKD
  • Phosphorus Goal
  • 2.7-4.5 g/dl
  • Optimal goal-lower half of RR

Phosphorus Binders

• Aluminum Salts
  • Most commonly used
  • Inexpensive
  • Good phosphorus binding
  • No known safe dose in humans
  • 30-100 mg/kg/day-divided with meals
  • GIVE WITH FOOD!
  • Monitor q10-14 days, then 4-6 weeks

• Side effects
  • Constipation
  • Hypophosphatemia
  • Reduced drug absorption
  • Fluoroquinolones, Tetracyclines, Steroids, Thyroid hormones, H-2 antagonists
  • Aluminum toxicity (chronic use)
  • Neuromuscular effects, Myocytosis
Calcium Salts

- Calcium Acetate (PhosLo, Calphron)
  - Good phosphorous binder
  - 2x more than Calcium Carbonate
  - Less Hypercalcemia
  - Caution with Calcitriol
  - Drug Interactions: Fluoroquinolones, Tetracyclines, Levothyroxine, Calcitriol
  - Dose 20-40 mg/kg each meal

- Calcium Carbonate (Epakitin/Tums)
  - Oral phosphorus binder, antacid
  - Dose 90-150 mg/kg/day
  - Divided and given with meals

Alternate Phosphorus Binders

- Sevelamer (Renagel)
  - No Calcium/Aluminum
  - Expensive
  - May reduce absorption of vitamins
  - Dose 200-1600 mg/dose q8-12

- Lanthanum Carbonate (Lantharenol/Renalzin)
  - Excellent phosphorus binder
  - No known toxicities
  - Really Expensive!
  - Dose 30-60 mg/kg/day

Alternate Phosphorus Binders

- Lenziaren (SBR759)
  - New oral phosphorus binder
  - Insoluble complex of iron oxide/hydroxide
  - Increased binding of iron to phosphate
  - Not yet commercially available
  - Dose 0.125-1.0 g/day

- Niacinamide
  - Safe and fairly effective
  - Contraindicated with liver dz, ulcers
  - Dose 125-500 mg/day
Calcitriol

- Why use Calcitriol with CKD?
  - Decreased PTH
  - Minimal increase in iCa
  - Correct absolute/relative deficiency
  - Occupy Vitamin D receptors
- Intra-renal effects
  - Anti-inflammatory
  - Anti-fibrotic
  - Reduce RAAS
- Increased survival for azotemic dogs (Polzin D et al, 2005)
- IRIS Stage 3-4
- Mean Creatinine 4.0
- MST 365 days vs 250 days

Calcitriol

- Ca and P levels should be normal
  - Prior to treatment (<6.0 mg/dl)
  - Do not use if hyperphosphatemic
  - Increased risk for tissue mineralization
  - Caution if susceptible to CaOx uroliths
  - Promotes hypercalciuria
- If hypercalcemia develops
  - Discontinue use (at least 1 week)
  - Therapy may be able to be reinstituted
  - Lower dose, altered dosing
  - Monitor Ca, P PTH
  - Assess after 1-2 weeks, then q 6 months
  - PTH also measure after 4-6 weeks
  - Increase dose if still elevated

Calcitriol-Emerging Protocol

- High Dose Twice Weekly
  - 9-12ng/kg q 3.5 days
  - 2.5-3.5 ng/kg q 3.5 days
  - Tuesday PM, Saturday AM
  - Wednesday AM, Saturday PM
  - Still Controls PTH
  - Lessens Concern for Hypercalcemia
- Daily Dosing
  - 2-2.5 ng/kg PO SID (initially)
  - Do not exceed 5 ng/kg/day
  - Preferably in evening/empty stomach

Specialized Veterinary Services 24 Hour Animal Emergency
Vitamin D and D-metabolite Options

- Vit D$_2$ - Ergocalciferol
  - Initial: 4,000-6,000 U/kg/day
  - Maintenance: 1,000-2,000 U/kg daily-weekly
  - Onset: 5-21 days
- 25(OH) Vit D - Calcidiol
- 1,25(OH)$_2$ VitD - Calcitriol
  - Initial: 20-30 ng/kg/day (3-4 days)
  - Maintenance: 5-15 ng/kg/day
  - Rapid onset (~1-4 days)
  - Short duration (2-3 days)

Hypokalemia

- Potassium depletion
  - Uncommon in dogs
  - Common in cats IRIS stage 2-3
- Negative effects
  - Reduced renal blood flow
  - Promotes polyuria
  - Hypokalemic polymyopathy
  - Muscle weakness, Cervical ventroflexion
- Oral supplementation
  - Potassium gluconate (2-6 mEq/cat/d)
  - Potassium citrate (40-60 mg/kg/d)
  - Alkalization therapy

Metabolic Acidosis

- When to supplement
  - HCO$_3$ < 15 mmol/L
- Treatment options
  - Renal diet
  - First step
  - Sodium bicarbonate
    - 0.22 mg/kg q8-12 hrs
  - Potassium citrate
    - Hypokalemia + Metabolic acidosis
    - 40-60 mg/kg q8-12 hrs
    - Risk for excessive alkalization
  - Parenteral NaHCO$_3$
    - pH > 7.10

- Oral supplementation
  - Potassium gluconate (2-6 mEq/cat/d)
  - Potassium citrate (40-60 mg/kg/d)
  - Alkalization therapy
Anemia

- Multifactorial
  - Latrogenic
  - Blood loss
  - Reduced lifespan
  - Poor nutrition/Fe deficiency
  - Decreased EPO

- Treatment
  - H2 blockers/Proton pump inhibitors + Sucralfate
  - Iron Dextran
    - 10-20 mg/kg IM
  - Ferrous sulfate
    - 100-300 mg per dog PO SID

- Erythropoietin
  - Erythropoietic agent
  - 100 units/kg SQ 3x weekly

- Darbepoietin (Chalhoub et al, 2012)
  - Recombinant human analog
  - Less immunogenic
  - Administer less frequently
  - More expensive
  - When to start?
    - PCV<20%
    - 0.25-1.0 mcg/kg SQ weekly

Other Management

- Drug Therapy
  - Use caution with renal metabolism
  - Antibiotics
    - Penicillins, cephalosporins, fluoroquinolones, aminoglycosides
  - Amphotericin B
  - Chemotherapy
    - Cisplatin, Carboplatin, Doxorubicin
  - Atenolol
  - Gabapentin
  - Other

- Subcutaneous fluids
  - As needed to maintain hydration
  - IRIS Stage 3-4

- Antihypertensive medications
  - Atenolol
  - Gabapentin

- Analgesia
  - Atenolol
  - Gabapentin

- Corticosteroids
  - As needed for IRIS Stage 3-4

- Other
  - Subcutaneous fluids
  - Analgesia
  - Corticosteroids
  - Antihypertensive medications
Summary CKD Treatment

- Diet
- Great phosphorus control
- Great proteinuria control
- Great blood pressure control
- RAAS Inactivation
- Calcitriol
- Other management

References

- Hall JA et al. JAVMA 2016; 11:e0153654
- Hall JA et al. JAVMA 2016; 11:e0153653

References

- Hoh CM, Smith SA, McMichael M, Byrne JE. Urinary thromboxane metabolites are inconsistently affected by low dose aspirin administration to healthy dogs. JAVMA 2011; 72:1038.