Chronic Kidney Disease in Cats

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Chronic Kidney Disease

- Most common kidney disease in geriatric cats
  - 30% - 40% of geriatric cats (Bartges 2012, Marino, 2014)
  - Mean age 12.6 yrs, range 1-26 yrs (Ettinger 2012, Bartges 2012)

- Irreversible
  - Functional and/or structural abnormalities

- Progressive
  - Stable periods with slow decline in function over time
  - Compensatory hypertrophy & hyperplasia has occurred (> 3 months following acute nephron loss)
Markers of Kidney Damage

- **Blood**
  - ↑ BUN, CREA, phosphorus, potassium
  - ↓ potassium, albumin
  - Metabolic acidosis

- **Urine**
  - Impaired concentration
  - Proteinuria, cylinduria, hematuria, cystinuria
  - Inappropriate pH or glucosuria

- **Abnormalities on imaging**
Staging CKD

- Proposed by International Renal Interest Society (IRIS)
- Guidelines for diagnosis, prognosis and treatment
- Based on level of kidney function
  - Best GFR
  - Creatinine more practical
    - Use ≥ 2 measurements over several weeks
    - Patient fasted and well hydrated
    - Reduced muscle mass
**CKD Stages**

**Stage 1** *(Nonazotemic)*
- Markers of renal disease present
- Creatinine <140 μmol/L (<1.6 mg/dl)

**Stage 2** *(Mild renal azotemia)*
- Markers of renal disease present, clinical signs mild or absent
- Creatinine 140-250 μmol/L (1.6-2.8 mg/dl)

**Stage 3** *(Moderate renal azotemia)*
- Creatinine 251-440 μmol/L (2.8-5.0 mg/dl)

**Stage 4** *(Severe renal azotemia) = Chronic kidney failure*
- Creatinine > 440 μmol/L (>5.0 mg/dl)
Proteinuria

Urine protein:creatinine ratio (UPC)

- Eliminate hemorrhage, infection, inflammation
- Examine 2-3 times over 1-2 months

- **Proteinuric (P)**
  - UPC > 0.4

- **Borderline proteinuric (BP)**
  - UPC 0.2-0.4
  - Re-evaluate after 2 months

- **Non-proteinuric (NP)**
  - UPC < 0.2
  - Role of microalbuminuria?

(ACVIM consensus, 2004; Lees, 2005)
Systemic Hypertension

- **Minimal (MN)**
  - < 150/95 mmHg
- **Low (L)**
  - 150/95 to 159/99 mmHg
- **Moderate (M)**
  - 160/100 to 179/119 mmHg
- **Severe (S)**
  - > 180/120 mmHg
- **Complicated (c)**
  - Evidence of end-organ hypertensive injury
- **Non-complicated (nc)**
  - No evidence of end-organ injury (ocular, neurologic, cardiac)

(2004 ACVIM Hypertension Consensus Group and IRIS)
Introducing SDMA: Symmetric Dimethylarginine

- New kidney function test
- Identifies kidney disease earlier
- Not impacted by lean muscle mass
- Opportunity for early kidney disease management
SDMA Increases Earlier than Serum Creatinine in Cats with CKD

Comparison of Serum Concentrations of Symmetric Dimethylarginine and Creatinine as Kidney Function Biomarkers in Cats with Chronic Kidney Disease

J.A. Hall, M. Yerramilli, E. Obare, M. Yerramilli, and D.E. Jewell

- Study published in JVIM 2014
- 21 cats with CKD living at Hill’s® Pet Nutrition cat colony
- SDMA earlier than creatinine mean of 17.0 months (range 1.5–48 months)
- SDMA detects as early on average with 40% loss of GFR and as little as 25% reduction
Tools for Early Detection of CKD

Using “old” tools better: trending creatinine with VetConnect Plus

New kidney function test: SDMA

(Modified from Heska®)
How to Interpret SDMA with Creatinine

- SDMA should always be interpreted along with creatinine and urinalysis.
- Diagnostic algorithms and interpretive comments promote complete kidney evaluation.

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- Kidney disease unlikely
- Early kidney disease
- Poor body condition
- Highly muscled
- Kidney disease possible
- Kidney disease likely
IRIS Updated CKD Guidelines include SDMA

- **Stage 1**
  - Persistent SDMA >14 ug/dl

- **Stage 2**
  - Consider as stage 3 if low BCS & SDMA >25 ug/dl

- **Stage 3**
  - Consider as stage 4 if low BCS & SDMA >45 ug/dl

Goals of Therapy

- Early intervention
- Enhance quality of life
- Free of adverse effects
- Reasonable demands
  - Owner’s time
  - Finances
- Not disrupt owner-pet relationship
- Based on randomized controlled clinical trials
Treatment CKD

- Conservative medical management
  - Ameliorate clinical signs of uremia
  - Nutritional support
  - Protect gastrointestinal tract
  - Correct fluid, electrolyte & acid-base disturbances
  - Minimize renal secondary hyperparathyroidism
  - Decreasing proteinuria and/or hypertension
  - Improve anemia
  - Renoprotective therapy
Dietary Therapy

- Most commonly recommended
  - Protein restriction
  - Reduced phosphorus & sodium
  - Increased B-vitamins, calories
  - Neutral effect on acid-base
  - Potassium supplementation in feline diets
  - Increased omega-3/omega-6 PUFA ratio

- Strong evidence - IRIS stage mid-2 to 4 in cats
  - Renal diets: MST 16 – 23 months vs 7 months (Plantinga, 2005)
  - Median survival 633 days vs 264 days (Ross, 2006)
Dietary Therapy

- Malnutrition major cause of morbidity & mortality
- Ideally maintain BCS of 2.5-3/5 or 4-5/9

- Appropriate renal diet
- Highly palatable diet
  - Increase palatability of diet
- Treatment to decrease anorexia and nausea
  - Uremic gastroenteritis, retained uremic toxins
  - Acidosis, electrolyte imbalances, dehydration
  - Anemia
- Feeding tube placement
Treatment of Gastrointestinal Signs

- Stage 3 & 4 CKD
- Treatment to ameliorate uremic gastritis
  - Antacids
    - H₂ blockers (ranitidine, famotidine)
    - Proton pump inhibitors (omeprazole)
  - Antiemetics (metoclopramide, ondansetron, maropitant)
    - Maropitant significantly reduced vomiting (Quimby, 2015)
  -Sucralfate
    - GI ulceration & phosphate binder
  - Appetite stimulant and anti-emetic (mirtazapine) (Quimby, 2013)
Maintain Hydration

- Stages 2-4 CKD in dogs and cats
  - Clinical evidence of dehydration (esp. cats)
- Acute dehydration
  - Intravenous balanced electrolyte solution (BES)
  - Oral or subcutaneous (mild dehydration)
- Chronic dehydration
  - Encourage water intake
  - Subcutaneous fluids
  - Feeding tube to provide water
Omega-3 fatty acid Supplementation

- Stages 2-4 CKD, Stage 1 CKD with proteinuria
  - Ideal quantity unknown
  - Ratio of 3:1 to 5:1 omega-6:omega-3 fatty acids
- Most renal diet supplemented
- Benefits?
  - Renoprotective (structure and function)
  - Reduce proteinuria and hypertension
  - Anti-inflammatory, anti-thrombotic & antioxidant effects
- Improved survival in cats fed diet highest omega-3 fatty acid content  
  (Plantiga et al, 2005)
Vitamin Supplementation

- Proposed vitamin B deficiency due to
  - Polyuria
  - Anorexia, decreased appetite
- No studies investigating in cats
- Majority of renal diets supplemented with B vitamins
- Vitamin E, vitamin C and β-carotene supplements as anti-oxidants maybe beneficial in CKD cats
  - Cats with CKD showed increased oxidative stress
  - Antioxidant supplements significantly reduced DNA damage

(Yu, 2006)
Supplements

- **Azodyl**
  - Probiotic-prebiotic combination
    - Bacteria metabolize uremic toxins to non-toxic metabolites
    - Combined with prebiotic (psyllium husk)
  - Clinical trial 10 cats: No reduction in azotemia in cats with stable CKD when combined with food  
    (Rishniw et al., 2011)

- **Rubenal**
  - Extract of medicinal rhubarb (*Rheum officinale*)
  - Study of CKD cats: No benefit when administered alone or in combination with benazepril  
    (Hanzlicek, 2014)
Supplements

- **Pronefra** (Virbac)

  - **Active ingredients:**
    - Two intestinal phosphate binders
    - Calcium & magnesium carbonate
    - Polysaccharides of *Astragalus membranaceus*
    - Protensin vasoactive peptides (fish protein hydrolysate)
    - Chitosan binds uremic toxins

  - Most palatable oral suspension *(Bernachon, 2014)*

  - 1 ml/4 kg q 12 hours with food

  - Iris stages 2, 3 & 4
Management of Serum Potassium

- Stages 1-4 CKD in cats
  - Outside of target range 3.5 to 5.5 mmol/L
- Hypokalemia: goal serum $K^+ > 4.0$ mmol/L
  - Renal tubular disorder
    - Parenteral potassium salts (KCl)
    - Supplement diet (potassium gluconate or citrate)
- Hyperkalemia
  - Stage 4 CKD or ACE inhibitor therapy
    - Diet restriction or dose reduction
- Weak evidence
Metabolic Acidosis Correction

- Stages 1-4 CKD in dogs and cats
  - Bicarbonate < 18 mmol/L, TCO₂ < 19 mmol/L

- Treatment with alkalinizing salt
  - Potassium citrate
  - Sodium bicarbonate
    - Risk of worsening systemic hypertension

- Weak evidence
Renal Secondary Hyperparathyroidism
Phosphorus Management

- Dietary phosphorus restriction
  - Stage 2 & 3
  - Effect apparent after 28-49 days (cats)
  - 12-hour fast
    - Avoids post-prandial ↑phosphorus
Renal Secondary Hyperparathyroidism
Phosphorus Management

- Intestinal phosphate binding agent
  - Some stage 3 & most stage 4 with renal diet
    - Aluminum (hydroxide, oxide or carbonate)
    - Calcium (carbonate, acetate, citrate)
      - Chitosan with calcium carbonate (Epakitan)
    - Sevalemer HCl (Renalgel)
    - Lanthanum carbonate (Fosrenal)
    - Lenziaren®
      - Insoluble complex of iron (III) oxide/hydroxide
      - Well tolerated, improved appetite
      - Significant reduction in phosphate  (King, 2015)
Renal Secondary Hyperparathyroidism
Calcitriol Therapy

- Stages 3-4 CKD
  - Treatment of hypovitaminosis D
  - Phosphorus < 1.9 mmol/L (<6.0 mg/dl)
  - May cause hypercalcemia

- Weak evidence
  - No survival benefit in randomized controlled clinical trial with any stage of CKD
    (Hostutler, 2006)
  - No benefit improving appetite, activity level or quality of life
Management of Proteinuria

- Stages 1-4 CKD in cats
  - UPC ratio > 2.0 in stage 1
  - UPC ratio > 0.4 in stages 2-4

- Protein-restricted diet
- ACE inhibitor therapy
- Angiotensin receptor blockers
- Omega-3 fatty acids
ACE Inhibitors

- **Benefits**
  - Lower UPC ratio with benazepril therapy
  - Increased appetite and trend prolonged survival *(Mizutani, 2006)*
  - UPC > 1.0 had MST 402 days vs 149 days *(King, 2006)*

- Benazepril preferred over enalapril
  - Hepatic metabolism

- **Discontinue therapy**
  - Increase creatinine >30% over baseline
  - Inappetence
Angiotensin Receptor Blockers

- **Semintra® (telmisartan)**
  - Boehringer Ingelheim
  - Selectively blocks AT₁ receptor
  - No angiotensin breakthrough
  - 1 mg/kg BW q 24 hours (4 mg/ml)
  - Licensed in cats
  - ‘Not inferior’ to benazepril in reduction proteinuria
    - Not recommended with ACE inhibitors
  - Comparison study in 8 healthy cats suggest advantages over benazepril for blood pressure attenuation *(Jenkins, 2015)*
Management of Systemic Hypertension

- Stages 1-4 CKD in dogs and cats
  - BP > 180/120 mmHg, stage 1
  - BP > 160/100 mmHg, stage 2-4

- Determine 3 separate blood pressure values
  - Except if retinal lesions or neurologic signs

- Goal: Reduce BP < 150-160 mmHg

- Retrospective study (265 CKD, 133 health cats)
  - Higher risk of hypertension in CKD vs healthy cats
  - Systolic BP significantly increased with age (Bijsmans, 2015)
Management of Systemic Hypertension

- **Amlodipine (calcium channel blockers)**
  - Most effective (reduce BP by 30-50 mmHg)
  - Significantly reduce development retinal lesions
  - Minimal side effects
  - Chewable amlodipine effectively reduced BP and well-tolerated (Huhtinen, 2015)

- **ACE Inhibitors**
  - Reduce intraglomerular hypertension
  - Decrease degree of proteinuria
  - Reduce systolic BP ~10 mmHg
  - Risk worsening azotemia and hyperkalemia
Management of systemic hypertension

- Other treatments
  - Beta-blockers (atenolol)
  - Alpha-blockers (prazosin)
  - Direct arteriolar vasodilators (hydralazine)
  - Aldosterone receptor antagonists (spironolactone)
  - Aliskiren (renin blockade)
  - Endothelin receptor blockers
    - Decreases vasoconstriction, glomerular hypertension, interstitial fibrosis

Taylor, 2013
Correction of Anemia

- Stage 3-4 CKD
  - PCV < 20%
  - Clinical signs
- Goals of treatment
  - Reduce renal cellular hypoxia
  - Target PCV 25-35%
    - Blood transfusion
    - Erythrocyte stimulating agents
      - B vitamin supplement
      - L-carnitine?
    - Management uremic gastroenteritis
Erythrocyte-Stimulating Agents

- **Epoetin**
  - 100 IU/kg SQ 3x/week
  - Target PCV ≥ 25%
  - Response 3-4 weeks
  - Maintenance dose 50-100 IU/kg 2x/week
  - Less expensive
  - PRCA 25-30%
  - Iron supplementation

- **Darbepoetin**
  - Hyperglycosylated rHuEPO
  - Longer half life
  - 1 ug/kg SQ 1x/week
  - Response 2-3 weeks
  - Target PCV 25-35%
  - Maintenance 1x/2-3 weeks
  - PRCA <10%
  - Iron supplementation
Erythrocyte-Stimulating Agents

- Monitoring
  - Weekly
    - PE, PCV, BP, reticulocyte count
  - 1-3 months
    - PE, Biochemical or renal profile, CBC, BP

- Complications
  - Iron deficiency anemia, hypertension, arthralgia, fever, seizures, pure red cell aplasia, polycythemia.

(Chalhoub, 2011)
Erythrocyte-Stimulating Agents

- Inadequate response to treatment (35-40%)
  - Iron deficiency
    - Functional iron deficiency in anemic CKD cats (Gest, 2015)
  - Infection/inflammation
  - Dose and correct administration
  - Deficiency B vitamins, L-carnitine
  - Aluminum toxicity, ACE inhibitors
  - Hyperparathyroidism
  - Bone marrow disease (PRCA, fibrosis, neoplasia)
Avoid Renal Injury

- Prevent dehydration

- Nephrotoxic drugs – avoid or use cautiously
  - i.e. NSAIDS, aminoglycosides, glucocorticoids

- Monitor urinary tract infection
Urinary Tract Infection

- Mayer-Roenne, 2007 – 77 cats
  - Higher incidence in cats with CKD (vs DM, hyperthyroid)
  - 22% bacterial UTI
  - Many cats no clinical signs or changes in laboratory values

- White et al, 2012 – 25 cats
  - 18 occult UTI
  - Increasing age & female cats significantly associated
  - No significant association with survival (when treated) or severity of azotemia
  - E.coli most common
Monitoring

- Serial monitoring important due to progressive nature
  - Body condition, musculature and weight
  - Assessment of hydration
  - Indirect measurement of systemic arterial BP
  - CBC, biochemical profile, UPC, urinalysis
  - Urine culture (cystocentesis)

- Monitoring once stable
  - Every 3-4 months stage 3-4 CKD
  - Every 4-6 months stage 1-2 CKD

- 7-10 days after changing anti-hypertensive therapy
Negative Prognostic Factors

- Studies - 190 cats (King, 2007); 50 CKD cats (Kuwahara, 2006); 214 cats (Geddes, 2015)
  - Increased creatinine, BUN, phosphate, WBC, UPC ratio
  - Decreased hemoglobin concentration & PCV
  - FGF-23 negatively associated with survival

- Hypertension significantly associated with lower GFR, higher UPC ratio, and kidney lesions (Finco, 2004)

- Proteinuria highly related to survival (Syme, 2006)
  - Creatinine and systolic BP positively related to magnitude
  - Associated with more severe renal lesions (McLeland, 2015)
Prognosis

- Factors shown not to affect CKD progression
  - Breed
  - Calcium
  - Bicarbonate
  - Potassium
  - Presence of UTI
  - PTH
Prognosis

- Median survival in cats with naturally occurring CKD – 733 cats, 2000-2002
  - 1,151 days  Stage II (b)
  - 778 days  Stage III
  - 103 days  Stage IV
  (Boyd et al, 2008)
Future Directions

- Early detection and intervention
  - Better quality of life and longer survival
  - Higher prevalence and severity of irreversible lesions in CKD stage 3 & 4 (McLeland, 2015)

- Cystatin C (Ghys, 2015)
  - Biomarker of GFR in early renal disease
  - Concerns with reference interval & previous studies CKD

- Mesenchymal stem cell therapy (Quimby, 2015)
  - Renoprotective: anti-inflammatory, pro-angiogenic, anti-apoptotic, anti-fibrotic & anti-oxidant
Questions?