Chronic kidney disease
CKD

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Diplomat ACVIM & ECVIM-CA

Terminology:
- Old: Chronic renal failure
- Old: Chronic renal insufficiency
- NEW: CHRONIC KIDNEY DISEASE (CKD)

Compensatory mechanisms of chronically diseased kidney can no longer:
- Excrete waste products (urea, creatinine, hormones, etc.)
- Regulate water homeostasis
- Produce hormones (erythropoetin, Vit-D)
- Regulate electrolyte and acid-base homeostasis
- Often pre- (and post-) renal complications

Third most common cause of death in dogs and second most common cause of death in cats with chronic disease
Cause most commonly unknown, many potential underlying diseases

Work-up of azotaemic patients:
1. Based on history and USG – decide if pre-renal, renal or post-renal azotaemia
2. Based on history, physical examination and many laboratory parameters (± diagnostic imaging) make a diagnosis of CKD (vs AKI)
3. If CKD → Staging according to IRIS
www.iris-kidney.com

IRIS is an international special interest group seeking to identify and disseminate information on better methods for the diagnosis and treatment of dogs and cats with renal disease!
IRIS has proposed a staging system for CKD based on the serum creatinine concentration of the stable patient on at least two occasions
Staging

- IRIS: International Renal Interest Society
  “The mission of IRIS is to help veterinary practitioners better diagnose, understand and treat renal disease in cats and dogs.”

- IRIS consensus statement 2006
  - Staging of chronic kidney disease (CKD) is undertaken following the diagnosis of CKD in order to facilitate appropriate treatment and monitoring of the patient. Staging is based initially on fasting plasma creatinine, assessed on at least two occasions in the stable patient. The patient is then substaged based on proteinuria and systemic blood pressure.

### Progression

- 33% compensation
- 25% loss of concentration mechanism (isosthenuria)
- 100% laboratory signs of renal disease (azotemia)

### Staging according to IRIS

<table>
<thead>
<tr>
<th>IRIS Stages</th>
<th>Creatinine in µmol/l</th>
<th>Creatinine in mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I Non-azotaemic CKD</td>
<td>&lt; 125</td>
<td>&lt; 1.4</td>
</tr>
<tr>
<td>Stage II Mild renal azotaemia CKD</td>
<td>125 - 179</td>
<td>1.4 - 2.0</td>
</tr>
<tr>
<td>Stage III Moderate renal azotaemia CKD</td>
<td>180 - 439</td>
<td>2.1 - 5.0</td>
</tr>
<tr>
<td>Stage IV Severe renal azotaemia CKD</td>
<td>&gt; 440</td>
<td>&gt; 6.0</td>
</tr>
</tbody>
</table>

*Diagrams and tables illustrate the staging system for dogs and cats, with creatinine levels in both units. Diagrams depict relationships between kidney mass, compensation, and loss of concentration mechanisms.*
### Substaging: Proteinuria

<table>
<thead>
<tr>
<th>Protein-Creatinine-Ratio (UPC)</th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>No proteinuria</td>
<td>&lt; 0,2</td>
<td>&lt; 0,2</td>
</tr>
<tr>
<td>Borderline proteinuria</td>
<td>0,2 - 0,5</td>
<td>0,2 - 0,4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&gt; 0,5</td>
<td>&gt; 0,4</td>
</tr>
</tbody>
</table>

### Sub-staging: Blood Pressure

- Hypertension = increased blood pressure leading to end-organ damage
  - Kidney (progression, proteinuria)
  - Eyes (blindness, bleeding, retinal detachment)
  - Brain (seizures, lethargy)
  - Cardiovascular (CHF, vessel rupture)
- Measure blood pressure (best with Doppler method)
- Examine end-organs carefully

### Substaging: Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Blood pressure in mmHg</th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>No to minimal risk</td>
<td>&lt; 150</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Mild risk</td>
<td>150 - 159</td>
<td>150 - 159</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>160 - 180</td>
<td>160 - 190</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 180</td>
<td>&gt; 190</td>
</tr>
</tbody>
</table>

### Causes of CRD

- Unknown
- Congenital
- Acquired

### Congenital Causes of CKD

- PKD (Cairn terrier, Persian and related breeds)
- Amyloidosis (Shar Pei, Abyssinian cat)
- Renal dysplasia (Newfoundland, Shih Tsu)
- Tubular dysfunction (Basenji, Norwegian elkhound)
- Tubulointestitial Nephritis (Boxer, Norwegian elkhound)
- Glomerular Dysfunktion (Bernese mountain dog)
- Cystadenocarcinoma (German shepherd dog)
Acquired causes of CKD

- Infectious (Bact, Leishmania, FIP, mycosis)
- Metabolic (hypercalcaemia, hypokalaemia, Diabetes mellitus)
- Neoplasia (lymphoma, carcinoma)
- Obstructive
- Nephrolithiasis
- Proteinuric (Amyloidosis, Glomerulonephritis)
- Drugs (NSAID, etc.)
- Chronic toxicity (environmental, food-associated)
- Primary systemic hypertension

Pathophysiology of CKD

- Hyperfiltration theory
- Trade off hypothesis
- Water balance alterations

Trade off hypothesis

Neil Bricker: „The biological price to be paid for maintaining external solute balance for a given solute as renal disease progresses is the induction of one or more abnormalities of the uraemic state”

- Calcium-phosphorus balance → secondary renal hyperparathyroidism
- Carbonate buffering → bone demineralisation
- Increased SNGFR → proteinuria

Diagnosis of CKD

- History
- Clinical examination
- Blood analysis
- Urinalysis (+ UPC)
- Blood pressure
- ± Diagnostic imaging
- ± GFR
- (Biopsy)
### Epidemiology

- **Prevalence of CKD**
  - Dog: 0.5-7%
  - Cat: 1.6-20%
- **Mainly elderly animals (50% > 7 Jahre)**
  - Range: 6 months–22 years
  - Dog:
    - 18% < 4 years,
    - 17% 4-7 years,
    - 20% 7-10 years,
    - 45% > 10 years

### Historic and clinical findings

- **PU/PD**
- **Gastrointestinal**
  - Anorexia
  - Vomiting (rarely diarrhoea)
- **Stomatitis**
- **Haematology**
  - Pale mucous membranes
  - Bleeding tendency
- **ZNS**
  - Lethargy
  - Uraemic encephalopathy
  - Peripheral neuropathy
  - Blindness
- **Sceleton**
  - Osteodystrophy
  - Calcification of soft tissue (kidney)
- **Endocrine**
  - Hypertension
  - Ren. 2° hyper-PTH
  - Insuline resistence
- **Dermatological**
  - Dehydratation
  - Edema
  - Pruritus
- **Respiratory**
  - Uremic pneumonitis

### Kidney palpation

- **Typical: small irregular kidneys**
- **BUT**
  - Also large kidneys
  - Lymphoma (other tumour)
  - PKD
  - Obstructive (Hydronephrosis)
  - Amyloidosis
  - FIP
- **Ultrasound in these cases**

### Anaemia

- **Non-regenerative, normocytic, normochromic**
- **May be masked by dehydration (check total protein, especially albumin)**
- **Causes:**
  - Decreased erythropoietin production
  - Decreased life span (<50%)
  - Insidious bleeding (gastritic, etc.)
  - Uraemic toxins impair erythropoesis

### Other haematological findings

- **May have stress leucogram**
- **Often thrombopathia**
  - Normal PLT numbers
  - Abnormal buccal mucosal bleeding time
- **Normal clotting tests (PT, PTT)**

### Chemistry profile

- **By definition: urea and creatinine increased**
  - Creatinine normal in muscle wasting
  - Urea higher than creatinine in GI bleeding
- **Potassium: often normal**
  - Hyperkalaemia in oliguria/anuria
  - Hypokalaemia in some cats/dogs with CKD
  - Muscle wasting, vomiting, PU/PD, anorexia as cause
  - Can lead to worsening CKD
  - Unclear what was first (CKD or hypokalaemia)
Chemistry profile

- Phosphorus: commonly increased in IRIS stage 3&4
  - Normal values <5.5 mEq/l (young animals have higher values)
  - Early stages have normal phosphorus
- Calcium: normal, rarely increased or decreased
  - Best measure ionized calcium
  - Mass law effect: Ca_{(mg/dl)} X P_{(mg/dl)} ≤ 70
  - Hypercalcaemia can result in CKD (what was first??)

Differentiating AKI vs CRD

- Occurrence of symptoms
  - AKI: quick
  - CRD: gradual
- General appearance
  - AKI: good
  - CRD: bad
- Urine volume
  - AKI: Normal to ↓
  - CRD: Often PU
- Haematocrit
  - AKI: Normal to ↑
  - CRD: Anaemia
- Potassium
  - AKI: ↑ (normal)
  - CRD: ↓ (normal)
- Urine sediment
  - AKI: Active
  - CRD: Non-active
- Therapeutic success
  - AKI: often
  - CRD: rarely
- Renal size
  - AKI: Normal/↑
  - CRD: Normal/↓

Blood pressure - Hypertension

- 9-93% of CKD dogs = hypertensive
- 19-63% of CKD cats = hypertensive

- Reason:
  - White coat effect
  - Different techniques and personnel
  - Various causes of CKD
  - Pathophysiology
  - Stage of CKD

Prognosis

- IRIS stage 2-3
  - Cats: 1-3 years
  - Dog: ½ - 1 years
- Factors of survival:
  - Primary cause of CKD
  - Severity of clinical symptoms
  - Probability of improvement
  - Rate of worsening
  - Response to therapy
  - Age
  - Risk factors (proteinuria, hypertension)

Survival of dogs with CKD

- Parker VJ, Freeman LM: Association between Body Condition and Survival in Dogs with Acquired Chronic Kidney Disease. JVIM 2011
- Median survival 174 days (3 – 921)
  - IRIS II & III no difference
  - IRIS IV significantly shorter than II or III
  - Hypoalbuminaemia – shorter survival
  - Reduced BCS – shorter survival
  - Renal diet – longer survival
Therapy of CKD

- Supportive
- Symptomatic
  - Correct fluid abnormality
  - Correct acid-base disturbance
  - Correct electrolyte abnormality
  - Treat endocrine and nutritional imbalance
- Specific
  - Hypercalcaemic nephropathy; UTI; obstruction, etc.

Goal of therapy for CKD

1. If possible: diagnose and treat underlying kidney disease
2. Avoid factors that can worsen underlying kidney disease
3. Halt progression of natural worsening
4. Manage uraemic syndrome
   - Decrease loss of vitamins (water soluble), electrolytes and minerals
   - Support caloric intake and protein requirements
   - Treat hormonal and metabolic alterations (anaemia, secondary hyperparathyroidism)

Therapeutic possibilities

- Diet
- Anti-hypertensive drugs
- Treat and avoid anaemia
- Management of hypokalaemia
- Treat ureaemic symptoms (vomiting, etc.)
- Avoid renal secondary hyperparathyroidism
- Treat dehydration
- Treat metabolic acidosis
- Emerging treatments?
- Dialysis & renal transplantation?

Diet

<table>
<thead>
<tr>
<th>Start: Dog</th>
<th>Stage</th>
<th>Cat</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>III, IV</td>
<td></td>
<td>II, III, IV</td>
<td></td>
</tr>
<tr>
<td>↓ Protein</td>
<td>↓ Symptoms of uraemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Phosphorous</td>
<td>↓ 2nd renal hyper-PTH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Sodium</td>
<td>↓ Arterial hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Vitamin B</td>
<td>Avoid loss via urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Calories</td>
<td>Due to ↓ Appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral acid-base content...</td>
<td>KD: ↓ acid secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Potassium</td>
<td>cat: often hypokalaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ ω3 to ω-6 PUFA ratio...</td>
<td>dog: may avoid progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Soluble fibre</td>
<td>Enteric dialysis ?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Polzin et al., CVT XIV, 2009

Why decreased protein content?

- Less waste products
  - improved well being, improved appetite
- Decreased Progression of CKD
  - ↓ risk of uremic crisis (cat: 26% versus 0%)
  - ↓ risk of CKD induced death (cat: 22% versus 0%)
- Median survival:
  - Dog: 594 days ↔ 188 days
  - Cat: 633 days ↔ 264 days

When to start protein restriction?

- As soon as CKD is recognised

Protein reduction – but how much?

- Worse symptoms dictate less protein
  - up to 16% on dry matter basis
- BUT – avoid malnutrition:
  - Mal nutrition worsened acidosis
  - Mal nutrition causes immune deficits
  - Use feeding tube (oesophagus, PEG)?
- Urea should decrease to only just above reference value

Jacob et al., 2002, Polzin et al., 2005, Ross et al., 2006
Phosphate restriction

Start: Dog & Cat Stage II, III, IV

- **Phosphate restriction: Why?**
  - Phosphate retention
    - Blocks 1α-hydroxylase activity → ↓ Calcitriol
  - Stimulate PTH secretion
  - Minimizes hyperparathyroidism
    - Damaging Effect of PTH
    - Progression of tubulointerstitial changes
    - Renal Osteodystrophy: skull & mandible
    - Anemia
    - Insulin resistence
  - Improved survival
  - Increased duration until GFR worsens
  - → Decreased progression of CKD

Polzin et al., CVT XIV, 2009

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Decrease dietary phosphate intake

- **Phosphate restriction: when?**
  - Serum Phosphat:
    - Stage II if < 4.5mg/dl < 1.45 mmol/l
    - Stage III if < 5mg/dl < 1.61 mmol/l
    - Stage IV if < 6mg/dl < 1.93 mmol/l

- **How to achieve:**
  - Phosphate restricted diet: KIDNEY DIET!
  - Intestinal phosphat binders
    - Cations, which bind Phosphat irreversibly
    - Must be given with food (every meal!)

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Phosphate binders

- They trap phosphat in GI lumen and increase excretion with faeces
- They do NOT decrease serum phosphate level

- Ipakitine ®
  - Contains Chitosan (80%) and calcium carbonate (10%)
  - Effect not proven but no side effects

- Lanthanum carbonate (Renalzin ®)
  - Acts similar to Ca-carbonat (but no risk of hypercalcaemia)

- Aluminum hydroxid
  - 30 mg/kg q8h
  - May cause constipation (mainly cats)

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Diet

- Provide good owner education (he must buy food)
- Implement food early
- Gradual transition (min. 7 days, better 3-4 weeks)
- Provide old and new food concurrently
- Use suitable food bowl in cats (whiskers)
- Avoid stressful periods (hospital, sick, etc.)
- Temperature (warm don’t heat)
- Try different texture and formulations (dry, wet)
- Add flavour enhancer (chicken broth, tuna juice, brewers yeast)
- Try other brand
**Tube feeding**

- In case of malnutrition (if everything else fails)
  - PEG tube
  - Osophageal feeding tube
  - Naso-oesophageal tube

**Antihypertensive therapy**

- Start: dog and cat: Stage II-IV
  - Systolic blood pressure > 160 mmHg
  - Signs of end-organ damage
- Cats:
  - Start with amiodipine
  - Add ACE-inhibitors and β-blockers if not successful
- Dogs:
  - Start with ACE-Inhibitors
  - Add Ca-Antagonists or β-Blockers if needed
  - Control blood pressure regularly

**Median survival (dog)**

- Stage IIb* (after rehydration) (death d/t CKD: 42%)
  - Normotensive: 504-1151 days
  - Hypertensive: 187 days
- Stage III (death d/t CKD: 68%)
  - Normotensive: 154-679 days
  - Hypertensive: 280 days
- Stage IV (death d/t CKD: 86%)
  - Normotensive: 35-57 days
  - Hypertensive: 21 days

* Creatinine > laboratory reference range

**Treat proteinuria**

- Start: Stage I – IV if UPC > 2
  - Dog: Stage II – IV if UPC > 0.5
  - Cat: Stage II – IV if UPC > 0.4

- Decrease proteinuria: Why?
  - Damage to kidney epithelium
  - Progression of CKD
  - Decreased risk of early death

- Therapy
  - Contraindicated in hypovolaemic patients
  - Need stable kidney disease (two UPC measurement)
  - ACE Hemmer: Benazepril, Ramipril

**Glomerular**

- Tubulo-interstitial inflammation
- Tubulo-interstitial fibrosis
- Decreased tubular function
- Decreased GFR
- Increased SNGFR
- Endothelin, NO, etc

**ACE Inhibitor**

- ACE-I (Ramipril, Benzapril, etc):
  - ↓ progression of CKD via
    - Decreased intraglomerular pressure
    - Reduced tubulo-interstitial remodeling
  - Decreases proteinuria: ↑ size selectivity of glomerular filtration slits
  - Will usually cause increase of urea and creatinine (up to 45 mmol/l creatinine)
  - => re-evaluate urea and creatinine regularly
## Antihypertensive Dosages

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Dose (cats)</th>
<th>Dose (dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplodipine</td>
<td>Ca-channel blocker</td>
<td>0.625-1.25 mg/cat q24h</td>
<td>0.1-0.4 mg/kg q24h</td>
</tr>
<tr>
<td>Diltazem</td>
<td>Ca-channel blocker</td>
<td>10 mg/cat q8h</td>
<td>0.5-3 mg/kg q8h</td>
</tr>
<tr>
<td>Benazapril</td>
<td>ACE-Inhibitor</td>
<td>0.5-1.0 mg/kg q12-24h</td>
<td>0.25-0.5 mg/kg q12-24h</td>
</tr>
<tr>
<td>Ramipril</td>
<td>ACE-Inhibitor</td>
<td>0.125 mg/kg q24h</td>
<td>0.125 mg/kg q24h</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β₁-Blocker</td>
<td>6.25-12.5 mg/cat q12-24h</td>
<td>0.25-1.0 mg/kg q12-24h</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Direct arteriolar dilator</td>
<td>1.0-2.5 mg/cat s.c. q24h</td>
<td>0.5-3.0 mg/kg q8-12h</td>
</tr>
<tr>
<td>Prazosin</td>
<td>α-adrenergic blocker</td>
<td>Not recommended</td>
<td>0.5-2.0 mg/dog q12h</td>
</tr>
</tbody>
</table>

## Treat anaemia of CKD
### Causes of anaemia
- Erythropoietin
- RBC survival
- Erythropoietin inhibitor substances
- GI blood loss
- Iron deficiency (nutritional)
- Bone marrow fibrosis

### Therapy of anaemia
Start: Dog & Cat Stage III, IV (if PCV < 15% and symptomatic)
- Replace iron
- Blood transfusion
- Erythropoietic hormone replacement
  - rHuEpo
  - Darbepoetin-α
  - Species-specific rEpo
- Anabolic steroids have no effect

Dose: Start with 100 U/kg 3x per week
Adjust based on PCV

### Therapy of uraemic symptoms
Start: Dog & cat: Stage III, IV
if GI symptoms due to CKD
- Proton pump inhibitors, sucralfat
  - Lessens and ameliorates GI symptoms due to uraemic gastritis
  - Omeprazole 1 mg/kg q24h orally
  - Sucralfate 20-40 mg/kg q8h orally
- Antiemetic drugs:
  - Decrease nausea => improved appetite
  - Decrease mal nutrition

## Summary of therapeutic management
- Diet
  - protein restriction
  - phosphate restriction (phosphate binders)
  - avoid mal nutrition → feeding tube?
- ACE-Inhibitor with proteinuria
- Treat hypertension
- Counteract GI symptoms
- Potassium (cats)
- Calcitriol ?
- rHuEpo (cats, small dogs)

## NOBODY MADE A GREATER MISTAKE THAN HE WHO DID NOTHING BECAUSE HE COULDN'T ONLY DO LITTLE
Edmund Burke