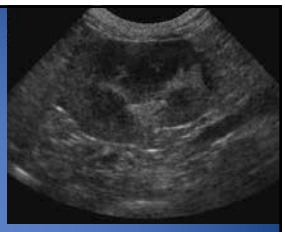


Chronic Kidney Disease

Paradigm shift from late diagnosis and treatment to earlier detection/intervention

Serge Chalhoub, DVM, Dipl. ACVIM (SAIM)

UNIVERSITY OF CALGARY
FACULTY OF VETERINARY MEDICINE

On the Menu

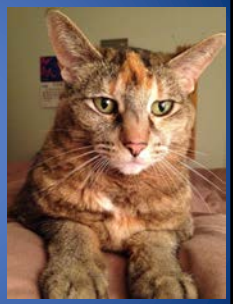
1. Diagnosis and prediction of feline CKD in every day practice (crystal ball?)
2. Pathogenesis of CKD (the great mystery)
3. Early diagnosis: Revenge of the biomarkers
4. Treatments (without getting scratched)

Thank you!

IDEXX LABORATORIES

Sketch

- 10 year old FS Calico
- Pre-dental exam: no concerns
  - "Getting older"
  - Weight 5.75kg (6.2kg 2y ago)
  - In-house labs:
    - USG 1.038



Feline Serum Chemistry	Result	Range
Phosphorus	1.3mmol/L	1.1-2.6 mmol/L
Calcium	2.75mmol/L	2-2.9 mmol/L
Total Protein	62g/L	54-78 g/L
Albumin	34g/L	25-39 g/L
Urea Nitrogen (BUN)	8.5mmol/L	3.6-10.7 mmol/L
Creatinine	132mol/L	44.2-180 mol/L
Sodium	152mmol/L	145-160 mmol/L
Potassium	4.2mmol/L	3.5-5.5 mmol/L
Chloride	124mmol/L	112-129 mmol/L

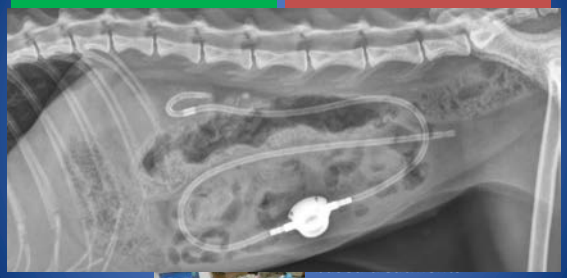
Brownie

- **12 year-old DSH MN, presents for weight loss over past year, on/-off anorexia for 3 months**
  - Exam: mild dehydration, dental disease, muscle loss around thighs
  - Labs: Mild NR anemia, mild hypokalemia, creatinine 240umol/L, USG 1.024, 1+ proteinuria
    - Last year: creatinine 130umol, no urine collected

What We Traditionally Do…

Well ☺	Not Well ☹
• IRIS Stage Feline CKD • Improve quality of life • Diagnose once a patient is symptomatic • Diet as therapy • Proteinuria and hypertension	• Early diagnosis and treatment, acute kidney injury (AKI) • We forget about post renal causes of azotemia • Understanding the pathophysiology • Still lots of grade 4 evidence-based treatments

Paradigm shift in our thinking



Paradigm Shift

A fundamental change in approach or underlying assumptions, a new way of thinking

Watson and Crick and DNA

Newton and theory of motion

Linnaeus and species concept

Copernicus and the solar system

Mendel inheritance and genetics

Darwin and natural selection

Veterinary CKD Paradigm Shifts

Elliott J, et al., *J Small Anim Practice,* 2000[1]: Cats with CRF fed the veterinary diet survived longer when compared with those that were not (633 died vs. 264 died).

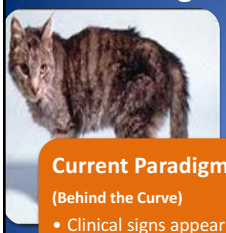
Ross SJ, et al., *JAVMA,* 2006[2]: CKD cats fed a renal diet survived longer and had fewer uremic crises.

Syme HM, et al., *JVIM,* 2006; King JN, et al., JVIM, 2007[3]: Survival of cats with CKD is related to severity of proteinuria and it is a negative prognostic indicator.

King JN, et al., *JVIM,* 2007[4]: Proteinuria significantly decreased with benazepril.

Jepson RE, et al., *JVIM,* 2009[5]: High normal creatinine predicted development of CKD, and 30% of cats aged 9+ likely to develop CKD.

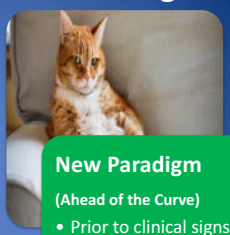
Paradigm Shift in our Thinking



Current Paradigm

(Behind the Curve)

- Clinical signs appear
- Azotemia present
- Slow progression
- Treat symptoms
- Quality of life



New Paradigm

(Ahead of the Curve)

- Prior to clinical signs
- Early diagnosis with new biomarkers
- Slow/prevent progression
- Early treatments

1. Diagnosis and Prediction of Feline CKD:

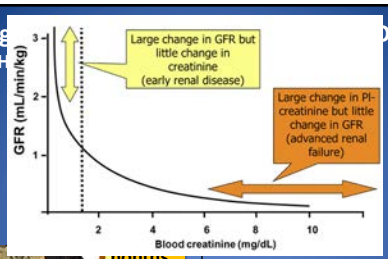
How do we do this in everyday practice?

CKD?

Decrease in renal function for at least 3 months

Renal azotemia and inappropriate USG	No azotemia but inappropriate USG	No azotemia, normal USG but structural changes
75% decrease of nephron mass[6]	68-70% decreased renal function	Unknown

1. Diag… D:



…months

No azotemia …
inappropriate …

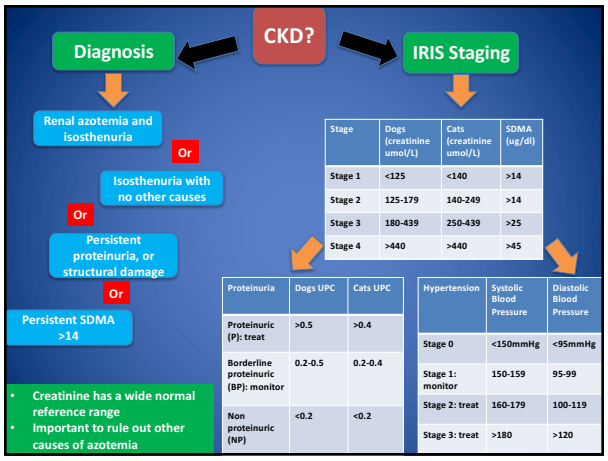
7… 68-70% decreased renal function Unknown

So we have not been good at diagnosing kidney disease when…

- Creatinine is in normal range.
- There is no changes in urine specific gravity (USG).
- There are no clinical signs.

- **Early CKD (IRIS Stage 1-2) has been a "mystery"**
  - Is it real? And who cares, can't do anything about it?
- **But CKD has a strong prevalence:**
  - Cats 30%–40% >10 years of age[7]
  - Dogs 0.37%–3.74%[8]

Hence the need for advanced biomarkers



Predicting CKD Prior to advanced biomarkers

Adams, et al., *Am J Vet Res,* 1993[11]; Finco, et al., *Am J Vet Res,* 1998[12]:
Diets: high protein, low potassium
Unlikely to be "real" diet

Jepson, Brodbelt, et al., *JVIM,* 2009[5]:
118 cats 9+y nonazotemic 12 months
30% became azotemic
High-end creatinine and UPC predicted

Greene, Lefebvre, et al., *JAVMA,* 2014[10]:
Thin BCS, recent anesthesia, male cat
Dental disease, cystitis

Finch, Syme, et al., *JVIM,* 2016[9]:
148 geriatric cats
Annual/frequent (every 2 years) vaccination
Moderate/severe dental disease

Piyarungsri and Pusoonthornthum, *J Fel Med Surg,* 2016[13]:
101 cats with CKD vs. normal cats >5y age
Increased risk: tap water, outdoor lifestyle, males
Decreased risk: eating commercial diet, filtered water, indoor lifestyle

Predicting CKD

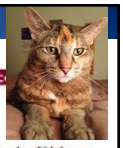
Prior to advanced biomarkers

Take home messages:

- Hard to predict CKD
- Unclear if diet has a role
- Chronic **inflammatory/ischemic diseases** and CKD?
- Weight loss
- UPC and high-end creatinine

Journal of Veterinary Internal Medicine

Open Ac



Standard Article

J Vet Intern Med 2016;30:1661–1666

Evaluation of Weight Loss Over Time in Cats with Chronic Kidney Disease

L.M. Freeman, M.-P. Lachaud, S. Matthews, L. Rhodes, and B. Zollers

- Median weight loss of -8.9% body weight in the 12 months prior to diagnosis of CKD[14]
- Weight loss already present 3 years prior to diagnosis
- Accelerated weight loss after diagnosis, association with IRIS stage

What IRIS stage are we talking about here?

The end game is tubulointerstitial nephritis

2. But… What's the Pathogenesis?

Environment, diet, vaccinations

RAAS, Hypertension

Primary renal diseases

Extra-Renal Diseases

Viruses

Age

Multiple AKIs?

s Progressive Chronic Kidney Disease a Slow Acute Kidney Injury?

Chronic Kidney Disease in Aged Cats: Clinical Features, Morphology, and Proposed Pathogeneses

Journal of Veterinary Internal Medicine
ACVIM
Open Access
Standard Article
J Vet Intern Med 2017;31:457–464

Acute-Phase Proteins and Iron Status in Cats with Chronic Kidney Disease

R. Javard, C. Grimes, L. Bau-Gaudreault, and M. Dunn

Background: The role of inflammation in the development and progression of chronic kidney disease (CKD) in cats is not well characterized. Hepcidin is a recently discovered acute-phase protein (APP) that plays an important role in iron metabolism and contributes to the development of anemia in humans with CKD.

Results: Mean SAA and hepcidin concentrations were significantly higher and mean total iron and TIBC were significantly lower in the CKD group ($P < .05$). There was a significant positive correlation between serum creatinine concentration (CRT) and 2 of the APPs (SAA and hepcidin; $P < .05$). Increases in SAA and hepcidin were associated with decreases in TIBC and hematocrit in the CKD group. Fourteen (37%) of the cats with CKD were anemic, and these cats had significantly lower TIBC ($P < .05$), suggesting a functional iron deficiency. There was no association between survival time and APP, iron status, or EPO concentrations.

Conclusions: Our data suggest that CKD in cats is associated with systemic inflammation and altered iron metabolism. With further validation in cats, hepcidin assays may help better characterize these relationships.

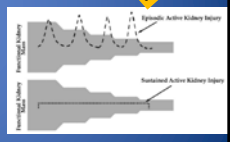
Key words: anemia; erythropoietin; ferritin; hepcidin; serum amyloid A.

CKD progression strongly associated with worsening inflammatory mediators[19]

2015 IRIS NAPA Meeting

- **AKI can initiate CKD in people and dogs; why not cats?**
  - AKIs (such as INFLAMMATION, TOXIC OR ISCHEMIA) likely cause maladaptive repair mechanisms, which initiate CKD.
  - Changes typical of ischemic AKI are present in experimental and naturally occurring CKD; AKI can lead to CKD in cats. (Brown, et al., *Vet Path*, 2015)[15]
- **Link between AKI/CKD pathologic processes?**
  - Likely interconnected entities **Progressive CKD associated to active episodic or ongoing AKI**
  - **AKI linked to CKD**

Paradigm shift in our thinking



Cowgill et al. Is progressive chronic kidney disease a slow acute kidney injury? Vet Clin Small Anim 46 (2016)

Maladaptation repairs even if traditional markers return to "normal"

3. Early Diagnosis: Biomarkers

Biomarker	Indication	Advantages	Disadvantages	Methodology
Cystatin C	GFR, AKI	Good for CKD detection	Effect related to age and weight	Immunoassay
Retinol Binding Protein	AKI, CKD	Stable	Large variation with cats and CKD	ELISA, Western Blot
A1- microglobulin	AK			ELISA, immunoassay
B2-microglobulin	AK			ELISA
Urinary clusterin	AKI	Early AKI, active AKI	Hemorrhage	Immunoassay
GGT	AKI	One urine sample	Unstable in acidic urine, hematuria, pyuria	Automated analyzer
NGAL	AKI, CKD	Urine, serum, plasma	Neoplasia, inflammation, hematuria, pyuria	ELISA

Most failed because:
- **Not readily available (benchtop)**
- **Not real-time (could take weeks)**
- **Not in-house (not accessible)**
- **Not affordable ($$$)**

Wait…Why Early Diagnosis?

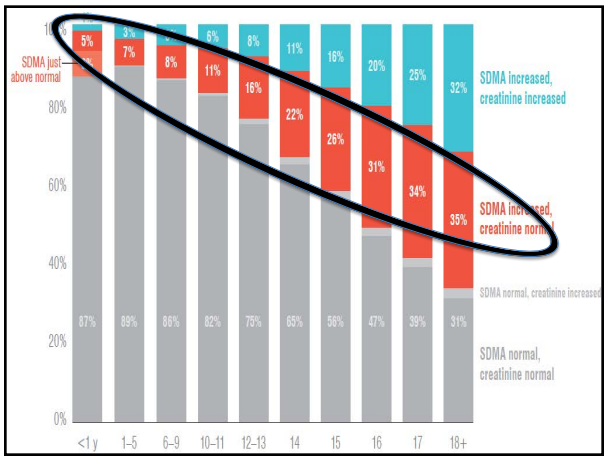
- **What's the fuss?**
  - Undetectable or difficult to detect changes in early kidney disease
    - Weight loss
    - Inflammation
    - Changes in appetite, activity
  - Ongoing damage
    - Multiple mini AKI model, inflammation
  - Breaking out of our current paradigm
    - Can be tough…
- **Maybe we should care…**
  - 30% of stage 1 cats will go into stage 2 within a year

IRIS Stage 1

- **Has been a mystery**
  - Low sensitivity in previous biomarkers (creatinine, BUN) in detection
  - Little to no research
  - No clinical signs
- **Paradigm shift: we now have the ability to reliably diagnose early kidney disease (both acute and chronic)**
  - In-house and at reference laboratory

SDMA

- **Symmetric dimethylarginine**
  - Methylated form of the amino acid arginine
  - Produced by all cells and released into circulation during protein degradation
    - Excreted almost exclusively by the kidneys
  - Increases at **40% of renal dysfunction (20%–40%)**[20]
    - Isosthenuria: 67-70% function loss
    - Azotemia: 75% function loss
  - Can identify CKD an average of **10 months earlier in dogs and 17 months sooner in cats**



Serum Creatinine[21]

- Increases at 75% function loss
- Specific
- Not sensitive 17%
- NPV 70%
- Decreases with age in cats
- Decreases with hyperthyroidism
- Biologic variability 15-20%
- Affected by hydration, diet (ex. meat)
- Variable reference ranges

Serum SDMA[21]

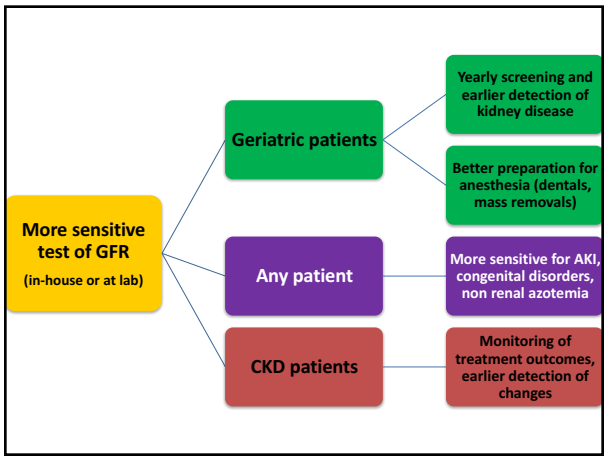
- Increases at 40% loss
- Specific
- Sensitive 100%
- NPV 100%
- Not affected by age or muscle mass
- Less affected by hyperthyroidism
- Biologic variability 15-20%
- Can be affected by hydration, not by diet
- One reference range

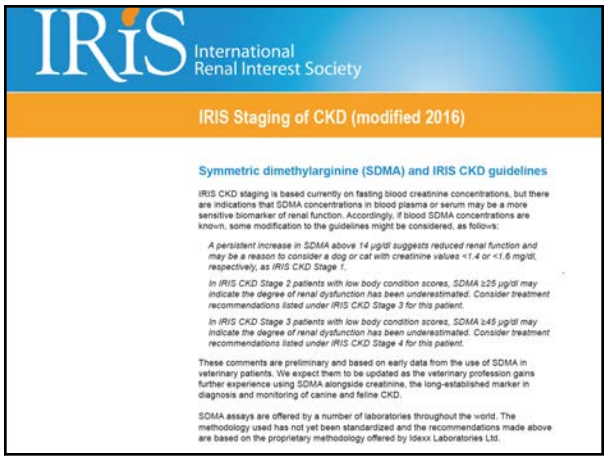
What Does It Mean

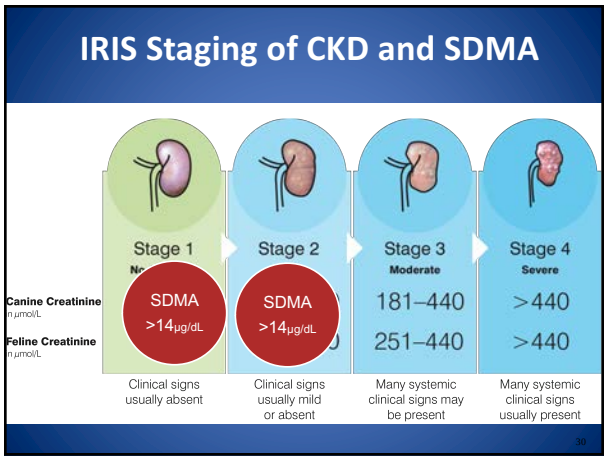
Paradigm shift in our thinking

- Detecting kidney disease in animals with poor BCS
  - Note: new reference range for dogs <2y (<16ug/dl)
- Detecting kidney diseases before azotemia or isosthenuria develops
- Monitoring of renal disease
  - Setting new guidelines for monitoring of IRIS Stage 1 patients
  - Setting the stage for monitoring of treatment outcomes
  - Developing earlier treatments and prevention
- Helpful with ARF/AKI
- BUT it does not tell you what disease you have (investigate, manage, monitor)

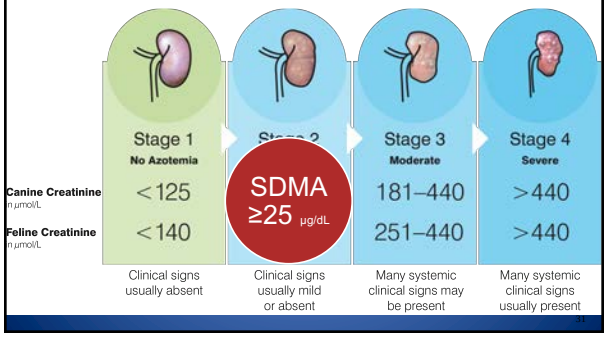
So SDMA helps with the diagnosis and the staging of CKD


More sensitive test of GFR
(in-house or at lab)
Geriatric patients
Yearly screening and earlier detection of kidney disease
Better preparation for anesthesia (dentals, mass removals)
Any patient
More sensitive for AKI, congenital disorders, non renal azotemia
CKD patients
Monitoring of treatment outcomes, earlier detection of changes

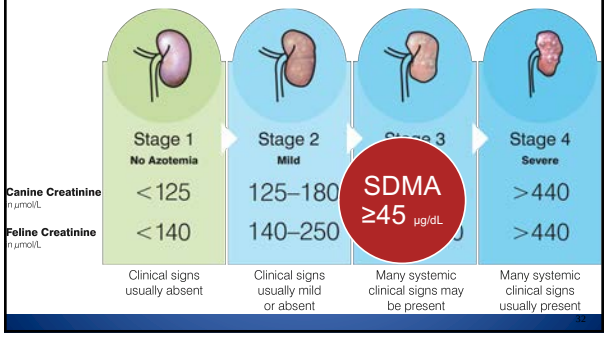

IRIS
International
Renal Interest Society
IRIS Staging of CKD (modified 2016)
Symmetric dimethylarginine (SDMA) and IRIS CKD guidelines
IRIS CKD staging is based currently on fasting blood creatinine concentrations, but there are indications that SDMA concentrations in blood plasma or serum may be a more sensitive biomarker of renal function. Accordingly, if blood SDMA concentrations are known, some modification to the guidelines might be considered, as follows:
A persistent increase in SDMA above 14 µg/dl suggests reduced renal function and may be a reason to consider a dog or cat with creatinine values <1.4 or <1.6 mg/dl, respectively, as IRIS CKD Stage 1.
In IRIS CKD Stage 2 patients with low body condition scores, SDMA ≥25 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 3 for this patient.
In IRIS CKD Stage 3 patients with low body condition scores, SDMA ≥45 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 4 for this patient.
These comments are preliminary and based on early data from the use of SDMA in veterinary patients. We expect them to be updated as the veterinary profession gains further experience using SDMA alongside creatinine, the long-established marker in diagnosis and monitoring of canine and feline CKD.
SDMA assays are offered by a number of laboratories throughout the world. The methodology used has not yet been standardized and the recommendations made above are based on the proprietary methodology offered by Idexx Laboratories Ltd.


IRIS Staging of CKD and SDMA
Stage 1
Stage 2
Stage 3
Moderate
Stage 4
Severe
Canine Creatinine
µmol/L
Feline Creatinine
µmol/L
SDMA
>14µg/dL
SDMA
>14µg/dL
181–440
251–440
>440
>440
Clinical signs usually absent
Clinical signs usually mild or absent
Many systemic clinical signs may be present
Many systemic clinical signs usually present

SDMA and Weight Loss Vs. Creatinine



SDMA and Progression of CKD with Weight Loss vs. Creatinine



Creatinine 300µmol/L

SDMA 52 µg/dl

So what stage is this cat in?

In-Hou… …m Chemistry	Result	Range
Phosphoru…	1.3mmol/L	1.1-2.6 mmol/L
Calcium	2.75mmol/L	2-2.9 mmol/L
Total Protein	…62g/L	54-78 g/L
Albumin		25-39 g/L
Urea Nitrogen (BUN)		3.6-10.7 mmol/L
Creatinine		44.2-180 mol/L
Sodium	152…	145-160 mmol/L
Potassium	4.2mmol/…	…5 mmol/L
Chloride	124mmol/L	…129 mmol/L
SDMA	16 µg/dl	<14 µg/dl

- Evidence of early kidney disease
- Paradigm shift in our thinking

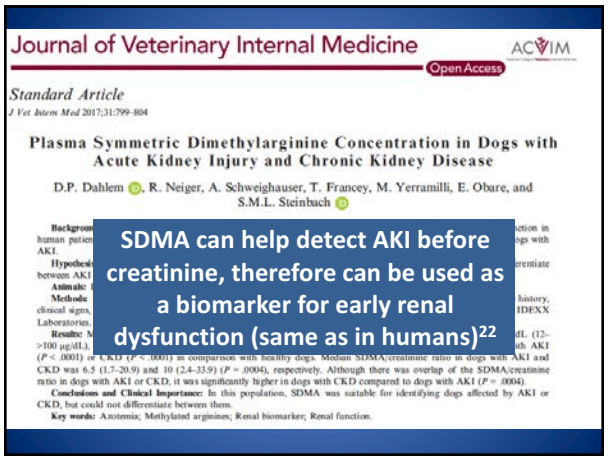
Suzie-Q

In-House Canine Renal Chemistry	Result	Range
Phosphorus	1.3mmol/L	1.1-2.6 mmol/L
Calcium	2.75mmol/L	2-2.9 mmol/L
Urea Nitrogen (BUN)	8.0mmol/L	3.6-10.7 mmol/L
Creatinine	126mol/L	44.2-180 mol/L
Sodium	152mmol/L	145-160 mmol/L
Potassium	4.2mmol/L	3.5-5.5 mmol/L
Chloride	124mmol/L	112-129 mmol/L

Suzie-Q

In-House Canine Renal Chemistry	Result	Range
Phosphorus	1.3mmol/L	1.1-2.6 mmol/L
Calcium	2.75mmol/L	2-2.9 mmol/L
Urea Nitrogen (BUN)	8.0mmol/L	3.6-10.7 mmol/L
Chloride	124mmol/L	112-129 mmol/L
SDMA	17 µg/dl	<14 µg/dl

- Evidence of AKI; Suzie-Q is in trouble
- Real-time analysis can change our approach
- Utility for monitoring



Journal of Veterinary Internal Medicine
ACVIM
Open Access

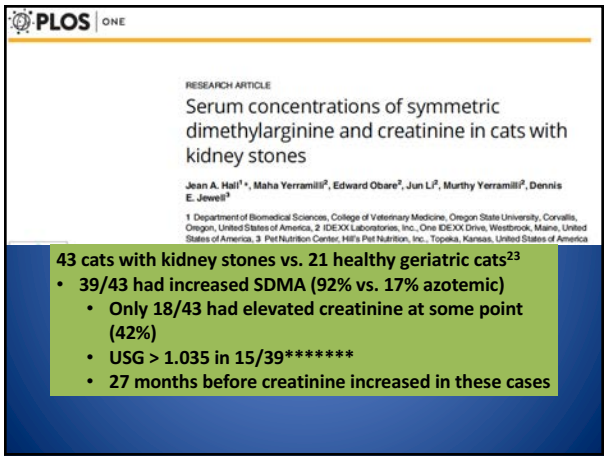
Standard Article

J Vet Intern Med 2017;31:799–804

Plasma Symmetric Dimethylarginine Concentration in Dogs with Acute Kidney Injury and Chronic Kidney Disease

D.P. Dahlem, R. Neiger, A. Schweighauser, T. Francey, M. Yerramilli, E. Obare, and S.M.L. Steinbuch

SDMA can help detect AKI before creatinine, therefore can be used as a biomarker for early renal dysfunction (same as in humans)[22]



PLOS ONE

RESEARCH ARTICLE

Serum concentrations of symmetric dimethylarginine and creatinine in cats with kidney stones

Jean A. Hall[1]*, Maha Yerramilli[2], Edward Obare[2], Jun Li[2], Murthy Yerramilli[2], Dennis E. Jewell[3]

1 Department of Biomedical Sciences, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon, United States of America, 2 IDEXX Laboratories, Inc., One IDEXX Drive, Westbrook, Maine, United States of America, 3 Pet Nutrition Center, Hill's Pet Nutrition, Inc., Topeka, Kansas, United States of America

43 cats with kidney stones vs. 21 healthy geriatric cats[23]

- **39/43 had increased SDMA (92% vs. 17% azotemic)**
  - **Only 18/43 had elevated creatinine at some point (42%)**
  - **USG > 1.035 in 15/39*******
  - **27 months before creatinine increased in these cases**

CKD Prognosis[24]

Cats

- **Depends on how fast disease progresses**
  - Can have stable disease for years
- **IRIS Upper Stage 2: median survival time 1151 days**
  - IF not proteinuric or hypertensive (both negative prognostic indicators)
  - IF treated appropriately
- **IRIS Stage 3: 679 days**
- **IRIS Stage 4: 35 days**

Dogs

- **CKD cats usually live longer than CKD dogs**
  - Proteinuric diseases more common in dogs and have worse prognosis
  - Arterial hypertension
- **Stage 3 + 4**
  - Usually more progressive
  - Months to years to death
  - Proteinuria and hypertension

Boyd, Langston 2008 JVIM

Predicting Progression

J Vet Intern Med 2012;26:275–281

Clinicopathological Variables Predicting Progression of Azotemia in Cats with Chronic Kidney Disease

S. Chakrabarti, H.M. Syme, and J. Elliott

Background: Chronic kidney disease (CKD) is common in geriatric cats, but often appears to be stable for long periods

- **High phosphorus and UPC predicted progression in all stages**[25]
- **Lower PCV and higher UPC predicted progression in stage 2**
  - UPC was 0.23 in progressive cases and 0.13 in stable cases
  - PCV was 33% in progressive cases and 36% in stable cases

Key words: Anemia; Hyperphosphatemia; Nephrology; Proteinuria.

4. Treatments

- **Goals**
  - Improve quality of life
    - Minimize uremic syndrome
  - Prolong life
  - Slow progression of disease
    - As disease progresses, more complications from azotemia + uremia
  - Prevent the disease?
  - Owner's quality of life

ISFM Consensus Guidelines on the Diagnosis and Management of Feline Chronic Kidney Disease[26]

isfm

Andrew H Sparkes BVetMed PhD DipECVIM MANZCVS MRCVS Veterinary Director, ISFM[1] *Panel Chair*[*]
Sarah Caney BVSc PhD DSAM (Feline) MRCVS[2]
Serge Chalhoub BSc DVM DipACVIM[3]
Jonathan Elliott MA VetMB PhD CertSAC DipECVPT MRCVS[4]
Natalie Finch BVSc PhD MRCVS[5]
Isuru Gajanayake BVSc CertSAM DipACVIM DipECVIM MRCVS[6]
Catherine Langston DVM DipACVIM[7]
Hervé P Lefebvre DVM PhD DipECVPT[8]
Joanna White BVSc DipACVIM PhD[9]
Jessica Quimby DVM PhD DACVIM[10]

Practical relevance: Chronic kidney disease (CKD) is one of the most commonly diagnosed diseases in older cats. In most cats, CKD is also a progressive disease and can be accompanied by a wide range of clinical and clinicopathological changes. These ISFM Consensus Guidelines have been developed by an independent panel of clinicians and academics to provide practical advice on the diagnosis and management of this complex disease.

Clinical challenges: Although CKD is a common clinical problem in cats, the manifestations of disease vary between individuals. Thus there is a need for careful and repeat evaluation of cats with CKD and adjustment of therapy according to individual needs. In addition to addressing problems arising from CKD and improving quality of life (QoL) for the patient, therapy may also target slowing the underlying progression of disease and hence prolonging life. While maintaining QoL is of paramount importance in our patients, this can be challenging when multiple therapies are indicated. In some cases it is necessary to prioritise therapy, given an understanding of what is likely to most benefit the individual patient.

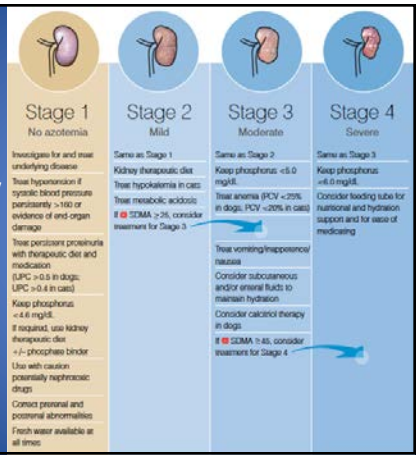
Evidence base: In preparing these Guidelines, the Panel has carefully reviewed the existing published literature, and has also graded the quality of evidence for different interventions to help to provide practical recommendations on the therapeutic options for feline CKD. This is a field of veterinary medicine that has benefited from some excellent published clinical research and further research findings will undoubtedly modify the recommendations contained in these Guidelines in the future.

As you will see, all current treatments are for IRIS 2 and above

- **Why???**
  - Poor ability to diagnose earlier
  - No clinical signs so why treat?
  - Minimal research up to this point

- **So what's the point of early diagnosis?**

Stage 1 has long been forgotten because cats rarely have visible clinical signs. But that is changing now.



Renal Diet

- **Cats**
  - 2006 Ross et al: Randomized study (24 months)[2]
  - Cats in mid-stage 2 or 3
  - Uremic crisis 0% vs. 26%
  - Death from renal cause 0% vs. 22%
  - No change in LBM

Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats

Sheri J. Ross, DVM, PhD, DACVIM; Carl A. Osborne, DVM, PhD, DACVIM; Claudia A. Kirk, DVM, PhD, DACVS, DACVIM; Stephen R. Lowry, PhD; Lori A. Koehler; David J. Polzin, DVM, PhD, DACVIM

Elliott et al 2000: Cats lived 2.5y longer at IRIS stage 3 on RD[1]
Plantinga et al 2005: RD survival 16 months vs. 7 months[27]

Renal Diet

- Nausea
- Appetite
- Hydration

Initially diagnosed CKD cats need to be treated as GI patients first

What If We Could Treat Prior to Clinical Signs (Stage 1)?

Jepson 2009: 30% cats in IRIS Stage 1 will progress within 1 year[5]

- 80 cats aged over 9 years age, all had normal creatinine at start[28]
  - Renoprotective test food vs. owner-choice food
- Over 6 months: SDMA did not change for cats fed renal diet vs. increase in SDMA in owner-fed diet
- In renal diet: BUN and creatinine dropped
- 30% started at or developed stage 1 CKD based on SDMA
  - SDMA increased in most cats on owner-fed diet
  - SDMA decreased or stayed stable on renal diet

Journal of Animal Physiology and Animal Nutrition

Hall JA, Fritsch DA, Yerramilli M, Obare E, Yerramilli M, Jewell DE. A longitudinal study on the acceptance and effects of a therapeutic renal food in pet dogs with IRIS-Stage 1 chronic kidney disease. *J Anim Physiol Anim Nutr*. http://onlinelibrary.wiley.com/doi/10.1111/jpn.12692/full. Accessed September 19, 2017.[29]

- Current IRIS guidelines: feed renal diet at stage 2+
- Unknown if earlier benefit or if detrimental:
  - Prospective 12 month trial of 36 dogs IRIS Stage 1 fed renal diet (44 clinical sites):
    - 97% of dogs transitioned successfully, majority enjoyed the new diet
    - *BUN, creatinine, SDMA significantly decreased from baseline at 3 months*
    - 12/16 dogs with proteinuria had significant decrease
    - Owners: overall health and quality of life attributes, hair coat

The Diet Controversy

The Pro and Con View of Renal Diets at Stage 2-4[32,33]

The Pro View

- Renal diets improve survival, decrease uremic crises
- Not just about the protein: phosphorus, sodium, omega-3, antioxidants, potassium, vitamin D, neutral effect on pH
- Protein restriction decreases uremia
- Phosphorus unlikely controlled with binders
- Phosphorus linked to CKD progression
- High protein leads to proteinuria and glomerular lesions
- Uremia causes weight loss, sarcopenia
- High protein diets untested and likely dangerous recommendation
- Promote eating

The Con View

- Obligatory carnivores that need high protein diets, lose LBM with lower protein diets
- Remnant kidney studies showed no association between high protein intake and renal lesions, proteinuria, or decreased GFR
- No study has looked just at protein
- CKD diet effect on proteinuria unclear (Ross 2006)
- Increased mortality with lower BW CKD
- Phosphorus restriction alone not studied
- Fatty acids?
- What about acid-base status correction
- Geriatric cats may need more than 32-34% of calories from protein

Vet Clin Small Anim 46 (2016)

The New Paradigm: Early diagnosis and intervention has benefits:

- May slow CKD progression
- <u>Early diagnosis = earlier intervention for proteinuria and hypertension</u>
- Stage 1: either a "renal friendly" diet: lower phosphorus and sodium, higher omega-3 fatty acids, not acidifying, anti-oxidants (geriatric diet), or an early-stage renal diet

Paradigm shift in our thinking

Appetite Stimulants

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

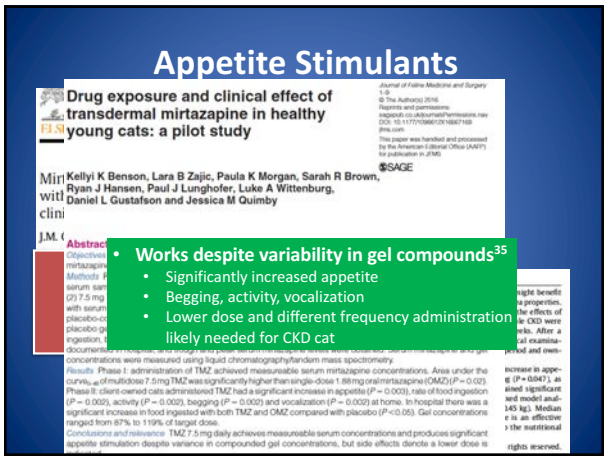
Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: A masked placebo-controlled crossover clinical trial

J.M. Quimby[a,*], K.F. Lunn[b]

[a] Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, 300 West Drake Road, Fort Collins, CO
[b] Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1060 William Moore Drive, Raleigh, NC 27607, USA

Significant increase in appetite, activity, and weight; decrease in vomiting[34]

Appetite Stimulants


Drug exposure and clinical effect of transdermal mirtazapine in healthy young cats: a pilot study

Kellyi K Benson, Lara B Zajic, Paula K Morgan, Sarah R Brown, Ryan J Hansen, Paul J Lunghofer, Luke A Wittenburg, Daniel L Gustafson and Jessica M Quimby

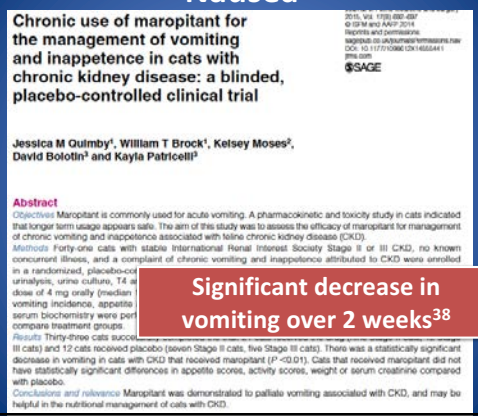
- **Works despite variability in gel compounds[35]**
  - Significantly increased appetite
  - Begging, activity, vocalization
  - Lower dose and different frequency administration likely needed for CKD cat

Ghrelin Receptor Agonists

- **Hormone mainly produced by stomach**
  - "Hunger hormone"
  - Homeostasis and energy metabolism
    - Distribution and rate of energy usage
  - Increased GH, IGF-1
    - Increase in lean muscle mass
      - Negative feedback on its own secretion
  - Anti-inflammatory properties
- **Ghrelin agonists**
  - Capromorelin
    - Beagles increase in weight and appetite
    - 200 dogs field study: significantly increased appetite and weight 70%[36]
    - 40 cats CKD pilot field study over 90 days: significant increase in weight vs. placebo[37]

Julie Allen ACVIM 2016

Nausea


Chronic use of maropitant for the management of vomiting and inappetence in cats with chronic kidney disease: a blinded, placebo-controlled clinical trial

Jessica M Quimby[1], William T Brock[1], Kelsey Moses[2], David Bolotin[3] and Kayla Patricelli[3]

Significant decrease in vomiting over 2 weeks[38]

Nausea

Original Article

Assessment of absorption of transdermal ondansetron in normal research cats

Lara B Zajic*, Andrea K Herndon, Liberty G Sieberg, Amber L Caress, Paula K Morgan, Ryan J Hansen, Luke A Wittenburg, Daniel L Gustafson and Jessica M Quimby

No significant serum concentration achieved[40]

Abstract

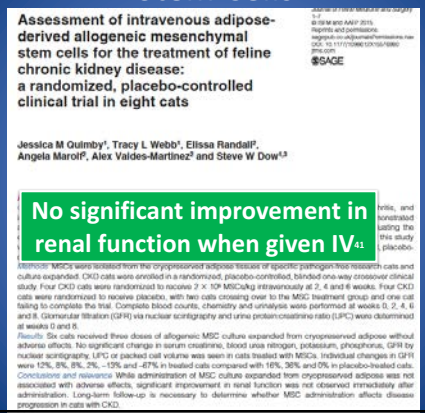
Objectives The objective of this study was to assess the absorption of transdermal ondansetron in healthy cats.

Methods Five research cats with unremarkable complete blood count, biochemistry and urinalysis were used for both single- and multiple-dose application studies. For single-dose application, 4 mg ondansetron in 0.1 ml Lipoderm gel was applied once to the internal ear pinna. Blood samples were collected via jugular catheter over a 48 h period following administration (0, 15 mins, 30 mins, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h and 48 h). For multiple-dose application, 4 mg ondansetron in 0.1 ml Lipoderm gel was applied for five consecutive days before blood samples were obtained in the same manner. Serum was separated and frozen prior to analysis. Ondansetron was measured via liquid chromatography coupled to tandem mass spectrometry.

Results Analysis revealed no clinically relevant drug levels in serum after either single- or multiple-dose administration of 4 mg transdermal ondansetron.

Conclusions and relevance Transdermal application of 4 mg ondansetron does not result in clinically relevant serum concentrations of drug. Despite characteristics of the drug that imply suitability for transdermal application, this does not appear to be an acceptable method of drug delivery for this medication at this dose. This study highlights the importance of assessing the suitability of each medication for transdermal administration.

Stem Cells



Assessment of intravenous adipose-derived allogeneic mesenchymal stem cells for the treatment of feline chronic kidney disease: a randomized, placebo-controlled clinical trial in eight cats

Jessica M Quimby, Tracy L Webb, Elissa Randall, Angela Marolf, Alex Valdes-Martinez and Steve W Dow

No significant improvement in renal function when given IV[41]

Secondary Renal Hyperparathyroidism

PHOSPHORUS CONTROL IS A REAL PROBLEM

- Secondary renal hyperparathyroidism common in CKD 76-84% dogs/cats, certainly in stage 4
- Geddes 2013 JVIM[42]: FGF-23 increases in cats with CKD and correlated with staging

If phosphorus control is so important, why would we feed a high protein diet?

- Finch 2012 JAVMA[43]: PTH higher in nonazotemic cats that developed azotemic CKD within 12 months and this prior to any changes in phosphorus
- Finch 2013[44]: FGF23 predicted development of azotemic CKD over 12 months
- Geddes 2015 JVIM[45]: FGF-23 associated with survival in azotemic CKD

Original Article

Effect of a high phosphorus diet on indicators of renal health in cats

Britta Dobenecker, Anna Webel, Sven Reese and Ellen Kienzle

- 13 healthy cats fed phosphorus excess diet (HP) vs. 13 control diet for 30 days[46]
  - High bioavailability
  - 9/13 HP cats had microalbuminuria and glucosuria
  - Endogenous creatinine clearance decreased significantly for HP group

clearance was significantly decreased after feeding HP. In the HP group phosphorus was highly available (apparent digestibility around 60%). Renal phosphorus excretion was significantly increased in the HP group (115 mg/kg body weight/

Paradigm shift in our thinking

Accepted: 26 April 2017

Evaluating Sucralfate as a Phosphate Binder in Normal Cats and Cats with Chronic Kidney Disease

Jessica Quimby, DVM, PhD, DACVIM, Michael Lappin, DVM, PhD, DACVIM

- Normal cats vomit with sucralfate
- CKD cats vomit even more with sucralfate
- No changes in phosphorus (study stopped)[47]

vomiting occurred after 14.7 % of administrations. Of the five normophosphatemic cats with CKD treated with sucralfate, three experienced clinical decompensation, including vomiting, anorexia, constipation, and increased azotemia. Administration of sucralfate did not result in significant changes in fecal phosphorus concentration in these cats. The effects of sucralfate administration on serum phosphorus concentration and urinary excretion of phosphorus in CKD cats was difficult to determine because of dehydration and worsening azotemia associated with decompensation. Due to side effects and the apparent lack of efficacy of the medication, the study was discontinued. This study was unable to confirm efficacy of this sucralfate formulation as a phosphate binder, and side effects were problematic during the study. (*J Am Anim Hosp Assoc* 2016; 52:8–12. DOI 10.5326/JAAHA-MS-6213)

Uremic Gastropathy

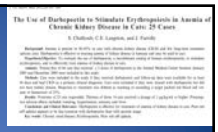
J Vet Intern Med 2014;28:827–837

Relationship among Serum Creatinine, Serum Gastrin, Calcium-phosphorus Product, and Uremic Gastropathy in Cats with Chronic Kidney Disease

S.M. McLeland, K.F. Lunn, C.G. Duncan, K.R. Refsal, and J.M. Quimby

- GI ulceration not found in any stage of CKD[48]
- But evidence of gastric mineralization especially in moderate/severe azotemia
- Ca X P product associated with disease severity and mineralization

Anemia of Renal Disease

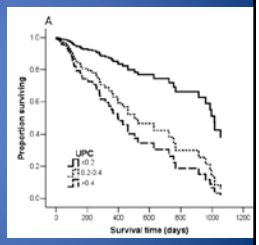


- Cats: renal anemia 30-65% of CKD patients
- Anemia independent predictor of progressive CKD, increased mortality
- Tx: Epogen, Darbepoetin
  - Darbe has MUCH lower pure red cell aplasia[50]
  - <10% vs. 25-40% Epogen

[50]Elliott J, Barber PJ. Feline chronic renal failure: clinical findings in 80 cases diagnosed between 1992 and 1995. Journal of Small Animal Practice 1998;39:78-85.

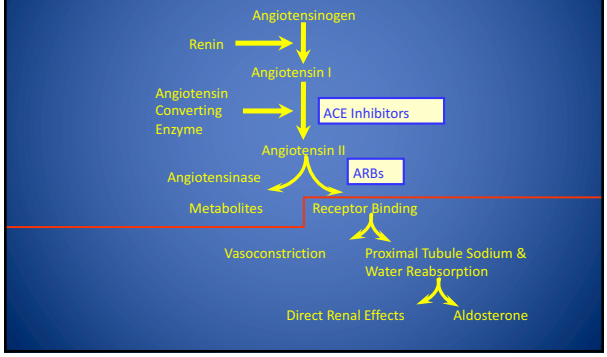
When to Treat Renal Proteinuria?

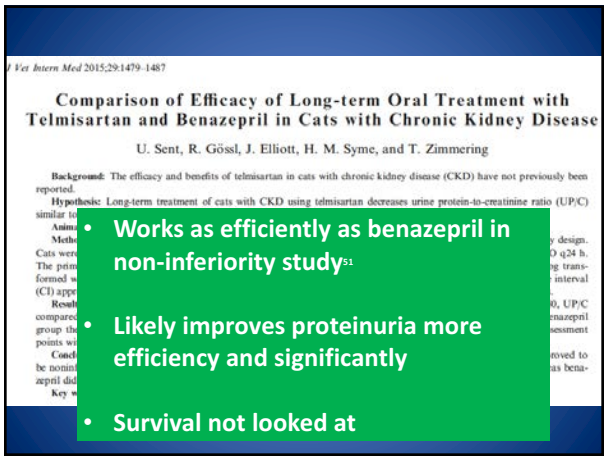
- IRIS currently recommends UPC >0.4 once azotemic
  - Syme 2006[3]: survival 1000d with UPC<0.2, 500d with UPC 0.2-0.4, 400d with UPC > 0.4
  - Chakrabarti 2012[25]: UPC was 0.23 in progressive cases and 0.13 in stable cases
  - Jepson 2009[5]: Group that developed azotemia had proteinuria at entry but in low levels (UPC 0.14 vs. 0.19)



Paradigm shift in our thinking

Renal Proteinuria Treatments





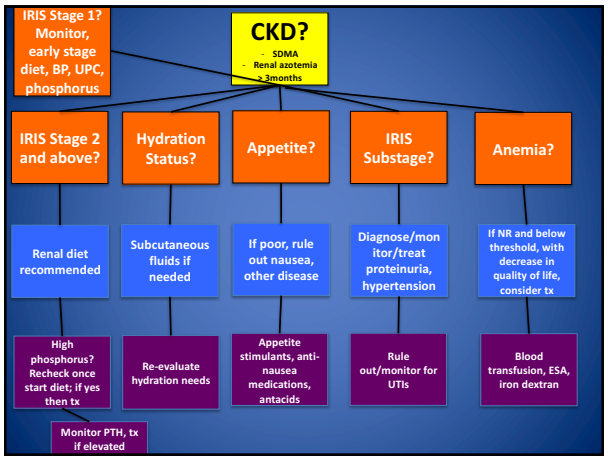
My CKD Monitoring

	Stage I-II	Stage III	Stage IV
Test	**Frequency**	**Frequency**	**Frequency**
Physical	q 6 months	q 3-6 months	Monthly
Biochemistry/SDMA	q 6 months	q 3-6 months	monthly
CBC	q 6 months	q 3-6 months	q 1-2 months
Urinalysis/UPC	q 6 months	q 6 months	q 3 months
Culture	q 12 months	q 12 months	q 3 months
BP	q 6 months	q 3-6 months	q 3 months
Ultrasound	As needed	As needed	As needed

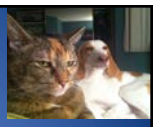
My Geriatric Cat Monitoring (age 8+)

Test	Frequency
Physical	q 12 months
Weight	q 6 months
Biochemistry/SDMA	q 12 months
CBC	q 12 months
Urinalysis/UPC	q 12 months
BP	q 12 months

How would have Sketch's care changed?
- Ruled out post renal causes
- Early renal diet
- Closer monitoring of UPC, BP
- More care with anesthesia, medications



Conclusion



- CKD is a progressive, serious disease
- Lots that we know, even more we don't know
- Early diagnosis important
- New treatments aimed at slowing disease down
- Change in paradigm from diagnosis/treatment when clinical signs are present, to earlier diagnosis/treatment and maybe prevention

schalhou@ucalgary.ca