Proteinuria: The Silent Killer

Serge Chalhoub, DVM, DACVIM

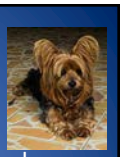
UNIVERSITY OF CALGARY
FACULTY OF VETERINARY MEDICINE

On the Menu

- **Proteinuria: types**
  - Pre-renal
  - Renal
    - CKD
    - GN
  - Post renal
- **Diagnosis**
- **Prognosis**
- **Treatment: Evidence-based**
  - CKD
  - GN

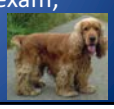
Thank you!

Proteinuria



Which one of these animals lived?

- 4 year-old MN Yorkie; pre-dental lab work indicated normal CBC/chemistry panel and had 4+ protein on urinalysis, no clinical signs
- 8 year-old FS Cocker mix presented for lethargy. CBC WNL, UA indicates 4+ proteinuria. Dull and dehydrated on exam, hypotensive

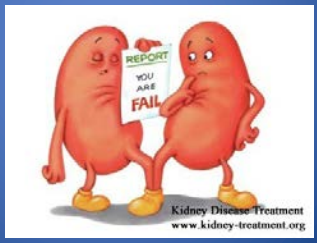


Proteinuria

- Who cares?
- Frequent finding on urinalysis
- Frequently ignored…
- May indicate different things
  - Should not be ignored especially if inactive sediment
  - Often not benign

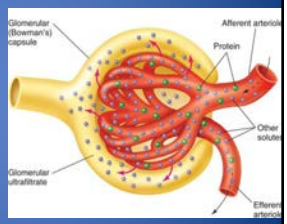
Proteinuria

- How does it happen?
  - Is it ALWAYS the fault of the kidneys?



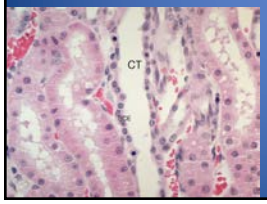
Glomerulus

- Fenestrated endothelium
  - 34nm
  - Negative charge basal membrane
  - Podocytes
  - Mesangial cells
- Maintains oncotic pressure



Normal Filtration

- **Tubular Protein Handling**
  - Reabsorption
    - Lysosomes
  - In excess…



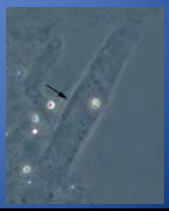
Proteinuria

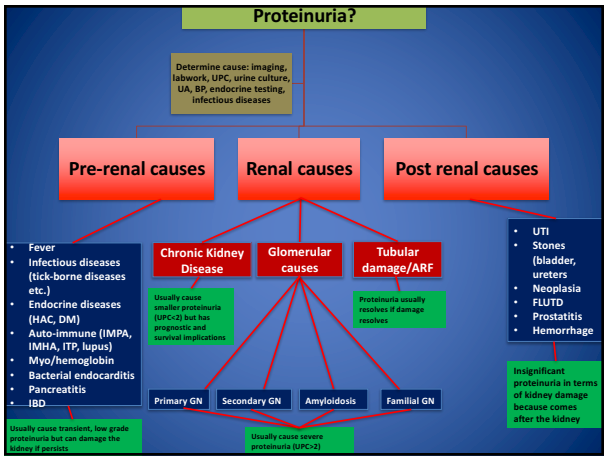
- **Clinical proteinuria results when:**
  - Too many smaller proteins are brought to the kidney
    - Transport maximum of tubules is exceeded
    - Excessive production and filtration of smaller proteins ex. Bence Jones proteinuria (multiple myeloma), myoglobinuria, hemoglobinuria
  - The glomerulus is injured, which means increased filtration of proteins
    - VERY important reason in dogs: glomerulonephritis (GN)
  - Tubular injury (decreased reabsorption, leakage)
    - For example: aminoglycosides, lilies, grapes, NSAIDs
  - Chronic kidney disease
    - #1 reason in cats
    - The entire kidney is compromised
  - Or, proteinuria is a result of the lower urinary tract
    - Which means no effect on the kidneys

Proteinuria and Kidney Damage

Proteinuria and Kidney Damage

- **Protein in general is not supposed to pass through the kidney**
  - Tubules become overwhelmed
  - Causes lysosomal bursting and tubulointerstitial damage, fibrosis
  - Leads to CKD
    - Protein or hyaline casts in urine



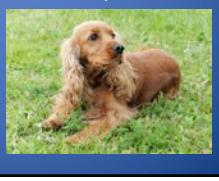


Causes

- **Pre-renal**
  - Most are transient and resolve with resolution of primary causes
    - So monitoring is important
  - Bust some persist or cause severe proteinuria and hurt the kidneys
- **Renal**
  - Glomerulonephritis, amyloidosis
    - DOGS mainly
  - Tubular damage
    - Toxic, ischemic damage
  - CKD
    - CATS mainly
- **Post renal**
  - The proteinuria is AFTER the kidneys so it doesn't hurt them

Pre-Renal Leading to Renal…

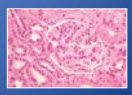
- **Pituitary-Dependant Hyperadrenocorticism**
  - Benji, 9 y.o Cocker mix MN
    - 2+ proteinuria and hypertensive prior to trilostane
      - Post trilostane: hypertension disappeared
      - Proteinuria not rechecked
        - » Developed PLN-associated CKD 1 year later



Glomerular Causes

Commonly referred to "Protein-losing nephropathies or PLN"

- **Categories:**
  - Glomerulonephritis (GN) (Primary/idiopathic, secondary)
  - Familial Glomerulopathy
  - Amyloidosis
- **Usually result in more severe proteinuria (UPC>>2)**
- **Glomerulonephritis (GN):**
  - We know that 50% of GN dogs have immune complexes that are in the kidney, which causes the damage But unfortunately the cause is unknown most of the time.
- **Glomerular proteinuria is usually seen dogs**
  - NOT cats



Secondary Glomerulonephritis

These are often pre-renal causes that can lead to glomerular damage

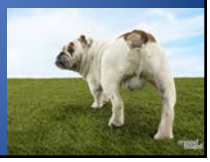
- **Infectious:**
  - Heartworm
  - RMSF
  - Ehrlichiosis
  - Lyme
  - Bartonella
  - Sepsis
  - Fungal disease
  - Pyometra
  - FIV, FIP

- **Immune-mediated:**
  - Lupus
  - Immune-mediated polyarthropathy
  - IMHA
  - Immune-mediated thrombocytopenia
- **Inflammatory:**
  - Prostatitis
  - IBD
  - Hepatitis
  - Pancreatitis

Secondary Glomerulonephritis

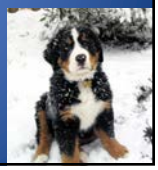
These are often pre-renal causes that can lead to glomerular damage

- **Medications:**
  - Glucocorticosteroids
  - Trimethoprim sulfa
- **Endocrinopathy:**
  - Hyperadrenocorticism
  - Diabetes mellitus
- **Hypertension**
- **Neoplasia:**
  - Lymphoma
  - Leukemia
  - TCC
  - Carcinoma
  - Mast cell tumors



Familial Glomerulonephropathy

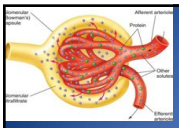
- Bernese mountain dog
- Bull terrier
- English cocker spaniel
- Dalmatian
- Doberman pinscher
- Samoyed
- Abyssinian
- Greyhound
- Newfoundland
- Rottweiler
- Soft-coated wheaten terrier
- Shar pei
- French Mastiff



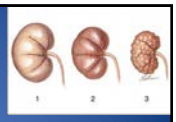
Amyloidosis

Causes severe PLN as well

- **Either secondary (reactive) or familial**
  - Beagles, Walker Hounds
  - Shar Pei (Shar Pei Fever)
  - Beagle
  - English foxhound
  - Abyssinian cat



GN vs. CKD



- **CKD**
  - An actual disease or the result of previous AKI/ARF
  - Patient is azotemic once in IRIS Stage 2
    - Relatively predictable disease process
  - Can develop proteinuria because of renal dysfunction
    - Negative prognostic indicator
    - Up to 50% of cats with CKD will develop proteinuria
- **GN**
  - Primary vs. secondary
  - The kidney itself is "fine" but the glomerulus is not, allows more protein to pass
    - Leads to severe tubular damage, then to CKD
    - But this CKD progresses MUCH faster

Proteinuria

- **Renal proteinuria, or pre-renal proteinuria that is significative, persistent or left unchecked, is very dangerous**
  - When you have CKD and proteinuria: it is a negative prognostic indicator (remember IRIS staging)
  - When you have any cause of renal proteinuria, your kidneys are being damaged

Clinical Presentation

- **Depends on the type of proteinuria**
  - Pre-renal
    - Primary clinical disease
  - Renal
    - Glomerulonephritis
    - CKD, ARF
  - Post-renal
    - UTI
    - Stones
    - Neoplasia
    - Prostatitis

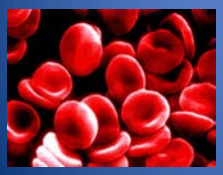
The proteinuria itself is silent, but pre-renal and renal proteinuria can lead to irreversible damage

Renal Proteinuria

- **Asymptomatic initially**
  - Can take months before they show signs related to the proteinuria
    - Silent killer
- **More classic signs of "CKD" once the damage happens:**
  - Often clinical at a ***lower degree*** of azotemia than traditional CKD
    - In other words, once they are azotemic, they are very sick

Diagnosis

- **CBC:**
  - Non regenerative anemia with CKD



- **Chemistry Panel:**
  - Normal in early stages
  - Hypercholesterolemia
  - Hypoalbuminemia
  - Azotemia, hyperphosphatemia
- **Infectious diseases, immune-mediated diseases etc.**
- **Urine culture**

Diagnosis

- **Urine proteinuria by dipstick**
  - Semi-quantitative, albumin 30mg/dl or more
  - 1-2+ in concentrated urine - may be normal
  - UTI or acute tubular injury may increase protein content
  - False positives:
    - Alkaline urine, hemoglobin, myoglobin, fever, stress
- **SSA turbidity test**
  - Less interference, better detection

Comparison of urine dipstick, sulfosalicylic acid, urine protein-to-creatinine ratio, and species-specific ELISA methods for detection of albumin in urine samples of cats and dogs

Shane D. Lyon, DVM; Michael W. Sanderson, DVM, MS, DACVPM; Shelly L. Vaden, DVM, PhD, DACVIM; Michael R. Lappin, DVM, PhD, DACVIM; Wayne A. Jensen, DVM, PhD; Gregory F. Grauer, DVM, MS, DACVIM

JAVMA, Vol 236, No. 8, April 15, 2010

Diagnosis

- **Urine Protein-Creatinine Ratio (UPC)**
  - Quantitative measure of protein excreted over 24h
  - Preferred test
    - Specific
  - IRIS Staging

Comparison of urine protein-to-creatinine ratio in urine samples collected by cystocentesis versus free catch in dogs

Laura Beatrice, DMV; Francesca Nizi, DMV; Daniela Callegari, DMV, PhD; Saverio Paltrinieri, DMV, PhD; Eric Zini, DMV, PhD; Paola D'Ippolito, DMV; Andrea Zatelli, DMV

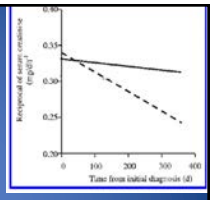
JAVMA, Vol 236, No. 11, June 1, 2010

Free-catch urine for UPC acceptable

Diagnosis

- **Microalbuminuria**
  - Humans: helps detect early nephropathy in diabetes and hypertensive diseases
  - Animals: rises prior to UPC
    - Too sensitive?
    - Functional vs. pathologic proteinuria
  - IRIS staging and treatment: based on UPC

Diagnosis



- **50-85% of renal proteinuric animals are hypertensive**
  - Organ/retinal damage in BP sustained >160mmHg; 3X more likely to die
  - What came first?

Diagnosis

- **Renal Biopsy: only for suspected GN cases**
  - Risks vs. benefits, and if will help in treatment
  - When to avoid:
    - Severe azotemia
    - CKD (DO NOT RECOMMEND BIOPSY IF CKD IS THE CAUSE OF PROTEINURIA)
    - Suspected pre-renal or post renal proteinuria
  - Procedures:
    - Ultrasound-guided
    - Laparoscopy
    - Laparotomy
  - Consider if:
    - Suspect GN
      - May find immune complexes, which means can treat

Treatment

1. **Treat underlying systemic disease**
   - With pre-renal and post renal proteinuria, you stop here
1. **Treat the azotemia and hypertension**
   - Renal causes
1. **Treat the renal proteinuria**
   - Nonazotemic dogs and cats
     - Investigate if UPC 0.5-2
     - Investigate and treat if UPC >2
   - Azotemic dogs and cats
     - Investigate with any abnormal UPC (>0.2)
     - Dogs: investigate and treat if UPC > 0.5
     - Cats: investigate and treat if UPC >0.4

Syme 2006: survival 1000d with UPC<0.2, 500d with UPC 0.2-0.4, 400d with UPC > 0.4

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

Journal of Feline Medicine and Surgery (2016) 18, 219–239

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.

isfm

Andrew H Sparkes BVetMed PhD DipECVIM MANZCVS MRCVS Veterinary Director, ISFM[1] *Panel Chair*[*]
Sarah Caney BVSc PhD DSAM (Feline) MRCVS[2]
Serge Chelhoub 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]

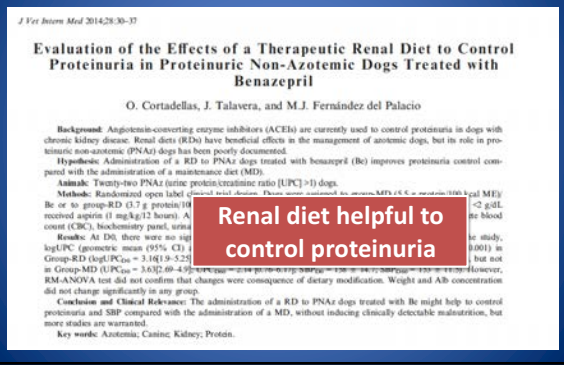
Renal Proteinuria Treatment Goals

- **UPC <0.4 (<0.2)**
  - Very achievable with CKD proteinuria
- **UPC decrease by 50%**
  - Especially with GN
  - Goal: reduce damage
  - UPC exceeding 2.0: worse structural renal outcome

Renal Proteinuria Treatment

- **Diet**
  - High protein diets exacerbate proteinuria
    - Increase intraglomerular pressure
  - Renal diets helpful
    - Protein restriction and better quality proteins
    - Phosphorous restriction, controlled potassium
  - Omega 3 fatty acids
    - Decrease renal inflammation
    - Many supplement extra
      - » 0.25-0.5g/kg daily of eicosapentanenoic acid (EPA)

Diet



J Vet Intern Med 2014;28:30–37

Evaluation of the Effects of a Therapeutic Renal Diet to Control Proteinuria in Proteinuric Non-Azotemic Dogs Treated with Benazepril

O. Cortadellas, J. Talavera, and M.J. Fernández del Palacio

Renal diet helpful to control proteinuria

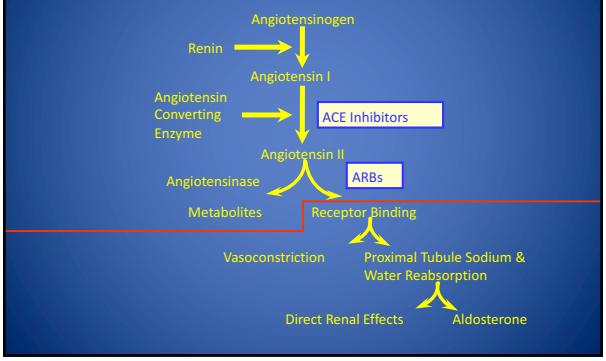
Renal Proteinuria Treatment

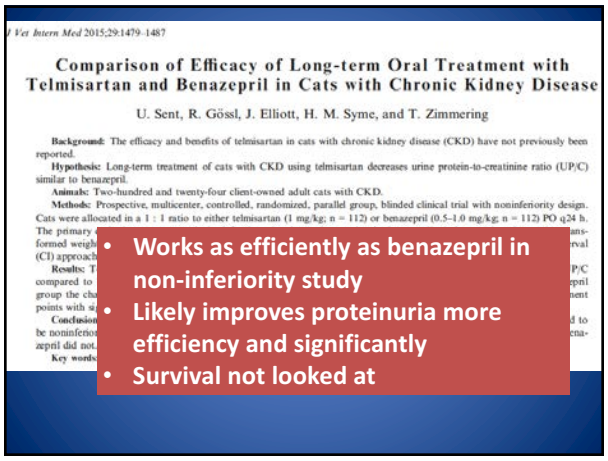
- **ACE inhibitors**
  - Oppose efferent arteriole constriction
    - Reduce glomerular pressure
    - Less protein gets "pushed" out
  - Enalapril, benazepril
    - 0.5-1 mg/kg SID-BID
      - >50% require BID
    - Start at 0.5mg/kg/day and reevaluate
    - Severe azotemia: Benefit?

Renal Proteinuria Treatment

- **Angiotensin Receptor Blockers (ARBs)**
  - Telmisartan (Semintra®)
  - 1mg/Kg/day, very palatable
  - Likely better at controlling RAAS-induced systolic pressor response
    - More complete and prolonged RAAS blockade

Angiotensin Receptor Blockers





J Vet Intern Med 2015;29:1479–1487

Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease

U. Sent, R. Gössl, J. Elliott, H. M. Syme, and T. Zimmering

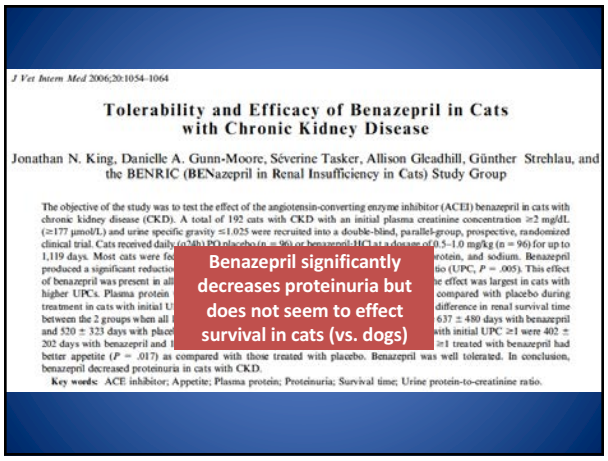
Background: The efficacy and benefits of telmisartan in cats with chronic kidney disease (CKD) have not previously been reported.

Hypothesis: Long-term treatment of cats with CKD using telmisartan decreases urine protein-to-creatinine ratio (UP/C) similar to benazepril.

Animals: Two-hundred and twenty-four client-owned adult cats with CKD.

Methods: Prospective, multicenter, controlled, randomized, parallel group, blinded clinical trial with noninferiority design. Cats were allocated in a 1 : 1 ratio to either telmisartan (1 mg/kg; n = 112) or benazepril (0.5–1.0 mg/kg; n = 112) PO q24 h. The primary

- Works as efficiently as benazepril in non-inferiority study
- Likely improves proteinuria more efficiency and significantly
- Survival not looked at



J Vet Intern Med 2006;20:1054–1064

Tolerability and Efficacy of Benazepril in Cats with Chronic Kidney Disease

Jonathan N. King, Danielle A. Gunn-Moore, Séverine Tasker, Allison Gleadhill, Günther Strehlau, and the BENRIC (BENazepril in Renal Insufficiency in Cats) Study Group

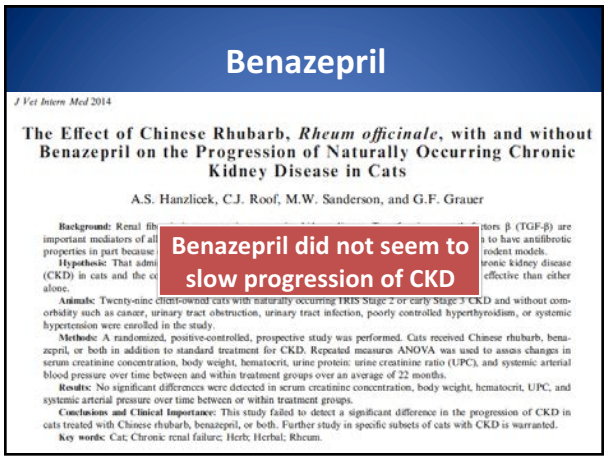
The objective of the study was to test the effect of the angiotensin-converting enzyme inhibitor (ACEI) benazepril in cats with chronic kidney disease (CKD). A total of 192 cats with CKD with an initial plasma creatinine concentration ≥2 mg/dL (≥177 μmol/L) and urine specific gravity ≤1.025 were recruited into a double-blind, parallel-group, prospective, randomized clinical trial. Cats received daily (q24h) PO placebo (n = 96) or benazepril-HCl at a dosage of 0.5–1.0 mg/kg (n = 96) for up to 1,119 days. Most cats were fe

Benazepril significantly decreases proteinuria but does not seem to effect survival in cats (vs. dogs)

rotein, and sodium. Benazepril tio (UPC, $P = .005$). This effect he effect was largest in cats with compared with placebo during difference in renal survival time 637 ± 480 days with benazepril with initial UPC ≥1 were 402 ± ≥1 treated with benazepril had better appetite ($P = .017$) as compared with those treated with placebo. Benazepril was well tolerated. In conclusion, benazepril decreased proteinuria in cats with CKD.

Key words: ACE inhibitor; Appetite; Plasma protein; Proteinuria; Survival time; Urine protein-to-creatinine ratio.

Benazepril



J Vet Intern Med 2014

The Effect of Chinese Rhubarb, *Rheum officinale*, with and without Benazepril on the Progression of Naturally Occurring Chronic Kidney Disease in Cats

A.S. Hanzlicek, C.J. Roof, M.W. Sanderson, and G.F. Grauer

Background: Renal fib tors β (TGF-β) are important mediators of all h to have antifibrotic properties in part because rodent models.

Hypothesis: That admi ronic kidney disease (CKD) in cats and the c effective than either alone.

Benazepril did not seem to slow progression of CKD

Animals: Twenty-nine client-owned cats with naturally occurring IRIS Stage 2 or early Stage 3 CKD and without comorbidity such as cancer, urinary tract obstruction, urinary tract infection, poorly controlled hyperthyroidism, or systemic hypertension were enrolled in the study.

Methods: A randomized, positive-controlled, prospective study was performed. Cats received Chinese rhubarb, benazepril, or both in addition to standard treatment for CKD. Repeated measures ANOVA was used to assess changes in serum creatinine concentration, body weight, hematocrit, urine protein: urine creatinine ratio (UPC), and systemic arterial blood pressure over time between and within treatment groups over an average of 22 months.

Results: No significant differences were detected in serum creatinine concentration, body weight, hematocrit, UPC, and systemic arterial pressure over time between or within treatment groups.

Conclusions and Clinical Importance: This study failed to detect a significant difference in the progression of CKD in cats treated with Chinese rhubarb, benazepril, or both. Further study in specific subsets of cats with CKD is warranted.

Key words: Cat; Chronic renal failure; Herb; Herbal; Rheum.

Case Report
J Vet Intern Med 2014;28:1871–1874

Telmisartan Treatment of Refractory Proteinuria in a Dog

A.C. Bugbee, A.E. Coleman, A. Wang, A.D. Woolcock, and S.A. Brown

Key words: Cardiology; Cardiovascular; Hemodynamics; Hypertension; Kidney; Pharmacology; Protein-losing nephropathy; Renal/Urinary tract.

- **Dog with GN refractory to benazepril**
- **ACEi decreased to SID and telmisartan added**

Treatment

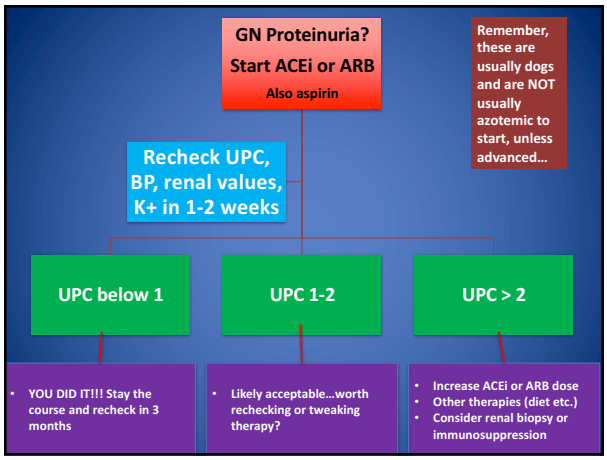
- **Important to monitor UPC, renal values**
  - ACEi and ARBs can worsen azotemia
    - 20-30% increase in creatinine "tolerable"
      - It's ok! As long as your patient feels ok
    - Euhydrated patients
  - ACEi and +/- ARBs can cause hyperkalemia
    - <6.0mEq/L: minimal consequences
- **Worsened azotemia vs. improved proteinuria**
  - What about the patient?

Recheck Schedule

- **Recheck UPC, renal values, potassium, BP at:**
  - 1-2 weeks
  - 4 weeks
  - 8 weeks
  - Then every 2 months

Goals Not Met?

- **Goals:**
  - UPC <0.5 (especially with CKD)
  - UPC reduction 50% (especially with GN)
  - Non clinical increase in azotemia, hyperkalemia
  - Control of hypertension
- **With CKD proteinuria targets usually met**
  - But important to recheck and monitor
- **With GN the proteinuria is often very difficult to treat**
- **What to do if goals not met?**
  - Usually with GN
  - Increasing dose of ACEi or ARB
  - +/- Adding another agent or changing agents
  - Consider immunosuppression



Cases

1. **Tony**
   - 12 y.o. FS DSH
   - Creatinine 1.9mg/dl, USG 1.016, well hydrated, BP 140mmHg, 4.8Kg
   - UA wnl, UPC 0.9
2. **Max**
   - 10 y.o. MN Pug
   - Creatinine 0.9mg/dl, BP 180mmHg, UPC 6.2
3. **Sage**
   - 3 y.o. FS Shar pei
   - Creatinine 4.2mg/dl, UPC 14

Thromboembolism and GN

- **Recognized complication with severe renal proteinuria**
  - Likely due to the loss of antithrombin
    - 25% of cases likely develop thromboembolism
- **Limited evidence for treatment in GN but we do try and prevent**
  - Aspirin - low dose inhibits platelet function
    - 1 mg/kg daily
  - Plavix – drug of choice? 1-2mg/Kg/day
    - As safe but not more effective
- **NOT FOR CKD CATS, JUST GN in DOGS**

What About Immunosuppression for GN?

- **Multiple GN cases have an immune cause or immune complex deposition**
  - If you have biopsies, then you will know
  - But if you can't get biopsies, we know that 50% of GN dogs have immune complexes in their kidneys and may benefit
- **Treat blindly?**
  - Not for CKD patients
  - Not for cats
  - But maybe for severe proteinuria that is not responding to ACEi/ARB therapy

No Pathologic Diagnosis

- **Targets not achieved, biopsy not realistic**
- **Inappropriate usage:**
  - NOT FOR CKD PROTEINURIA, cats, DM, Cushing's, infectious, pancreatitis, uncontrolled hypertension, liver disease
  - Familial GN, amyloidosis:
    - Unresponsive to steroids
- **Evidence?**
  - Based on current evidence 48% of biopsies submitted for proteinuria/GN had evidence of immune complexes

GN No Pathologic Diagnosis

- **Azotemia + GN proteinuria survival: <60d**
- **Non azotemic proteinuric GN dogs 605d**
  - Therefore, 50/50 chance
  - Must discuss pros and cons
    - Use same agents as biopsied confirmed cases
  - Recommend mycophenolate
    - 10mg/kg BID PO

Prognosis

- **GN cases presenting with moderate to severe azotemia has poor prognosis**
  - Weeks
  - Lyme nephropathy shorter survival time
- **Animals with proteinuria and CKD**
  - Survival time shortened vs. non-proteinuric CKD; negative prognostic indicator

Prognosis

- **Proteinuria leads to azotemia and CKD in cats: Jepson *et al* JVIM 2009;23 6–813**
- **Cats with CKD a uria survive less longer: Syme *et al* JVIM 2006 20:**
- **Proteinuria at initial diagn KD poor prognosis for survival: Jacob *et al* JAVMA 2 393-400**
- **Benazepril decreases proteinuria in but may not increase survival: King *et al* JVIM 2006 20: 1054-1064**

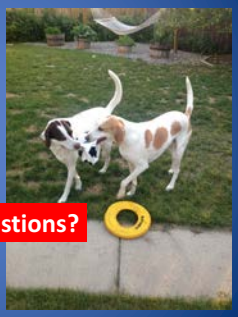
Proteinuria = BAD

So, Who Lived?

Hmmmm…

Conclusions

- Proteinuria not to be ignored
- Origin
  - Pre-renal, renal, post renal
  - CKD, GN
- Diagnostic tests
- Treatment
- Prognosis



Thanks!!! Questions?