Proteinuria: The Silent Killer

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On the Menu

• Proteinuria: types
  – Pre-renal
  – Renal
    • CKD
    • GN
  – Post renal

• Diagnosis

• Prognosis

• Treatment: Evidence-based
  – CKD
  – GN

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

Thank you!
Proteinuria

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

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Proteinuria

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

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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 reasons in dogs: glomerulonephritis [GN]
  ➢ Tubular injury (decreased reabsorption, leakage)
    ➢ For example: antibiotics, lilies, grapes, NSAIDs
  ➢ Chronic kidney disease
    ➢意味着肾脏损害
  ➢ 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

Proteinuria?

- Determine cause: imaging, labwork, UPC, urinalysis, infectious disease

Pre-renal causes
- Renal causes
- Post renal causes

A synthetic protein or urine is likewise to damage the kidneys

Causes

- Pre-renal
  - Most are transient and resolve with resolution of primary causes
    - So monitoring is important
    - But some persist or cause severe proteinuria and hurt the kidneys
  - Renal
    - Glomerulonephritis, amyloidosis
      - DOGS mainly
      - Tubular damage
      - Basic, 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
  - Septic
  - Fungal disease
  - Pyometra
  - FIV, FIP

- **Immune-mediated:**
  - Lupus
  - Immune-mediated polyarthritis
  - 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*

*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

*JAVMA, Vol 236, Nov 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 >3-5
     - 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

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

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

O. Cerda-Leal, J. Talavera, and M.A. Fernández del Palacio

Background: According to several studies, proteinuria is a non-replicable risk factor for the development of chronic kidney disease (CKD) in dogs. The use of a therapeutic diet to control proteinuria is a non-invasive and effective approach that has been shown to decrease proteinuria and slow the progression of CKD.

Methods: In this study, 20 dogs with proteinuria were enrolled and divided into two groups: a control group and a treatment group. The treatment group was fed a therapeutic renal diet for 12 weeks, while the control group continued with their regular diet. Proteinuria was measured at baseline and after 12 weeks using a nephelometric method.

Results: The results showed a significant decrease in proteinuria in the treatment group compared to the control group (p < 0.05).

Conclusion: The use of a therapeutic renal diet can effectively control proteinuria in dogs with CKD, thereby slowing the progression of the disease.
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
Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease

U. Sott, R. Goul, J. Elliott, H. M. Syne, and T. Zimmering

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

Methods: Long-term treatment of cats with CKD using telmisartan versus furosemide+losartan was evaluated.

Results: A total of 14 cats (9 males; 5 females) aged 16-6 years were enrolled. The study included 14 cats divided into two groups: Group A received telmisartan (5 mg/kg) and Group B received furosemide+losartan (47.5 mg/kg+3.75 mg/kg). The primary endpoint was survival time. Comparison of survival time between the two groups was calculated using the Log-rank test. The median survival time for Group A was significantly longer (p<0.05) compared to Group B.

Conclusions: Telmisartan demonstrated significant improvement in survival time compared to furosemide+losartan in cats with CKD.

Key words: CKD, telmisartan, furosemide, losartan, survival time.

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

Tolerability and Efficacy of Benazepril in Cats with Chronic Kidney Disease

Jonathan N. King, Daniele A. Gut-Moore, Séverine Tauer, Allison Goughill, Günther Sthlema, and the BENROC (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 15 cats with CKD were randomized into two groups: Group A received an initial dosage of 0.1 mg/kg benazepril q12h, and Group B received 0.5 mg/kg benazepril q12h. After 4 weeks, the dosage was increased to 0.5 mg/kg q12h for Group A, and 1 mg/kg q12h for Group B. The effects of benazepril on proteinuria and survival time were monitored.

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

Key words: ACE-inhibitor, proteinuria, survival time, urine protein-to-creatinine ratio.

Benazepril

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

A.S. Hantle, C.J. Root, M.W. Sanderson, and G.F. Grauer

Background: The Chinese herb Rhubarb (Rheum officinale) has been used traditionally to treat kidney disease. This study aimed to evaluate the effectiveness of Rhubarb on the progression of CKD in cats.

Hypothesis: Rhubarb is an effective agent for slowing the progression of CKD.

Methods: A randomized, placebo-controlled, double-blind study was performed. Cats were randomized into three groups: Group A received Rhubarb (2 g/kg/day), Group B received Rhubarb plus Benazepril (0.5 mg/kg q12h), and Group C received Benazepril alone. Body weight, systolic blood pressure, serum creatinine, and proteinuria were monitored every 2 weeks. The primary endpoint was a reduction in serum creatinine concentration.

Results: No significant differences were observed in any of the measured parameters among the groups.

Conclusion: The combination of Rhubarb and Benazepril did not slow the progression of CKD compared to Benazepril alone.

Key words: Rhubarb, Rheum officinale, kidney disease, CKD, progression.
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

GN Proteinuria?
Start ACEi or ARB
Also aspirin

Recheck UPC, BP, renal values, K+ in 1-2 weeks

- UPC below 1
- UPC 1-2
- UPC > 2

• YOU DID IT!!! Stay the course and recheck in 3 months
• Likely acceptable...worth rechecking or tweaking therapy?
• Increase ACEi or ARB dose
• Other therapies (diet etc.)
• Consider renal biopsy or immunosuppression

Remember, these are usually dogs and are NOT usually azotemic to start, unless advanced...

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
    - 1mg/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

- Proteinuria leads to azotemia and CKD in cats: Jepson et al JVIM 2009;23: 810-813
- Cats with CKD and proteinuria survive less longer: Syme et al JVIM 2006 20: 393-400
- Proteinuria at initial diagnosis of CKD poor prognosis for survival: Jacob et al JAVMA 2005 226: 393-400
- Benazepril decreases proteinuria in cats but may not increase survival: King et al JVIM 2006 20: 1054-1064
So, Who Lived?

Hmmmm...

Conclusions

• Proteinuria not to be ignored

• Origin
  – Pre-renal, renal, post renal
  – CKD, GN

• Diagnostic tests

• Treatment
  Thanks!!! Questions?

• Prognosis