Approach to the Proteinuric Canine Patient

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Introduction

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Introduction

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Aphorisms of Hippocrates
Hippocrates of Cos (460–377 BCE)

- “Bubbles appearing on the surface of the urine indicate disease of the kidneys and a prolonged illness.”
- Nobody’s perfect!

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Current Methods: Proteinuria

At USG of 1.060, 2+ on dipstick protein can be ~ 100 mg/dl
Dilute to 1.030, sample has 50 mg/dl and reads 1+ on dipstick
Dilute to 1.015, sample has 25 mg/dl & reads trace on dipstick

Screening For Proteinuria

- Urine dipsticks
  - Most sensitive to albumin
  - Very Alkaline pH = false positive
- Precipitation methods
  - Sulfosalicylic acid (SSA)
  - False +: radiocast agents, penicillins, sulfasoxazole, cephaloridine
  - In addition to albumin, will detect Bence-Jones proteins and globulins

Concentration/Dilution & Proteinuria

- At USG of 1.060, 2+ on dipstick protein can be ~ 100 mg/dl
- Dilute to 1.030, sample has 50 mg/dl and reads 1+ on dipstick
- Dilute to 1.015, sample has 25 mg/dl & reads trace on dipstick

Urine concentration/dilution alters the quantity of water extracted from filtrate, but has no effect on protein content of the filtrate
Screening For Proteinuria

- Both tests can have false positive & negatives
  - Advantage when both are reported
  - Causes for false positive & negative findings differ
- Positive findings should be followed-up by urine protein:urine creatinine (UPC)

What Dipstick Level Indicates That A UPC Should be Performed?

- Generalization: 1+ at any specific gravity
- Trace protein
  - Look at urine specific gravity
  - The lower the USG, the more significant you should considered the finding of a “trace” protein

The earlier you recognize and treat GN – the better the chance of a favorable outcome

UPC - Concept

- Creatinine filtered but neither absorbed nor secreted
- Glomerular proteinuria
  - Exits glomerular filter with creatinine
  - Some reabsorption of small protein molecules & albumin
- Net: eliminates impact of urine concentration & dilution of urine

Fates of Filtered Proteins

Pathological Renal Proteinuria

- Glomerular
  - Glomerular permeability defect (UPC >0.2 up)
  - Small to large quantity
  - Albumin-sized proteins and larger
- Tubular
  - Failure of tubules to reabsorb proteins
  - Small quantity (UPC less than about 2)
  - Small proteins up to approaching the size of albumin
- Interstitial
  - Traffic from peritubular capillaries
  - Usually of inflammatory origin
  - Small to large amounts

Why Is It Important to Differentiate the Type of Renal Proteinuria?

- UPC in a urine with a quiet urinary sediment = 5.6 & 4.9. The dog has minimal clinical signs other than PU/PD.
- Should I treat this dog with benazepril?
- Not yet ... need to seek causation:
  - Leptospirosis
  - Cushing’s syndrome
  - Others ...
Quantify Proteinuria – UPC

- Urine protein:creatinine ratio
- Calculation: Urine protein (mg/dl)/Urine creatinine (mg/dl) = unit-less ratio estimating urinary protein loss
- Interpretation:

UPC Confounders

- Protein could enter urine throughout the urinary tract
- Inflammation in the urinary tract
- Urinary tract infection
- Blood
- [Serum creatinine]
- Math!

Confirming that UPC is Valid

- UPC Ratio Uninterpretable with Gross Hematuria, Pyuria, or Bacterial UTI
- Recommend urinalysis & urine culture before UPC
  - Urinalysis
    - Pyuria
    - Gross hematuria
  - Urine culture

3-Day Urine Collections

- Improve reliability of UPC values
- Test-test variability not clearly established
- Method:
  - Serial for 3 days collect 1st morning urine samples
  - Combine equal volumes from each sample and mix well (e.g. 5 ml from each collection → 15 ml)
  - Submit for UPC determination

3y10m F Ches. Bay Retriever

Would “trace” protein be interpreted differently if the urine specific gravity were higher (e.g. 1.035)?
Should an UPC have been performed?

Repeat to confirm!

Has the UPC increased (clinical interpretation)?

No!

What & when should you do next?

Proteinuria! What Now?

Detect proteinuria
 Confirm proteinuria
 Establish the magnitude of proteinuria
 Determine origin (in the urinary tract) of the proteinuria
 If renal...
   – Glomerular proteinuria
   – Tubular proteinuria
   – Interstitial proteinuria

Guideline for Monitoring

- Urine P:Cr ratio should be reconfirmed
  – 3 times if UPC < 3.0
  – 2 times if UPC > 2.9
  – At 2 to 4 week intervals
- Clinically important changes in urine P:Cr may require a 30% to 50% change
Pathologic Renal Interstitial Proteinuria ... Some Causes

- Inflammatory cells, hematuria, infection - of renal origin (casts)
- Positive leptospirosis test
- Physical evidence of renal origin – enlarged, painful kidney(s), etc.
- Biochemical evidence of kidney disease?

SDS Page Electrophoresis of Urine

- Can be used to assess size of proteins in urine
- Localizing
  - Small = tubular
  - Large = glomerular

Magnitude of UPC and Action Plans

- UPC > 0.5

Monitoring – What? Why?

- Magnitude
- Pattern →
  - Static
  - Progressive
  - Regressive
- Persistence
- To determine if investigation needed
- Prognosis

Investigation of Proteinuric Dogs

- Medical history: include family details, environment, travel history, drug exposure, and prior or concurrent illnesses
- Physical exam: include: BCS, fundic exam, at least 2 blood pressure measurements
- Laboratory tests:
  - CBC including platelets
  - Comprehensive chemistry profile
  - Complete urinalysis (with sediment exam)
  - Urine Protein: Creatinine Ratio
  - (±) Urine culture

Hypertension!

- Recommend that dogs with proteinuria have blood pressure measured
- Hypertension is “common” in dogs and cats with kidney diseases
  - More frequent in glomerular diseases?
  - ~30-60% prevalence overall dogs glomerular Dz
White Coat Effect

- Serial Measurements
- Techniques

Blood Pressure Ranges for Dogs

Possible Associations with Renal Proteinuria

- AKI
- CKD
- Glomerular disease
- Acute pancreatitis
- Viral disease
- Drug reactions
- Systemic hypertension
- Diabetes mellitus (?)
- Hyperadrenocorticism
- Immune-mediated disease
- Tick-borne disease
- Leptospirosis
- Endocarditis
- Heartworm disease
- Exogenous steroid use
- Any severe inflammation
- Neoplasia

From: Harley & Langston, 2012

8 Year-Old FS Golden Retriever

- Polyuria, Polydipsia, Panting
- Laboratory findings:
  - Serum creatinine – 1.4 mg/dl
  - Serum albumin – 2.1 mg/dl
  - SAP – 972 U/dl
  - ALT – 211 U/dl
  - Urine specific gravity – 1.017 / UPC – 10.1
- **Diagnosis: Hyperadreocorticism**

9 Year-Old M/C Labrador Retriever

- Dry, dull hair coat
- Progressive lethargy over past 3-4 months
- Laboratory findings:
  - Hypoalbuminemia – 2.1 mg/dl
  - UPC - 7.6
  - Serum creatinine – 1.4 mg/dl
  - Hypercholesterism – 1163
- **Diagnosis: Hypothyroidism**

Tiers of Canine Glomerular Disease

- **Tier I:** Persistent subclinical renal proteinuria
  - Absent azotemia & hypoalbuminemia
  - No apparent renal-related clinical signs/sequelae
  - Non-hypertensive (A) or Hypertensive (B)
- **Tier II:** Renal proteinuria with hypoalbuminemia but not azotemic
  - Clinical signs typically due to edema or thromboembolic complications
  - Non-hypertensive (A) or Hypertensive (B)
Tiers of Canine Glomerular Disease

- **Tier III: Renal proteinuria with renal azotemia**
  - (A): No hypertension or hypoalbuminemia
  - (B): With hypertension, not hypoalbuminemic
  - (C): With hypoalbuminemia
    - With or without clinical signs/sequellae of hypoalbuminemia
    - Often hypertensive but not consistently

6 year old Labrador Retriever

- "Jake" - medical history
  - Losing weight last ~6 weeks
  - Still eating, but appetite has been declining
  - More lethargic
- Physical examination
  - Jake is thin (body condition score 3/9) and lethargic
  - Otherwise unremarkable

"Jake" - Initial Evaluation

- CBC: Hematocrit = 37%
  ...normal leukocyte count & differential count
- Chemistry profile:
  - Albumin: 1.6 g/dl
  - Total protein: 4.7 g/dl
  - ALT: 26 U/L
  - ALP: 35 U/L
  - BUN: 11 mg/dl
  - Creatinine: 1.4 mg/dl
  - Ca: 9.4 mg/dl
  - Phosphorus: 5.4 mg/dl
  - tCO₂: 20.1 meq/L
  - Na⁺: 148 meq/L
  - K⁺: 4.8 meq/L
  - Cl⁻: 116 meq/L
  - Cholesterol: 347 mg/dl

"Jake" — Urinalysis, BP, US & Culture

- Urinalysis:
  - Specific gravity: 1.034
  - Chemistries:
    - 4+ protein
    - Negative for occult blood
  - Sediment: 0-3 RBC/0-1 WBC
- Urine culture: Negative
- Blood pressure: systolic mean — 175/120

Jakes Tier?

- **Tier II: Renal proteinuria with hypoalbuminemia, hypertension & non-azotemia**
- **Key Initial Goals:**
  - Diagnostics to find causation → Specific therapy?
  - Reduce proteinuria
  - Increase serum albumin concentration
  - Normalize hypertension (HT may promote proteinuria & cardiovascular complications)

Proteinuria: Additional Studies

- Additional Strategies to identify the cause for proteinuria:
  - Serology for possible infectious diseases (local & travel)
    - Borreliosis
    - Ehrlichiosis
    - Heartworm disease
    - Leptospirosis (proteinuric early)
  - Imaging:
    - Ultrasound & Advanced Imaging
    - Neoplasia
    - Inflammatory lesions
    - Lipid profile (especially hypertriglyceridemia)
  - Endocrine tests: Hyperadrenocorticism, hypothyroidism
- Renal Biopsy?
**“Jake” – Further Evaluation**

- Abdominal Ultrasound: No Abnormalities
- Positive for Borrelia (Lyme Disease agent)

**What Does A Positive Test for Lyme Dz Mean in A Dogs With Glomerular Dz?**

- Presumed that the glomerular disease is a consequence of Borreliosis infection (but not 100% proof)
- Administering doxycycline to dogs with presumed Borreliosis-associated GN is very unlikely to improve the glomerular disease
  - But we still treat it this way
  - One month, six months, until the titer drops by at least 50% - no conclusive evidence

**In Minnesota & Northeast USA**

- Borreliosis appears to have a significant association with proteinuria & glomerular disease
- Of dogs that test positive for Borreliosis, a relatively small number have or will develop glomerular disease
- Nonetheless – Early recognition of glomerular disease improves probability of better outcome with appropriate treatment

**Intervention**

- Reduce magnitude of the proteinuria
- Minimize complications of proteinuria
  - Hypercoagulable condition
  - Hypertension
- Treat initiating causation (if known)
- Treat the primary glomerular disease

**Standard Therapy of Protein-Losing Nephropathy**

**Reducing the Magnitude of Proteinuria**

**Effect of Proteinuria on Survival**

![Graph showing the cumulative survival of dogs with CKD compared to non-proteinuric dogs.](image)
Goals

• Reduce magnitude of proteinuria
• Secondary -- ↑ serum albumin if hypoalbuminemia is present
• Therapy needs to continue so long as proteinuria persists

Standard Therapy of Glomerular Disease

Limiting Proteinuria: Inhibition of RAAS & Renal Diet

Effect of ACEI on Glomerular Hemodynamics

Why Does Blocking the RAAS Decrease Glomerular Proteinuria?

• Decreased pressure in the glomerular capillaries
  -- Higher pressure in glomerular capillaries → increased production of glomerular filtrate
  -- Protein swept out through larger “holes” by solute drag
• Restore slit diaphragm integrity & increase negative charge on glomerular membrane

Benefits of Reducing Proteinuria

• Slow progression of glomerular disease
  -- The higher baseline proteinuria – greater potential benefit
  -- Magnitude of benefit appears to be related to magnitude of reduction in proteinuria (humans)
• Effects on GFR and renal pathology in dogs???
• To date, little evidence that standard therapy alone is likely to consistently reverse or resolve lesions of glomerular disease in dogs.

Drugs Reducing Activity of the RAAS

• Angiotensin converting enzyme inhibitors
  -- Enalapril or Benazepril
• Angiotensin receptor blockers
  -- Telmisartan or Losartan (?)
• ACEI + ARB Combination
ACE Inhibitors in Dogs

Grauer et al, 2000

Effects of Enalapril in Samoyed Dogs with Hereditary Nephritis

- Slowed the rate of increase of proteinuria ($P < 0.01$)
- Delayed the onset of increase in serum creatinine concentration ($P < 0.05$)
- Treated dogs survived 1.36 times longer ($P < 0.05$).

Grodecki et al, 1997

Using ACEI in Glomerular Disease

- Side Effects:
  - Azotemia
  - Reduced BP
  - Hyperkalemia
- Starting ACEI:
  - Monitor serum creatinine & K⁺, UPC, BP
  - Starting dose (~0.25-0.5 mg/kg/day)

Adjust ACEI Dose “To Effect”

- Goal:
  - Minimally: Reduce UPC by 50%
  - Ideal → Reduce UPC to < 0.5
- If UPC not at target, increase dose (usually 50-100%) to target or maximum dose (~2 mg/kg/day)
- Carefully monitor ramp up to end-point

Potassium Management

- Managing potassium may allow higher dosages of ACEi and ARB
- Options
  - Limit dietary potassium intake
  - Enhance distal tubular flow:
    - Avoid dehydration
    - Supplement fluids (Caution!)

Should You Start with ACEi or ARB?

- ACEi is commonly first choice
  - Typical practice – more comfortable with drugs?
  - Usually well tolerated (if hydrated)
  - Commonly need to increase ACEi dosages
- When might you use ARB
  - No firm guidelines yet
  - ACEi fails to reduce proteinuria by at least 50%
  - Patient is hypertensive?
Observational Evidence ...

• Options when ACEi has not achieved goal
  – Switch to ARB (Telmisartan)
  – Add ARB (dual therapy)
    • May reduce proteinuria, but ...
    • Increased risk of adverse effects in people

Efficacy & Safety of Dual Blockade of the RAAS

• Potential adverse effects:
  – Impaired renal function
  – Hyperkalemia
• Benefits:
  – Reduce proteinuria
  – Increase survival

Makani, (BMJ) 2013

Observational Evidence ...

• Options when ACEi has not achieved goal
  – Switch to ARB (Telmisartan)
  – Add ARB (dual therapy)
    • May reduce proteinuria, but ...
    • Increased risk of adverse effects in people
• Observations:
  – In selected cases, where ACEi have failed, Telmisartan may profoundly reduce proteinuria
  – So far “better” drug has been unpredictable

3 (Related) Yorkshire Terriers

• 9 year old 5lb Yorkshire terrier
  – ACEi (Benazepril – 2 mg/kg) + Losartan: UPC > 7
  – Replaced Losartan with Telmisartan 1 mg/kg once daily.
  – UPC declined within first month from >7 to <0.6
• Previous dog’s brother UPC ~ 2+ on ACEi
  – Replace ACEi with Telmisartan
• 3rd (unrelated) Yorkshire terrier – no change in UPC on Telmisartan

Key to Success with ACEI/ARB

• Drug must reduce proteinuria!
  – Starting dose
  – Progressive ACEI dosing to ~ 2.0 mg/kg/day
  – ARB dosing 0.5-2 mg/kg
• How Long Should You Treat?
  – At least while the patient is proteinuric
  – Proteinuric means UPC ≥ 0.5
• How long should you keep monitoring?
  – Regularly ~ every 3 month (UPC, Scr, K, Albumin)

Diet: Limiting Protein Intake

• Limiting protein intake reduces proteinuria
• High protein feeding increases proteinuria (glomerular hyperfiltration)
• In rats – high protein feeding actually impairs protein nutrition status
• Other diet factors:
  – Salt
  – n-6:n-3 PUFA ratio ~ 5
  – Antioxidants

Burkholder, 2004
Standard Therapy of Protein-Losing Nephropathy

Management of Hypertension and Thromboembolism

Hypertension and the Kidney

- Nephron loss → impaired ability to adjust NaCl excretion rapidly and quantitatively as intake changes
  - ↑ ECFV → increasing blood pressure
  - Diuretics mainstay of therapy in humans
- Other major contributors
  - Activation of RAAS
  - Increased sympathetic NS activity

What Are The Effects of HT?

- In Kidney Patients: Hypertension promotes ...
  - Progression of renal dysfunction
  - Proteinuria
  - Polyuria
- Heart
  - Recent – Biomarkers indicated association between kidney disease and cardiac disease
  - “Cardio-renal syndrome”

What Are The Effects of HT?

- Ophthalmological
  - Retinal detachment
  - Retinal hemorrhage
  - Hyphema
  - Vitreal hemorrhage
  - Retinal effusion
  - Vascular tortuosity
- Neurological
  - Sudden change in mentation
  - Seizures
  - Behavioral
  - Appetite

Antihypertensive Therapy in CKD

- Goals:
  - Lower blood pressure (To < 150/95 ???)
  - Slow progression of CKD
  - Prevent/treat hypertensive end-organ injuries
  - Reduce cardiac impact (cardiorenal axis)
- Consider:
  - Proteinuria
  - Coordinate with other therapies (e.g. ACEI)

Drug Therapy for Hypertension

- Amlodipine
  - Dogs: 0.1-0.6 mg/kg/day
  - Cats: 0.625-1.25 mg/day for cats < 5 kg
- ARB – Telmesartan
  - 0.5-2 mg/kg/day
  - Protects the kidneys
- ACEI (benazepril, enalapril)
  - 0.25-2.0 mg/kg q 12-24 h
  - Protects the kidneys

Treatment is “to effect”
Multidrug Approach May Be Required

- Dogs – Amlodipine + ACEI ➔
  - Commonly used together in dogs
  - Protect the glomeruli ➔ Monitor proteinuria
- Telmisartan may be good starting choice when hypertension AND significant proteinuria
- Other options (multi-drug):
  - Hydralazine (vasodilator) - β-blockers
  - Diuretics

General Plan for Hypertension Rx

- Establish BP Dx with multiple readings
- Begin Rx based on BP & Creatinine
- Goal: Systolic BP < 150 mmHg (ideal)
- Monitor q 1-3 weeks, adjust dosage as indicated
- At Target BP ➔ monitor q 3 months

Thrombosis Prophylaxis in GN

- Justification
  - Thromboembolism
  - Fewer thromboembolic events?
- Aspirin dosage: 1.0 to 5.0 mg/kg/day
  - Efficacy unproven (dose ?)
  - Appears to be safe
  - Plavix (clopidogrel; 1.1 mg/kg/d)
- Indication?
  - Hypoalbuminemia
  - Low AT III levels?

Immunotherapy of Glomerular Disease

Immunomodulatory Therapy

- Standard therapy does not “cure” glomerular disease!
- Immunomodulatory therapy – justification?
  - Pathophysiologic reasoning
  - The human experience with glomerular diseases
  - Preliminary evidence in dogs
- ~50% of dogs with glomerular disease have glomerular immune complexes (50% do not!)
“First do no harm”
&
Risk is a two-way street!

Immunotherapy
- Mycophenolate:
  – 5-10 mg/kg PO q 12-24 h
  – Use generic (works/less expensive)

- Glucocorticoids:
  – Immunosuppressive dose
  – Single “pulse” dose or < 7 days therapy
  – Sole Therapy or Concurrent Therapy

Does Mycophenolate Work?
- 10 dogs with biopsy-proven MPGN (proliferative)
- Mycophenolate 5-20 mg/kg + Standard Therapy
- Mean baseline values (pre-treatment):
  – Serum creatinine concentration: 2.4 mg/dl (range 1.9 to 4.2) (normal value: ≤ 1.4 mg/dl)
  – Serum albumin concentration: 1.6 g/dl (range 1.1 to 1.9) (normal value: > 2.5 g/L)
  – UPC: 9.1 (range 3.7 to 16.2) Five of the 10 dogs were Lyme positive (Borreliosis)

Mycophenolate Rx of MPGN - Survival
- Standard therapy mean survival time for dogs with MPGN: 104.5 days
  (Klosterman, 2011)
- Of 10 dogs, 9 survived beyond 104.5 days
- Six of 10 alive and clinically well with survival times of 4.5 (135 d), 6, 8.5, 10, 22.5 and 48 months

Mycophenolate Rx of MPGN - Survival
- Outcome for the 7th dog unknown, but last known data:
  – Serum creatinine had declined to 0.7 mg/dl from 2.1
  – Serum albumin had increased from 1.6 to 3.2
  – UPC ratio had declined from 8.8 to 2.0
- Survival times for the 3 dogs known to be dead were 3, 8, and 39.6 months.

Mycophenolate Treatment of MPGN
- Mean (median) changes for 10 dogs with MPGN treated with mycophenolate:
  - Reduction in serum creatinine concentration
  = 0.9 mg/dl (0.9) – mean was 2.4 mg/dl
  - Reduction in serum albumin concentration
  = 1.1 g/dL (0.6) – mean was 1.6 g/dL
  - Reduction in UPC ratio was 6.0 (6.7)
  - Percent reduction in UPC was 67% (75%).
Summary

• What is known:
  – About 50% dogs with proteinuric kidney disease have Immune Complex Glomerulonephritis (ICGN)
  – Many dogs with ICGN respond to immunotherapy
  – Mycophenolate generally appears to be safe
  – Steroids may be effective, but need further study
  – At least some treated dogs that achieve partial or complete remission will recrudesce with GN

• Needed: Appropriate therapeutic clinical trials

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