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PROTEINURIA: PATHOPHYSIOLOGY, DIAGNOSTIC APPROACH AND TREATMENT

Description: This lecture will discuss diseases that cause proteinuria, with an emphasis on the dog. A brief review of pathophysiology will put diagnosis and management of proteinuria into perspective. Diagnostic approaches and therapeutic strategies, including recent experience with telmisartan will be emphasized. Lyme nephritis will be briefly discussed. Cases will reinforce the topic.

Learning objectives:

1) *Formulate a differential diagnosis list for proteinuria and generate a diagnostic plan.*

2) *Develop treatment and monitoring plans for patients with proteinuria.*

3) *Recognize presumptive Lyme nephritis and know treatment options and prognosis.*

BACKGROUND: Pathologic proteinuria can be associated with various disease conditions. Proteinuria can be considered pre-renal, renal, or post-renal. Renal proteinuria can be further divided into glomerular and/or tubular in origin. Many causes of pre-renal proteinuria may not require treatment. For example, strenuous exercise or significant anxiety can provoke pre-renal proteinuria. Alternatively, pre-renal proteinuria can be an indicator of significant disease, for example multiple myeloma. Once proteinuria is identified, consideration of the magnitude, history and physical findings and other clinicopathologic data will aid in deciding if immediate diagnostic pursuit versus confirmation of proteinuria is appropriate. For example, in an ill, edematous patient, if proteinuria is identified in combination with inappropriate USG, azotemia, hypoalbuminemia, it would be ill-advised to simply confirm proteinuria on an early morning sample. Alternatively, mild to moderate proteinuria detected on screening urinalysis without other abnormalities or signs of disease could be re-evaluated before exhaustive diagnostics are performed.

Renal proteinuria can be derived from injury or dysfunction of glomerular filtration or tubular protein transport mechanisms. The magnitude of proteinuria can be useful in identifying glomerular disease. A urine protein:creatinine ratio (UPC) greater than 2.0 is consistent with some degree of glomerular dysfunction. However, a UPC of > 2.0 does not exclude concurrent tubular disease. Evidence of tubular disease includes isosthenuria (or reduced USG vs expected), azotemia, and glucosuria.

DIAGNOSIS: In many cases of proteinuria or protein losing nephropathy (PLN), a definitive underlying diagnosis or histologic diagnosis is not achieved. However, a thorough diagnostic approach is essential to identifying any provocative disease. Broad disease categories that are associated with pathologic renal proteinuria include familial, infectious, inflammatory, and neoplasia. Therefore, the general diagnostic approach is aimed largely at identifying or ruling out infectious, inflammatory or neoplastic processes. Infectious disease testing may vary considerably depending on location and travel history.

The following are diagnostic tests that are generally appropriate in the course of diagnosis and monitoring of a patient with renal proteinuria. International Renal Interest Society (IRIS) staging is appropriate in all cases of renal proteinuria: www.iris-kidney.com

- **Complete blood count:** a CBC may disclose evidence of an infectious or inflammatory disease.
- **Biochemistry profile:** Characterization of a proteinuric patient requires evaluation of renal values, albumin, globulin and cholesterol values, in particular.
- **Urinalysis:** USG evaluation may be critical in trying to determine etiology (tubular vs glomerular) of renal proteinuria.
- **Urine protein:creatinine ratio (UPC):** Whenever possible, this should be performed on a voided, first-morning sample collected by the client at home. This minimizes contribution of pre-renal causes of proteinuria. Pooling three days of urine collection further enhances diagnostic value. At lower UPC values (e.g. 0.5) an approximately 80% change in UPC is required to make an assessment of a clinically relevant change in UPC. For higher UPC values, only about a 35% change is required for a similar assessment.
- **Urine culture:** Urine culture is generally recommended to rule out occult urinary tract infection as a cause or contributor to proteinuria.
- **Thoracic and abdominal imaging:** Screening for intrathoracic and intrabdominal diseases that could provoke proteinuria is typically best achieved by thoracic radiography and abdominal ultrasonography. Abdominal radiography is appropriate if abdominal ultrasound cannot be pursued. Advanced imaging may be appropriate in some cases, but generally not indicated.
- **Blood pressure:** Blood pressure measurement is important for patients with renal proteinuria as i) many patients have systemic hypertension and ii) medical treatment of proteinuria involves drugs that affect systemic blood pressure.
- **Coagulation parameters:** Loss of anti-coagulant regulatory proteins (such as antithrombin, protein C and protein S) in the urine predisposes patients with renal proteinuria to hypercoagulability.
- **Anti-nuclear antibody (ANA) test:** A positive ANA may support an immune-mediated process that would require immunomodulatory therapy.
- **Renal biopsy:** Although rarely performed by many practitioners, this may provide additional information for

TREATMENT: The ACVIM has issued the following consensus statements for:

Standard Therapy of Glomerular Disease in Dogs
(https://onlinelibrary.wiley.com/doi/pdf/10.1111/jvim.12230)

Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis
(https://onlinelibrary.wiley.com/doi/pdf/10.1111/jvim.12222).

- **Standard medical management:** The following medications are nearly always appropriate for patients with glomerular disease. Angiotensin converting enzyme inhibitors (ACEi) are generally the first-line therapy primary therapy; however, angiotensin receptor blockers (ARB) may have an advantage over ACEi and telmisartan is now becoming my drug of choice. Dogs not responding to an ACEi could be switched directly to an ARB, in some cases addition of an ARB with a reduction in ACEi dose may be appropriate with a goal to convert to ARB alone.

- **ACEi/ARB:** ACEi. Drugs in these classes modulate renal blood flow such that glomerular pressure is reduced. Reduction in glomerular pressure subsequently reduces proteinuria. Other drug effects can include modulation of inflammation, antifibrotic effects, etc.
    - **Enalapril:** Dose at 0.5 – 2 mg/kg/day PO. Generally divide BID. 100% elimination by kidneys.
    - **Benazepril:** ACEi. Dose at 0.5 – 2 mg/kg/day PO. Generally administer SID. 50% elimination by kidneys, 50% hepatic elimination, thus may have advantage in azotemic patients with respect to theoretic dose reductions.
    - **Telmisartan:** ARB. Dose at 1 mg/kg SID if non-azotemic. If azotemic, dose at 0.25 – 0.5 mg/kg SID initially with the possibility to increase. This drug has superior pharmacology properties in dogs compared to other ARB class drugs and also works as a PPARγ agonist, which imparts additional renoprotective effects to this drug. Use caution in combination with diuretics (particularly spironolactone) as dangerous reductions in GFR could occur.

- **Monitoring for ACEi/ARB:**
    - **Blood pressure:** Check BP 1 week after starting or changing dose.
    - **Electrolytes & Renal Values:** Check BP 1 week after starting or changing dose.
    - **UPC:** Recheck UPC 1 month after starting or changing dose. Ideally assess a 3-day pooled, voided sample collected at home, first morning.
    - **Once optimal doses are established based on response, quarterly monitoring is appropriate.**

- **Anti-platelet therapy:** Generally, ONE of the following drugs is chosen. Clopidogrel is increasingly becoming the drug of choice; however, data directly comparing clopidogrel to ultra-low dose aspirin in dogs with renal proteinuria is lacking.
    - **Clopidogrel:** Trace name Plavix, dose at 2 mg/kg PO SID. Irreversibly blocks P2Y12 ADP receptor on platelets. Activation by P450 enzymes.
    - **Aspirin/acetylsalicylic acid:** Dose at 0.5-1 mg/kg PO SID. COX inhibitor, blocks thromboxane synthesis. Has other drug effects/interactions that clopidogrel may not, e.g. anti-inflammatory effects and changes to protein binding of other drugs. *This dose is safe to use in combination with glucocorticoid therapy.*

- **Dietary management:** Data is limited; however, protein restriction is thought to reduce glomerular hypertension and there are studies that demonstrate a beneficial effect. Omega-3 fatty acids result in the elaboration of inert or anti-inflammatory lipid mediators (e.g. prostaglandins, leukotrienes, resolvins). Sodium restriction may be beneficial.

    - **Therapeutic veterinary renal diets:** Renal diets are available through major pet food manufacturers including: Blue Buffalo, Hill's Science Diet, Purina, Rayne Clinical Nutrition, and Royal Canin. Additionally, Hill's g/d may be an appropriate choice, particularly for patients requiring a lower fat diet.
    - **Omega-3 fatty acids:** A target for total EPA/DHA in the daily diet is ~150 mg/kg0.75. This may be difficult to easily calculate in most cases. A more straightforward way to dose is to give 1-2 capsules/10 lbs BW daily if using 1000 mg fish oil capsules that contain ~300 mg EPA/DHA.

- **Case-specific management:** Common causes of glomerular disease and the high frequency of systemic hypertension warrants consideration of the following treatments on a case-by-case basis.

    - **Antimicrobial therapy:** Cases of suspected Lyme nephritis should receive at least 28 days (4 weeks) of doxycycline therapy (10 mg/kg daily PO, may divide BID), but may optimally require 45 days (6 weeks) of treatment.
    - **Immunomodulatory therapy:** Concurrent evidence of immune-mediated disease, for example a positive ANA, or other steroid-responsive condition should prompt consideration of immunomodulatory therapy. I generally consider steroids as the first-line drug, followed by mycophenolate mofetil as the secondary agent, for glomerular disease in dogs that may benefit from immunomodulation. Consideration of side-effects and potential for underlying untreated infectious disease is essential.
    - **Fluid therapy:** Synthetic colloid therapy is generally contra-indicated. Judicious use of fluids may be appropriate on a case-by-case basis. Body weight, hydration status via physical exam and systemic blood pressure monitoring is essential to promptly identify overhydration and fluid overload.
    - **Management of systemic hypertension:** ACEi/ARB therapy alone may be insufficient to control most cases of significant hypertension. These classes of drugs generally only reduce systolic blood pressure by 10-15 mmHg. The most commonly used drug to treat systemic hypertension in these patients is amlodipine. The dose is 0.1- 0.75 mg/kg/day PO. Start at the lower end of the dose range and titrate up. In-hospital cases can be dosed at 0.1 mg/kg, with at least ~2 hours between doses, throughout the day (up to maximum dosing) as blood pressure is monitored and the total dose required to control BP can be used to determine daily dose. Dogs treated with amlodipine should be concurrently treated with an ACEi or ARB to counteract RAAS activation associated with this drug.

PROGNOSIS: The prognosis for glomerular disease in dogs is variable and depends on the underlying cause. Response to treatment can guide in estimating a prognosis early in disease treatment. Dogs with suspected Lyme nephritis are considered to have a grave prognosis. Dogs with stable glomerular disease may have a good prognosis and many are successfully treated for years. Most cases require life-long treatment unless there was a specific inciting cause the was eliminated and the glomerular damage was reversible. The prognosis in cats is often unclear given the rarity of glomerular disease in this species, but certainly also depends on the underlying cause.

HEPATOCUTANEOUS SYNDROME: A DISEASE THAT IS MORE THAN SKIN DEEP

Description: This lecture will review historical information regarding hepatocutaneous syndrome (HCS) and recent advances in diagnosis and treatment. A case example will illustrate the potential for good outcomes in patients that are aggressively treated. I am available for consultation regarding these cases.

Learning objectives:

1) *To understand that HCS appears to emerge first as a hepatopathy (hepatocutaneous hepatopathy), followed by cutaneous lesion development. Thus, aiding in early diagnosis in cases of hepatocutaneous hepatopathy alone.*

2) *Know options for diagnosis beyond biopsy of liver and/or skin.*

3) *Gain an understanding of treatment, monitoring, and prognosis.*

BACKGROUND: Hepatocutaneous syndrome is a rare or uncommon disease that is characterized by skin lesions and a concurrent unique hepatopathy. The unique skin lesions are representative of Necrolytic Migratory Erythema (NME) or Superficial Necrolytic Dermatitis (SND), which can manifest as part of HCS or other disease. In human beings, NME is most commonly associated with glucagonoma. Other conditions that have been associated with NME/SND include phenobarbital administration and gastrointestinal disease (e.g. Crohn's disease). Another central feature of HCS is hypoaminoacidemia, which has implications for treatment and diagnosis. Males are over-represented in some studies. Small breeds are over-represented and include: Shetland Sheepdog, Cocker Spaniel, Shih Tzu, etc. Our group has recently discovered aminoaciduria is a feature of the disease.

DIAGNOSIS: A definitive diagnosis of NME requires skin biopsy. If coupled with appropriate features of hepatic disease it is reasonable to conclude HCS. Appropriate features are increased ALP, hypoechoic nodules ("Swiss cheese" or "honeycomb" liver) identified by abdominal ultrasonography, and hypoaminoacidemia. Liver biopsy could provide definitive diagnosis of hepatocutaneous hepatopathy. Recognition of hepatocutaneous hepatopathy (a severe vacuolar hepatopathy, glycogen and lipid type, w/ parenchymal extinction) may be overlooked in cases without skin lesions. Insulin resistant diabetes mellitus is present in many cases. A clinical diagnosis of HCS can be considered without biopsy confirmation if all of following are present:

1) skin lesions that are consistent with NME/SND (crusting paw pads; erythematous crusting lesions at sites of mechanical trauma, commonly including inguinal region, elbows, axilla and mucocutaneous junctions
2) Increased ALP activity
3) Characteristic ultrasound findings
4) Hypoaminoacidemia.
    a. I recommend plasma amino acid profiles are performed by the UC Davis Amino Acid Laboratory. https://www.vetmed.ucdavis.edu/labs/amino-acid-laboratory
    b. Although not currently common practice, urine amino acid profile analysis by UC Davis would provide further support for HCS if lysinuria is present.

TREATMENT: The gold-standard treatment for HCS is parenteral administration of an amino acid solution. Additional treatment includes parenteral lipid infusions, enteral protein and amino acid provision, and supportive care.

- **Parenteral amino acid solutions:** 8-10% Aminosyn or Travasol is typically used (our warehouse sources from Cardinal Health). Procalamine is acceptable, but the lower concentration (3%) requires a larger volume to provide a similar amount of amino acids.

    - **8-10% Amino Acid solution** (ideally w/o electrolytes)**:** 25 ml/kg given over 6-8 hours. I routinely administer through a peripheral catheter (the osmolarity is in the range of partial/peripheral parenteral nutrition solutions).

    - **3% Procalamine:** I generally recommend administering 50 ml/kg and extending the infusion time to 8-12 hours if possible. Consideration of fluid rate is of greater importance than more concentrated solutions.

    - **20% lipid solution (e.g. Intralipid):** Administered at 7 ml/kg over 6-8 hours. We generally administer through the same catheter as the AA solution, using a mini-bifuse to merge separate administration lines. Do not include if patient is hyperlipidemic.

  The frequency of administration can range from weekly to as-needed depending on patient status, remission history/status, client financial status, etc. For patients that are diagnosed without skin lesions, I typically recommend quarterly infusions. For patients with skin lesions, I recommend weekly injections until remission is achieved or client finances or patient quality of life is limiting. Once in remission monthly infusions may be optimal; however, data are lacking, and this is not feasible for all patients or clients.

- **Dietary management:** A high protein diet is essential for all HCS cases that can tolerate it. Dietary protein restriction should only be considered in cases the develop hepatic encephalopathy (rarely encountered with this hepatopathy) or another concurrent nutritionally responsive disease (e.g. renal disease). ***Performance diets (i.e. a 30/20 protein/fat diet), 95% meat diets, cat food or high protein therapeutic diets such as Purina JM*** are examples of higher protein diets appropriate for most HCS patients. A high protein home-cooked diet appears to be beneficial for many patients I have managed. The addition of egg/egg yolk, whey protein or meat is often beneficial. I recommend aiming for providing 50% of the patient's calories derived from protein (i.e. $\geq$ 50% ME from protein). Consultation with a veterinary nutritionist can aid in developing an optimal diet plan.

- **Dietary supplements:** The following supplement regimen is targeted for an approximately 5-15 kg dog. Scale appropriately for larger dogs. Although appropriate for most HCS patients, I use plasma and urine AA profile results to customize when appropriate.

    - **Amino acid supplements** (available from health food stores, Amazon.com, etc.)**:**

        - Proline – 500 mg/day orally
        - Glutathione – 500 mg/day orally
        - Arginine/Ornithine – 1500 mg/day orally
        - Lysine – 500 mg/day orally

- **Other supplements:**

    - Zinc – 10 mg/10 lbs daily, orally (mg based on elemental zinc content)
    - Fish oil – 1000 mg/10 lbs daily, orally (may use other marine source such as krill oil, squid, etc.)
    - Denosyl – generally use manufacturer dosing (up to 40 mg/kg/day acceptable). Denamarin is acceptable, but the benefit of milk thistle extracts unclear in this disease. Other SAMe formulations may not have optimal bioavailability.

- **Ancillary treatments:**
    - Analgesics as appropriate (avoid NSAIDs and glucocorticoids in HCS cases)
    - Epsom salt soaks
    - Control secondary infection (may have cutaneous bacterial and yeast infections)

PROGNOSIS: The historical prognosis for HCS is grave to guarded, with a MST of ~6 months in most studies. Dogs treated at our facility have a MST of 785 days. One patient with severe lesions required 10-15 AA+lipid infusions approximately 7-10 days apart to achieve remission. That patient is now maintained on monthly infusions and is doing well over 3 years from diagnosis.