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The 1-2-3s of CKD

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Chronic kidney disease (CKD) is clinically characterized by the development of variably progressive, irreversible, intra-renal lesions and loss of renal functions. A variety of interventions may slow the progression of this disease and improve the quality of and extend the quantity of life for the patient. The International Renal Interest Society (IRIS) has proposed a staging system for CKD based on the serum creatinine concentration for the stable patient (well hydrated) on at least two (2) occasions.

IRIS Stage	Serum [CREA] – Dog	Serum [CREA] – Cat
Stage 1	<1.4 mg/dL	<1.6 mg/dL
Stage 2	1.4–2.0 mg/dL	1.6–2.8 mg/dL
Stage 3	2.1–5.0 mg/dL	2.9–5.0 mg/dL
Stage 4	>5.0 mg/dL	>5.0 mg/dL

IRIS Sub-Stage by UPC	Dog	Cat
Non-Proteinuric (NP)	<0.2	<0.2
Borderline Proteinuric (BP)	0.2–0.5	0.2–0.4
Proteinuric (P)	>0.5	0.4

IRIS Sub-Stage by BP Risk for Renal Injury	Systolic (mmHg)	Diastolic (mmHg)
Minimal	<150	<95
Low	150–159	95–99
Moderate	160–179	0.4
High	≥180	≥120

Staging allows utilization of rational treatment strategies based on stage of disease. Obviously, the objective of treatment is to slow or prevent the disease from progressing. General goals for management of CRF are to:

- Reduce uremic signs
- Provide optimal nutrition
- Slow progression of CRF
- Provide endocrine replacement when possible

1. Dietary Intervention

Evidence in clinical cats and dogs with CKD shows dietary modification increases survival time and decreases the number of uremic crises. Recommended renal friendly diets are generally restricted in protein, phosphorus, calcium, and sodium, and are supplemented with carbohydrates, sources of alkali, and polyunsaturated fatty acids in a favorable ratio of $\omega 6:\omega 3$. Traditionally, benefits of such diets are attributed to the effects of dietary phosphorus restriction, but diets with higher eicosapentaenoic acid content may also confer protection. Regardless of the type of diet fed, it is more important that dogs and cats with mild-to-moderate CKD maintain adequate caloric intake to avoid protein-calorie malnutrition.

2. Antacid Therapy

Dogs and cats with CKD have increased serum gastrin concentrations that contribute to the pathogenesis of uremic gastritis. Unfortunately, many with uremic gastritis only show partial to complete anorexia as the clinical signs of this problem rather than vomiting. Therefore, proton pump inhibitors or H_2 receptor antagonists are recommended for treatment of uremic gastritis secondary to CKD once the serum creatinine is above 2.5 mg/dL. Anti-emetic medications such as a 5-HT₃-serotonergic antagonist or neurokinin (NK-1) antagonist may be required as uremia progresses.

If therapy for uremic gastroenteritis fails to restore normal appetite, administration of an appetite stimulant should be considered. As renal disease may affect drug elimination, reducing the dosage or prescribing longer dosing intervals may be necessary. If food intake remains inadequate, long-term use of percutaneous gastrostomy or esophagostomy tubes should be considered, and has been successful for delivering food, extra water, and medications to patients with CKD.

3. Intestinal Phosphate Binders and Phosphate Restriction

Early phosphorus restriction may help blunt or reverse renal secondary hyperparathyroidism. Renal friendly diets may provide sufficient dietary phosphate restriction during early stages of CKD, but dietary phosphate binders are

The 1-2-3s of CKD (Continued)

frequently needed. Diet and binders should be prescribed to help achieve serum phosphorus and parathyroid hormone (PTH) levels. Normal serum phosphorus concentrations are desirable but do not guarantee PTH is normal. Phosphorus-binding agents should be given with meals or within two (2) hours of feeding to maximize their binding of dietary phosphorus. Commonly employed oral phosphorus binders include aluminum hydroxide, calcium carbonate, and calcium acetate, but no drug is licensed for phosphate binding in veterinary medicine. Animals should be monitored for development of hypercalcemia whenever phosphorus binders containing calcium are used, especially if calcitriol is being administered concurrently.

4. ACE-Inhibition

Angiotensin-II plays a pathophysiologic role in proteinuria and the progression of renal disease. Angiotensin-converting enzyme (ACE) inhibitors may have protective effects in patients with chronic renal disease due to their ability to block adverse effects of angiotensin II. ACE-inhibition reduces glomerular capillary hydraulic pressure by decreasing post-glomerular arteriolar resistance. Proteinuria is decreased secondary to reduced glomerular hydraulic forces and development of glomerulosclerosis is limited when protein loss across the glomerulus is ameliorated. This beneficial effect must be balanced against the potential to worsen azotemia.

5. Calcitriol

Calcitriol treatments help decrease PTH or prevent its increase in those with renal secondary hyperparathyroidism. During calcitriol therapy, simultaneous monitoring of serum ionized calcium, serum phosphorus, and PTH concentrations is essential to document successful and safe control of renal secondary hyperparathyroidism. Calcitriol should not be administered until hyperphosphatemia has been controlled. If the calcium x phosphorus solubility product exceeds 60-70, calcitriol should be avoided because of the risk of soft-tissue mineralization.

6. Erythropoietin Replacement

Recombinant human erythropoietin (rhEPO) and darbopoietin have been used to successfully correct non-regenerative anemia in dogs and cats with CKD. Treated animals demonstrate resolution of anemia, weight gain, improved appetite, improved haircoat, increased alertness, and increased activity. Therapy should be considered in patients with PCV values <20% and problematic clinical

signs of anemia. Although initially effective in correcting the anemia of CKD, erythropoietin replacement may result in antibody formation in up to 50% of treated dogs and cats after 1-3 months of treatment. The resulting anemia may be more severe than that present before treatment because the induced antibodies may cross-react with the animal's native EPO. Other adverse effects have been observed during administration of rhEPO to dogs and cats including vomiting, seizures, hypertension, uveitis, and a hypersensitivity-like mucocutaneous reaction.

7. Control of Systemic Hypertension

Systemic hypertension occurs in 30 to 75% of cats and dogs with chronic kidney disease. The correlation of unregulated arterial hypertension to the progression of CKD has not been established in cats, but there are some studies in dogs and humans that suggest a positive relationship. It is likely systemic hypertension is transmitted to the glomerular vessels to promote further injury. Enalapril has not been very effective for treatment of hypertensive cats, but the calcium channel blocker amlodipine has been used quite successfully; indeed, it is this author's first choice anti-hypertensive medication for patient's living with CKD. Follow-up evaluations should be scheduled for one week after beginning treatment with amlodipine and happily, adverse effects are very uncommon with the use of this medication.

8. Control of Proteinuria

The detection of proteinuria is a diagnostic index in cats and dogs with CKD. The magnitude of proteinuria is a function of the integrity of the glomerular barrier, GFR, tubular reabsorptive capacity, and effects from elevated systemic and intra-glomerular blood pressure. Evidence shows cats with CKD had an increased risk for death or euthanasia when the UPC was 0.2 to 0.4 compared to <0.2, and the risk was increased even further in cats with UPC of >0.4 (Syme HM, et al. *J Vet Intern Med*, 2006). In a study of dogs with naturally occurring CRF, the relative risks for the development of uremic crises and death were approximately three times higher when coupled with urinary protein to creatinine ratios (UPC) >1.0, compared with UPC <1.0 (Jacob F, et al. *J Am Vet Med Assoc*, 2003). Because low-level proteinuria is a risk factor for survival, it is prudent to consider treatments that lower the amount of proteinuria in those with CKD. However, the effect of treatments that lower proteinuria has not been specifically studied.

Case Study

Chronic Diarrhea – Not Always the Gut's Fault

By Christopher G. Byers, DVM, DACVECC, DACVIM

PATIENT HISTORY

Signalment: Allegheny, 1.5 yr MN Border Collie (20 kg)

Chief Complaint: 4 months' duration of weight loss and small bowel diarrhea

Salient Points: Allegheny's history included small bowel diarrhea of 3 months' duration approximately 9 months prior to the current presentation that was minimally responsive to metronidazole therapy and dietary manipulation. His current diet is novel protein (venison) formula with occasional apple slices for training treats. Allegheny has always lived in Maryland, and received RV, DA2PP/CV, and Bordetella vaccinations 6 months prior to presentation.

PHYSICAL EXAMINATION

On examination, Allegheny was bright, alert, responsive, well-hydrated, and afebrile. His body condition score (BCS) was 2/9 and generalized cachexia was noted. Rectal examination identified soft, light brown feces. After rectal examination, the patient was observed to defecate a large volume of malodorous, similarly colored feces.

INITIAL DIAGNOSTIC EVALUATION

The initial diagnostic plan included:

- Complete blood count (CBC), serum biochemical profile, and urinalysis to provide a minimum database
- Fecal flotation by zinc sulfate sedimentation to evaluate for ova and parasites evaluation identified no abnormalities
- *Giardia* ELISA
- Fecal cytology to evaluate bacterial populations and presence of inflammatory cells

RESULTS

The CBC identified an absolute mature neutrophil count of 15,265 (reference range: 2060-10600) and an absolute monocyte count of 1011 (reference range: 0-840). Serum biochemical profile documented an alanine aminotransferase (ALT) of 132 U/L (reference range: 12-118 U/L) and asparagine aminotransferase (AST) of 88 U/L (reference range: 15-66 U/L). Urinalysis, *Giardia* ELISA, and fecal flotation were all negative. Fecal cytology identified colonic epithelial cells, and a mixed population of bacteria, yeast, and unidentifiable debris.

Given the patient's history, signalment, and cumulative test results, differential diagnoses for his weight loss and chronic small bowel diarrhea included:

- Intestinal parasitism (i.e.: giardiasis, hookworms, roundworms)

- Inflammatory gastrointestinal disease (inflammatory bowel disease)
- Lymphangiectasia
- Small intestinal bacterial overgrowth
- Histoplasmosis
- Stagnant loop syndrome
- Occult gastrointestinal parasitism
- Neoplasia
- Exocrine pancreatic insufficiency (EPI)
- Highly digestible diet responsive

DIAGNOSTIC PLAN

The updated diagnostic plan included:

- Abdominal ultrasound (AUS) examination to look for any changes in the intra-abdominal organs, particularly the gastrointestinal tract, liver, and pancreas
- Fasting trypsin-like immunoreactivity assay to screen for EPI
- Fasting cobalamin and folate levels to screen for deficiencies and/or hypersyntheses

ADDITIONAL RESULTS

The AUS examination identified no architectural abnormalities. Fasting TLI was 1.2 ug/dL (reference range: 5.7-45.2 ug/L) and the cobalamin level was 175 ng/L (reference range: 251-908 ng/L). The serum folate level was normal.

PROBLEM LIST

- Weight loss
- Chronic small bowel diarrhea
- Mature neutrophilia
- Monocytosis
- Elevated hepatocellular enzymes
- Hypocobalaminemia
- Decreased TLI

DIAGNOSIS

- Exocrine Pancreatic Insufficiency (EPI)

TREATMENT

Allegheny was prescribed a powdered pancreatic extract (Pancreazyme; 2 teaspoons per 20 kg body weight), cobalamin parenteral, and oral Vitamin E supplementation. At a 3-week recheck examination, his weight had slightly increased, his appetite had normalized, and his fecal consistency was markedly improved.

DISCUSSION

Exocrine pancreatic insufficiency (EPI) is caused by insufficient synthesis and secretion of exocrine pancreatic digestive enzymes.¹ Subsequently, there is insufficient digestive enzyme activity in the lumen of the small intestine. Pancreatic acinar atrophy (PAA) is the most common cause of EPI in dogs. Canine PAA occurs secondary to subclinical immune-mediated pancreatitis in German Shepherd Dogs and Border Collies.^{2,3}

Clinical signs of EPI develop following loss of approximately 90% of the exocrine pancreas. Nutrient malabsorption may lead to both protein-calorie malnutrition and vitamin deficiencies. Serum cobalamin concentrations are markedly decreased in many dogs with EPI, and serum folate concentrations are often increased, suggesting concurrent small intestinal bacterial overgrowth (SIBO).⁴ Vitamin K deficiency and a resultant coagulopathy may develop rarely.⁵ In patients with EPI caused by chronic pancreatitis, pancreatic tissue destruction may not be limited to the acinar cells, and concurrent diabetes mellitus may be present.

Clinical signs most commonly reported in dogs with exocrine pancreatic insufficiency are polyphagia, weight loss, and diarrhea. Feces from dogs with EPI are commonly pale, loose, voluminous, and malodorous. However, dietary modification may mask these expected fecal changes.¹ Results of routine blood/urine tests are within the normal range in most cases, although lymphopenia, lymphocytosis, neutrophilia, eosinophilia, and elevations of hepatic enzymes may be seen.^{6,7} Abdominal radiography and ultrasonography are frequently unremarkable. The serum trypsin-like immunoreactivity (TLI) is recognized as the most sensitive and specific non-invasive screening assay for EPI. Serum TLI concentrations are markedly subnormal in affected patients.⁸

Most dogs with EPI may be successfully managed by supplementing each meal with pancreatic enzymes present in commercially available dried pancreatic extracts.⁹ Adding two teaspoons of powdered pancreatic extract per 20 kg of body weight to each meal is generally an effective starting dose, and this can be mixed with a maintenance food immediately prior to feeding. When available, use of 85-115 g/20 kg of body weight of chopped raw ox, pig, or other pancreas obtained from animals certified as healthy following appropriate inspection is a more economical alternative.¹⁰ As soon as clinical improvement is apparent, owners can determine a minimum effective dose of enzyme supplement. Rarely, oral bleeding has been correlated with pancreatic enzyme replacement therapy with resolution of clinical signs with dose reduction.¹¹

Only a small proportion of the oral dose of each enzyme is delivered functionally intact to the small intestine. As such, attempts have been made to increase the effectiveness

of enzyme supplementation, including pre-incubation of enzymes with food prior to feeding, bile salts supplementation, inhibition of gastric acid secretion, and use of enteric-coated preparations. None have been shown to consistently improve clinical response.

Nutrient absorption does not return to normal despite appropriate enzyme therapy. As such, patients usually compensate by eating more than usual in order to maintain ideal body weight. Feeding a highly digestible, low-fiber diet helps to compensate for residual digestive deficits.¹²

Dogs with EPI may have severely subnormal concentrations of serum cobalamin and Vitamin E.^{1,3,13} Clinical signs associated with naturally occurring Vitamin E deficiency and/or hypocobalaminemia have not been well documented in the dog, but supplementation of these vitamins if serum levels are decreased is prudent. Administration of 400 IU/20 kg body weight Vitamin E once daily with food for a month frequently normalizes serum concentrations. Several protocols for cobalamin supplementation have been suggested, and this author supplements according to the following schedule:

- 250-1000 mcg SQ q7 days x 6 weeks;
then 250-1000 mcg SQ q14 days x indefinitely

Long-term monitoring of serum cobalamin concentration is warranted. Parenteral cobalamin replacement at intervals as frequently as every 1 week may be required for a long-term optimal clinical response.

Dogs with PAA commonly have SIBO, but in most cases this is a subclinical abnormality and affected individuals respond very well to treatment with oral enzyme replacement alone even though the overgrowth usually persists.^{1,3,6,13} In those patients who do not respond to oral enzyme supplementation, antibiotic therapy may be appropriate. Dogs with EPI that do not respond adequately to standard therapies (enzyme supplementation, cobalamin supplementation when hypocobalaminemia is present, antibiotic therapy when SIBO is suspected) should be evaluated further for additional gastrointestinal disease(s), most commonly lymphoplasmacytic gastroenteritis.

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Testimonials

“Dr. Byers did work miracles. He is a specialist in dealing with hemolytic anemia because one of his own dogs has a similar problem and we were able to benefit from his expertise in this area. He successfully has treated Casey and he’s a healthy and happy dog. I and my wife would personally like to thank everyone at MidWest Veterinary Specialty Hospital, Dr. Byers and his staff have treated us with a great deal of professionalism and empathy. The bright little light of Casey continues to shine.”

- *Edward and Judith Brodnicki*

“Our little dog Max had 2 surgeries and an extended recovery due to a ruptured cervical disc. He was unable to walk or sit when he came to you and was in severe pain. Everyone at MidWestVET was wonderful. Today you would never know how sick Max was by looking at him. The doctors and staff are great!”

- *Mike and Karen Curry, “Max”*

“THANK YOU! THANK YOU! THANK YOU to Dr. Thoesen, Molly, and your wonderful staff. On November 21st, 2010, both of our dogs were shot on our land by roadside hunters. Luckily, they both made it home, alive! We took them to our local vet, Dr. Lynn Guthmiller, who was amazing. He stabilized them and referred us on to MidWestVET. Hunter was shot in the chest and Bo was shot in the jaw, shattering it and destroying his tongue. We were not sure if they would make it through all of the trauma they sustained. This was very hard on our family, but your team took WONDERFUL care of our boys! Dr. Thoesen reassured us every step of the way that we would get through this and they would heal and come home, but we had to take one step at a time. They have come a long way and there are not enough words to express our appreciation for all you have done for our boys and our family!”

- *The Wortmans, “Hunter and Bo”*



Technician Tips

By James K. Roush, DVM, MS, Diplomate, ACVS

Help Your Clients Keep Their Pets’ Hips Healthy

Hip Dysplasia in dogs is caused by a combination of genetic, nutritional, and environmental factors. Genes transmitted from the parents are only responsible for 30% of the clinical expression of hip dysplasia. The quality and quantity of food provided to the puppy during growth also plays a big role in hip dysplasia development.

Prevention tips you can share to improve the odds:

1. Keep the puppy thin. This means you need to see a definition between the ribs and loins of the dog. Feeding too many calories to a puppy actually increases the likelihood of hip dysplasia. Obese puppies **are not** healthier puppies in terms of their hip development.
2. Feed a quality diet that is recommended by your veterinarian for puppies and young adults.
3. Do not give calcium supplements to rapidly-growing large breed puppies. Commercial diets contain sufficient calcium for growth. Oversupplementation increases the risk of hip dysplasia and other juvenile orthopedic diseases.



Management Memo

Are You the Leader?

In light of the recent passing of Apple founder Steve Jobs, business owners everywhere can learn from his leadership tactics and use his example to make a positive difference on their industry, and for customers and colleagues, according to the Harvard Business Review. Writing for the Review, Bill Taylor says the true legacy of the legendary Apple founder is not his contribution to the tech industry, but rather the influence he had on his employees as a high-impact leader. “Attracting and maintaining great people is necessary to a successful company or team,” Taylor writes.

Taylor suggests following Jobs’ example by asking yourself five important questions:

1. **Why should great people want to work with you?**
2. **Do you know a great person when you see one?**
3. **Can you find great people who aren’t looking for you?**
4. **Are you great at teaching people how your team or company works and wins?**
5. **Are you as tough on yourself as you are on your people?**

To read more on how to follow in Jobs’ footsteps and be a great leader, check out the Harvard Business Review blog online at www.hbr.com.

Not Your Typical Cause of Abdominal Fluid

By Mike Thoesen, DVM, DACVS

A four year-old intact male Small Munsterlander presented to MidWestVET for further evaluation of a suspected caudal thoracic mass and abdominal effusion. The history included four months of lethargy, decreased appetite, elevated WBC counts ranging between $40.0-60.0 \times 10^3/\mu\text{l}$, and recent abdominal fluid accumulation.

On presentation, the patient had abdominal distention, a cachectic appearance, and a moderate increase in respiratory rate and effort. Three view chest radiographs revealed a large midline caudal thoracic soft tissue/fluid opacity between the heart and diaphragm (**figures 1 and 2**). Differential diagnoses for this finding included diaphragmatic hernia, neoplastic process and infectious/cystic lesion. A focal ultrasound revealed a fluid-filled structure that was aspirated. A fluid sample was submitted for analysis. Abdominal fluid was collected via abdominocentesis and sent for analysis. Analysis of fluid from the thoracic structure was consistent with a neutrophilic exudate and the abdominal fluid was a transudate.

The patient was scheduled for a computed tomography scan followed by an exploratory thoracotomy if indicated. The CT scan confirmed the presence of an encapsulated fluid-filled structure measuring 8.5cm x 14cm at its largest point positioned between the heart and diaphragm. The structure was compressing the caudal vena cava (**figure 3**). The liver had a mottled appearance and was enlarged. An exploratory thoracotomy via a median sternotomy approach was performed. The capsule wall of the fluid-filled structure was resected followed by copious thoracic lavage and drainage. Samples of the capsule wall were obtained for tissue culture and histopathologic analysis. A liver biopsy was submitted for histopathologic analysis.

Tissue culture revealed microbial growth of *Actinomyces bovis*. Histopathologic analysis of the capsule wall revealed pyogranulomatous inflammation with intralesional bacterial organisms compatible with a thoracic abscess. The liver had benign chronic congestion, likely the result of increased venous hydrostatic pressure secondary to compression of the caudal vena cava by the thoracic abscess.

Three days postoperatively the abdominal fluid had completely resolved. The patient was treated with long-term amoxicillin trihydrate/clavulanate potassium based on culture and sensitivity testing. Two weeks postoperatively the patient had gained 1 kilogram and was clinically normal.

Thoracic actinomycosis typically presents as a generalized pyothorax rather than a localized, encapsulated abscess. This is an infection often associated with puncture wounds and environmental foreign bodies such as plant fragments and grass awns. The treatment of choice for actinomycosis is aggressive surgical drainage and debridement followed by weeks to months of antibiotic therapy based on culture and sensitivity testing.

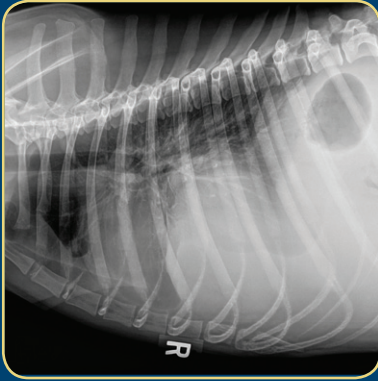


Figure 1. Lateral radiograph showing increased soft tissue/fluid density in the caudoventral thorax causing diaphragm border effacement.

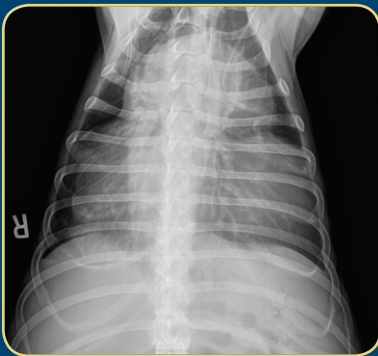


Figure 2. Ventrodorsal radiograph showing a midline soft tissue/fluid density between the heart and diaphragm.

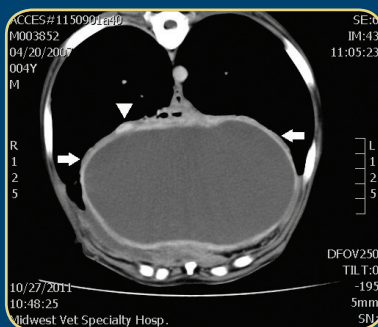


Figure 3. Transverse computed tomography image further defines the thin walled fluid-filled structure (white arrows) and caudal vena cava compression (white arrow head).