

V E T E R I N A R Y R E F E R R A L N E W S F R O M A N G E L L A N I M A L M E D I C A L C E N T E R



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EMERGENCY & CRITICAL CARE

A Closer Look at Panoquell-CA1 in Dogs

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Acute pancreatitis (AP) is a common but often challenging disease to treat in our canine patients due to the variability in the severity of the disease and the response to treatment. In the past, the mainstay of treatment has been supportive care (intravenous fluids, anti-emetics, dietary changes).

The etiology and pathogenesis of spontaneous pancreatitis are poorly understood in humans and dogs.¹ Often, in dogs, the cause of pancreatitis is thought to be idiopathic. Spontaneous disease is likely far more complex and dependent on multiple genetic and environmental factors, some of which might be unknown.¹ Potential risk factors in dogs are divided into categories in Cridge et al.'s paper (table on page 2).¹



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SURGERY

The Limping Labrador

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Labrador Retrievers (LR) and LR crosses frequently present to veterinary surgeons for orthopedic problems, most often hind leg lameness. It is not surprising that we see a lot of LR, as they were the most popular breed of dog for 31 years before being dethroned by the French Bulldog in 2022 in the AKC rankings. Rupture of the cranial cruciate ligament (CCL) is a leading cause of

hind leg lameness in dogs, accounting for about 20% of cases presenting to veterinary surgeons. (Johnson 1994) Although hip dysplasia (HD) is the most common orthopedic problem seen in dogs, many dogs (76% to 86%) with HD are asymptomatic. (Powers 2005) In a population of dogs presenting to a university hospital for hip dysplasia, 32% were found to have a rupture of the CCL as the cause of the

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TABLE 1. Suggested risk factors for pancreatitis in dogs¹

Category	Potential Risk Factor
Dietary factors	High-fat diet Ingestion of unusual food items Ingestion of table scraps Ingestion of trash
Drugs/toxins	L-asparaginase Phenobarbital and potassium bromide ^a Azathioprine Potentiated sulfonamides Organophosphates Corticosteroids ^b Furosemide Atovaquone/proguanil (Malarone) N-methyl-glucamine (Meglumine) ^b Clomipramine Zinc
Endocrinopathies	Hyperadrenocorticism ^a Hypothyroidism ^a Diabetes mellitus ^{ac}
Hereditary/breed predispositions	SPINK 1 mutation ^b Acute: Terrier breeds, miniature poodles, dachshunds, cocker spaniels, Alaskan malamute, laika, miniature schnauzer Chronic: Cavalier King Charles spaniel, collies, boxers
Lipid disorders	Hypertriglyceridemia
Miscellaneous	Babesiosis Canine monocytic ehrlichiosis Schistosomiasis (<i>Heterobilharzia americana</i>) Honeybee envenomation Organic acidemias Immunoglobulin G4-related disease Increasing age Obesity/overweight status Neutered status Previous surgery Hepatitis/cholangitis

Note: Potential risk factors for AP in dogs. Many of these factors are implied by a temporal association alone, and causation has not been established for many of these factors. Additionally, various definitions and indicators of AP were utilized in the referenced studies, and clinical signs of AP were not always noted. Thus, some of these risk factors might represent risk factors for subclinical pancreatic injury rather than primary clinical AP. The relationship between the proposed risk factors and

pancreatitis is often challenging to determine clinically, and for some risk factors, the direction of causation cannot be determined.

- ^aMay be due to secondary lipid abnormalities.
- ^bContradictory evidence exists.
- ^cReverse direction of causation has been suggested.

Cridge et al. discuss the balance between stressors and protective mechanisms determining clinical evidence of acute pancreatitis.

Panoquell-CA1 (fuzapladib sodium) is the first and only drug conditionally approved in the U.S.³ to treat acute canine pancreatitis. It is a leukocyte function-associated antigen 1 (LFA-1) activation inhibitor that is given to block the specific pathway of inflammation associated with acute pancreatitis.³

The drug is given IV at a dose of 0.4 mg/kg once daily for three days. The product comes in two vials. One vial contains 14 mg of fuzapladib sodium, 52.5 mg of mannitol, and 21 mg of tromethamine as a sterile lyophilized powder. The second vial of 3.9 ml sterile diluent (bacteriostatic water for injection), containing 1.8% w/v benzyl alcohol, is for reconstituting the sterile lyophilized powder before use. No other diluent should be used, and only 3.5 mL is needed for the reconstitution.⁴ The resulting concentration is 4 mg/ml and given in a bolus injection over 15 seconds to a minute. The product is good for 28 days once reconstituted and refrigerated.

Panoquell-CA1 is a highly protein-bound drug, and caution should be used with other highly protein-bound drugs (NSAIDs, anti-emetics, antibiotics, diuretics, behavior modifying medications).⁵ The safe use of Panoquell-CA1 has not been evaluated in dogs with cardiac disease, hepatic failure, renal impairment, pregnant, lactating, or breeding dogs, or less than six months of age.³

Neutrophils and macrophages are key in local and SIR (systemic inflammatory response) in acute pancreatitis.¹ Neutrophils within the capillaries enter pancreatic tissue by adhering when LFA-1 binds to ICAM-1, resulting in tissue inflammation. Panoquell-CA1 blocks LFA-1 and the process of neutrophils entering the tissue.¹

The cost of one 3.5 ml vial of Panoquell-CA1 in our hospital is a few hundred dollars. This is relatively inexpensive if it decreases the length of hospital stay.

Possible side effects include anorexia, digestive tract disorders, respiratory tract disorders, hepatopathy, and jaundice. Swelling and bruising may occur at the injection site.⁵

Panoquell-CA1 has been approved in Japan since 2018 for treating acute pancreatitis in dogs. This drug received temporary approval on November 15, 2022, and must meet the requirements for full approval within five years. This paper includes the freedom of information summary application⁴, which describes the pilot field study that concluded that the drug is safe and has a reasonable expectation of effectiveness when

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used according to the labeling.⁴ On day three of the study, the clinical scores (activity, appetite, vomiting, etc.) in the treatment group were improved compared to those of the control group.

Panoquell-CA1 is still in the initial stages of its clinical use. The drug has been used in a few cases at Angell Animal Medical Center. Further research must be conducted to determine its efficacy and when it is best to administer the medication during the disease process. A multicenter clinical trial in spontaneous pancreatitis in dogs is ongoing in the United States.¹

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- 3 <https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/13134>
- 4 <https://vetmed.illinois.edu/2023/08/29/panoquell-ca1-conditionally-approved-for-management-of-pancreatitis-in-dogs/>

› Emergency & Critical Care Service at Angell West; Urgent Care Available by Appointment

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lameness. (Powers 2005) The overall incidence of CCL rupture in dogs is about 2.5%, according to data from 2003. (Witsberger 2008) That study also showed that certain breeds are at higher risk, with Newfoundlands and Rottweilers having the highest risk. Labrador Retrievers have the third highest risk at almost 6%, about twice the average dog. Greyhounds only have a prevalence of 0.55%, making them one of the lowest-risk breeds. In that study, the prevalence of CCL rupture was calculated for each decade between 1964 and 2003, significantly increasing each decade. (Witsberger 2008) During that time, the prevalence statistically considerably increased over each period. Cruciate ligament rupture in dogs has a tremendous economic impact in the United States, with estimates that owners spent \$1.32 billion on treating CCL rupture in 2003. (Wilke 2005)

ACL Disease in People

In people, anterior cruciate ligament (ACL) rupture is also a common and severe condition, with estimates of over \$1 billion spent annually on surgery alone. (Flynn 2005) ACL ruptures in people have many similarities to CCL ruptures in



dogs. Ruptures are most common in female athletes in their late teens or early twenties. (Sutton 2013) Greater than 70% of cases are caused by non-contact injuries and are characterized by progressive fiber tearing, which eventually progresses to complete tears. (Pfeifer 2018) People also have a high risk of contralateral rupture. ACL rupture is also a complex disease with both genetic and environmental risks. Familial risk for rupture of the anterior cruciate ligament (ACL) was first suggested in 2005. (Flynn 2005) 2.9% of patients with an ACL tear had a relative who had experienced a tear as well, which is higher than the prevalence in the overall population, making a familial predisposition likely. The same study showed that a person with an ACL tear is twice as likely to have a relative (first, second, or third-degree) who also has an ACL tear and more than twice as likely to have a first-degree relative (sibling, parent, or child) with an ACL tear. (Flynn 2005) Because the canine CCL and the human ACL are anatomically equal, the dog is often used as a model for research on cruciate ligaments in people.

CCL Anatomy

The CCL is a ligament of twisted collagenous fascicles and fiber bundles and runs cranially, medially, and distally from the femur to the tibia. (Hayashi 2004) It has a narrow mid-region, which fans out proximally and distally. Two bands make up the CCL: the craniomedial and caudolateral bands. The craniomedial band is the major contributor to the craniocaudal stability of the stifle joint. It is long and spiral but smaller than the caudolateral band. (De Rooster 2006) It is taut through range of motion, unlike the caudolateral band. The caudolateral band has a straighter course and is taut only in extension and lax in flexion. (De Rooster 2006) The craniomedial band is often torn in partial CCL tears. The blood supply to the CCL is marginal to the ligament's core and predominantly from the surrounding soft tissue, making it vulnerable. (Hayashi 2004) There is a large amount of joint inflammation in dogs with CCL disease, which may be secondary to ligament rupture; however, in 25% of cases, synovitis is present prior to ligament fraying. (Bleedhorn 2011)



This may indicate that synovitis may cause ligament degeneration in some dogs. (Bleedhorn 2011, Muir 2011) CCL rupture in dogs is a syndrome of progressive fiber tearing in the presence of knee synovitis. Joint inflammation, mechanical overloading, ligament micro-injury, and ischemia all result in diminished typical crimped structure of collagen fibrils and disruption of ligament fascicles. (Hayashi 2004, De Rooster 2006) The increased collagen remodeling leads to increased laxity and progressive degenerative joint disease. Most cases involve a mid-substance rupture, which is the narrowest region of the ligament and has the weakest blood supply. (Bennett 1988, Hayashi 2004)

Risk Factors for CCL Disease

CCL tears typically occur as a non-contact injury during normal activity. (Pfeifer 2018) Normal running, fetching, and playing with other dogs should not be enough force to rupture a healthy ligament. (Buote 2006) High-level activities such as agility, dock jumping, racing, and lure coursing do not increase the risk of CCL rupture. (Sellon 2022) In fact, competing frequently and participating in more challenging events was associated with a lower risk of CCL rupture, while



novice-level agility was associated with an increased risk. Other studies also found that activity level was not a risk for CCL rupture in Labrador Retrievers. (Terhaar 2020) That same study and a second study showed that dogs who were obese or overweight, on a weight management plan, or fed premium dog food were at increased risk. (Lampman, 2003) CCL rupture is a multifactorial disease; many studies have evaluated risk factors. Age, sex, neuter status, weight, conformation, and breed have all been implicated as influencing the risk; however, many studies have found contradictory results. Early studies on the CCL found microscopic degenerative disease in the cranial and caudal cruciate ligament as dogs age. (Zahm 1965, Vassuer 1986) The degeneration progressed, and no attempt was made at repair. (Vassuer 1986) This degeneration leads to the weakening of the ligaments in older dogs but does not explain the ruptures seen in young dogs. In

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1988, it was suggested that there is a syndrome of CCL disease in younger large breed dogs where dogs less than four years of age and greater than 22kg experience partial ruptures that progress to complete tears over time. (Bennett 1988)

CCL Disease and Genetics

A decade later, researchers started investigating the breeds experiencing early CCL tears. Newfoundlands were found to have an increased risk for CCL, while Golden Retrievers and German Shepherds had decreased risk. (Duval 1999) This suggested heritability in cruciate disease. Greyhounds rarely rupture their CCL, so they have served as controls in many studies. Both Rottweilers and LR were found to have weaker CCLs when compared to greyhounds. (Wingfield 2000, Comerford 2005) Numerous studies describe a high risk of bilateral tears in young, high-risk breeds. Increased weight bearing on the contralateral side is not the cause of bilateral tears, as dogs with experimentally transected cruciate ligaments had normal contralateral joints after being followed for over two years. (Campbell 1982) Bilateral rupture on initial presentation has been reported in as many as 27% of dogs. Dogs presenting with unilateral disease have a 37% to 48% risk of tearing the other side. (Doverspike 1993, Buote 2009, Cabrera 2009) Degenerative

change or joint effusion in the contralateral stifle is associated with an even higher risk (59% to 61%), especially in younger dogs. (Fuller 2014) Dogs over eight years of age are less likely to experience a contralateral tear (19%). (Murphy 2023) Labrador Retrievers had an even lower risk after eight years of age with only 6% rupturing the contralateral side. (Cook 2020) A genetic basis for CCL rupture was first suggested in 2003 when pedigree analysis showed genetic heritability in both boxers and Newfoundlands. (Nielen 2003, Wilke 2006) In 2009, chromosomal regions associated with CCL rupture were identified, and in 2014, three chromosomal regions associated with CCL disease were found in Newfoundlands, confirming a genetic basis in that breed. (Baird 2014) That same year, single nucleotide polymorphisms (SNPs) were examined in four breeds: Newfoundlands, Rottweilers, LR, and Staffordshire Terriers. (Baird 2014) SNPs are a substitution of a single nucleotide at a specific position in the genome that is present in varying numbers within a population. They may influence the development of a disease and control how a patient will respond to pathogens or medications. The authors looked at 196 SNPs across 28 genes and found 17 were associated with the CCL, most within collagen genes. Genes involved in ligament strength, stability, and extracellular matrix formation were all associated with rupture of the CCL. (Baird 2014) The authors

concluded that the structure and strength of the CCL may be compromised by these mutations, leading to an increased risk of CCL rupture. (Baird 2014) SNP-based heritability in LR was investigated, and heritability ranged from 0.55 to 0.886. (Cook 2020) This means that 55% to 89% of the risk of developing CCL rupture is genetic in LR, with environmental factors accounting for the remainder. That study also found that less than 6% of LR ruptured their CCL after eight years of age, so dogs older than eight were used as controls. (Cook 2020) Another study found that yellow LR had an increased risk of CCL rupture while black LR had a decreased risk. (Terhaar 2020) This was the first time coat color influencing the risk of CCL was described. That same group analyzed 679 SNPs and found that multiple SNPs are associated with both CCL disease and coat color. (Lee 2023) Inheritance of coat color is controlled by two genes, MC1R and TYRP1. A mutation within MC1R is responsible for the yellow color in LR. Dogs that are homozygous for the MC1R mutation produce pheomelanin, which creates a yellow coat color. In contrast, dogs with at least one gene without the mutation will produce eumelanin, resulting in a black or chocolate coloring. (Lee 2023) It is possible that the selection for coat color inadvertently selected risk variants for other phenotypes, including CCL disease. Coat color does influence behavior and other disease processes, such as skin and ear disease, which is statistically more frequent in chocolate LR. (McGreevy 2018). Chocolate color is also associated with a higher body condition score. (Wallis 2023)

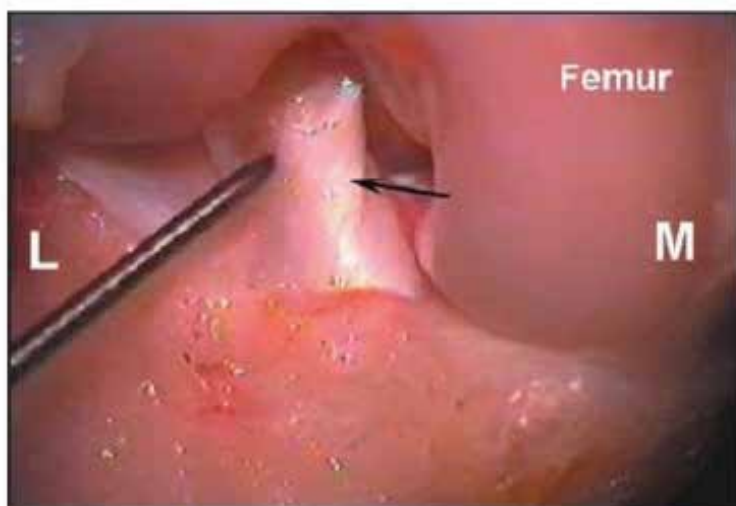


Figure 1—Photographic view of the canine stifle joint illustrating the cranial medial and caudal lateral bands of the cranial cruciate ligament (CCL). The probe is placed on the caudal lateral band, which comprises the bulk of the CCL. The twist in the fascicles of the cranial medial band is clearly visible (arrow). (L=lateral; M=medial)

Testing for CCL Disease

Recently, genetic testing became available specifically for LR and CCL disease. The test uses SNP markers and sex to determine risk so it can be performed at any age. The test is currently only available for LR, but additional breeds should eventually be available. Many genetic markers across the genome are examined. Although each variant may have a small to moderate effect, they act additively, and a higher number of DNA risk variants increases the genetic risk of developing CCL rupture. The results are reported as “predicted to be a case” if marker genotypes associated with CCL disease are present and “predicted to be control” if marker genotypes protective from CCL rupture are present. Patients predicted to be a case are very likely to rupture their CCL, while dogs “predicted to be control” are unlikely to rupture their CCL. The test is available from the University of Wisconsin Comparative Genetics and Orthopedic Research Lab. Blood or saliva can be submitted, and results take approximately four to six weeks. The test costs about \$250 and is 98% accurate. It can be ordered through genetics@vetmed.wisc.edu. The most significant

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benefit of this test is for breeders, and it should be completed along with screening for eyes, elbows, and hips; only low-risk dogs should be bred. Puppies intended for hunting or athletic work should also be screened prior to investing in training. Pets may also benefit from testing so lifestyle changes can be undertaken and treatment can be pursued with early signs of disease prior to the development of osteoarthritis. The impact of a positive test on insurance coverage may need to be considered.



Conclusion

CCL rupture is a disease that is the leading cause of hind limb lameness in dogs, with numbers steadily increasing in frequency. In Labrador Retrievers, most of the risk of CCL rupture is genetic, and testing breeding dogs will help select dogs with lower risk. Most CCL ruptures occur in dogs under eight years of age, and LR have a decreased risk after eight years of age compared to other dogs.

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Feline Hyperaldosteronism

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Aldosterone Physiology

The zona glomerulosa is the layer of the adrenal gland that secretes aldosterone, the principal mineralocorticoid responsible for regulating sodium and potassium. An increase in potassium directly stimulates aldosterone secretion from the adrenal glands. In addition to a decrease in potassium, a decrease in blood pressure will stimulate the renin-angiotensin-aldosterone system (RAAS), leading to increased sodium resorption and potassium and hydrogen excretion. The sodium resorption leads to the conservation of water, raising blood volume. The RAAS system will also increase systemic vascular resistance due to angiotensin II. The vast majority of physiologic actions in the RAAS system are mediated by angiotensin II. In addition to regulating vascular resistance, angiotensin II contributes to cell growth, aldosterone production, and controlling the glomerular filtration rate and renal blood flow.

Mineralocorticoids have two essential roles: they regulate extracellular fluid volume and are the major regulator of potassium homeostasis. The kidney is the primary target tissue for mineralocorticoids, the distal convoluted tubule specifically. They bind to receptors in the epithelial cells, activating sodium channels and stimulating the Na⁺, K⁺-ATPase. An electrochemical gradient is established, leading to passive excretion of potassium into the urine.

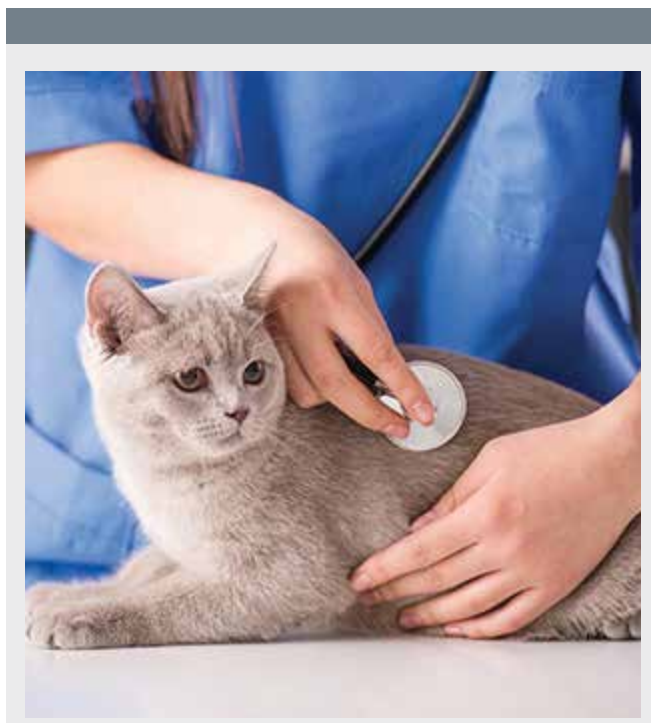
Feline Hyperaldosteronism

Hyperaldosteronism can be classified as primary (PHA) or secondary. Primary hyperaldosteronism occurs when adrenocortical cell secretion of aldosterone is autonomous and does not respond to negative feedback, i.e., an adrenocortical tumor. The tumor is usually unilateral and can have varying degrees of malignancy, ranging from well-capsulated adenomas to carcinomas with caudal vena cava invasion. Secondary hyperaldosteronism occurs when some other disease process, such as congestive heart failure renal panel, stimulates RAAS activation, leading to aldosterone production.

The incidence and recognition of feline PHA have been increasing over the past 20 years. There is no breed predisposition. The median age at diagnosis is around 13 years old; the majority are over 10. There is no sex predisposition. Clinical signs are primarily related to hypokalemia (hindlimb weakness, ventroflexion, ataxia, etc.) and hypertension (sudden blindness, retinal detachment, seizures). Weakness is usually apparent on physical examination.

Diagnosis

Routine laboratory testing reveals hypokalemia. An increased urinary fraction of potassium can confirm that the hypokalemia is renal in origin, but this is rarely performed. Hypernatremia is uncommon due to the “Aldosterone escape” phenomenon, which is volume or pressure natriuresis. Creatine Kinase levels are variably elevated with hypokalemic myopathy. Imaging is of variable helpfulness. A large tumor may be detected on ultrasound unilaterally with a small contralateral adrenal gland. Bilateral



adrenal tumors and pulmonary metastasis are both rare. Abdominal CT and MRI may be helpful, but the number of reports is limited. Confirmation of hyperaldosteronism is obtained by measuring a high basal aldosterone in the face of hypokalemia. This is not a useful test to determine whether the hyperaldosteronism is primary and secondary, as results overlap. Plasma renin activity could be used to determine if it is primary (decreased or normal due to negative feedback) or secondary (increased due to RAAS activation), but this test is not available in the United States.

Treatment and Prognosis

The treatment of choice for a feline aldosteronoma or other adrenal tumors is an adrenalectomy. This is potentially curative but requires highly skilled surgeons and is highly risky. An increase in anesthesia time has been associated with decreased survival. The hypokalemia should be corrected with parenteral or oral potassium. It is also essential to assess for metastasis and tumor thrombi. It is crucial post-operatively to monitor electrolytes as the negative feedback has put the zone glomerulosa cells of the contralateral adrenal gland into dormancy.

Medical management for cats that do not undergo an adrenalectomy focuses on increasing the potassium and regulating the blood pressure. Potassium supplementation (2-6 meq PO q12h) has been effective. Amlodipine (0.625-

INTERNAL MEDICINE

Feline Hyperaldosteronism

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1.25 mg/cat PO q24h) is the treatment of choice for hypertension. Up to 2.5 mg/cat can be used if the blood pressure is not controlled on the conventional doses. Spironolactone can be used (2-4 mg/kg PO q24h) to decrease blood pressure and increase serum potassium. Medical management has yielded a median survival time of several months to a couple of years.

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According to the 2023 updated ACVIM Consensus Statement on Leptospirosis, **early dialytic intervention is recommended to prevent the morbidity of acute kidney injury rather than as a delayed salvage for failed conventional management.** Early referral to centers providing dialytic therapy should be considered for dogs in IRIS AKI Grade 4, when serum creatinine concentration exceeds 5mg/dL.

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Contact Shawn Kearns, DVM, DACVIM and Courtney Peck, DVM, DACVECC at internalmedicine@angell.org or 617-541-5186.





Malignant Ear Tumors in Cats: Contrasting Literature

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Introduction

Tumors within the ear canals of cats are uncommon, with studies showing anywhere from 1% to 2% of all tumors in cats. However, they can be a persistent and frustrating source of discomfort and recurrent infection once they occur. A broad range of space-occupying lesions can occur in the ear canal, ranging from non-neoplastic benign to malignant entities. The ear is an extensive combination of anatomic structures, allowing for inflammation or neoplasia arising from different tissue types: epithelial, mesenchymal, or nervous tissue.

Review of Clinical Cases

Common external ear canal tumors in cats are nasopharyngeal polyps, squamous cell carcinomas, and ceruminous gland adenocarcinomas, with ceruminous gland tumors being the most common. In some cases, squamous cell carcinoma, fibrosarcoma, or lymphoma can also be identified in the middle ear. One comprehensive study assessed feline aural tumors over 14 years, including 56 malignant and eight benign tumors. Three out of four cats with benign otic tumors had radiography of the skull, which showed concurrent otitis media. Unfortunately, 48% of the 56 cats were diagnosed with malignant tumors had further imaging, showing lysis of the bulla in 19% of the cats and sclerosis of the bulla in 19% of the cats. No changes were noted in 26% of the cats. Researchers found 9% cytologic evidence of lymph node metastasis at the time of diagnosis, and no evidence of paraneoplastic syndromes was noted in any cats.



Survival time data was limited in this retrospective study, with 11 cats not having viable data. Five cats were euthanized at the time of the diagnosis, and the median survival time of the remaining 40 cases was approximately 11 to 12 months. Sixty-five percent of cats died as a result of other causes. Cats with neurologic signs at the time of diagnosis had a marked decrease in survival time, averaging 1.5 months.

The exception to this is the diagnosis of ceruminous gland adenocarcinoma, having a survival time of around 49 months (significantly different than other aggressive tumors such as squamous cell carcinoma or carcinoma in general).

Age, of course, plays a role in these numbers. Inflammatory polyps are still reported as the most common aural tumor in cats, developing anywhere from ages three months to five years of age. These arise from the epithelial lining of the external or middle ear canal and can result in recurrent/persistent otitis externa and, in some cases, extension into otitis media. This should be a consideration for younger cats over more aggressive diagnoses.

In the previous study mentioned, ceruminous gland tumors were more likely to be malignant adenocarcinoma vs. benign adenoma. Still, different studies assessing feline aural tumors have had contrasting findings (one indicated an equal proportion of ceruminous gland adenocarcinoma and squamous cell carcinoma diagnoses, vs. a separate study showing ceruminous gland adenocarcinoma being the more common malignant tumor in the ear canals of cats, mainly males).

Malignant tumors in cats have the inclination to have extensive local involvement/invasion into local tissue, with squamous cell carcinoma being the most aggressive. Overall, cats have a significantly shorter survival time than dogs diagnosed with and similarly affected by malignant tumors; however, this may be because squamous cell carcinoma and other carcinoma types



DERMATOLOGY

Malignant Ear Tumors in Cats: Contrasting Literature

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develop more frequently in cats. Unfortunately, squamous cell carcinoma in cats (found in the outer, middle, or inner ear) had a median survival time of 168 days with aggressive surgery vs. 68 days if treated with radiation/chemotherapy or through medical management.

Surgery of some form is the most commonly used treatment for aural tumors in cats, regardless of malignancy, similar to dogs. Aggressive surgical management tended to increase survival time in some cases. Papers assessing survival times in cats and dogs with ceruminous gland adenocarcinoma showed aggressive surgical management substantially increased survival times when compared to the use of conservative surgical excision.

However, given that aggressive surgical management may not always be feasible either through patient stability for anesthesia or through cost, or if a diagnosis of tumor type has not been defined, this author finds that video otoscopy and tumor debulking/histopathology an acceptable first approach to some aural tumors before considering more aggressive surgical intervention if possible. In some cases, tumors are slower growing, less aggressive, and take time to recur, and the patient's comfort level is temporarily improved. Chronic otitis externa is common in the ear that has the tumor present. So, maintenance ear medications may be necessary to control chronic bacterial or yeast otitis externa secondary to tumor development.

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Canine Malocclusion

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Malocclusion of the oral cavity is a common finding noted in dogs and has been reported in 13.7% to 26% of dogs seen.^{1,2} Puppies as young as 8 weeks of age² have been identified with malocclusion. As the majority of maxillofacial development occurs within the first 36 after birth, the relationship between the maxilla and mandible continues to change during this time, so close monitoring throughout the first year of life is necessary.

So, what is malocclusion? Occlusion is the relationship of dentition when the upper and lower jaws contact. It is determined by both the skeletal and dental relationship of the maxilla and mandible. Dental and skeletal occlusion should be symmetrical on the dog's right and left sides. Maxillary incisors should be just rostral to mandibular incisors so that the coronal tips of the mandibular incisors are actually resting on the palatal (portion of the incisors that face the roof of the mouth) base of the maxillary incisors. Mandibular canines are mesial (rostral in the oral cavity) to the maxillary canines and rest between the diastema of the maxillary third incisor and canine. The premolars are interdigitated, meaning they do not sit in the same transverse plane but are offset so they don't touch each other when the mouth is closed. Mandibular premolars should be lingual and just rostral to their maxillary counterparts. Lastly, the molars are defined as such so that both mandibular and maxillary molars meet to create a grinding surface. It's important to note that the maxillary fourth premolar does align with the mandibular first molar, but they do not touch. The mandibular first molar is offset to be palatal to the fourth premolar, so it still acts as a shearing tooth, not a grinding tooth in this occlusion, while contacting the maxillary first molar more caudally for grinding.

Malocclusions are categorized into four different classes. Class 1 malocclusions involve a normal skeletal alignment, but one or multiple teeth

> This is an example of a class 1 and class 2 where the mandibular right canine is lingually deviated and the entire mandibular dentition is slightly distally deviated (increased space between mandibular and maxillary incisors).



> Post-orthodontic device to shift mandibular canine rostral and lateral to create an atraumatic occlusion.



are out of alignment. An example is a mesioverted canine or 'lance tooth' seen in Shetland Sheepdogs or 'base narrow' canines. A Class 2 malocclusion is described as mandibular distocclusion. Essentially, the teeth of the mandible align more caudally than expected due to a skeletal mismatch in the length of the maxilla and the mandible. Similarly, Class 3 malocclusions have a mandibular mesiocclusion where the mandible is longer than expected for the maxilla. It is important to note that it may be the maxilla that is shortened (such as in brachycephalic dogs), but the classification is still based on mandibular position relative to the maxilla. A Class 4 malocclusion shows asymmetry between the left and right sides of either the maxilla or mandible or both and can be described as a 'wry' bite where the jaw looks curved to one side. The term 'wry' bite is not recommended as it does not indicate how or where the asymmetry lies. Class 4 malocclusion is most commonly seen after trauma to young dogs. It is important to note that one patient can also have multiple malocclusions. While a simultaneous Class 2 and Class 3 cannot exist, a Class 1 and a Class 2 (shown below) or 4 can exist together.

Treatment for malocclusions falls into three general categories. Options include extraction of teeth, endodontics, and orthodontics. Selective extractions can be considered to prevent self-trauma in an occlusion. While the skeletal abnormality may not be addressed, the goal is comfort and function. One should always recheck the occlusion after a tooth of interest is removed. The new occlusion may yield trauma from other dentitions that could not occur due to the inability to close the mouth thoroughly. For puppies with deciduous dentition, some evidence supports the extraction of traumatic deciduous teeth to promote eventual normocclusion of the permanent dentition.³



Endodontics can be considered for cases where a client would like to retain at least some structure of the tooth while limiting or exterminating self-trauma. Most commonly, the endodontic procedure is a crown reduction with vital pulp therapy. Chronic follow-up is necessary to monitor the health of the reduced teeth for continued maturation. Failure to do so can result in abscess formation and necessitate further treatment, such as root canal therapy or extraction. Lastly, orthodontic movement is an option for some cases of malocclusion. Devices can range from passive devices (shown below) to active devices with rubber chains to pull teeth into position. While malocclusion may be a permanent change to a dog's conformation, many options exist to provide functional, pain-free use of the oral cavity.

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Internal Medicine Pearls for the General Practitioner

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Introduction

Today's doctors are fortunate to practice veterinary medicine at a time when quality, comprehensive primary care practice is expected by clients whose pets have earned their place as family members in households near and far. Specialty care is readily available, particularly in urban areas, and it may be a choice for some clients. Many clients prefer to extend care with their primary clinicians for numerous reasons. Management of chronic and/or advanced medical conditions may excite or overwhelm you as a primary care veterinarian. The author of this article is an internist turned primary care veterinarian, and she hopes to highlight some practical and accessible Internal Medicine tips for managing a few common conditions.

Diabetes Mellitus Management Updates

In 2023, many new exciting pharmaceutical products emerged in veterinary practices. A true game-changer is the class of SGLT-2 inhibitors for managing feline diabetes mellitus. The "gliflozins" are the standard of care in human

medicine for managing insulin-resistant diabetes mellitus and are also recognized for their benefits in cardiovascular and renal conditions. Bexacat (Elanco) and Senvelgo (Boehringer Ingelheim) are the two medications in this class for feline patients.

SGLT2 inhibitors work by inhibiting sodium-glucose cotransporter-2 found in the kidney's proximal tubule. This blockade prevents the reabsorption of glucose that typically occurs via the SGLT2 cotransporter, thus resulting in increased glucose excretion into the urine, as depicted in this relatively simple picture (left).

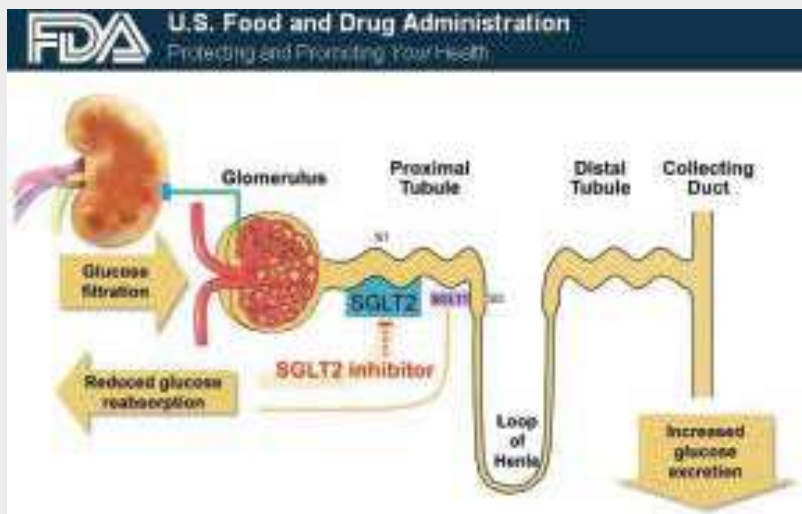
Hypoglycemia is prevented because additional sodium-glucose cotransporters are found primarily in the intestines (SGLT1). SGLT2 inhibitors are selective, and although some cross-reactivity may occur, the degree to which it is unknown is usually mild and could differ amongst specific medications.

SGLT2 inhibitors rely on some amount of insulin to be effective and to prevent the most concerning potential side-effect, ketoacidosis. Thus these medications are only for use in cats. An estimated 90% of feline diabetics fall into the "Type 2"

category, characterized by insulin resistance, Beta cell exhaustion, and decreased insulin sensitivity. Successful use of this medication does require some thoughtful patient selection. "Sick" diabetics should be started on insulin instead. Both Bexacat and Senvelgo have comprehensive algorithms to guide a doctor through baseline testing and considerations before prescribing them. That being said, the author suggests screening as much as a client will allow. If the choice is between treatment with one of these medications and euthanasia, the author might still consider one of these medications instead.

The main difference between these two medications is that Bexacat is a flavored tablet and Senvelgo is a flavored liquid. Bexacat is one tablet per cat 3.0 kg or greater, while Senvelgo is 1 mg/kg with no minimum weight restriction, and the product insert recommendations for ketone screening differ at this time. Both medications are only given once daily to naive diabetics, have a similar side effect profile, and should work generally interchangeably otherwise. Screen for ketones the day you start treatment (or as close to it as possible). How you screen for ketones is less important than the fact that it should be done. That being said, patient-side ketone readers are readily available online, have been validated for use in cats, are inexpensive (currently ~ \$28), are easy to use, require just a drop of blood, and may make sense if you are already checking a blood glucose level. Additionally, they may detect increases in ketone bodies earlier than urine screening based on the ketone body they detect. The product insert cut-off of 2.4 for a ketone reading might be a little high. Most non-ketotic cats will have baseline ketone levels of 0.5 or lower.

This class of medications truly inspiring. Clients have been indeed held captive by twice-daily insulin schedules for decades (though some cats can be treated with once-daily insulin). Gliflozins almost completely eliminate the risk of clinical hypoglycemia. Storage and handling are both easier and safer. Management by veterinarians may also become much less complicated. (And finding cat-sitters may also be easier for clients!) The mechanism of action results in sustained euglycemia in most treated cats, completely





eliminating the need for blood glucose curves. It also permits exhausted pancreatic Beta cells a chance to recover, potentially leading to remission.

Although not a new test, serum fructosamine levels may appreciate increased popularity due to the advent of SGLT2 inhibitor use. Fructosamine measures glycated serum proteins (primarily albumin), and past studies have demonstrated that quantifying serum fructosamine concentration is a meaningful test for the diagnosis of diabetes and for differentiating diabetes from stress hyperglycemia. Fructosamine levels may be the most useful test for monitoring cats on SGLT2 inhibitors since stress hyperglycemia could still impact spot blood glucose measurement.

Of course, not all cats will be candidates for or successfully managed on Bexacat or Senvelgo. There is still a place for serial blood glucose measurements in these cats. Continuous glucose monitoring seems to be a divisive topic since the author finds that clinicians have either strongly positive or negative anecdotal experiences with their use. Doctors should prepare themselves and the client as much as possible for the goal of monitoring. In some instances, 12 to 24 hours

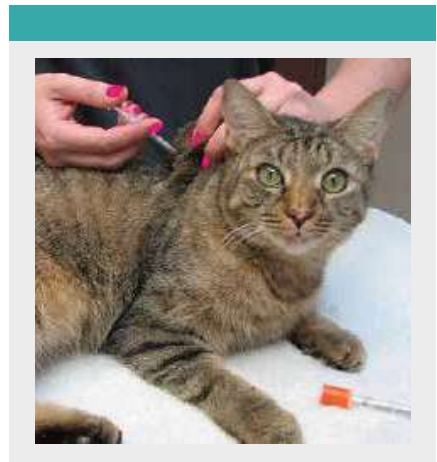


worth of data trends can be beneficial. Sometimes, it can be a great way to get clients involved, but setting up expectations surrounding data interpretation and treatment adjustments is also helpful. Another suggestion is to set up a clinic policy that everyone knows before using it. What will a doctor do if the monitor falls off or doesn't seem to be reading accurately? Assign one or two clinic assistants to be well-learned to apply the sensors themselves since there is a bit of a learning curve applying them. Commercially available wipes may help prep shaved skin to make the sensors adhere better, as can a judicious use of skin glue (one tiny drop at each 12, 3, 6, and 9 o'clock). Clients and cats may better tolerate Stockinette or small fleece shirts than E-collars if you find cats bothered by the sensors. The author uses LibreView to manage patient data instead of asking clients to send screenshots or isolated reports; setting up an account and sending invitations to clients to start this process is straightforward.

Speaking of insulin selection, although veterinarians are not mandated to choose FDA-approved products as first-choice treatments, the author tends to lean toward Vetsulin as first choice for dogs and glargine (Lantus) for cats, as AAHA's Diabetes Mellitus guidelines also support this <https://www.aaha.org/aaha-guidelines/diabetes-management/treatment/insulin-therapies/>. The advantage of these approved insulins is that client and practitioner support materials are well-established. Vetsulin is available in a pen for easier administration, and the author has used Vetsulin's home care instructions document and finds it very user-friendly and client-friendly: <https://www.merck-animal-health-usa.com/vetsulin/client-discharge-form>.

(There is speculation that Detemir will be discontinued by the end of 2024, so the author does not select this as a first-choice insulin, nor would it be helpful to transition patients who need a different insulin to Detemir or Levemir at this time, given the availability may become extremely limited in the near future.)

Insulin Glargine is a recombinant human insulin analog; most veterinarians are more familiar with using Lantus. Toujeo is also Glargine, but it is not bioequivalent to Lantus and, therefore, is not interchangeable. Toujeo has three times the active ingredient and zinc and has been shown in people to have a flatter ("peakless") and more prolonged profile of glucose-lowering activity compared with Lantus at the same dose (up to 36 hours). It may have a longer duration of action in cats and dogs, making it a reasonable choice for patients with insulin that is too short or where twice-daily injections are not possible. A 2022 ACVIM abstract from Professor Chen Gilor showed in a



multi-institutional study including newly diagnosed dogs and dogs previously treated with other insulin formulations that, overall, dogs were well controlled on Toujeo and that half of them could be maintained on once-daily injections. He also noted that the required dosages ranged greatly to achieve good control and that a higher dose of Toujeo is required compared to doses standardly reported for other types of insulin. The starting dose was 0.5 U/Kg q24h for newly diagnosed dogs and 0.8 U/Kg (0.2 to 2.5) q24h for the dogs transitioned from other insulins. Of the half of dogs requiring twice daily injections, their total daily insulin requirements ranged from 0.6 to 5.0 U/kg/day. Only one dog in the study required less than 0.5 units/kg/day; therefore, 0.5 units/kg/day is a reasonable starting dose. This study also suggests Toujeo is less potent in dogs than in people (who often require the same dose as Lantus glargine, for example). Toujeo seems to have a similarly "peakless" profile in cats and a long duration of action (16 hours). Minimal data suggests cats can be managed highly effectively on twice-daily injections (0.5 U/kg/dose), and as mentioned previously, Toujeo could be a good choice if once-daily injections are your only option.

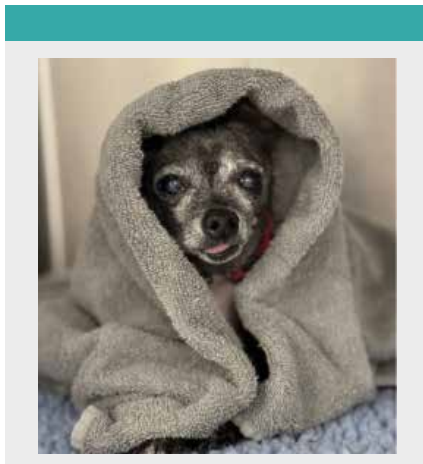


Diabetes mellitus and hyperadrenocorticism are two relatively common endocrinopathies that can be managed successfully by primary care veterinarians. However, throwing the conditions together in the same patient can become more challenging and frustrating for all involved. There is a lot of overlap between the clinical signs and laboratory abnormalities, making it harder for veterinarians to know how successfully they manage either or both conditions. Here are some tips for success:

1. Unregulated diabetics typically experience weight loss, and patients with hyperadrenocorticism typically do not; therefore, try to manage the patient's diabetes "well enough" to stop weight loss before tackling their Cushing's.
2. Excess glucocorticoids can result in a shorter duration of insulin action in dogs (very frustrating), but a "pro" of this scenario is that clinical hypoglycemia is rare. With a typical intermediate-acting insulin, a BG curve might very well show decreased glucose levels for only a few hours after injection and then marked hyperglycemia. A strategy for this can be to supplement the intermediate-acting insulin with a "background" long-acting insulin such as glargine. If a veterinarian decides to try this, the author suggests keeping the same total insulin dose in units the patient is already receiving, so decrease the current dose to account for the new addition of a second insulin.
3. Although many patients with hyperadrenocorticism alone can be managed successfully on once-daily trilostane, diabetic dogs with hyperadrenocorticism may do better with BID or even TID trilostane. This relates to point #2 above, which provides more stable serum cortisol over the course of a day to achieve a more stable and predictable insulin requirement. Some patients may even need TID insulin based on their glucose curve results and clinical picture assessment.
4. If ALP continues to rise on serum chemistry profiles in the face of management for hyperadrenocorticism and diabetes, that can be a clue to assess the chosen Cushing's treatment strategy further.

Geriatric Patient "Potpourri"

Having been a veterinarian for 20 years, the author has realized the significant frequency with which clients wish to discuss concerns related to the aging of their pets. Some clients may feel guilt complaining about their pet's frequent night-waking or accidents in the house, but all pet owners know how sleepless nights and cleaning up various messes can lead to resentment,



sadness, or desperation. For a multitude of new symptoms, the author suggests trying to eliminate pain as a cause first. Some clients still believe pets are only in pain if they are overtly lame or vocalizing. Clients may also be embarrassed to think they might have ignored signs of pain in their pets. Clients also may project their own personal beliefs about aging and/or the use of pain relief in themselves onto their pets (both in favor of treating pain and withholding treatment). Although chronic pain can require more than one approach and persistence to un-do "wind-up," the author suggests starting with a finite trial of pain relief of some kind for a multitude of symptoms, including restlessness, sometimes increased panting, night-waking, and on occasion, inappropriate eliminations (after a physical exam and minimum database plus urine culture if there are urinary accidents). Judicious use of NSAIDs can be tolerated in many canine patients, even those with some stable/mild co-morbidities. (The author does not personally use NSAIDs in geriatric cats, but data suggests this fear may be unfounded.) However, the advent of anti-NGF monoclonal antibodies (Solensia in cats, Librela in dogs) provides an alternative option for many cats and dogs. Gabapentin is also widely used due to its safety profile, dosing range, and a multitude of benefits. The author has found some senior dogs, in particular, more sensitive to the sedation and ataxia side effects of Gabapentin; one suggestion is to start Gabapentin at a lower dose and possibly once daily at night, just in case. Some pets may need to have their Gabapentin discontinued or reduced in dose or frequency in case of side effects.

Chronic pain management is way beyond daily NSAID or Gabapentin use, however. (The author suggests AAHA Pain management guidelines for a comprehensive review of acute and chronic pain assessment and treatment options.) A multimodal approach is ideal. Do not underestimate the power of weight loss to ameliorate chronic osteoarthritis pain. Weight loss goals for improvement in OA

symptoms tend to be relatively modest (~5-7% weight loss), and modest weight loss goals may be more attainable and palatable to clients. The author also suggests that clients find a rehabilitation program for pain management; they are particularly beneficial for geriatric patients suffering from chronic pain, anxiety, and weight gain.

Nutrition is a daunting topic for many veterinarians during all life stages of their patients. Although there are therapeutic diets for probably every diagnosis or even a combination of diagnoses, the author often takes a "don't rock the boat" approach, particularly for geriatric patients who may have more finicky appetites. Weight issues (both over and under-conditioning) and loss of lean muscle mass should be addressed with calorie, fat, and protein management in particular, ideally after minimum diagnostics establish any specific nutritional needs or contraindications (renal disease features prominently here in terms of avoidance of excessive protein diets and phosphorus restriction). In terms of diabetes, the author notes that she does not typically change a dog's diet if they are otherwise doing well, and the diet is generally not "offensive" to managing their diabetes. If marked post-prandial hyperglycemia is occurring or persistent hypertriglyceridemia, then therapeutic diets may be helpful. The author does not change cats to diabetic diets while at the same time starting insulin or SGLT2 inhibitors and suggests that veterinarians save diet changes for future recheck appointments. It's best not to change too many things simultaneously, particularly in geriatric patients, but this approach can vary significantly from clinician to clinician.

› Angell Fall 2024 Continuing Education

Register at angell.org/ce

Sunday, October 27, 2024

8:15am – 2:45pm

Live Webinar

5 CE Credits (*pending RACE approval*)

TOPICS AND SPEAKERS:

- **Speed, Strength and Stamina: Our Reliance on Muscle in Health and Conditions of Failure in our Veterinary Patients** – *Rob Daniel, DVM, DACVIM (Neurology)*
- **Neuro-pharmacology Myth Busters: Common Misconceptions of Medications in Neurological Patients** – *Jennifer Michaels, DVM, DACVIM (Neurology)*
- **Snakes and Pains: Recognizing and Managing Pain in Exotic Animal Species** – *Anne Staudenmaier, VMD, DABVP (Avian Practice)*
- **It's all Jawesome! Cracking a Grin While Managing Oral Fractures in a GP Setting** – *Joyce Tai, DVM, DAVDC (Dentistry)*
- **The "Tea" on TCC: Update on Diagnosis and Management of Bladder/Prostate Tumors for the General Practitioner** – *Jillian Walz, DVM, DACVIM (Medical Oncology), DACVR (Radiation Oncology)*

Wednesday, November 6, 2024

6:15pm – 8:45pm

Live Webinar

2 CE Credits (*pending RACE approval*)

TOPICS AND SPEAKERS:

- **Habits, Tricks, and Interesting Cases from the ER** – *Kiko Bracker, DVM, DACVECC-SA (Emergency & Critical Care)*
- **Feline Allergic Skin Syndrome (FASS)** – *Klaus Loft, DVM (Dermatology)*



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