PEER REVIEWED

CANINE CRANIAL CRUCIATE DISEASE

Updating Our Knowledge about Pathogenesis & Diagnosis

James K. Roush, DVM, MS, Diplomate ACVS

This is the first article in a 2-part series that will discuss the pathogenesis, diagnosis, management, and prognosis of canine cranial cruciate disease, focusing on the latest information and innovations available.

Cranial cruciate ligament rupture (CrCLR) is the most common cause of hindlimb lameness in dogs and, in my experience, the most common misdiagnosed or overlooked cause of canine lameness. Of 369 dogs referred to a teaching hospital for treatment of hip dysplasia, 32% had CrCLR as the primary cause of hindlimb lameness.[1]

In most dogs, undiagnosed or untreated CrCLR results in rapid advancement of osteoarthritis (OA). Radiographs taken within 6 weeks of acute cruciate rupture often display signs of OA, including peripatellar and peritrochlear osteophytes, joint effusion, and joint space collapse. Timely, accurate diagnosis and treatment of CrCLRs are likely very important to minimize progression of OA and optimize surgical outcomes.[2]

> The annual economic impact of CrCLR in dogs was estimated to be 1.32 billion dollars in 2003.[3]

DIAGNOSIS OF CRANIAL CRUCIATE DISEASE

Why Is CrCLR Underdiagnosed So Frequently?

Veterinary school instruction has traditionally emphasized teaching subtle and difficult manipulative physical examination procedures, such as *cranial drawer sign* and *cranial tibial thrust*, to definitively diagnose CrCLR. Cranial tibial thrust is the stifle vector force created by the dog when weight-bearing, which results in cranial translation of the tibia with each step in a dog with CrCLR. The correct performance of either test is a learned skill, mastered only after much experience and practice on healthy dogs as well as those with partial or complete CrCLRs.

Immature dogs are often misdiagnosed with CrCLR because they have greater than expected cranial drawer sign due to normal puppy laxity. Lameness in immature dogs is rarely due to CrCLR because young ligaments are often stronger than bone physes and fracture occurs first. CrCLR can occur in young dogs but the history usually includes severe trauma, such as vehicular trauma.

Even with 25 years of experience as a veterinary orthopedic surgeon, I would estimate that examination with the cranial drawer sign or tibial thrust allows me to diagnose CrCLR in only about 80% of the dogs that subsequently undergo surgery, even though virtually 100% of these dogs have visible cruciate damage at arthrotomy.

How Can Clinical Detection Be Improved?

Hindlimb Lameness. A diagnosis of CrCLR should be considered in any dog with hindlimb lameness until proven otherwise. This is due to the fact that a high percentage of hindlimb lameness in dogs is caused by CrCLR, especially in patients with recent or sudden development or worsening of hindlimb lameness.

Extension & Range of Motion. Dogs with CrCLR often show pain during extension of the hip: it is a common error to inadvertently extend the stifle while extending the hip, resulting in stifle pain misattributed as hip pain. On the other hand, many dogs with CrCLR are not overtly painful during non–weight-bearing stifle range of motion or palpation, further complicating lameness localization.

Medial Buttress Sign. All veterinarians should learn and recognize the appearance of the *medial buttress sign*. Shortly after CrCLR, most, if not all patients, develop a distinct, firm swelling over the proximo-medial tibia in the region of insertion of the medial collateral ligament

Figure 1. Medial buttress is a firm swelling palpable on the medial aspect of the proximal tibia; presence of medial buttress is a characteristic clinical sign of CrCLR.

(**Figure 1**). Palpation of a medial buttress over the proximal tibia of the affected leg:

- Is a reliable clinical sign of cruciate rupture
- Occurs rapidly after ligament rupture in most dogs
- Provides ample indication for surgical joint exploration even in the absence of a cranial drawer sign.

This swelling can be best detected by simultaneously palpating the medial tibial plateau of both hindlimbs, comparing the swelling of the lame limb to lack of swelling in the normal limb. My preference is to position myself at the caudal aspect of a standing dog, with my hands simultaneously wrapped around from the cranial to the medial aspect of both hindlimbs (**Figure 2**).

In patients with suspected bilateral CrCLR, remain aware that a bilateral medial buttress will be present and must be considered during diagnosis.

Figure 2. To evaluate medial buttress, the dog should be standing and the examiner should simultaneously reach around the cranial aspect of both stifles and palpate the proximal-medial tibia.

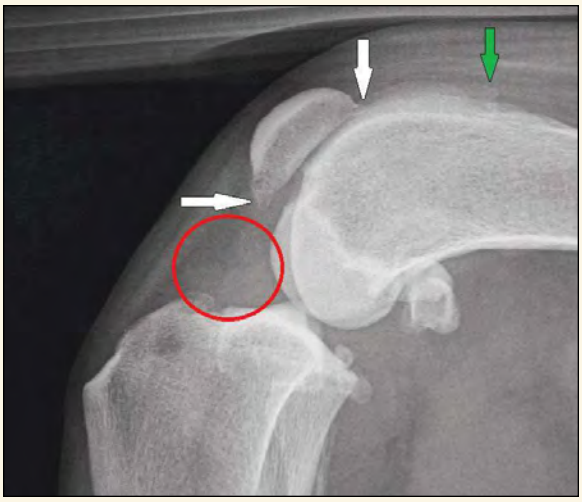

*Figure 3. Radiographic signs of stifle OA secondary to CrCLR include periarticular osteophytes on the patella (**white arrows**) and trochlear ridge (**green arrow**) and a compressed infrapatellar fat pad (**circled**). These radiographic signs strongly suggest stifle instability in dogs without other evidence of septic arthritis or visible trauma.*

What Role Does Radiography Play in Diagnosis?

On orthogonal stifle radiographs, the following findings are highly suggestive of CrCLR (**Figure 3**):

- Joint effusion (characterized by compression of infrapatellar fat pad)
- Peripatellar or peritrochlear osteophyte formation.

Either finding alone is sufficient indication for joint arthrocentesis, arthroscopy, or arthrotomy for further diagnosis and treatment.

Increasing severity of radiographic signs of OA is an even stronger indication for further diagnostic attention and treatment. Other less frequent causes of joint pathology, such as septic arthritis, distal femoral osteochondritis dissecans, or chronic fracture, can cause similar radiographic changes; however, their relative rarity and differing clinical histories make inadvertent surgery of these conditions unlikely.

Severity of OA is not of value in treatment determinations because OA scores are not related to kinetic gait parameters and lameness in dogs.[4]

PATHOGENESIS OF CRANIAL CRUCIATE DISEASE

Are Certain Breeds Predisposed to CrCLR?

Our understanding of CrCLR remains a chicken-or-egg-first quandary. Recent information suggests that CrCLR disease is heritable as a recessive trait in certain breeds, such as Newfoundlands, in which there is an identified heritability index of 0.27.[5]

Bilateral CrCLR is present at initial diagnosis in up to 30% of large breed dogs presented for CrCLR. Bilateral disease in small breeds is much less frequent than in large breed dogs.

How Does a Rupture Develop?

In small breed dogs, CrCLR is often associated with long-standing patella luxation or acute trauma. In large breed dogs, CrCLR occurs as 2 distinct disease types:

1. A small percentage of large breed dogs *acutely develop CrCLR*, with no preexisting evidence of OA and often during strenuous activity in which the cruciate rupture occurs as a result of hyperextension and/or excessive strain on the cranial cruciate ligament.
2. The majority of large breed dogs, however, have preexisting radiographic OA at the time of complete CrCLR, suggesting that an unknown etiology causes slow degeneration of the ligament before functional failure occurs.

What Are the Risk Factors for CrCLR?

Risk factors for increased prevalence of cranial cruciate ligament (CCL) injury include:[6]

- Obesity
- Neutering

Degeneration of the CCL is associated with:[7]

- Aging
- Excessively straight hindlimb conformation
- Immune-mediated arthropathies.

In some studies[8,9] but not others,[10,11] degeneration of the CCL has also been associated with:

- Increased tibial plateau angle (TPA)
- Excessive patellar ligament-plateau angle.

Think of correction of **TPA** by tibial plateau leveling osteotomy (TPLO) and **patellar ligament-plateau angle** by tibial tuberosity advancement (TTA) **as changes in stifle biomechanics to limit tibial thrust** rather than as corrections of abnormal angles.

How Likely Is Rupture of the Contralateral CCL?

In 1 study, 48% of Labrador retrievers ruptured the contralateral CCL within a median time of 5.5 months.[12] Therefore, it is prudent to warn owners of large breed dogs with unilateral CrCLR that these dogs have a high probability of contralateral CrCLR.

TPA is not a useful predictor of contralateral CrCLR in dogs with existing unilateral CrCLR.[13] Consequently, any measures that decrease stress on the remaining intact ligaments are important therapy additions, including careful weight management of the patient and exercise restriction.

What Is the Focus of Current Research Efforts?

After CrCLR, there are:

- Increased matrix turnover with increased collagen and glycosaminoglycan synthesis[14]
- Increased matrix metalloproteinases and changes in proteinase location within the ligament and synovial membrane[15-17]
- Histologic changes, including decreased typical fibroblasts and increased chondroid cells in the ruptured ligament core.[18]

A great degree of research effort has been directed at understanding and comparing changes in the extracellular matrix of ruptured ligaments and cytokines in stifles affected by CrCLR versus intact ligaments, but few findings have been relevant to prevention or treatment of ligament rupture.

Findings of recent in-depth summaries[19,20] on the pathogenesis of CCL disease and those of future studies may ultimately lead to better anti-inflammatory joint therapies and shed some light on disease progression and prevention. Surgical intervention after CrCLR will still be a necessary part of therapy for the foreseeable future. ■

State-of-the-art treatment considerations for CrCLR will be discussed in the second article in this series, ***Canine Cranial Cruciate Disease: Updating Our Knowledge about Therapy & Prognosis****.*

CCL = cranial cruciate ligament; CrCLR = cranial cruciate ligament rupture; OA = osteoarthritis; TPA = tibial plateau angle; TPLO = tibial plateau leveling osteotomy; TTA = tibial tuberosity advancement

References

1. Powers MY, Martinez SA, Lincoln JD, et al. Prevalence of cranial cruciate ligament rupture in a population of dogs with lameness previously attributed to hip dysplasia: 369 cases (1994-2003). *JAVMA* 2005; 227:1109-1111.
2. Hulse D, Beale B, Kerwin S. Second look arthroscopic findings after tibial plateau leveling osteotomy. *Vet Surg* 2010; 39:350-354.
3. Wilke VL, Robinson DA, Evans RB, et al. Estimate of the annual economic impact of treatment of cranial cruciate ligament injury in dogs in the United States. *JAVMA* 2005; 227:1604-1606.

James K. Roush*, DVM, MS, Diplomate ACVS, is the Doughman Professor of Surgery at the Kansas State University College of Veterinary Medicine. Prior to his current position, he was a clinical instructor at the University of Wisconsin–Madison School of Veterinary Medicine. His research interests include osteoarthritis therapy, gait kinetics, and canine fracture healing. Dr. Roush received his DVM from Purdue University; then worked in private practice before completing a small animal surgical residency and MS degree from University of Wisconsin–Madison.*

COMFORTIS®-Cats (spinosad)
Chewable Tablets
Before using COMFORTIS chewable tablets, please consult the product insert, a summary of which follows:
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Indications:
COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*), for one month, on cats and kittens 14 weeks of age and older and two pounds of body weight or greater.
Dosage and Administration:
COMFORTIS is given orally once a month, at the minimum dosage of 22.5 mg/lb (50 mg/kg). Administer COMFORTIS with food for maximum effectiveness. If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.
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There are no known contraindications for the use of COMFORTIS.
Warnings:
Not for human use. Keep this and all drugs out of the reach of children.
Precautions:
Use with caution with concomitant extra-label use of ivermectin. The safe use of COMFORTIS in breeding, pregnant, or lactating cats has not been evaluated.
Adverse Reactions:
In a well-controlled US field study, which included a total of 211 cats (139 treated with COMFORTIS and 72 treated with an active topical control once a month for 3 treatments), no serious adverse reactions were attributed to the administration of COMFORTIS. The most frequently reported adverse reaction in cats was vomiting.
Percentage of Cats (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS (n=139)	Active Topical Control (n=72)	COMFORTIS (n=135)	Active Topical Control (n=69)	COMFORTIS (n=132)	Active Topical Control (n=67)
Vomiting	14.4	1.4	14.8	1.4	13.6	4.5
Lethargy	3.6	0	0.7	0	1.5	1.5
Anorexia	2.2	0	0.7	0	2.3	1.5
Weight Loss	1.4	0	0	0	3	0
Diarrhea	1.4	1.4	0.7	2.9	2.3	1.5

Over the 3-month (3-dose) study, vomiting occurred on the day of or the day after at least one dose in 28.1% (39/139) of the cats treated with COMFORTIS and in 2.8% (2/72) of the cats treated with the active topical control. Three of the 139 cats treated with COMFORTIS vomited on the day of or the day after all three doses. Two cats that received extra-label topical otic ivermectin on Day -1 of the field study developed lethargy on Day 1 after COMFORTIS administration on Day 0.
For technical assistance or to report an adverse drug experience, call Elanco at 1-888-545-5973. Additional information can be found at www.comfortis.com. For a complete listing of adverse reactions for spinosad reported to the Center for Veterinary Medicine, see Adverse Drug Experience Reports under http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation
Effectiveness:
In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 98% effectiveness within 4 hours. COMFORTIS kills fleas before they can lay eggs. In a separate well-controlled laboratory study, COMFORTIS demonstrated 100% effectiveness on the first day following treatment and >90% effectiveness on Day 30.
If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In a field study conducted in households with existing flea infestations, flea count reductions of 97.5% were observed one month after the first treatment and 99.3% after three monthly treatments with COMFORTIS. Cats with pre-existing signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermatitis, and pruritus as a direct result of eliminating the fleas.
Storage Information:
Store at 20 to 25˚C (68 to 77˚F), excursions permitted between 15 to 30˚C (59 to 86˚F).
How Supplied:
COMFORTIS is available in four tablet sizes for use in cats: 90, 140, 270 or 560 mg. Each tablet size is available in color-coded packages of 6 tablets.
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Indications:
COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month, on dogs and puppies 14 weeks of age and older and 3.3 pounds of body weight or greater.
Dosage and Administration:
COMFORTIS is given orally once a month, at the recommended minimum dosage of 13.5 mg/lb (30 mg/kg). Administer COMFORTIS with food for maximum effectiveness. If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.
Contraindications:
There are no known contraindications for the use of COMFORTIS.
Warnings:
Not for human use. Keep this and all drugs out of the reach of children.
Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with COMFORTIS (see POST APPROVAL EXPERIENCE).
Precautions:
COMFORTIS is for use in dogs and puppies 14 weeks of age and older.
Use with caution in breeding females and in dogs with pre-existing epilepsy. The safe use of COMFORTIS in breeding males has not been evaluated.
Adverse Reactions:
In a well-controlled US field study, which included a total of 470 dogs (330 dogs treated with COMFORTIS and 140 dogs treated with an active control), no serious adverse reactions were observed with COMFORTIS. All reactions were regarded as mild and did not result in any dog being removed from the study. The most frequently reported adverse reaction in dogs in the COMFORTIS and active control groups was vomiting. The occurrence of vomiting, most commonly within 48 hours after treatment, decreased with repeated doses of COMFORTIS.
Percentage of Dogs (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS Chewable Tablets (N=330)	Active Topical Control (N=139)[a]	COMFORTIS Chewable Tablets (N=282)	Active Topical Control (N=124)	COMFORTIS Chewable Tablets (N=260)	Active Topical Control (N=125)
Vomiting	12.7	12.2	7.8	3.2	5.8	4.8
Decreased Appetite	9.1	5	2.8	1.6	1.9	0.8
Lethargy	7.6	5	3.5	4	1.2	0.8
Diarrhea	6.7	5	4.3	0.8	1.2	0
Cough	3.9	5	0.4	2.4	0	0
Polydipsia	2.4	1.4	0.7	0	0.4	0
Vocalization	1.8	0	0.4	0	0.4	0
Increased Appetite	1.5	0	0.4	0.8	0.4	0
Erythema	1.5	0	0.4	0	0.4	0
Hyperactivity	1.2	1.4	0	0	0.4	0
Excessive Salivation	1.2	0	0.4	0	0	0

[a] This number (n=139) is less than the total number of dogs in the safety population for the active control group (n=140) because one dog joined the study late and was only dosed at Month 3.
In US and European field studies, no dogs experienced seizures when dosed with COMFORTIS at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of COMFORTIS, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.
Post Approval Experience (June 2009):
The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, anorexia, ataxia, diarrhea, pruritus, trembling, hypersalivation and seizures.
Following concomitant extra-label use of ivermectin with COMFORTIS, some dogs have experienced the following clinical signs: trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation. Post approval experience continues to support the safety of COMFORTIS when used concurrently with heartworm preventatives according to label directions.
For technical assistance or to report an adverse drug experience, call Elanco at 1-888-545-5973. Additional information can be found at www.comfortis.com. For a complete listing of adverse reactions for spinosad reported to the Center for Veterinary Medicine, see Adverse Drug Experience Reports under http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation.
Effectiveness:
In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. COMFORTIS kill fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with COMFORTIS. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermatitis and pruritus as a direct result of eliminating the fleas.
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EP085610AMA V01-07-2012

4. Gordon WJ, Conzemius MG, Riedesel E, et al. The relationship between limb function and radiographic osteoarthrosis in dogs with stifle osteoarthrosis. *Vet Surg* 2003; 32:451-454.
5. Wilke VL, Conzemius MG, Kinghorn BP, et al. Inheritance of rupture of the cranial cruciate ligament in Newfoundlands. *JAVMA* 2006; 228:61-64.
6. Slauterbeck JR, Pankratz K, Xu KT, et al. Canine ovariohysterectomy and orchiectomy increases the prevalence of ACL injury. *Clin Orthop Rel Res* 2004; 429:301-305.
7. Shultz K. Diseases of the joints and stifle. In Fossum TW (ed): *Small Animal Surgery*, 3rd ed. Philadelphia: Mosby Elsevier, 2007, pp 1254-1300.
8. Wilke VL, Conzemius MG, Besancon MF, et al. Comparison of tibial plateau angle between clinically normal Greyhounds and Labrador Retrievers with and without rupture of the cranial cruciate ligament. *JAVMA* 2002; 221:1426-1429.
9. Schwandt CS, Bohorquez-Vanelli A, Tepic S, et al. Angle between the patellar ligament and tibial plateau in dogs with partial rupture of the cranial cruciate ligament. *Am J Vet Res* 2006; 67:1855-1860.
10. Reif U, Probst CW. Comparison of tibial plateau angles in normal and cranial cruciate deficient stifles of Labrador retrievers. *Vet Surg* 2003; 32(4):385-389.
11. Venzin C, Howard J, Rytz U, et al. Tibial plateau angles with and without cranial cruciate ligament rupture. *Vet Comp Orthop Trauma* 2004; 17:232-236.
12. Buote N, Fusco J, Radasch R. Age, tibial plateau angle, sex, and weight as risk factors for contralateral rupture of the cranial cruciate ligament in Labradors. *Vet Surg* 2009; 38:481-489.
13. Cabrera SY, Owen TJ, Mueller MG, Kass PH. Comparison of tibial plateau angles in dogs with unilateral versus bilateral cranial cruciate ligament rupture: 150 cases (2000-2006). *JAVMA* 2008; 232:889-892.
14. Comerford EJ, Innes JF, Tarlton JF, Bailey AJ. Investigation of the composition, turnover, and thermal properties of ruptured cranial cruciate ligaments in dogs. *Am J Vet Res* 2004; 65:1136-1141.
15. Muir P, Danova NA, Argyle DJ, et al. Collagenolytic protease expression in cranial cruciate ligament and stifle synovial fluid in dogs with cranial cruciate ligament rupture. *Vet Surg* 2005; 34:482-490.
16. Muir P, Schamberger GM, Manley PA, Hao Z. Localization of cathepsin K and tartrate-resistant acid phosphatase in synovium and cranial cruciate ligament in dogs with cruciate disease. *Vet Surg* 2005; 34:239-246.
17. Barrett JG, Hao Z, Graf BK, et al. Inflammatory changes in ruptured canine cranial and human anterior cruciate ligaments. *Am J Vet Res* 2005; 66:2073-2080.
18. Hayashi K, Frank JD, Dubinsky C, et al. Histologic changes in ruptured canine cranial cruciate ligament. *Vet Surg* 2003; 32:269-277.
19. Comerford EJ, Smith K, Hayashi K. Update on the aetiopathogenesis of cranine cranial cruciate ligament disease. *Vet Comp Orthop Trauma* 2011; 24:91-98.
20. Cook JL. Cranial cruciate ligament disease in dogs; biology versus biomechanics. *Vet Surg* 2010; 39:270-277.