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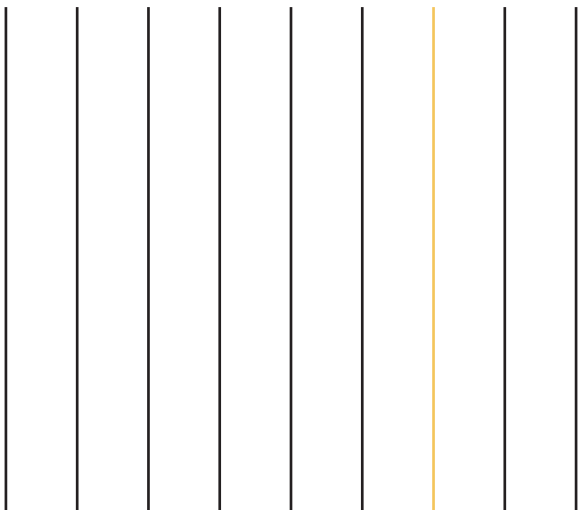

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CONFERENCE EVALUATION

Thank you for joining us!

OSTEOARTHRITIS & OTHER CHRONIC PAIN SYNDROMES: RECOGNITION, ASSESSMENT, MANAGEMENT

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SMALL ANIMAL

CANINE & FELINE OSTEOARTHRITIS & CHRONIC PAIN SYNDROMES
RECOGNITION, ASSESSMENT, AND MANAGEMENT
Kansas State Univ 2024

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It can be argued that chronic pain is the most ubiquitous disease process in all of medicine. All animals, whether human and veterinary should they live long enough, will probably experience it. And of all chronic pain syndromes, osteoarthritis (OA) remains the most predictable cause in both dogs and cats. Indeed, in dogs the pathophysiology of OA is commonly heritable and conformational, to include, joint incongruity, joint malalignment, and intrinsic cartilaginous defects. For these dogs, the disease process begins at a very young age and is progressive and lifelong. At least 30-40% of dogs may be affected clinically,[1] with a higher percentage (up to 60%) having radiographic changes associated with degenerative joint disease.[2] Other common causes include acquired conditions such as trauma, including not insignificantly chronic cranial cruciate ligament (CCL) injury and acute-on-chronic CCL rupture. Nearly half of musculoskeletal disorders identified during a 10-year span in 16 veterinary hospitals resulted from joint disease.[3] The etiology of OA in cats is uncertain, with less attributable to conformation (exception: hip dysplasia in Maine Coons[4]) than dogs. Cats, both young and old, appear to have a very high incidence of OA, with up to 60% of all cats have radiographic OA changes and 90% over 10 years old.[5] Although the pathophysiology of OA may be different in dogs and cats, this means that OA in both these species can initiate early in life, far earlier (relatively speaking) than routinely in humans, and how we intervene in OA may be quite different from one life stage to another.

Risk factors for OA begins with breed predisposition (see Table 1) and extend to breed dispositions for a variety of other painful orthopedic conditions, injuries, and inflammatory joint diseases (see Tables 2, 3).

For example the highest prevalence of canine hip dysplasia (CHD) is in those that tend to be stocky, round, and heavy. The lowest prevalence is in slender, trim, fleet-footed, and highly coordinated breeds (e.g. greyhound, whippet). However, one report failed to support the hypothesis that heavy, fast-growing dogs from four large-sized breeds were at increased risk for CHD, and other unknown risk factors and genetic variances within litters may have played a role in this cohort of dogs.[6]

Interestingly, CHD is not reported in wild, undomesticated carnivores, speculatively because they often mature slowly due to poor nutrition, although again other genetic variances may play important roles.[7] Nutrition clearly can play a role, evidenced by one study that limited feeding of domestic dogs at risk for CHD over a 5-year period, revealing minimal development of coxofemoral joint osteoarthritis.[8] [6]

Table 1: Heritable Conformational conditions resulting in OA:

		Common breeds with Highest Odds Ratio [9],[10] (Alphabetical)
Hip Dysplasia		Burnese Mtn Dog, Chow chow, German Shepherd, Kuvasz, Labrador retriever, Newfoundland, Rottweiler, St. Bernard
Legg-Calves-Perthes		Australian Shepherd, Chihuahua, Miniature Pinscher, Pug, Toy Poodle, West Highland white terrier, Yorkshire terrier

Elbow Dysplasia	Fragmented medial coronoid	Burnese Mtn Dog, Bullmastiff, German Shepherd, Irish Wolfhound, Labrador retriever, Rottweiler, St. Bernard.
	United anconeal process	Burnese Mtn Dog, Mastiff, Rottweiler
OCD	Shoulder	Burnese Mtn Dog, Great Dane, Great Pyrenees, Irish Wolfhound, Labrador large breed especially German Shepherd, Rottweiler; sporting breeds
	Elbow	Chow, Golden Retriever, Great Dane, Labrador Retriever, Newfoundland, Rottweiler
	Stifle	Boxer, Bulldog, Great Dane, Irish Wolfhound, Mastiff, Rottweiler
	hock	Bullmastiff, Labrador Retriever, Rottweiler
Medial shoulder instability/subluxation[11]	Congenital	Dachshund, Chihuahua, Pekinese, Shetland sheepdog, toy poodle
Angular limb deformity (premature growth plate closure)[12]	Pes varus	Dachshund
	Pes valgus	Collies, Shetland sheepdogs, Newfoundland, Rottweiler
	Genu valgum (knock knee)	Small breeds[13]
	Genu varum (bow-leg)	Large breeds[14]
Luxating Patella[15]	Medial	Maltese, Pomeranian, Toy Poodle, Yorkshire Terrier
	Lateral	Akita, Bulldog, Cavalier King Charles Spaniel, Chihuahua, Chinese Sharpei, Great Pyrenees
Poor tibial plateau angle resulting in Cranial Cruciate injury/rupture		Newfoundland, Rottweiler, Labrador retriever, Boxer, Chow chow, American Staffordshire terrier, St. Bernard, Alaskan malamute, Airedale terrier. Sexually altered and females predisposed.[16] Akita, Mastiff, and Chesapeake Bay retriever were also predisposed, and obesity a significant risk factor.[17]

Other historical, environmental factors will also impact the development of CHD. One report of 501 dogs found increased risk of development of a dysplastic phenotype in puppies allowed to take stairs at or before 3 months of age, and diminished radiographic CHD in puppies that were allowed off-leash before 3 months of age; those born on a farm, and in the spring or summer.[18]

OA is typically envisioned as a disease of bone and cartilage. And of course, physical examination – or even just movement - often will easily elicit the crepitace attributable to osteophytes and bone-on-bone grating. But it is instructive to point out that the pain of OA is not felt at the articular surfaces or what is left of them. Rather, the pain is felt in the peri-articular structures, from an inflamed synovium, when tension is placed on a fibrotic joint capsule, and when patients are asked to exert (even if just by standing or walking) weakened ligaments, tendons, and muscle. Thus OA is a disease of the entire joint organ, including dramatic synovitis, fibrosis, and atrophy…and the result is not just pain but progressive disability. Physical examination and clinical measurement instruments (CMIs) can be designed to illuminate and document these findings.

Several validated CMIs are available and can be use to semi-quantify patient comfort, mobility, and abilities, e.g.

a. CODI: Cincinnati Orthopedic Disability Index:[19] Includes a client-specific outcome measure (CSOM), whereby the pet owners are asked not only standard questions but also to volunteer specific activities of daily living that have become difficult for their dog, the degree of impairment, and the final score is normalized to a 0-100 scale. Based on the human MACTAR (McMaster-Toronto Arthritis) and WOMAC (Western Ontario McMaster) arthritis index in humans, variations of CSOMs have been applied to a number of OA pain studies in dogs.

b. CBPI: Canine Brief Pain Inventory.[20] Derived from the human Brief Pain Inventory, the CBPI questionnaire asks owners to place their dogs on a 0 best-10 worst scale in 3 domains, a Pain Severity Score (4 subdomains of pain its present and least, worst, and average over the previous week), a Pain Interference Score (7 subdomains of general life enjoyment plus ability of general activity, to rise, walk, run, climb stairs), with a combined overall best score of 0 and worst of 100; and an Overall quality of life impression Poor to Excellent).

c. LOAD: Liverpool Osteoarthritis in Dogs.[21] The questionnaire asks owners to scale (0 best-5 worst) 5 areas of mobility Generally (general, lameness disability, activity, affect of cold/damp weather on lameness, stiffness after lying down) and 8 areas of mobility at Exercise (how active in exercise, how keen, ability, affect on lameness, how often stopping/resting, effect of cold/damp weather, stiffness after lying down, effect of lameness). The maximum best score is 0, maximum worst/most affect score is 65).

d. COAST: Canine Osteoarthritis Staging Tool.[22] This novel CMI not only gives an OA "score" but defines the stages of OA for assessment and monitoring of dogs either 'at risk' or with clinical signs of the disease. It consists of two key steps (grading and staging), performed by both owner and veterinarian, which are repeated at monitoring intervals tailored to the requirements of the individual dog. Unique to COAST, it has a key focus on "at risk" dogs (e.g. breed, conformation, body condition score predispositions, history of joint injury, etc.) and not merely symptomatic patients, which minimizes the risk of underdiagnosing OA, and allows for prospectively earlier diagnosis of OA. A two-pronged approach to grading ('grade the dog' and then 'grade the joint') ensures that the impact of OA on the joints and on the dog as a whole is evaluated. The resulting grades are consolidated to provide an overall measure of disease severity. This correlates with the stage of OA which is useful for guiding treatment and monitoring disease progression. The individual grades may also provide useful supplementary information.

And in cats:

a. FMPLI: Feline Musculoskeletal Pain Index[23] www.painfreecats.org
b. MICAT: Montreal Instrument for Cat Arthritis Testing[24]

Owners may recognize orthopedic pain only when the gait is asymetric (only 1 limb affected, or far worse than a contralateral limb, thus "lameness"), but bilateral disease (e.g. osteoarthritis) may not reveal a single limb being favored (i.e. no lameness reported). Instead the patient may merely shift weight forward or back w/ resultant muscle atrophy and hypertrophy accordingly. Changing the rise from lying down, a shortened stride, stiff gait, or improving gait when "warmed out" also points to osteoarthritis pain. Decreased range of motion (ROM) may indicate joint capsule fibrosis and/or osteophytes.

An orthopedic exam can be both brisk and thorough when part of a routine wellness visit. It begins and can be halfway completed upon knowing signalment e.g. age, breed (see Table 1), gender (males over-represented), lifestyle (agility & sporting vs. sedentary) dispositions, history (previous trauma or h/o lameness?), and first walking in the room, chatting with the owner, and watching/interacting with the pet.

- Visible conformation: Body condition score; kyphosis of back, diminished angle to stifle & hock, obvious muscle atrophy (denotes a patient that has been shifting weight forward for considerable time); cow-hock, base narrow or wide, chondrodyplasia – all evident at a glance.
- Dog sitting "square", or cheating on one hip?
- When stands from a laying position, should be all 4 legs simultaneously; vs. rising up first on forelimbs and fololwed by hoisting up the rear quarters.
- Gait if possible – stilted or fluid? Lameness: look for a "quick step" and it is the contralateral limb affected; look for classic 'wiggle' of rear quarters seen as the dog rotates its pelvis to reduce painful extension of the hip.
- Jumping up or standing on back legs easily, partially, or unable/unwilling?

In the cooperative patient, the hands-on orthopedic exam can be completed in less than two minutes and of course can be incorporated to the rest of the physical exam as hands are run over the body. If there is a reported lameness or disability then more time may need to be spent on the affected area to fully characterize.

Focusing on the orthopedic aspect of the PE:[25] A consistent routine back to front or vece versa, with attention "lame" leg last if reported. Although not required, an assistant is recommended to aid with maneuvering, restraint if necessary, and identification of painful response (body shift, change of facial expression). The clinician can focus mindfulness towards: symmetry (atrophy or thickening relative to contralateral limb), ROM (full or limited/resistance; crepitation), and pain (hyperalgesia upon palpation). Individual regions and maneuvers:

Scapula: prominent scapular spine suggests disuse atrophy; abducted limb may suggest infraspinatus contracture;

Shoulder: Flexion, extension, adduction, abduction, internal/external rotation, drawer maneuver. Pain at cranial aspect shoulder and in extension consistent w/ supraspinatus tendonopathy (*note: avoid placing forelimb into extension w/ hand placed caudal/behind or distal to elbow join*t during should extension which also forces elbow into extension and a painful response could be shoulder OR elbow). Instead place hand above elbow which is held in neutral position. Bicipital tenosynovitis: pain upon deep palpation, or palpation during simultaneous flexion of shoulder then elbow (max stretch on bicipital tendon). Medial glenohumeral laxity (excessive shoulder abduction and pain at end of maneuver).

Elbow: ROM including extension/flexion and varus/valgus; thumb & forefinger caudal to humeral condyle in front of olecranon: effusion will cause a distension rather than concave depression; pain upon digital pressure on medial as indicates r/o ununited anconeal process, Fragmented coronoid process

Long bone: pain on digital pressure? (puppies/young large breed dogs r/o panosteitis, hypertrophic osteodystrophy; older large breed dogs primary r/o osteosarcoma, metastatic bone neoplasia)

Carpus: ROM including varus/valgus and extension/flexion (pad should touch or nearly touch caudal antebrachium).

Spine: deep palpation (hyperalgesia?), symmetry, atrophy? Cervical gentle ROM, any resistance? Digital pressure at lumbosacral w/ and without extension of tail (best if hind limbs somewhat elevated (pain elicited r/o LS stenosis)

Hip: Puppy: Ortolani: hand on flexed stifle and femur is forced in a dorsal/axial direction with other hand on hip/pelvis → abducted: clunk when subluxated femoral head moves "up and over" the acetabular rim. Adult: Should be able to elicit comfortable 3 second hold in extension (via pulling back on hock or stifle).

Stifle: cupping from behind; medial buttress consistent with chronic cranial cruciate ligament injury and instability; luxating patella through extension and flexion (Grade IVs hardest to detect due to false impression of proper seating since cannot be displaced; follow patellar ligament from tibial tuberosity, will be ectopic for luxating patella and puffy if any effusion). Clicking or popping in ROM (meniscus); tibial thrust and cranial drawer for CCL.

Tarsus: popping during ROM may be displacement of superficial digital tendon post-retinaculum tear (→hyperflexion of tarsus, digits; also calcaneal tendon damage can lead to hyperextension); joint capsule distension, palpable on dorsal as well as caudomedial, caudolateral joint surfaces (suggests OCD).

Early Management (COAST Stage 1-2): REDO the PARAGRAPHS

Several Systematic Reviews reveal the most predictably effective, evidence-based means of canine OA management[26],[27],[28],[29] and are summarized in industry guidelines such as the Global Pain Council[30] and AAHA Pain Management Guidelines.[31] However the most cogent consensus of treatment guidelines are based on COAST Stages.[32],[33]

1. Weight Optimization: keep the patient lean! The evidence is clear that #1 preventative measure to slow the progression of OA in at-risk dogs is to maintain a lean body condition score.[34],[35],[36],[37],[38] The role of adipose tissue as a mediator of systemic inflammation, the contribution of central obesity to chronic pain in humans (doubling the risk for it[39]), and the primacy of weight loss to diminish chronic pain signs and symptoms- is now a settled matter. In dogs with osteoarthritis, several studies illuminate the benefit of improving pain scores, mobility, and NSAID reduction with weight loss alone (even modest, i.e. only 6%[40]). Indeed, it is probably not an overstatement to say that in an overweight patient, both the clinician and pet owner are wasting time and money on other interventions until and unless weight optimization is achieved.
2. NSAID (including EP4 receptor antagonists): for the early OA patient may be in an intermittent or pulse dose fashion – several weeks on, several weeks off. Multiple systematic reviews describe safety of efficacy of NSAID use in dogs and their highest and wisest use.[41],[42],[43] See the separate discussion on NSAID in dogs and cats.
3. Chondroprotectants: The evidence for glucosamine and chondroitin in OA remains mixed at best, although some other ingredients of oral neutraceuticals such as Bosswelia, egg shell membrane, avocado soybean unsuponafiables, MSM, green-lipped mussel, microlactin, and others offer suggestions for varying degrees of immunomodulating, chondroprotective, and pain-modifying effect (with one combination product in an well-designed but unpublished study revealing statistical improvement in biomarkers and LOAD[44]). A recent review of nutritional supplements for canine OA concludes that even if additional investigation is needed, dietary supplements should be considered in OA management.[45],[46] It can be argued that these neutraceuticals, due to their ease, relative safety, low cost, and easy acceptance by pet owners, should be deployed with earliest onset of OA signs, or even in at-risk patients before symptomatic. Parenteral polysulfated glycosaminoglycans (PSGAG), in particular Adequan® which is FDA-approved "Disease-modifying osteoarthritis agent" (DMOAD) for dogs with bioavailability and efficacy supported by independent studies.[47] One abstract in cats demonstrates bioavailability and distribution to joints with SC administration.[48] Another injectable glycosaminoglycan for horses, pentosan polysulfate (PPS, Cartrophen®), also has some evidence for benefit in canine OA[49] although not available in the U.S.
4. Eicosapentaenoic acid (EPA)-rich diets in dogs,[50] Docosahexaenoic acid (DHA)-rich diet in cats.[51] There is an emerging body of evidence to support other nutritional supplements such as eggshell membrane and many others.
5. Exercise, especially controlled. Therapeutic exercise is hypoalgesic[52] and considered to play a crucial role in the management of osteoarthritis in dogs.[53],[54]

Note: The AAHA/AAFP Pain Management Guidelines[55] strongly emphasizes the role of low-stress handling and fear-free environment (especially in the clinic setting). For dogs and cats, a superior resource is Dr. Sophia Yin's *Low Stress Handling, Restraint and Behavior Modification of Dogs and Cats: Techniques for Developing Patients Who Love Their Visits* and website, www.drsophiayin.com. For cats in particular, the *AAFP/ISFM Feline-Friendly Handling Guidelines*[56] is an excellent place to begin, and the manuscript is accompanied by video demonstrations: http://www.catvets.com/guidelines/practice-guidelines/handling-guidelines. In

addition, pheromones are increasingly recognized for their integral role in diminishing stress, with its attendant contribution to pain. All of this is globally part of the Fear-Free experience for cats, www.fearfreepets.com.

Additional modalities for more advanced OA (COAST Stages 2-4):

1. Pain-modifying analgesic drugs: PMAD – one or more
    a. amantadine: exerts a pain-modifying effect as an NMDA receptor antagonist[57] and remains an interest in humans with chronic and neuropathic pain (but not specifically osteoarthritis) in humans, with mixed results.[58],[59] One study at 3 mg/kg once daily does demonstrate utility as an adjunct to NSAID in dogs with refractory osteoarthritis within 3 weeks,[60] and there is one case report of using amantadine to treat neuropathic pain in a dog.[61] More recent pharmacokinetic studies suggest that 3-5 mg/kg every 12 hours may be more appropriate.[62] Toxicity and kinetic studies have been performed in humans[63] and cats[64] but not in dogs. In dogs, anecdotal reports of amantadine-induced ADE's include agitation and other behavioral changes, and GI signs especially diarrhea. In humans QT-syndrome is reported, and in dogs a recent study demonstrated a moderate risk of arrhythmia and decreased cardiac output in halothane-anesthetized dogs receiving IV amantadine.[65] The clinical significance of this finding in awake dogs receiving PO amantadine remains unknown.
    b. gabapentin or pregabalin: anti-convulsant that analgesic properties predominantly by down-regulating pre-synaptic voltage-dependent calcium channels in the dorsal horn of the spinal cord[66] but other mechanisms probably exist as well (while structurally similar to GABA, it is not a direct agonist, although it may have indirect effects on GABA metabolism such as increasing intracellular stores). Because of its effectiveness and tolerability, it is approved for post-herpetic neuralgia and is in widespread use for humans with a variety of neuropathic and other maladaptive pain conditions,[67],[68],[69],[70],[71] and this suggests, along with published veterinary case reports,[72],[73],[74] a strong rationale for the utilization of gabapentin in analogous conditions experienced by dogs and cats. The utility of gabapentin for osteoarthritis in demonstrable in rodent models,[75],[76] one canine study suggests a disease-modifying effect (not a pain study) in experimental osteoarthritis,[77] but no clinical studies have been published investigating gabapentin canine OA. However, case reports exist of successful use in treating non-OA neuropathic pain conditions in both dogs[78],[79],[80] and cats.[81] In cats, one study demonstrated a benefit of gabapentin in naturally-occurring osteoarthritis,[82] in addition to a case series of chronic musculoskeletal pain.[83] Pharmacokinetics of gabapentin are well established in dogs[84],[85],[86] and cats,[87] with a half-life suggesting TID administration schedule, although anecdotally BID appears to be useful. The primary adverse effect in dogs appears to be somnolescence (as in humans) which usually will spontaneously resolve over a few days' acclimation time. For chronic pain dosing, a general consensus is that doses are initiated at 3-5 mg/kg and gradually tapered upwards as the patient can tolerate to a target dose range of 20+ mg/kg. Pregabalin is a gabapentin-like analogue and is thought to have a similar mechanism of action for both its pain-modifying (the labeled indication) and anticonvulsant (down-regulates calcium channels, diminishing action potential propagation) activity. In the U.S. it is available as Lyrica® labeled in humans for pain associated with diabetic neuropathy, fibromyalgia, and post-herpetic neuralgia (Shingles) and is a scheduled Class IV drug. It appears to have a superior kinetic profile relative to gabapentin: higher oral bioavailability, longer T ½, and with a linear GI absorption profile suggesting a dose of 4 mg/kg twice daily in the dog.[88] A case series describes its use in canine syringomyelia,[89] but its expense may currently limit its use in veterinary medicine.
    c. note: tramadol has been shown to be ineffective in modifying OA-related pain[90]
    d. SS(N)RI's: These compounds exert their effect by increasing serotonin +/- norepinephrine in the synaptic cleft. At least one popular SSNRI, duloxetine, has a chronic pain label in humans (including osteoarthritis and low back pain, in addition to fibromyalgia and diabetic neuropathy); one evaluation in dogs revealed poor bioavailability (4%),[91] but another study appears to reveal a dose-dependent effect with more favorable plasma levels at high doses (30 & 60 mg to laboratory beagles, equivalent to 100 & 200 mg in humans respectively which 2-4x customary dosing), but with a much shorter plasma T1/2 (2.5 H in dogs, vs. 10-12 H in humans).[92] Another SSNRI, venlafaxine (which has evidence for efficacy in human OA[93]), is reported to have bioavailability approaching 50% of that of humans and T ½ of 3 hours with a suggested dose of 4 mg/kg PO Q 8-12H.[94] Evidence of a clinical pain-modifying effect for either molecule is currently lacking in animals, and there are no dosed-titration data for either

drug. Note: many drugs and compounds enhance monoamines and/or serotonin and caution should be undertaken when or if used in combination. Examples include: tramadol, TCA's including amitriptyline and clomipramine, SS(N)RI's, amantadine, metoclopramide, selegiline, amitraz, mirtazapine.

2. Biologic therapies:
    a. Anti-Nerve Growth Factor Monoclonal Antibodies (monthly SC injection).[95],[96] The feline version is available as Solensia™, and Librela™ in the dog
    b. Intra-articular injections – some commercially available, others investigational
        i. Stem Cells (autologous mesenchymal vs. allogeneic)[97],[98]
        ii. Platelet-rich Plasma (PRP)[99],[100]
        iii. Stromal-vascular fraction[101]
        iv. Autologous Protein Solution[102]
        v. Tn-117 – under investigation as anti-synovitis medical device (Synovetin OA™)
        vi. Resiniferotxin – TRPV1 agonist under investigation[103] ("molecular neurosurgery")

3. Physical Modalities
    a. Physical Therapy – beyond therapeutic exercise as described above, referral for more advanced modalities e.g. hydrotherapy[104]
    b. Energy-based modalities – Embraced by many but most evidence is molecular, cellular, tissue; clinical evidence limited and conflicting, and outcome measures not always pain.
    c. Low-Level Laser
    d. TENS
    e. Extracorporeal Shock Wave Therapy
    f. Pulsed Electromagnetic Field Therapy[105]
    g. Acupuncture
    h. Myofascial Trigger Point Therapy

Table 2: Other heritable non-joint but painful orthopedic disorders:[106]

panosteitis	Basset Hound, Burnese Mtn Dog, Chinese Sharpei, Dalmatian, English Springer Spaniel, Giant Schnauzer, German Shepherd, Great Dane, Great Pyrenees, Irish Wolfhound, Mastiff, St Bernard. Males are affected four times more often than females. Age: 6 mos – 2 years.
Hypertrophic Osteodystrophy	Boxer, Great Dane, Irish Setter, Weimaraner

Table 3: Other Acquired painful orthopedic conditions with breed dispositions:

Tendonopathy, mineralization, myopathy/contractures	Supraspinatus tendonopathy/ mineralization[107]	Performance, sporting dogs, almost 60% agility dogs; median age 6.5 years.
	Infraspinatus contracture[108]	Working and sporting dogs, e.g. "bird" dogs (pointers, setters) in US, Elkhound in Europe
	Bicipital tenosynovitis[109]	No breed or gender disposition but trend mean wt 33 kg, mean age 4.6y.
	Gracilis, semitendinosus myopathy/contracture[110]	German shepherd
	Achilles tendon injury[111]	Doberman, Labrador, Border collie
	Iliopsoas injury[112]	Sporting, working breeds

Medial shoulder instability/subluxation[113]	Congenital		Dachshund, Chihuahua, Pekinese, Shetland sheepdog, and toy poodle
	Acquired		Sporting, agility breeds
Intervertebral Disc	Hansen 1[114]		Chondrodysplastic breeds
	Hansen 2[115]		Non-chondrodysplastic breeds
Lumbosacral stenosis[116]			German shepherd dog, Airedale terrier, Boxer, English Springer spaniel, Golden retriever, Great Dane, Irish setter, Labrador retriever.
Osteosarcoma[117]			Bernese Mountain dog, Doberman pinscher, German shepherd, Golden retriever, Great Dane, Greyhound, Irish setter, Labrador retriever, Rottweiler Saint Bernard, other large and giant breeds
Inflammatory Polyarthritis	Infectious, especially vector-borne		No breed predisposition but outdoor (vector-exposed) dogs at higher risk
	Immune-mediated[118]	Erosive (Rheumatoid Arthritis)	Small, toy breeds; Sheltie
		Non-erosive (Idiopathic)	Labrador Retriever, Golden Retriever, German Shepherd, Cocker Spaniels, Akita, American Eskimo, Shar Pei, other Sporting and large-breed dogs; age 2-5 years.

Note: Odds ratios reflect the likelihood of a particular dog within a breed being affected by a given condition; it does not necessarily predict the most common breeds to walk through the door with that condition, since some breeds are far more popular (e.g. Labradors) than others (e.g. Kuvasz, Irish Wolfhound). An informal survey among 5 veterinary rehab professionals identified the following breeds as the most commonly encountered with orthopedic conditions in their practices, in order of frequency cited: Labrador retriever, German shepherd, Rottweiler, Golden Retriever, Newfoundland, St. Bernard, Great Dane, Burnese Mtn Dog, Border Collie, Doberman pinscher.[119]

Management of non-OA, non-OSA pain

- Adjunctive Pain-modifying analgesic drugs, including but not limited to:
  - gabapentinoids, amantadine, amitriptyline, SSRI/SSNRI, acetaminophen? (dog only), maropitant, ketamine,, cannabinoid?, low-dose naltrexone?
- NSAID
- opioids (oral bioavailability low; be aware of potential diversion)
- weight optimization
- Biophysical modalities
  - Therapeutic Laser, PEMF, etc.
  - Acupuncture
  - Myofasical Trigger Point

Osteosarcoma (and potentially other neoplasms) :To the above,

- Bisphosophonate infusion: zoledronate[120] 0.1 - 0.15 mg/kg IV in 60 ml (or 10ml/kg) saline over 15min q 4wks. Monitor renal values
- Palliative radiation therapy

References

[1] Johnson JA, Austin C, Bruer GJ. Incidence of Canine Appendicular Musculoskeletal Disorders in 16 Veterinary Teaching Hospitals from 1980 through 1989. Vet Compar OrthTrauma, 1994 (7): 56-69.

[2] Bland SD. Canine osteoarthritis and treatments: a review. Vet Sci Dev, 43 Refs ed. 2015 Vol 5 (2) pp. 5931, 84-89.

[3] JA, Austin C, Breur GJ. Incidence of canine appendicular musculoskeletal disorders in 16 veterinary teaching hospitals from 1980 through 1989. Johnson Vet Comp Orthop Trauma 7:56-69, 1994.

[4] Loder RT, Todhunter RJ. Demographics of hip dysplasia in the Maine Coon cat. J Feline Med Surg. 2018 Apr;20(4):302-307.

[5] Lascelles BD, Henry JB 3rd, Brown J, Robertson I, Sumrell AT, Simpson W, Wheeler S, Hansen BD, Zamprogno H, Freire M, Pease A. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. Vet Surg. 2010 Jul;39(5):535-44.

[6] Krontveit RI, Nodtvedt A, Saevik BK, et al: A prospective study on canine hip dysplasia and growth in a cohort of four large breeds in Norway (1998-2001). Prev Vet Med 2010 Vol 97 (3-4) pp. 252-63.

[7] McCarthy RJ: Hip Dysplasia Management in Younger Dogs. Western Vet Conf 2007.

[8] Kealy RD, Lawler DF, Ballam JM, et al: Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs . J Am Vet Med Assoc 1997 Vol 210 (2) pp. 222-5

[9] LaFond E, Breur GJ, Austin CC. Breed susceptibility for developmental orthopedic diseases in dogs. J Am Anim Hosp Assoc. 2002 Sep-Oct;38(5):467-77.

[10] Clements DN, Carter SD, Innes JF, Ollier WE. Genetic basis of secondary osteoarthritis in dogs with joint dysplasia. Am J Vet Res. 2006 May;67(5):909-18.

[11] Kowaleski MP: Diseases of ligaments and joints. In Morgan RV (ed): Handbook of Small Animal Practice. 5th Ed. Saunders Elsevier, ST. Louis, MO 2008 pp. 764-765.

[12] Piermattei DL, Flo G, DeCamp C: Correction of Abnormal Bone Growth and Healing. Handbook of Small Animal Orthopedics and Fracture Repair, 4th ed. Ed, Saunders Elsevier 2006 pp. 747-72.

[13] Woods S. Non-traumatic Diseases of the Canine Stifle. WSAVA Congress Proceedings, 2016

[14] Riser WH, Parkes LJ, Rhodes WH et al: Genu valgum: A stifle defomlity of giant dogs. J Am Vet Radiol Soc 10:28, 1969

[15] Kowaleski MP: Diseases of ligaments and joints. In Morgan RV (ed): Handbook of Small Animal Practice. 5th Ed. Saunders Elsevier, ST. Louis, MO 2008 pp. 764-765.

[16] Witsberger T H, Villamil J A, Schultz L G, et al: Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. J Am Vet Med Assoc 2008 Vol 232 (12) pp. 1818-24.

[17] Duval J M, Budsberg S C, Flo G L, et al: Breed, sex, and body weight as risk factors for rupture of the cranial cruciate ligament in young dogs. J Am Vet Med Assoc 1999 Vol 215 (6) pp. 811-4.

[18] Krontveit RI, Nodtvedt A, Saevik BK, et al: Housing and exercise-related risk factors associated with the development of hip dysplasia as determined by radiographic evaluation in a prospective cohort of Newfoundlands, Labrador Retrievers, Leonbergers, and Irish Wolfhounds in Norway. Am J Vet Res 2012 Vol 73 (6) pp. 838-46

[19] Gingerich DA, Strobel JD. Use of client-specific outcome measures to assess treatment effects in geriatric, arthritic dogs: controlled clinical evaluation of a nutraceutical. Vet Ther. 2003 Winter;4(4):376-86.

[20] Brown DC, Boston RC, Coyne JC, Farrar JT. Ability of the canine brief pain inventory to detect response to treatment in dogs with osteoarthritis. J Am Vet Med Assoc. 2008 Oct 15;233(8):1278-83.

[21] Walton MB, Cowderoy E, Lascelles D, Innes JF. Evaluation of construct and criterion validity for the 'Liverpool Osteoarthritis in Dogs' (LOAD) clinical metrology instrument and comparison to two other instruments. PLoS One. 2013;8(3):e58125.

[22] Cachon T, Frykman O, Innes JF, Lascelles BDX, Okumura M, Sousa P, Staffieri F, Steagall PV, Van Ryssen B; COAST Development Group. Face validity of a proposed tool for staging canine osteoarthritis: Canine OsteoArthritis Staging Tool (COAST). Vet J. 2018 May;235:1-8.

[23] Benito J, Hansen B, Depuy V, Davidson GS, Thomson A, Simpson W, Roe S, Hardie E, Lascelles BD. Feline musculoskeletal pain index: responsiveness and testing of criterion validity. J Vet Intern Med. 2013 May-Jun;27(3):474-82.

[24] Klinck MP, Monteiro BP, Lussier B, Guillot M, Moreau M, Otis C, Steagall PV, Frank D, Martel-Pelletier J, Pelletier JP, Del Castillo JR, Troncy E. Refinement of the Montreal Instrument for Cat Arthritis Testing, for Use by Veterinarians: detection of naturally occurring osteoarthritis in laboratory cats. J Feline Med Surg. 2017 Sep 1:1098612X17730172.

[25] Multimodal Management of Canine Osteoarthritis. Fox SM, Millis D. 2010 Manson Publishing/The Veterinary Press. London, UK

[26] Innes JF, Clayton J, Lascelles BD. Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. Vet Rec. 2010 Feb 20;166(8):226-30.

[27] Sanderson RO, Beata C, Flipo RM, Genevois JP, Macias C, Tacke S, Vezzoni A, Innes JF. Systematic review of the management of canine osteoarthritis. Vet Rec. 2009 Apr 4;164(14):418-24.

[28] Aragon CL, Hofmeister EH, Budsberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. J Am Vet Med Assoc. 2007 Feb 15;230(4):514-21.

[29] Kirkby KA, Lewis DD. Canine Hip Dysplasia: Reviewing the Evidence for Nonsurgical Management. Vet Surg. 2011 Dec 8.

[30] Monteiro BP, Lascelles BDX, Murrell J, Robertson S, Steagall BPV, Wright B. 2022 WSAVA guidelines for the recognition, assessment and treatment of pain. J Sm Anim Pract. 27 October 2022, pp. 1-79.

[31] Gruen ME, Lascelles BDX, Colleran E, Gottlieb A, Johnson J, Lotsikas P, Marcellin-Little D, Wright B. 2022 AAHA Pain Management Guidelines for Dogs and Cats. J Am Anim Hosp Assoc. 2022 Mar 1;58(2):55-76.

[32] Mosley C, Edwards T, Romano L, Truchetti G, Dunbar L, Schiller T, Gibson T, Bruce C, Troncy E. Proposed Canadian Consensus Guidelines on Osteoarthritis Treatment Based on OA-COAST Stages 1-4. Front Vet Sci. 2022 Apr 26;9:830098..

[33] Cachon T, Frykman O, Innes JF, Lascelles BDX, Okumura M, Sousa P, Staffieri F, Steagall PV, Van Ryssen B. COAST Development Group's international consensus guidelines for the treatment of canine osteoarthritis. Front Vet Sci. 2023 Aug 3;10:1137888.

[34] Smith GK, Paster ER, Powers MY, et al. Lifelong diet restriction and radiographic evidence of osteoarthritis of the hip joint in dogs. J Am Vet Med Assoc. 2006;229(5):690–693.

[35] Kealy RD, Lawler DF, Ballam JM, Mantz SL, Biery DN, Greeley EH, Lust G, Segre M, Smith GK, Stowe HD. Effects of diet restriction on life span and age-related changes in dogs. J Am Vet Med Assoc. 2002 May 1;220(9):1315-20.

[36] Lawler DF, Evans RH, Larson BT, Spitznagel EL, Ellersieck MR, Kealy RD. Influence of lifetime food restriction on causes, time, and predictors of death in dogs. J Am Vet Med Assoc. 2005 Jan 15;226(2):225-31.

[37] Lawler DF, Larson BT, Ballam JM, Smith GK, Biery DN, Evans RH, Greeley EH, Segre M, Stowe HD, Kealy RD. Diet restriction and ageing in the dog: major observations over two decades. Br J Nutr. 2008 Apr;99(4):793-805.

[38] Kirkby KA1, Lewis DD. Canine Hip Dysplasia: Reviewing the Evidence for Nonsurgical Management. Vet Surg. 2012 Jan;41(1):2-9.

[39] Ray L, Lipton RB, Zimmerman ME, Katz MJ, Derby CA. Mechanisms of association between obesity and chronic pain in the elderly. Pain 2011 Jan;152(1):53-9.

[40] Marshall WG, Hazewinkel, HA, Mullen D, De Meyer G, Baert K, Carmichael S. Vet Res Commun. The effect of weight loss on lameness in obese dogs with osteoarthritis. 2010 Mar;34(3):241-53

[41] Lomas AL, Grauer GF. The renal effects of NSAIDs in dogs. J Am Anim Hosp Assoc. 2015 May-Jun;51(3):197-203

[42] Innes JF, Clayton J, Lascelles BD. Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. Vet Rec. 2010 Feb 20;166(8):226-30.

[43] Monteiro-Steagall BP, Steagall PV, Lascelles BD. Systematic Review of Nonsteroidal Anti-Inflammatory Drug-Induced Adverse Effects in Dogs. J Vet Intern Med. J Vet Intern Med. 2013 Sep-Oct;27(5):1011-9.

[44] Muller C, Enomoto M, Meyers R, Steiner J, Lascelles BDX Randomized pilot trial of 'Movoflex' supplementation on biomarkers of inflammation in dogs with degenerative joint disease Comparative Pain Research Laboratory, NCSU; TAMU Gastrointestinal Research Laboratory

[45] Comblain F, Serisier S, Barthelemy N, Balligand M, Henrotin Y. Review of dietary supplements for the management of osteoarthritis in dogs in studies from 2004 to 2014. J Vet Pharmacol Ther. 2016 Feb;39(1):1-15

[46] Barbeau-Grégoire M, Otis C, Cournoyer A, Moreau M, Lussier B, Troncy E. A 2022 Systematic Review and Meta-Analysis of Enriched Therapeutic Diets and Nutraceuticals in Canine and Feline Osteoarthritis. Int J Mol Sci. 2022 Sep 8;23(18):10384.

[47] Fujiki M, Shineha J, Yamanokuchi K, Misumi K, Sakamoto H. Effects of treatment with polysulfated glycosaminoglycan on serum cartilage oligomeric matrix protein and C-reactive protein concentrations, serum matrix metalloproteinase-2 and -9 activities, and lameness in dogs with osteoarthritis. Am J Vet Res. 2007 Aug;68(8):827-33.

[48] Heidrich. Fluorescein-labeled polysulfated glycosaminoglycan in a feline acute traumatic knee model. 2008 VOS Proceedings.

[49] Read RA, Cullis-Hill D, Jones MP. Systemic use of pentosan polysulphate in the treatment of osteoarthritis. J Small Anim Pract. March 1996;37(3):108-14.

[50]Vandeweerd JM, Coisnon C, Clegg P, Cambier C, Pierson A, Hontoir F, Saegerman C, Gustin P, Buczinski S. Systematic review of efficacy of nutraceuticals to alleviate clinical signs of osteoarthritis. J Vet Intern Med. 2012 May;26(3):448-56.

[51] Corbee RJ, Barnier MM, van de Lest CH, Hazewinkel HA. The effect of dietary long-chain omega-3 fatty acid supplementation on owner's perception of behaviour and locomotion in cats with naturally occurring osteoarthritis. J Anim Physiol Anim Nutr (Berl). 2013 Oct;97(5):846-53

[52] Koltyn KF, Brellenthin AG, Cook DB, Sehgal N, Hillard C. Mechanisms of exercise-induced hypoalgesia. J Pain. 2014 Dec;15(12):1294-1304.

[53] Harper TAM. Conservative Management of Hip Dysplasia. Vet Clin North Am Small Anim Pract. 2017 Jul;47(4):807-821.

[54] Dycus DL, Levine D, Marcellin-Little DJ. Physical Rehabilitation for the Management of Canine Hip Dysplasia. Vet Clin North Am Small Anim Pract. 2017 Jul;47(4):823-850.

[55] Gruen ME, Lascelles BDX, Colleran E, Gottlieb A, Johnson J, Lotsikas P, Marcellin-Little D, Wright B. 2022 AAHA Pain Management Guidelines for Dogs and Cats. J Am Anim Hosp Assoc. 2022 Mar 1;58(2):55-76..

[56] Rodan I, Sundahl E, Carney H, Gagnon AC, Heath S, Landsberg G, Seksel K, Yin S; American Animal Hospital Association. AAFP and ISFM feline-friendly handling guidelines. J Feline Med Surg. 2011 May;13(5):364-75.

[57] Plumb's Veterinary Drug Handbook, 5th ed. Plumb DC, Blackwell Publishing Limited, 2005

[58] Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. *J Pain Symptom Manage* 2000;20:358-373.

[59] Collins S, Sigtermans MJ, Dahan A, Zuurmond WW, Perez RS. NMDA receptor antagonists for the treatment of neuropathic pain. Pain Med. 2010 Nov;11(11):1726-42.

[60] Lascelles BD, Gaynor JS, Smith ES, Roe SC, Marcellin-Little DJ, Davidson G, Boland E, Carr J. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. J Vet Intern Med. 2008 Jan-Feb;22(1):53-9.

[61] Madden M, Gurney M, Bright S. Amantadine, an N-Methyl-D-Aspartate antagonist, for treatment of chronic neuropathic pain in a dog. Vet Anaesth Analg. 2014 Jul;41(4):440-1

[62] Norkus C, Rankin D, Warner M, KuKanich B. Pharmacokinetics of oral amantadine in greyhound dogs. J Vet Pharmacol Ther. 2015 Jun;38(3):305-8.

[63] Vernier VG, Harmon JB, Stump JM, *et al*. The toxicologic and pharmacologic properties of amantadine hydrochloride. *Toxicol Appl Pharmacol* 1969;15:642-665

[64] Siao KT, Pypendop BH, Stanley SD, Ilkiw JE. Pharmacokinetics of amantadine in cats. J Vet Pharmacol Ther. 2011 Dec;34(6):599-604.

[65] Cao X, Nakamura Y, Wada T, Izumi-Nakaseko H, Ando K, Sugiyama A. Electropharmacological effects of amantadine on cardiovascular system assessed with J-Tpeak and Tpeak-Tend analysis in the halothane-anesthetized beagle dogs. J Toxicol Sci. 2016;41(3):439-47.
[66] Longmire DR, Jay GW, Boswell MV. Neuropathic Pain. In: Weiner's Pain Management, A Practical Guide for Clinicians, 7th ed. Boswell MV, Cole BE ed. Taylor & Francis, Boca Raton FL 2006, p. 305.
[67] Solak O, Metin M, et al, Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain, Eur J Cardiothorac Surg. 2007 Jul;32(1):9-12. Epub 2007 Apr 17
[68] Ahn SH, Park HW. Gabapentin effect on neuropathic pain compared among patients with spinal cord injury and different durations of symptoms. Spine. 2003 Feb 15;28(4):341-6; discussion 346-7
[69] Rowbotham M, Harden M. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998 Dec 2;280(21):1837-42
[70] Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther. 2003 Jan;25(1):81-104
[71] Lascelles BDX. Drug therapy for acute and chronic pain the cat. Int J Pharm Compounding. 2002;6:338-343.
[72] Plessas IN, Rusbridge C, Driver CJ, Chandler KE, Craig A, McGonnell IM, Brodbelt DC, Volk HA. Long-term outcome of Cavalier King Charles spaniel dogs with clinical signs associated with Chiari-like malformation and syringomyelia. Vet Rec. 2012 Nov 17;171(20):501.
[73] Wolfe KC, Poma R. Syringomyelia in the Cavalier King Charles spaniel (CKCS) dog. Can Vet J. 2010 Jan;51(1):95-102.
[74] Rusbridge C, Heath S, Gunn-Moore DA, Knowler SP, Johnston N, McFadyen AK. Feline orofacial pain syndrome (FOPS): a retrospective study of 113 cases. J Feline Med Surg. 2010 Jun;12(6):498-508.
[75] Lu Y, Westlund K. Gabapentin Attenuates Nociceptive Behaviors in an Acute Arthritis Model in Rats JPET 290:214–219, 1999
[76]Hanesch U, et al Gabapentin reduces the mechanosensitivity of fine afferent nerve fibres in normal and inflamed rat knee joints. Pain. 2003 Jul;104(1-2):363-6
[77] Boileau et al, Oral treatment with PD-0200347, an alpha2delta ligand, reduces the development of experimental osteoarthritis by inhibiting metalloproteinases and inducible nitric oxide synthase gene expression and synthesis in cartilage chondrocytes, Arthritis Rheum 2005 Feb; 52(2):488-500
[78] Plessas IN, Rusbridge C, Driver CJ, Chandler KE, Craig A, McGonnell IM, Brodbelt DC, Volk HA.
Long-term outcome of Cavalier King Charles spaniel dogs with clinical signs associated with Chiari-like malformation and syringomyelia. Vet Rec. 2012 Nov 17;171(20):501.
[79] Wolfe KC, Poma R. Syringomyelia in the Cavalier King Charles spaniel (CKCS) dog. Can Vet J. 2010 Jan;51(1):95-102.
[80] Cashmore RG, Harcourt-Brown TR, Freeman PM, Jeffery ND, Granger N. Clinical diagnosis and treatment of suspected neuropathic pain in three dogs. Aust Vet J. 2009 Jan-Feb;87(1):45-50
[81] Clare Rusbridge1, Sarah Heath, Danièlle A Gunn-Moore, Susan Penelope Knowler, Norman Johnston, Angus Kennedy McFadyen. Feline orofacial pain syndrome (FOPS): a retrospective study of 113 cases. J Feline Med Surg. June 2010;12(6):498-508.
[82] Guillot M, Taylor PM, Rialland P, Klinck MP, Moreau MM, Martel-Pelletier J, Pelletier JP, Troncy E. Evoked temporal summation in cats to highlight central sensitization related to osteoarthritis-associated chronic pain: a preliminary study. PLoS One. 2014 May 23;9(5):e97347.
[83] Lorenz ND, Comerford EJ, Iff I. Lorenz 2012: Long-term use of gabapentin for musculoskeletal disease and trauma in three cats. J Feline Med Surg. 2012 Dec 19.
[84] Kukanich B, Cohen RL Pharmacokinetics of oral gabapentin in greyhound dogs. Vet J. 2009 Oct 22
[85]Vollmer KO, Parmacokinetics and metabolism of gabapentin in rat, dog and man, Arzneimittelforschung, 1986; 36(5):830-9
[86] Radulovic LL, Türck D, von Hodenberg A, et al. Disposition of gabapentin (neurontin) in mice, rats, dogs, and monkeys. Drug Metab Dispos. 1995 Apr;23(4):441-8.
[87] Siao KT, Pypendop BH, Ilkiw JE. Pharmacokinetics of gabapentin in cats. Am J Vet Res. 2010 Jul;71(7):817-21.
[88] Salazar V, Dewey CW, Schwark W, Badgley L, Gleed RD, Horne W, Ludders JW. Pharmacokinetics of single-dose oral pregabalin administration in normal dogs. Vet Anaesth Analg. 2009 Nov;36(6):574-80.

[89] Plessas IN, Rusbridge C, Driver CJ, Chandler KE, Craig A, McGonnell IM, Brodbelt DC, Volk HA. Long-term outcome of Cavalier King Charles spaniel dogs with clinical signs associated with Chiari-like malformation and syringomyelia. Vet Rec. 2012 Nov 17;171(20):501.

[90] Budsberg SC, Torres BT, Kleine SA, Sandberg GS, Berjeski AK. Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis. J Am Vet Med Assoc. 2018 Feb 15;252(4):427-432.

[91] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000572/WC500036776.pdf

[92] Baek IH, Lee BY, Kang W, Kwon KI. doi: 10.1055/s-0033-1341493. Epub 2013 Apr 18. Pharmacokinetic analysis of two different doses of duloxetine following oral administration in dogs. Drug Res (Stuttg). 2013 Aug;63(8):404-8.

[93] Sullivan M, Bentley S, Fan MY, Gardner G. A single-blind placebo run-in study of venlafaxine XR for activity-limiting osteoarthritis pain. Pain Med. 2009 Jul-Aug;10(5):806-12.

[94] Howell SR, Hicks DR, Scatina JA, Sisenwine SF. Pharmacokinetics of venlafaxine and O-desmethylvenlafaxine in laboratory animals. Xenobiotica. 1994 Apr;24(4):315-27.

[95] Webster RP1, Anderson GI, Gearing DP. Canine Brief Pain Inventory scores for dogs with osteoarthritis before and after administration of a monoclonal antibody against nerve growth factor. Am J Vet Res. 2014 Jun;75(6):532-5.

[96] Vet Rec. 2018 Oct 27. pii: vetrec-2017-104590

[97] Vilar JM1, Batista M, Morales M, Santana A, Cuervo B, Rubio M, Cugat R, Sopena J, Carrillo JM. Assessment of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells in osteoarthritic dogs using a double blinded force platform analysis. BMC Vet Res. 2014 Jul 1;10:143.

[98] Vilar JM, Morales M, Santana A, Spinella G, Rubio M, Cuervo B, Cugat R, Carrillo JM. Controlled, blinded force platform analysis of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells associated to PRGF-Endoret in osteoarthritic dogs. BMC Vet Res. 2013 Jul 2;9:131.

[99] Upchurch DA, Renberg WC, Roush JK, Milliken GA, Weiss ML. Effects of administration of adipose-derived stromal vascular fraction and platelet-rich plasma to dogs with osteoarthritis of the hip joints. Am J Vet Res. 2016 Sep;77(9):940-51.

[100] Vilar JM, Manera ME, Santana A, Spinella G, Rodriguez O, Rubio M, Carrillo JM, Sopena J, Batista M. Effect of leukocyte-reduced platelet-rich plasma on osteoarthritis caused by cranial cruciate ligament rupture: A canine gait analysis model. PLoS One. 2018 Mar 19;13(3):e0194752.

[101] Marx C, Silveira MD, Selbach I, da Silva AS, Braga LM, Camassola M, Nardi NB. Acupoint injection of autologous stromal vascular fraction and allogeneic adipose-derived stem cells to treat hip dysplasia in dogs.

[102] Wanstrath AW, Hettlich BF, Su L, Smith A, Zekas LJ, Allen MJ, Bertone AL. Evaluation of a Single Intra-Articular Injection of Autologous Protein Solution for Treatment of Osteoarthritis in a Canine Population. Vet Surg. 2016 Aug;45(6):764-74.

[103] Iadarola MJ, Sapio MR, Raithel SJ, Mannes AJ, Brown DC. Long-term pain relief in canine osteoarthritis by a single intra-articular injection of resiniferatoxin, a potent TRPV1 agonist. Pain. 2018 Oct;159(10):2105-2114.

[104] Dycus DL, Levine D, Marcellin-Little DJ. Physical Rehabilitation for the Management of Canine Hip Dysplasia. Vet Clin North Am Small Anim Pract. 2017 Jul;47(4):823-850.

[105] Sullivan MO, Gordon-Evans WJ, Knap KE, Evans RB. Randomized, controlled clinical trial evaluating the efficacy of pulsed signal therapy in dogs with osteoarthritis. Vet Surg. 2013 Apr;42(3):250-4.

[106] LaFond E, Breur GJ, Austin CC. Breed susceptibility for developmental orthopedic diseases in dogs. J Am Anim Hosp Assoc. 2002 Sep-Oct;38(5):467-77.

[107] Canapp SO, Canapp DA, Carr BC, Cox C, Barrett JG. Supraspinatus Tendinopathy in 327 Dogs: A Retrospective Study. Vet Evid. September 2016;1(3):32. 1-14.

[108] Devor M, Sorby R: Fibrotic contracture of the canine infraspinatus muscle. Vet Compar Orthop Traumatol 2006 Vol 19 (2) pp. 117-21.

[109] Stobie D, Wallace LJ, Lipowitz AJ, King V, Lund EM. Chronic bicipital tenosynovitis in dogs: 29 cases (1985-1992). J Am Vet Med Assoc. July 1995;207(2):201-7.

[110] Hamilton M. Musculotendinous Injuries in the Hindlimb . Br Small Anim Vet Cong 2018.

[111] Corr SA, Draffan D, Kulendra E, Carmichael S, Brodbelt D. Retrospective study of Achilles mechanism disruption in 45 dogs. Vet Rec. 2010 Sep 11;167(11):407-11.
[112] Cabon Q, Bollinger C. Iliopsoas injury in dogs. Compend Contin Educ Vet. 2013 May;35(5):E2.
[113] Kowaleski MP: Diseases of ligaments and joints. In Morgan RV (ed): Handbook of Small Animal Practice. 5th Ed. Saunders Elsevier, ST. Louis, MO 2008 pp. 764-765.
[114] Bergknut N, Egenvall A, Hagman R, et al: Incidence of intervertebral disk degeneration-related diseases and associated mortality rates in dogs. J Am Vet Med Assoc 2012 Vol 240 (11) pp. 1300-9.
[115] Jeffery ND, Levine JM, Olby NJ, et al: Intervertebral disk degeneration in dogs: consequences, diagnosis, treatment, and future directions. J Vet Intern Med 2013 Vol 27 (6) pp. 1318-33
[116] Meij BP, Bergknut N: Degenerative lumbosacral stenosis in dogs. Vet Clin North Am Samll Anim Pract 2010 Vol 40 (5) pp. 983-1009.
[117] Ru G, Terracini B, Glickman L T: Host related risk factors for canine osteosarcoma. Vet J 1998 Vol 156 (1) pp. 31-39.
[118] Mackin A: Immune-Mediated Polyarthritis. Pacific Veterinary Conference 2016.
[119] Goldberg ME. Top 5 most common orthopedic conditions in dogs. August 2015 Vet Team Brief Aug 2015 p 27-30
[120] Spugnini EP, Vincenzi, B, Caruso G, Baldi, A, Citro G, Santini D, Tonini G. Zoledronic acid for the treatment of appendicular osteosarcoma in a dog. Case Reports J Small Anim Pract. 2009 Jan;50(1):44-6.

CPR BASIC LIFE SUPPORT (BLS) GUIDELINES BASED ON THE RECOVER (REASSESSMENT CAMPAIGN ON VETERINARY RESUSCITATION) INITIATIVE

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SMALL ANIMAL

SEDATION & ANALGESIA FOR THE EMERGENCY CRITICAL CARE PATIENT

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PATHOPHYSIOLOGY OF PAIN AND MALADAPTIVE PAIN SYNDROMES

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Pathophysiology of Pain and Maladaptive Pain Syndromes
Kansas State Univ 2024

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In the last 10 years, the veterinary profession has undergone what can only be described as a sea change in perspectives about animal pain and pain control. In many ways the issue of pain management in animals closely parallels that in human pediatrics, whereby the patient is non-verbal and the clinician must rely on personal/staff observations and the reports of the patient's advocate (in some ways this parallel extends to human geriatrics, whereby the patients may be once again non-verbal and a caregiver is the patient's advocate). Thus it is that physicians have also long struggled with the critique of under-managing pain in children[1],[2] the cognitively impaired,[3] and the elderly.[4],[5]

Under- (or un-) managed pain elicits a cascade of debilitating neuro-hormonal effects that result in hypertension, catabolism, immunosuppression, and in what can be a terminal event, bacterial translocation and sepsis. This is called the "stress response." With under- (or un-) managed pain, patients at best recover more slowly from their condition, and at worst, may develop severe, even life-threatening complications.

However, the effect is not limited to pain of an acute nature. In addition to discomfort and physical disability, the capacity of chronic pain to impair cognition is becoming increasingly recognized in humans. A global summary of statistically significant findings in 42 studies of patients with chronic musculoskeletal pain revealed that deficits of memory, attention, psychomotor speed, and mental flexibility all can be attributed as a consequence of chronic pain, independent of other causes.[6] In animals, for all of these reasons, under-attended, under-managed pain can become a criterion for euthanasia.

Pain itself is normal, and when physiologic it is protective. But undermanaged pain, as it becomes extended in time and intensity, becomes maladaptive and debilitating. And the younger the patient, the more long-term consequences of undermanaged pain because of the enhanced plasticity of the spinal cord: hypersensitivity to thermal stimuli can be documented years after the initial sets of painful experiences in both animals and humans.[7] Thus for clinicians in a veterinary practice, their staff, and their clients, the first step to developing an aggressive, integrative pain management system is to internalize how dangerous and damaging undermanaged pain is to their patients. In fact, until so convinced, stocking drugs on a shelf and writing down protocols stands little chance of successful hospital-wide implementation.

The neuro-anatomic, physiologic, and molecular basis of nociception is a rapidly evolving field of study. Once-simple models are now understood to be highly complex and supremely inter-related sets of dynamics. The "Gate Control Theory", offered in 1965 by Melzak and Wall, proposes a feedback mechanism that controls activation of pain fibers by allowing or inhibiting impulses through the "gate."[8] Nothing that we now understand about nociception challenges the basic operational premise of the Gate Theory. What is new and growing is the illumination of its details.

Nociceptors are specialized nerve fibers that have their dendritic endings in peripheral tissue, with several different subtypes identified. These nerve fibers have receptors that respond to mechanical and chemical stimuli but may be polymodal for touch, pressure, heat, cold, itch, and other sensations. When activated by the appropriate stimulus, a signal is said to be *transducted*, and the nerve endings depolarize. The signal is then conducted, or *transmitted*, electrobiochemically in an afferent direction, that is, towards the spinal cord. There, in the dorsal horn, the signal is *modulated*, that is either enhanced or dampened. Synapses are made with secondary neurons which ascend up the spinothalamic tract of the spinal cord to the thalamus, where another synapse occurs with tertiary neurons, which then project to the

cerebral cortex where *perception* occurs. However, in addition to these ascending pathways to the brain are descending, inhibitory pathways; and under the proper conditions conduction can occur from the spinal cord down the peripheral nerve fibers in an anti-dromic fashion to the site of original transduction.

The fastest of the nerve fibers are the small but fully-myelinated A-beta sensory fibers which involve the sensations of touch, pressure, vibration, and proprioception. Somewhat slower are the thinly-myelinated A-delta fibers which stem from mechano-, thermo-, and nociceptors involved in sharp physiologic and acute pain. C-fibers are large and unmyelinated and hence very slow conductors of mechanoreceptors and nociceptors involved in dull, aching chronic pain. From somatic sites the cell bodies of these nerve fibers are located in the dorsal root ganglia, and from visceral sites, the sympathetic ganglia. The terminal endings of these fibers are highly tropic in the dorsal horn, with somatic A-delta and C fibers occurring in the most dorso-lateral aspect (Laminae I and II), somatic A-beta fibers terminating in the deeper Laminae II, IV, and V, and visceral A-delta and C fibers scattered throughout each of these Laminae.[9] However, the tropism, inter-connectivity, and even phenotype of these various neurons is not static, rather the dorsal horn can exhibit dramatic plasticity, changing and altering form and function depending on a wide variety of factors: age (the younger the more plasticity), type and duration of stimulus, gender (or sexual status i.e. presence or absence of androgenic hormones), and others.

At the peripheral site of transduction, stimulus comes in the form of heat (transient vanilloid receptor 1, TRPV1), cold (cold- and menthol receptor 1, CMR1), membrane distortion, or cell damage releasing fatty acids and free ions from cell membranes. Each of these stimuli open non-specific cation channels on the peripheral endings of A-delta and C-fibers, which allows an inward Na+, K+, or Ca+ current. When a critical threshold of intracellular Na+ and/or Ca+ is reached, then activation and opening of voltage-gated cation channels occurs, which propagates depolarization afferently along the nerve fiber membrane.[10] In addition, the free fatty acids are catalyzed by phospholipase-A2 into arachadonic acid, providing the substrate for cyclo-oxygenase metabolism and the initiation of the inflammatory cascade through a number of mediators e.g. prostaglandins, H+ ions, cholecystikinin, histamines, Substance P, bradykinins, leukotrienes, and many more,[11] all highly noxious stimuli that bind to their own receptors on the nociceptor nerve ending, exacerbating or continuing the cation influx. The peripheral nerve fiber transmits its signal to the spinal cord, terminating in the dorsal horn.

In the dorsal horn, the nociceptors terminate and release various highly bioactive molecules across synapses to interneurons (also called *second-order* neurons). Chief among many of these in the classic model is the excitatory amino acid glutamate, which binds to AMPA receptors on the interneuron. This binding causes a sodium/potassium channel to open, allowing Na+ to flow freely through the cell membrane into cytoplasm (and K+ out into the extracellular space), which elicits an action potential: the interneuron depolarizes and the impulse is transmitted afferently to the brain. However, as quickly as it opens, an AMPA receptor will close, unless the stimulus is sustained. If the stimulus is in fact sustained, not only will the AMPA receptor remain open, but the accumulation of intracellular Na+, will phosphorylate adjacent NMDA receptors, releasing a magnesium “plug.” The NMDA receptor is now open and free to allow calcium to inflow into the neuron, further depolarizing it for an extended period of time.[12] NMDA activation is now well-established in its role of potentiating hypersensitization and neuropathic pain.[13]

The second-order, or projection neurons, upon which the peripheral A- and C-fibers synapse, are characterized as wide dynamic range (WDR, sensitive to a variety of sensations, including pain) and nociceptive-specific (NS, pain-only) neurons. They ascend the spino-thalamic tract to terminate in the thalamus, with projections (via third-order neurons) to the reticular, limbic, homeostatic-control, and cortical somatosensory regions of the brain[14]. Here the spatial and temporal qualities of pain become more than an unpleasant sensation, but transcends to a physical and emotional experience as well.

Inhibitory neurons, some intraspinal and some descending from the brain, synapse on the second-order neurons as well. Here the neurotransmitters are inhibitory in nature and include gamma amino butyric acid (GABA), norepinephrine (NE), certain serotonins (5-HT3), B-endosyn, and others[15]. Furthermore, circulating endogenous opioids bind to kappa and delta (less so mu) receptors (closing Ca+ channels, and opening K+ channels, respectively), hyperpolarizing the cell. A basal level of interconnectivity occurs between afferent A-beta, A-delta, C-fibers, interneurons, and intra- and descending inhibitory neurons.[16] Lastly, the supporting glial cells (astrocytes, microglia, oligodendrocytes) in the spinal cord, whose purpose was once thought to be merely structural in nature (providing synaptic architecture, host defense, and myelin, respectively), are now thought to be highly integrated into the pain process, particularly with regards to chronic pain.[17] Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal terminal.[18] A recently isolated chemokine, fractalkine, appears to be a neuron-glial cell signal, activating glially-dependent pain facilitation (in a recent rat model, blocking the one known fractalkine receptor in rats diminished the development of neuropathic pain).[19] Indeed, the glia may play a primary role with regards to synaptic strength, plasticity, and sensitization in the spinal cord, which does exhibit substantial change under the influence of chronic pain.[20]

Sustained nociception begins to alter the dynamic considerably, and pain can quickly move from its physiologic, protective nature to a maladaptive one. The constant presence of inflammatory and bioactive mediators at a peripheral site forms a “sensitizing soup” that creates a constant barrage of excitatory neurotransmitters in the dorsal horn. The opening of the calcium channel begins a cascade of events that in some cases becomes irreversible. An influx of calcium ion causes activation of Protein Kinase C (PKC), which in turn elicits production of nitrous oxide (NO), which then diffuses back across the synapse and through the terminal ending of the afferent nociceptor. This causes K+ channels to close and also the production of Substance P, a profoundly excitatory bioactive molecule, which then flows back across the synapse once more to bind on neurokinase (NK-1) receptors of the interneuron[21] (expression of the NK-1 receptor appears to also contribute to opioid-induced hyperalgesia and tolerance[22]). Not only does the interneuron stay depolarized, but a phenotypic change may be induced where it may not reset. Expression of *c-fos*, *c-jun*, and *Knox-24* genes transcribe new (probably aberrant) proteins that produce permanent microstructural changes of the neuron that result in reduced firing threshold, upregulation of central neuronal activity, downregulation of inhibitory activity, expansion of the receptive field, peripheral hypersensitivity and intensified pain responses to further stimulation.[23]

Furthermore, the afferent nociceptor will conduct a signal efferently, in an anti-dromic fashion. There, at the peripheral site of original stimulus, it releases Substance P and calcitonin gene-related peptide (CGRP), another highly bioactive excitatory compound, which elicits further release of inflammatory mediators and recruiting and activating other previously innocent-bystanding nociceptors, further bombarding the dorsal horn with impulses.[24] As the feedback loop persists, more and more cells express *c-fos* and other genes, Nerve Growth Factor is stimulated into production (suspected to be from glial cells), and more interconnections are made between types and locations of neurons in the spinal cord.[25] These interconnections are not isolated to somatosensory neurons, for they have been shown to newly express adrenoceptors which are activated by catecholamines. Sympathetic stimulation may then result in nociception,[26],[27] and may in fact be central to the pathophysiology of neuropathic pain. Moreover, neuropathic pain is associated with alterations in receptor location (more places on more axons) and sensitivity to excitatory amino acids (greater) throughout the nervous system.[28] Eventually, when the process of pain is located centrally (in the spinal cord) rather than at the site of the original stimulus, the pain is said to be “neuropathic” in origin. Once neural pathways are thus sensitized, the physiologic (and physical) responses to pain may persist, even when the peripheral nerves themselves are blocked (or even transected).[29] Clearly, at this point, pain has become a disease unto itself.

Summary of terminology used to describe this sensitized state:
Peripheral hypersensitization: generation of an ever-present "sensitizing soup" of inflammatory mediators (prostaglandins, bradykinin, cytokines, neuropeptides), activation of quiescent (silent/sleeping) bystanding nociceptors from non-injured tissue, reduction of threshold in normally-high threshold nociceptors.

Central hypersensitization: increase in the excitability of neurons in dorsal horn of spinal cord, cumulative depolarization ("wind up") amplifying the neuronal activity in dorsal horn, generation of Nerve Growth Factor which promotes interconnections between formerly segregated types and locations of neurons, expression of new receptors, and phenotypic modification of nerve function.

Neuropathic pain: the extension of hypersensitization which is the initiation of transmitting a pain impulse (spontaneous depolarization) in the absence of noxious stimuli, or out of proportion to it.

In both acute and chronic pain, other non-neural peripheral tissues are not exempt from physical changes as well. Reflex muscular spasms are not only themselves painful, they may compromise vascular supply, and the resulting ischemia can result in release hydrogen ions and ATP, which are also highly sensitizing agents. This can result in altered, maladaptive conformation and gait, leading to abnormal stresses on ligament, tendon, cartilage, as well as and hyperirritable bands of contracted muscle (myofascial trigger points, TrP).[30]

Glial cells (astrocytes, microglia, oligodendrocytes) in the spinal cord, whose purpose was once thought to be merely structural and macrophage-like in nature (providing synaptic architecture, host defense, and myelin, respectively), are now thought to be highly integrated into the pain process, particularly with regards to chronic pain.[31] Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal terminal.[32] A recently isolated chemokine, fractalkine, appears to be a neuron-glial cell signal, activating glially-dependent pain facilitation (in a recent rat model, blocking the one known fractalkine receptor in rats diminished the development of neuropathic pain).[33] Indeed, the glia may play a primary role with regards to synaptic strength, plasticity, and sensitization in the spinal cord, which does exhibit substantial change under the influence of chronic pain.[34] There is no one moment when pain is transformed from physiologic to "acute" to "chronic" to "hyperesthetic" to "allodynic" to "neuropathic". Rather it exists on a continuum with a high degree of biologic variation from patient to patient. There is also recent evidence that anxiety in the acute setting, mediated by cholecystikinin rather than mobilization of the hypothalamic-pituitary-adrenal axis, plays a major role in creating a chronic, hyperalgesic state.[35]

Historically, the focus of analgesia has been to diminish transduction (e.g. local anesthesia, anti-inflammatories) and perception (e.g. opioids), and indeed these remain crucial components of a multi modal approach to pain management. The most exciting area of attention today however is in the dorsal horn, by enhancement of inhibitory modulation of nociception and interrupting the feedback loop that results in exaggerated pain responses and perception. As greater understandings emerge of the molecular and physiologic bases of pain emerges, new opportunities for intervention also emerge.[36]

Clinical Features and definitions of Neuropathic Pain state:

- Hyperesthesia: exaggerated pain out of proportion to a noxious stimulus
- Allodynia: pain from a non-noxious stimulus (e.g. touch, pressure)
- Extended duration: pain persisting past the time of expected tissue inflammation and healing
- Expanded field: pain at site(s) distant to the damaged tissue
- Spontaneous pain: in the absence of known tissue injury

- Dysesthesias: pain with other sensations including itch, tingling, even numbness
- Exaggerated character of pain: stabbing, "lancinating" (cutting, piercing), radiating, pulsing, burning
- Sympathetic signs: pain that worsens with stress, or the painful site exhibits autonomic signs (vasodilation, edema, vasoconstriction, etc.)

What might this look like in a dog or cat?

Think of the cat that:

- no longer wishes to be stroked or petted, or have feet touched
- grooms less
- conversely, abruptly grooms, perhaps down to extremity, or chronically overgrooms a region
- dislikes being held, objects to restraint
- spontaneously rubs its mouth
- reacts to (runs from) an invisible stimulus
- spontaneous panniculus

And dog or cat that:

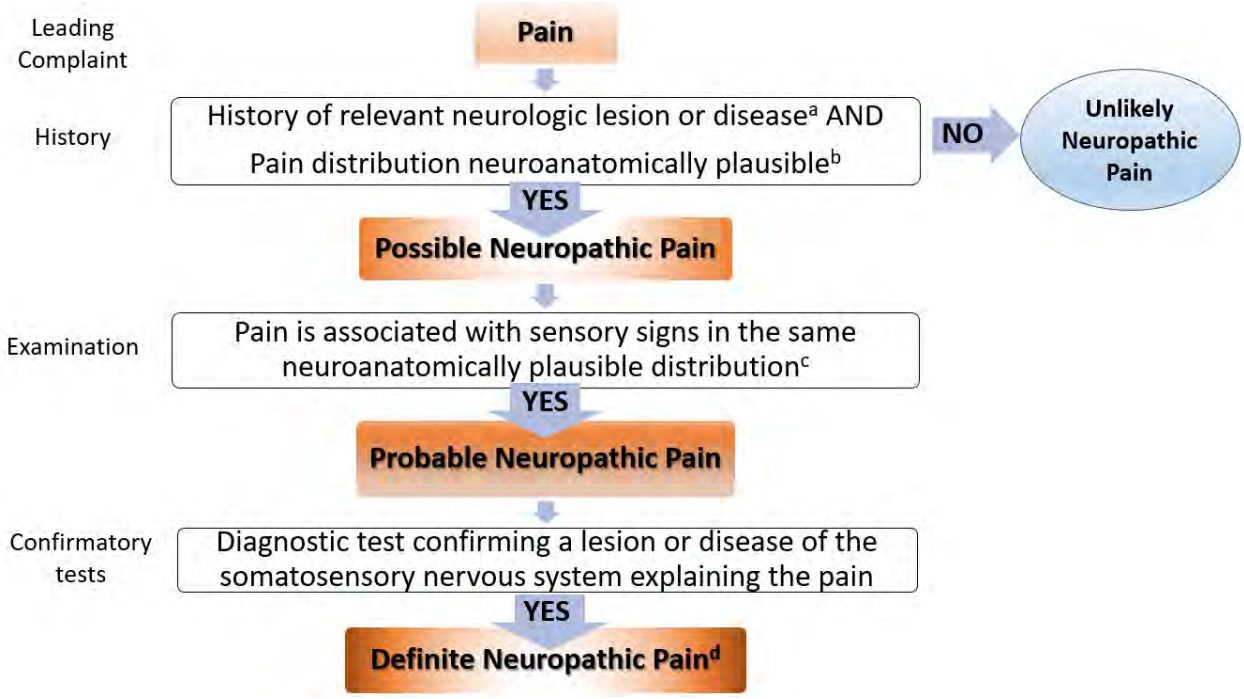
- exhibits avoidance behavior
- increasingly objects to nail trims and/or venipuncture
- progressively interacts less with owners
- or becomes increasingly grouchy/self-defensive

Diagnosis in Humans, Diagnosis in Animals

Confirming neuropathic pain in humans involves validated self-reporting questionnaires and Quantitative Sensory Testing (QST). Some patients may be assumed to have neuropathic pain if they are diagnosed with a known such condition e.g. post-herpetic neuralgia (Shingles) or diabetic neuropathy. Intermediary criteria have been established, wherein a patient showing some of 8 criteria is described as having "possible," "probable," or (if 5 of 8 are present) "definite" neuropathic pain.[37] Since it exists along a spectrum, another descriptor is that a patient may have "pain with a neuropathic component" (PNC).

A grading system in humans defines criteria for neuropathic pain on a probability spectrum (Figure 1).[38] In this schema, history and clinical observations are enough to speculate that a patient has "possible" neuropathic pain. Additional examination may reveal signs consistent with "probable" neuropathic pain, and confirmatory testing (often advanced diagnostics not available to the clinical generalist) can lend a diagnosis of "definite" neuropathic pain; however (and importantly), *known direct nerve damage qualifies as a confirmatory test.*

Figure 1



From: Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain. 2016;157(8):1599-606.

In dogs and cats, validated Clinical Metrology Instruments (CMIs) exist for post-operative and chronic osteoarthritis-related pain (See Chapter XX Steagall, or Chapter XX Monteiro). However, none of these specifically address the presence or absence of a neuropathic pain component. A semi-objective sensory testing rubric for hyperalgesia and allodynia in dogs and cats has been proposed (Table 1).

Table 1: Semi-objective sensory testing in dogs and cats[39]	
Hyperalgesia: Produces exaggerated response in affected area compared to unaffected	Allodynia: Normally non-painful but elicits pain in affected area compared to unaffected
Manual pinprick w/ needle	Manual light pressure
Thermal cold (acetone, cold metal 0°C)	Light manual prick (sharpened wooden stick, stiff von Frey hair)
Thermal heat (object at 46°C)	Stroking (brush, gauze, cotton applicator)
Algometry: lowered threshold and tolerance	Thermal cool (objects at 20°C)
	Thermal warm (objects at 40°C)

QST, although not a "pain measurement" per se, evaluates sensory changes (gain or loss of function) elicited in and contributing to a pain state with central and/or peripheral sensitization. QST modalities include mechanical and thermal threshold analyses among others. Current work with QST is beset by a lack of standardization of instruments, modalities, methods, and outcome measures used. Such standardization in veterinary patients must be established before QST can become a clinical cage-side tool.

Prevalence of Neuropathic Pain in Dogs & Cats

One study in a teaching hospital evaluated cats for the presence of pain with neuropathic features. Among outpatients, 92 of 652 (14%) cats and 20% of dogs exhibited pain, with 1/3 – ½ of these (7-8%%) exhibiting a neuropathic component for 1 to 12 months (1% experienced pain >1 year) [40]

This represents a somewhat similar prevalence as found in the human general population (6.9-10%)[41] although some specific sub-populations have much higher rates. In the emergency setting, 23% of both cats and dogs experienced a combination of inflammatory and neuropathic pain.[42]

Recognized or Suspect Neuropathic Pain Conditions in Dogs and Cats[10]

- Feline Orofacial Pain Syndrome (FOPS)[43] – characterized by episodic, spontaneous unilateral pawing at the mouth, excessive and exaggerated licking movements, growling when eating, drinking, or grooming, and food aversion anorexia. More severe cases will involve self-mutilation of tongue, lips, and buccal mucosa. In the UK there appears to be genetic disposition (Burmese cats, < 1year old). In the USA it has been observed in many breeds (excluding Burmese cats, the median age of onset is 9 years old), and a majority (63%) were associated with erupting teeth or oral pathology such as odontoclastic resorptive lesions, periodontal disease, lymphoplasmacytic gingivitis/stomatitis, and post-extraction surgery. Environmental stress may precipitate episodes. Understanding at the present time suggests a neuropathic pain condition analogous to trigeminal neuralgia and/or glossodynia in humans, with involvement from the sympathetic nervous system (SNS).

- Feline Hyperesthesia Syndrome (FHS)[44] - characterized by skin twitching and muscle spasm in the lumbar area, licking of lumbar, flank, tail regions, tail-chasing, exaggerated response to a non-noxious stimulus (e.g., stroking), and reactive (including vocalization) avoidance behavior to a non-apparent stimulus. In extreme cases, a non-noxious stimulus can elicit a seizure-like tetany response or self-mutilation (especially of the tail). Affected cats are generally younger (median age 1 year, range 1-7years) and male cats (both intact and altered) may be overrepresented. Episodes are intermittent, ranging from several times per day or per week. Proposed etiologies include an idiopathic focal epilepsy, primary (and idiopathic) neuropathic pain disorders,

- Feline Idiopathic/Interstitial/Sterile Cystitis (FIC, FSC)[45] - under various names, including Pandora Syndrome for its complex (and evil) nature,[46] this condition mirrors an analogous syndrome in women (Interstitial Cystitis, IC) more broadly called Bladder or Pelvic Pain Syndrome (BPS, PPS). Indeed the term “cystitis” is inappropriate, since significant inflammation is not a feature of the condition in cats or humans.[23] In both species there are similar clinical signs and abnormalities of afferent sensory neurons (lowered firing threshold, recruitment of otherwise “silent” mechanoreceptors; and increased norepinephrine (NE) content and activity in bladder wall,[47] increased peripheral nerve and CNS excitability[48], enhanced sympathetic efferent neuronal function, upregulation of bladder mucosal Substance P and NK-1 receptors.[49] The result of this cascade represents peripheral and central hypersensitization along with disrupted epithelial excretion of glycosaminoglycan (GAG). Several subtypes of lower urinary tract disease are described in both cats and women, but both species almost always express a Type 1, non-ulcerative form that is considered neuropathic in origin.[50] The complex etiology appears to include early-life (both pre- and postnatal) stressors, presumptively due to a strong sympathetic

response on the developing pituitary-adrenal axis and high plasticity of the developing CNS. Later in life, chronic activation of the central threat response system (CTRS), the condition becomes a clinical entity and can involve other extra-bladder comorbidities in addition to their LUT signs.[51] Fundamentally, FIC and IC appear to represent a neuropathic phenomenon whereby the SNS gets wired into nociceptive pathways.

- Feline herpesvirus[52] - Post-herpetic neuralgia (PHN, Shingles) is an extremely common and painful neuropathic pain condition in humans. Herpes zoster virus infects and damages peripheral nerve endings creating the cascade of sensitization events characteristic of peripheral nerve injury. Viral activation elicits painful erupting skin lesions most often on the back, neck, and face; however, the hyperalgesia and allodynia of PHN can be present without the dermatologic lesions. Cats are infected by a different virus, FHV-1, but it shares similarities including permanency of infection, propensity to re-activation, and dermatoses. These lesions are often mistaken for a variety of other dermatologic conditions including military dermatitis, eosinophilic granuloma complex, pemphigus, dermatophytosis, and squamous cell carcinoma. Biopsy, dermatohistopathology and PCR can correctly identify lesions that are herpetic in origin.[53] Treatment focuses on antiviral therapy and managing secondary bacterial infection. Although the degree of discomfort cannot be known with certainty, it is most likely not minor and analgesic strategies should be considered.

- Feline gingivostomatitis (FGS) - FGS is a common, often severe and refractory disorder of uncertain etiology but thought to involve an immune-mediated response to dental plaque and correlated with a variety of organisms with indeterminate causality.[54] FGS can be exquisitely painful, and it is plausible, if not likely, that peripheral and central sensitization processes are involved (to include an anti-dromic, efferent neurogenic component, contributing to a self-perpetuating viscous cycle of inflammation causing pain, and pain worsening inflammation).

- Osteoarthritis (OA) - Many experimental models demonstrate that OA can be accompanied by peripheral[55] and central[56] sensitization consistent with a neuropathic component. In humans with OA, approximately 25% have a neuropathic component to their pain.[57] A study of cats with *hip* OA identified temporal summation and a lower mechanical threshold in the *feet* of 25% of the patients.[58] This study illustrates two classic features of peripheral and central sensitization: increased tactile sensitivity, and expanded field (distant from the affected site).

- Syringomyelia (Chiari-like Malformation)[59] – a congenital condition especially affecting the Cavalier King Charles Spaniel, the CNS maldevelopment is essentially “punched out” lesions in the spinal cord (especially cervical) and brain, eliciting exquisite neuropathic pain symptoms.

- Inflammatory Bowel Disease (IBD)[60] - The chronic inflammatory state of IBD produces an ongoing afferent barrage of visceral nociceptors producing changes in the dorsal horn of the spinal cord consistent with central sensitization. Furthermore, intestinal high- and low-threshold mechanoreceptors can undergo a phenotypic alteration into nociceptive function, with normal motility eliciting visceral pain. Chronicity may also elicit a neurogenic component to the pathophysiology: neurons begin to carry efferent signals from the dorsal horn back to the intestine, enhancing inflammation. In humans, IBDs are characterized by debilitating painful flare-ups (presumably from cross-innervation with the SNS), and are comorbid with other hyperalgesic syndromes such as Interstitial Cystitis (now more accurately called Urologic Pelvic

Pain syndrome).[61] The extent to which cats and dogs with IBD experience visceral pain, "cramping," and/or hyperalgesia may be difficult to discern.

- Pancreatitis (acute and chronic[62]) - Abdominal pain is a classic feature of acute and chronic pancreatitis in humans; it is less well appreciated in cats. In humans the "neuro-immune" response is especially robust in pancreatitis (and pancreatic cancer) leading to remarkable visceral discomfort. Inflammatory cells and a unique brew of local neurotrophins and neuropeptides active pancreatic afferent nociceptors leading to central changes consistent with hypersensitization and somatic neuropathic pain disorders. Due to the diffuse projections of afferent nociceptors in the spinal cord, pain may not be confined to the upper/cranial right quadrant where the pancreas is located; humans with pancreatitis (and cholecystitis; perhaps similar to feline "triaditis") report pain in the back and even the shoulder. Additionally, as with other inflammatory states, a neurogenic component may additionally contribute to the pathophysiology of pancreatitis.

- Diabetic Neuropathy (DN) - In humans with diabetes mellitus (DM), DN is so common and debilitating that several drugs are labeled specifically for this indication. Reported sensations include walking on glass shards or barbed wire, and spontaneous tingling and itch without evoked stimulus; these signs are also reported in the hands (i.e., "Diabetic Hand and Foot Syndrome"). In cats (less so in dogs, but may be under-appreciated), DM is associated with motor neuropathy and a classic plantigrade stance in the rear legs (less often in the forelimbs) and a posture and gait associated with generalized weakness. However, classic sensory neuropathic changes in peripheral nociceptors and along the entire length to the spinal cord dorsal horn, have been found in cats like those in humans,[63] including endoneural microvascular pathology.[64] This likely accounts for anecdotal observations of diabetic cats and dogs objecting to handling of paws, being held or stroked, and/or objecting increasingly to their insulin injections.

- Gross nerve injury: entrapment, transection - Nerve injury so reliably produces central and peripheral sensitization that ligation of major nerve bundles is a prime neuropathic pain model. One case report describes neuropathic pain in a cat whose sciatic nerve had inadvertently been ligated during rear limb amputation.[65] This patient experienced both hyperalgesia and hypoesthesia (numbness) in different aspects of the surgical region. Any amputation requires severing of major nerves, and in humans, post-amputation neuropathic pain signs occur in a high proportion (45-85%) of patients, medically managed or resolved in most cases but remaining persistent in 5-10% of patients.[66] Manifestations of post-amputation neuropathic pain in dogs and cats may also include persistent tactile sensitivity and constant grooming at the stump site (it is possible that a subset are experiencing dysesthesia – tingling or itch). Cats experiencing chronic lameness months or years post-onychectomy may be experiencing neuropathic pain in their feet.[67] Pathophysiology of post-amputation neuropathic pain, including phantom limb pain, may include micro- or macroscopic neuroma formation, the sprouting of nerve endings at the transaction site into a bundle of hyperexcitable, cross-linking neurons classic of peripheral sensitization. Changes are also detectable in peripheral axons, dorsal root ganglia, spinal cord, and even the cerebral cortex. Similarly, nerve root compression or injury from intervertebral disc disease and/or lumbosacral stenosis are likely confer a neuropathic pain component to these conditions

- Spinal cord injury (SCI) - Damage or compression to the spinal cord is known to create a neuropathic pain component with hyperalgesia and tactile allodynia in a majority of human post-SCI patients. Etiologies in the cat may include blunt force trauma, forced sacrococcygeal tail avulsion, intervertebral disc disease/herniation (IVDD, although much less common in cats, affecting <0.3%, both cervical and thoracolumbar (TL) are reported, with a possible pure-bred breed disposition [Persians, British Shorthairs] in the latter[68]) , lumbosacral stenosis (LSS), neoplasia, congenital malformations, infectious disease, and iatrogenic injury from epidural injection. Radiographic changes suggesting LSS may be more common than clinically relevant, but affected dogs and cats present with signs such as low tail carriage, hyperalgesia of the lumbosacral region and/or upon dorsoflexion of the tail, reluctance to jump and/or ambulate, elimination outside the litter box, pelvic-limb paresis, urinary incontinence, constipation, and in the exam room, raising of tail and taking a rectal temperature.[69] Pudendal nerve entrapment with neuropathic pain is described in humans with LSS, with chronic disabling perineal discomfort (anorectal, urogenital) especially upon sitting or urgency to urinate or defecate; in cats this may be shown as or newly objecting to insertion of a rectal thermometer.[70] Advanced imaging, specifically MRI, is more likely to pick up lesions not apparent radiographically, and the condition may be more common in cats than currently appreciated. The presence of transitional lumbosacral vertebrae is a risk factor for LSS, with affected cats having a 9-fold increased risk of developing the condition over cats without transitional vertebrae (54% vs. 6% in the general population).[71]

- CNS infection and neoplasia - Any disease of cerebral cortex, meninges, or spinal cord involving inflammation, vascular changes, ischemia, or necrosis can potentially induce pain with a neuropathic component. This may include profound headache with migraine-like features. Migraines themselves, whether primary idiopathic or comorbid to another disorder, are essentially a neuropathic pain condition that happens to involve blood vessels in addition to afferent and efferent neurons[72]. Head pressing associated with intra-cranial disease, including brain tumor, may be in part from severe debilitating headache. Infectious agents known to cause encephalitis and/or myelitis in cats include viruses (Feline Infectious Peritonitis (FIP), rabies, Feline Leukemia Virus (FeLV), and Feline Immunodeficiency Virus (FIV)), protozoa (toxoplasmosis), systemic fungi (most commonly *Cryptococcus neoformans)*, and parasites (*Cuterebra* myiasis*)*. Granulomatous Meningoencephalitis, Pug Encephalitis are idiopathic immune-mediated conditions, and Feline nonsuppurative meningoencephalomyelitis and eosinophilic meningoencephalitis (EME) are idiopathic but likely involve an as-yet-unidentified infectious agents.[73],[74]

- Vascular disorders: - Aortic thromboembolism elicits sudden, massive ischemic myopathy and neuropathy and can be considered chief among feline vascular disorders to induce neuropathic pain.[75] Cerebrovascular disease (including “ministroke”) and other vascular ischemic events may be under-appreciated in dogs and cats. Migraine is considered a neuropathic pain disorder (with similar pathophysiology that simply includes a blood vessel involved at the interface between primary and second-order neurons.[76] One case report of suspected migraine treated in a dog appears in the literature.[77]

- Persistent Post-Surgical Pain (PPSP) - PPSP is a significant and well-described neuropathic phenomenon in humans, with up to half of patients developing chronic pain after surgery (even common outpatient procedures), and signs of neuropathic pain present in 35 to 57%. 11.8% of

patients still experienced moderate to severe pain 12 months post-operatively.[78] Veterinary metrics are not available but if PPSP exists in even a fraction of cats and dogs as reported in humans, it would represent a potentially significant unrecognized clinical problem. In humans, the degree of trauma[79] (surgical and otherwise) and the degree of acute postoperative pain[80] are predictive factors for chronic pain with neuropathic components. In humans every 10% increase in the time spent in severe postoperative pain was associated with a 30% increase in chronic pain 12 months after surgery.[80]

- Bone Disease - Trabecular bone and periosteum are richly innervated. Upon fracture, infection, or neoplasia, periosteal and intrinsic mechanosensitive neurons are damaged, followed by massive release of excitatory neuropeptides which activate and sensitize neurons and promote ectopic nerve sprouting (including sympathetic fibers) at the callous. With proper healing these factors return to baseline and pain subsides, but if proper healing does not occur, chronic bone pain results.[81] Complex Regional Pain Syndrome (CRPS) is a poorly understood *sympathomimetic* neuropathic pain syndrome reported as a complication of fracture (and other trauma) in humans and several animal species including a dog.[82] Pelvic fractures are especially prone to severe and chronic maladaptive pain complications.[83] A case series describes idiopathic musculoskeletal pain in 3 dogs.[84] Osteosarcoma and any metastatic cancer to bone elicits neuropathic pain through classic mechanisms but also includes massive central glial hypertrophy, peripheral upregulation of cyclooxygenase, and a unique proalgesic neurochemical signature from osteoclastic activity.[85] The effect of such changes has been detected via QST in canine OSA.[86]

- Allergic inflammation - Allergic inflammation has been established as potential cause of neuropathic pain in mice,[87] and implications for this in dogs and cats (as established in mice) include well-recognized syndromes such as flea allergy dermatitis, atopic and flood allergy dermatitis, possibly eosinophilic granuloma complex, feline asthma, and canine eosinophilic pneumopathy. In the extreme, the phenomenon of "neuropathic itch" is well described in humans and animal models.[88]

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[1] Schechter NL. The undertreatment of pain in children: An overview. Pediatric Clinics of North America, 1989 36(4): 781-794
[2] Mather, The incidence of postop pain in children, Pain 1983 15:271-82
[3] Cook AK, Niven CA, Downs MG. Assessing the pain of people with cognitive impairment. Int J Geriatr Psychiatry. 1999 Jun;14(6):421-5.
[4] Lovheim H, Sandman PO, et al. Poor staff awareness of analgesic treatment jeopardises adequate pain control in the care of older people. Age Ageing. 2006 May;35(3):257-61. Epub 2006 Mar 17.
[5] Miller LL, Talerico KA. Pain in older adults. Annu Rev Nurs Res. 2002;20:63-88.
[6] IASP Pain Clinical Updates, Carr DB ed. July 2007, XV:4
[7] Hermann C, et al. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain 2006 124:278-285
[8] Melzack R, Wall P, Pain mechanism: A new theory. Science 150:951, 1965
[9] Light AR, Perl ER. Spinal terminations of functionally identified primary afferent neurons with slowly conducted myelinated fibers. J Compar Neuro 1979; 186:133-150.
[10] Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7th ed. Taylor & Francis, Boca Raton FL 2006
[11] Levine JD et al, Peptides and the primary afferent nociceptor. J Neurosci 1993; 13:2272-2286
[12] Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7th ed. Taylor & Francis, Boca Raton FL 2006, p. 15-22
[13] Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;44:293-299.
[14] Yaksh TL. Anatomical systems associated with pain processing, in The 15th annual review of pain and its management, Vol. I Dannemiller Memorial Education Foundation 2005; 101:1-16
[15] Cousins M, Power I. Acute and post operative pain. In: Wall PD, Melzak R eds. Textbook of Pain 4th ed. New York: Churchill-Livingston, 1999; 447-491.

[16] Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7th ed. Taylor & Francis, Boca Raton FL 2006
[17] Watkins L, Milligan ED, Maier SF. Spinal glia: New players in pain, Pain 93:201, 2001
[18] De Leo JA, Tawfik VL, LaCroix-Fralish ML. The tetrapartitie synapse: Path to CNS sensitization and chronic pain. Pain 2006 122(1-2): 17-21
[19] Shan S, New evidence for the involvement of spinal fractalkine receptor in pain facilitation and spinal glial activation in rat model of monoarthritis, Pain 129(1-2) May 2007: 64-75
[20] Honore P, Menning PM, Rogers SD, et al. Neurochemical plasticity in persistent inflammatory pain. Prog Brain Res. 2000;129:357-363.
[21] Yaksh TL. Post-tissue-injury pain states, in The 15th annual review of pain and its management, Vol. I Dannemiller Memorial Education Foundation 2005; 102:1-13
[22] Louis PV et al, Spinal NK-1 receptor expressing neurons mediate opioid-induced hyperalgesia and anti-nociceptive tolerance via activation of descending pathways Pain 129(1-2) May 2007:33-45
[23] Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7th ed. Taylor & Francis, Boca Raton FL 2006
[24] ibid
[25] Doubell TP et al. The dorsal horn: state-dependent sensory processing, plasticity, and the generation of pain. In: Wall PD, Melzak R, eds. Textbook of Pain 4th ed. New York: Churchill-Livingston, 1999;165-82
[26] Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. Clin J Pain 2000; 16:S12-20
[27] Ramer MS et al. causes and consequences of sympathetic basket formation in dorsal root ganglia. Pain 1999; 6:S111-120
[28] Devor M, Govrin-Lippmann R, Angelides K. Na+ channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neurosci* 1993;13:1976-1992
[29] Lascelles BDX et al, Efficacy and kinetics of carprofen, administered preoperatively or postoperatively for the prevention of pain in dogs undergoing ovariohysterectomy. Vet surg 1998 27:568-82.
[30] Simons DG, te al (ed.) General Overview. In: Myofascial Pain and Dysfunction: Vol 1, 2nd ed. 1999, Philadelphia, Lippincott Williams and Wilkins, pp. 11-93.
[31] Watkins L, Milligan ED, Maier SF. Spinal glia: New players in pain, Pain 93:201, 2001
[32] De Leo JA, Tawfik VL, LaCroix-Fralish ML. The tetrapartitie synapse: Path to CNS sensitization and chronic pain. Pain 2006 122(1-2): 17-21
[33] Shan S, New evidence for the involvement of spinal fractalkine receptor in pain facilitation and spinal glial activation in rat model of monoarthritis, Pain 129(1-2) May 2007: 64-75
[34] Honore P, Menning PM, Rogers SD, et al. Neurochemical plasticity in persistent inflammatory pain. Prog Brain Res. 2000;129:357-363.
[35] Benedetti F, et al. J Neruosci 2006;12014-12022, IASP Pain Clinical Updates XV:1 March 2007

[37] Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008 Apr 29;70(18):1630-5.
[38] Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain. 2016 Aug;157(8):1599-606.
[39] Mathews KA. Neuropathic pain in dogs and cats: if only they could tell us if they hurt. Vet Clin North Am Small Anim Pract. 2008 Nov;38(6):1365-414, vii-viii.
[40] Muir WW III, Weise AJ, Wittum TE. Prevalence and characteristics of pain in dogs and cats examined as outpatients at a veterinary teaching hospital. J Am Vet Med Assoc 2004;224:1459-63.
[41] van Hecke O, Austin SK, Khan RA, et al. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014 Apr;155(4):654-62.
[42] Wiese AJ, Muir WWW III, et al. Characteristics of pain and response to analgesic treatment in dos and cats examined at a veterinary teaching hospital emergency service. J Am Vet Med Assoc 2005;226: 2004-9.
[43] Rusbridge C Heath S, Gunn-Moore DA, et al. Feline orofacial pain syndrome (FOPS): a retrospective study of 113 cases. J Feline Med Surg. June 2010;12(6):498-508.
[44] Ciribassi J. Understanding behavior: feline hyperesthesia syndrome. Compend Contin Educ Vet. 2009 Mar;31(3):E10.
[45] Westropp JL, Delgado M, Buffington CAT. Chronic Lower Urinary Tract Signs in Cats: Current Understanding of Pathophysiology and Management. Vet Clin North Am Small Anim Pract. 2019 Mar;49(2):187-209.
[46] Buffington, CAT. Idiopathic Cystitis in Domestic Cats—Beyond the Lower Urinary Tract. J Vet Intern Med 2011;25:784–796
[47] Buffington CA, Teng B, Somogyi GT. Norepinephrine content and adrenoceptor function in the bladder of cats with feline interstitial cystitis. J Urol. 2002 Apr;167(4):1876-80.
[48] Sculptoreanu A, de Groat WC, Buffington CA, et al. Abnormal excitability in capsaicin-responsive DRG neurons from cats with feline interstitial cystitis. Exp Neurol 2005;193:437–43.
[49] Buffington CAT, Wofle SA. High affinity binding sites for [3H] substance P in urinary bladders of cats with interstitial cystitis. J Urol 2000; 163:1112-5.
[50] Potts JM, Payne CK. Urologic chronic pelvic pain. Pain. 2012 Apr;153(4):755-8.
[51] Stella JL, Lord LK, Buffington CA. Sickness behaviors in response to unusual external events in healthy cats and cats with feline interstitial cystitis. J Am Vet Med Assoc 2011;238:67–73.
[52] Perisco, et al. Detection of F-HV1 via PCR and IHC in cats with ulcerative facial dermatitis. Vet Dermatol 2011
[53] Mazzei M, Vascellari M, Zanardello C, et al. Quantitative real time polymerase chain reaction (qRT-PCR) and RNAscope in situ hybridization (RNA-ISH) as effective tools to diagnose feline herpesvirus-1-associated dermatitis. Vet Dermatol. 2019 Sep 5. [Epub ahead of print]
[54] Rolim VM, Pavarini SP, Campos FS, Pignone V, et al. Clinical, pathological, immunohistochemical and molecular characterization of feline chronic gingivostomatitis. J Feline Med Surg. 2017 Apr;19(4):403-409.
[55] Thakur M, Rahman W, Hobbs C, et al. Characterisation of a peripheral neuropathic component of the rat monoiodoacetate

model of osteoarthritis. PLoS One. 2012;7(3):e33730.
[56] Havelin J, Imbert I, Cormier J, et al. Central Sensitization and Neuropathic Features of Ongoing Pain in a Rat Model of Advanced Osteoarthritis. J Pain. 2016 Mar;17(3):374-82.
[57] Hochman JR, Neuropathic pain symptoms in a community knee OA cohort. Osteoarthritis Cartilage. 2011 Jun;19(6):647-54.
[58] Guillot M, Taylor PM, Rialland P, et al. Evoked temporal summation in cats to highlight central sensitization related to osteoarthritis-associated chronic pain: a preliminary study. PLoS One. 2014; 9(5): e97347.
[59] Plessas IN, Rusbridge C, Driver CJ, et al. Long-term outcome of Cavalier King Charles spaniel dogs with clinical signs associated with Chiari-like malformation and syringomyelia. Vet Rec. 2012 Nov 17;171(20):501.
[60] Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. Inflamm Bowel Dis. 2009 May;15(5):778-88
[61]Potts, JM, Payne CK. Urologic Pelvic Pain. 2012 (153): 755-758
[62] Goulden MR. The pain of chronic pancreatitis: a persistent clinical challenge. Br J Pain. 2013 Feb;7(1):8-22.
[63]Mizisin AP, Nelson RW, Sturges BK, et al. Comparable myelinated nerve pathology in feline and human diabetes mellitus. Acta Neuropathol. 2007 Apr;113(4):431-42
[64] Estrella JS, Nelson RN, Sturges BK, et al. Endoneurial microvascular pathology in feline diabetic neuropathy. Microvasc Res. 2008 Apr;75(3):403-10.
[65] O'Hagan BJ. Neuropathic pain in a cat post-amputation. Aust Vet J 2006:84:83-6
[66] Kuffler DP. Origins of Phantom Limb Pain. Mol Neurobiol. 2018 Jan;55(1):60-69.
[67] Gaynor JS. Chronic pain syndrome of feline onychectomy. NAVC Clinician's Brief. 2005;63:11-3.
[68] De Decker S, Warner AS, Volk HA. Prevalence and breed predisposition for thoracolumbar intervertebral disc disease in cats. J Feline Med Surg. 2017 Apr;19(4):419-423.
[69] Harris JE, Dhupa S. Lumbosacral intervertebral disk disease in six cats. J Am Anim Hosp Assoc. 2008 May-Jun;44(3):109-15.
[70] Popeny C, Ansell A, Renny K. Pudendal entrapment as an etiology of chronic perineal pain: diagnosis and treatment. Neurol Urodyn 2007; 26(6): 820-7.
[71] Harris G, Ball J, De Decker S. Lumbosacral transitional vertebrae in cats and its relationship to lumbosacral vertebral canal stenosis. J Feline Med Surg. 2019 Apr;21(4):286-292.
[72] Chakravarty A, Sen A. Migraine, neuropathic pain and nociceptive pain: towards a unifying concept. Med Hypotheses. 2010 Feb;74(2):225-31.
[73] Nowotny N, Weissenböck H. Description of feline nonsuppurative meningoencephalomyelitis ("staggering disease") and studies of its etiology. J Clin Microbiol. 1995 Jun;33(6):1668-9.
[74] Williams JH, Köster LS, Naidoo V, et al. Review of idiopathic eosinophilic meningitis in dogs and cats, with a detailed description of two recent cases in dogs. J S Afr Vet Assoc. 2008 Dec;79(4):194-204.
[75] Fuentes LV. Arterial thromboembolism: risks, realities and a rational first-line approach. J Feline Med Surg. 2012 Jul;14(7):459-70.
[76] Chakravarty A, Sen A. Migraine, neuropathic pain and nociceptive pain: towards a unifying concept. Med Hypotheses. 2010 Feb;74(2):225-31.
[77] Plessas IN, Volk HA, Kenny PJ. Migraine-like Episodic Pain Behavior in a Dog: Can Dogs Suffer From Migraines? J Vet Intern Med 27 (5), 1034-40 Sep-Oct 2013
[78] Richebé P, Capdevila X, Rivat C. Persistent Postsurgical Pain: Pathophysiology and Preventative Pharmacologic Considerations. Anesthesiology. 2018 Sep;129(3):590-607.
[79] Powelson EB, Mills B, Henderson-Drager W, Boyd M, Vavilala MS, Curatolo M. Predicting chronic pain after major traumatic injury. Scand J Pain. 2019 Jul 26;19(3):453-464.
[80] Fletcher D, Stamer UM, Pogatzki-Zahn E, et al; euCPSP group for the Clinical Trial Network group of the European Society of Anaesthesiology: Chronic postsurgical pain in Europe: An observational study. Eur J Anaesthesiol 2015; 32:725–34
[81]Mitchell SAT, Majuta LA, Mantyh PW. New Insights in Understanding and Treating Bone Fracture Pain. Curr Osteoporos Rep. 2018 Aug;16(4):325-332.
[82] LaBarre A, Coyne BE. Reflex sympathetic dystrophy in a dog. J Am Anim Hosp. Assoc. 1999 May-Jun;35(3):229-31.
[83] Meyhoff CS, Thomsen CH, Rasmussen LS, et al. High incidence of chronic pain following surgery for pelvic fracture. Clin J Pain. 2006 Feb;22(2):167-72.
[84] Cashmore RG, Harcourt-Brown TR, Freeman PM, Jeffery ND, Granger N. Clinical diagnosis and treatment of suspected neuropathic pain in three dogs. Aust Vet J. 2009 Jan-Feb;87(1):45-50
[85] Schwei MJ, Honore P. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. J Neurosci. 1999 Dec 15;19(24):10886-97.
[86] Monteiro BP, de Lorimier LP, Moreau M, Beauchamp G, Blair J, Lussier B, Pelletier JP, Troncy E. Pain characterization and response to palliative care in dogs with naturally-occurring appendicular osteosarcoma: An open label clinical trial. PLoS One. 2018 Dec 6;13(12):e0207200.
[87] Yamasaki R, Fujii T, Wang B, et al. Allergic Inflammation Leads to Neuropathic Pain via Glial Cell Activation. J Neurosci. 2016 Nov 23;36(47):11929-11945.
[88] Hachisuka J, Chiang MC, Ross SE. Itch and neuropathic itch. Pain. 2018 Mar;159(3):603-609.

PAIN MANAGEMENT FOR THE LOW-SURGICAL DOSE PATIENTS

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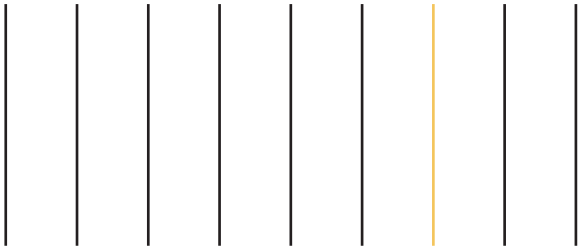

SMALL ANIMAL

Trans Operative Pain Management for The Low-Surgical Dose Patient
Kansas State 2024

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The robust advances in pain management for companion animals underlie the decision of AAHA and AAFP to expand on the information provided in the 2007 AAHA/AAFP Pain Management Guidelines for Dogs and Cats.The 2015 Guidelines can be found at these URL's: (https://www.aaha.org/public_documents/professional/guidelines/2015_aaha_aafp_pain_management_guidelines_for_dogs_and_cats.pdf and http://jfm.sagepub.com/content/17/3/251.full.pdf+html), and the 2022 AAHA Guidelines can be found at 2022 AAHA Pain Management Guidelines for Dogs and Cats

The Guidelines continue the trend in all branches of medicine toward evidence-based consensus statements that address key issues in clinical practice. Although not a review article, the Guidelines represent a force multiplier for the busy practitioner, consolidating in a single place current recommendations and insights from experts in pain management. The recommendations of the guidelines Task Force are evidence based insofar as possible and otherwise represent a consensus of expert opinion. These notes contain the key applied principals for veterinary clinicians.

Devising an evidence-based top-tier trans-operative pain management strategy is within the scope of any practice to achieve. The framework of effective pain management systems rests solidly on the foundation of recognition/assessment, pre-emption, and using multiple modalities. Multiple modalities allow for intervention at several different places of the nociceptive pathway, increasing effectiveness and minimizing the need for high or protracted doses of any one particular drug (including, perhaps especially, opioids), and minimizes the likelihood or severity of peripheral and central sensitization which contributes to maladaptive (exaggerated) pain. Veterinary medicine would do well to emulate a recent trend in human transpoerative care called ERAS – Enhanced Recovery After Surgery,[a] which aims for evidence-based measures to 1. Reduce Surgical stress, 2. Maintain physiologic functions, and 3. Enhance mobilization after Sx; outcomes measured include: 1. Reduced morbidity rates, 2. Faster recovery, 3. Shorter hospital stays. Chief among the strategies to achieve the ERAS goals is to minimize the minimization of opioid use.[1]

The basic construct for low-surgical dose patients is a 4-legged stool:

1. ANXIOLYTICS

Anxiety contributes directly to the hyperalgesic state through cholecystikinin-mediated "nocebo" effect.2 A number of studies in humans support the idea that patients who are highly anxious or stressed pre-operatively experience higher pain scores post-operatively. These observations are also found in many animals studies, where restraint, social defeat, rotation – all things veterinary patients experience in the normal pre-surgical setting in order to draw blood, place catheters, etc. – contribute to hyperalgesia.[3] Thus the first leg of a strong transoperative pain management protocol does not involve the use of analgesics in and of themselves, but anxiolytics and not just pharmacologic ones i.e. low-stress handling techniques,[b] the Fear Free™,[c] experience to include (but not limited to) pheromones and addition to tranquilizers/sedatives such as trazodone (8-10mg/kg) or gabapentin (15 mg/kg) for the owner to administer at home pre-visit. In hospital, clinicians may choose between phenothiazines (e.g. acepromazine), benzodiazepines (midazolam or diazepam), or alpha2 agonists (dex/medetomidine).

2. OPIOIDS

[a] https://erassociety.org/
[b] http://drsophiayin.com/lowstress, http://www.catvets.com/guidelines/practice-guidelines/handling-guidelines
[c] https://fearfreepets.com/

Opioid receptors are distributed ubiquitously throughout the body and can be found in most central and peripheral tissues. Several opioid different receptor types and subtypes have been isolated, each with a variant effect; activation of an opioid receptor inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters. The proposed mechanism includes opioid receptor coupling with the membrane-associated G protein; this leads to decreased intracellular formation of cAMP which diminishes calcium channel phosphorylation (closing off the channel) and opens potassium channels enhancing potassium influx. The resulting effect is hyperpolarization of the neuron and blockade of Substance P release. Nociceptive transmission is thus greatly impeded. Opioids in combination with anxiolytics discussed above can induce a profound sedating neurolopetanalgesic effect to the patient's benefit. However, recent efforts to reduce the frequency, duration, and dosing of full mu agonists (e.g. morphine, hydromorphone, fentanyl) in favor (while still maintaining patient comfort) of partial mu agonists (buprenorphine) and mu-antagonist/kappa agonist (butorphanol) in human medicine are being mirrored in the veterinary profession https://ivapm.org/wp-content/uploads/2018/12/Op-Sparring-Task-Force-WP.pdf.

Different opioid drugs are available which vary in their relative potency and receptor affinity, and a complete discussion of their similarities and differences are available in a number of resources. Full-mu agonists have the most significant analgesic punch, but in low-surgical dose patients it can be argued should be used only short-term (e.g. hydromorphone as a pre-medication). Full mu agonists do not have a ceiling effect which means higher doses can achieve more profound analgesic but with accompanying increases in adverse effects (dysphoria, suppressed appetite and in the extreme constipation, hyperalgesia, and potentially fatal respiratory suppression however uncommon this might be in animals). Recognizing and having strategies for counteracting their signs will minimize the complications that they present.[4]

Buprenorphine is a partial mu agonist so less potent an analgesic than full mu agonists and can be considered suitable for low-surgical dose patients. It has a ceiling effect, meaning higher doses elicit neither additional analgesia nor much more in the way of adverse effect. Buprenorphine does have a higher affinity for the mu receptor than full mu agonists and will displace those molecules if both are present. Buprenorphine also has the unique feature of taking significant time to achieve maximum effect (1 hour IM, 30 min IV); and it is the least sedating of commonly used opioids in veterinary medicine.

Butorphanol is a mu agonist and a kappa antagonist; like buprenorphine it has a ceiling effect. However its short duration of action in the dog (approx. 30-40 min) generally makes it a poor choice for surgical analgesia in this species, although co-administered with alpha-2 agonists (e.g. dexmedtomidine) it will act syngergistically for both pain and sedation and this combination can be appropriate for low-surgical dose procedures.

Tramadol, in contradistinction to humans, does has negligible opioid activity in the dog, but cats have opioid (and serotonin, norepinephrine) metabolites similar to humans.

3. NSAID

The primary mode of action is to inhibit cyclooxygenase 2 (COX2), the enzyme that is expressed at site of inflammation and results in the production of pro-inflammatory and vasoactive prostaglandins. Also, through poorly understood mechanisms, likely by modulating multiple gene expression pathways,5 it may inhibit central perception of pain. Several superior products are now labeled for use in dogs and cats (meloxicam and robenacoxib are metabolized through oxidative rather than glucuronidase pathways), making them among the most popular of pain management medications in veterinary medicine. Pre-operative use of NSAID appears to be safe in healthy dogs (even in the face of modest hypotension; but hypotension should be avoided with the use of IV fluids and careful blood pressure monitoring); robenacoxib is specifically labeled for pre-op use. However it is satisfactory to administer post-operatively should that be the clinician's preference. The adverse event profile however is well-established and results from metabolites of COX1 metabolism (especially in the GI tract), and also PGE2 from COX2 metabolism (especially in the renal tubules) do have normal homeostatic, tissue-protective, and tissue-healing effects. However, the frequency and severity of NSAID ADE can be minimized through well-established means. The GI and renal adverse effects can be expected to occur most commonly in higher

risk patients, e.g.: hypovolemia, hypotension (including anesthetic procedures especially those not supported by intravenous fluids), pre-existing GI or renal disease, overusage, and the inappropriate combination with other NSAID's or corticosteroids. Notable in this last category is client use of aspirin in their pets, which may be unbeknownst to the clinician unless specifically queried in a thorough history (uniquely, this NSAID produces a cyto-protective lipoxin through the COX pathway;[6] thus when COX is inhibited through the use of another, concurrently-given NSAID, the potential for GI toxicity is considerably enhanced). The very rare hepatic issues are idiosyncratic reactions of that dog to that molecule, and can not be prevented or predicted based on liver enzymes (do avoid in liver dysfunction however).

Grapiprant is not COX-inhibiting but rather antagonizes just the EP4-receptor of PGE2 (responsible for activating nociceptors), sparing the EP1, EP2, EP3 subunits largely concerned with normal tissue function and repair. Galliprant™ is labeled for osteoarthritis in dogs, and its use in acute, post-surgical pain remains to be determined (conflicting data as of this writing).

Robenacoxib (Onsior™, Elanco) has been approved for 3 days of post-operative pain relief in cats. It is COX2-selective with the unique feature of having a very short plasma elimination half life of 1.7 hours (compared to meloxicam at approx. 20 hours), yet (because it like all NSAID is highly protein-bound) stays at the site inflammation/effusion for >24 hours. It is presumed that this novel PK profile lends itself to impressive safety data including up to 5 & 10X labeled dose.[7]

4. LOCOREGIONAL ANESTHESIA

Local anesthetics were once a mainstay of pain management in veterinary medicine, and may now be one of the most under-utilized modalities. Administered locally or regionally, they are the only modality that renders complete anesthesia to a site, i.e. no transmission of nociceptive impulses as long as the drug exerts its effect. Initially used as a means of desensitizing tissues in order to "invade" tissues with scalpels; local anesthetics are enjoying a rebirth as powerful tools to prevent or reduce perioperative pain (as well as procedural and even chronic pain) and to reduce general anesthetic and concurrent analgesic (especially systemic opioid) requirements. There is no longer a reason to hold an "either-or" position; "for surgery either I use local anesthetics *or* I use general anesthesia", in fact, there are many reasons to combine general and local anesthetic for surgical pain relief.[8] Simple techniques for the low-surgical dose patients include: topical/dermal/epidermal local anesthetics for IV catheter placement (e.g. EMLA®, LMX4®, or their generic equivalents), incisional line blocks, field blocks for lumpectomies or laceration repairs, intra-abdominal (peritoneal) blocks before laparotomy closure, orofacial blocks for extractions and mesovarium and intra-testicular blocks for spay and neuter respectively, are well described in the literature.

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[1] Echeverria-Villalobos M, Stoicea N, Todeschini AB, Fiorda-Diaz J, Uribe AA, Weaver T, Bergese SD. Enhanced Recovery After Surgery (ERAS): A Perspective Review of Postoperative Pain Management Under ERAS Pathways and Its Role on Opioid Crisis in the United States. Clin J Pain. 2020 Mar;36(3):219-226.

[2] Benedetti F, et al. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect, J Neruosci 2006 Nov 15;26(46):12014-22, IASP Pain Clinical Updates XV:1 March 2007

[3] Martenson ME, Cetas JS, Heinricher MM A possible neural basis for stress-induced hyperalgesia. Pain 142 (2009): 236-244

[4] Carr, DB (Ed.) Opioid Side Effects, In: IASP Pain Clinical Updates, April 2007 XV:2

[5] Xiao-Min W et al Rofecoxib modulates multiple gene expression pathways in a clinical model of acute inflammatory pain, Pain 128(1-2) March 2007: 136-147

[6] Schottelius AJ, Giesen C, et al. An aspirin-triggered lipoxin A4 stable analog displays a unique topical anti-inflammatory profile. J Immunol. December 2002;169(12):7063-70.

[7] King JN, Hotz R, Reagen EL, Roth DR, Lees WS. Safety of oral robenacoxib in the cat. J Vet Pharmacol Ther. 2012 Jun;35(3):290-300.

[8] Jones RS. Combining local and general anesthesia for better pain relief in dogs and cats. Vet J. 2008 Nov. 178(2):161-2

PAIN MANAGEMENT FOR THE HIGH-SURGICAL DOSE PATIENTS

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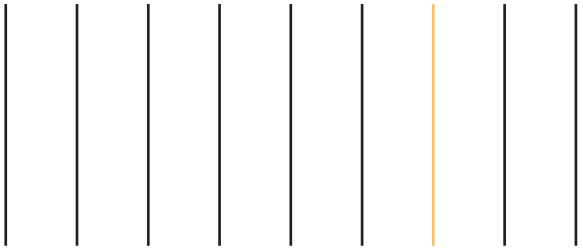

SMALL ANIMAL

Trans Operative Pain Management for The High-Surgical Dose Patient
Kansas State Univ 2024

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Industry Pain Management Guidelines include:
2014 & 2022 WSAVA Global Pain Council: https://wsava.org/Global-Guidelines/Global-Pain-Council-Guidelines/
2015 & 2022 AAHA

- https://www.aaha.org/public_documents/professional/guidelines/2015_aaha_aafp_pain_management_guidelines_for_dogs_and_cats.pdf
- https://www.aaha.org/aaha-guidelines/2022-aaha-pain-management-guidelines-for-dogs-and-cats/home/

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The basic construct is a 4-legged stool even for Low-Surgical Dose Patients (covered in that session) include

- **ANXIOLYTICS** (pharmacologic, non-pharmacologic)
- **OPIOIDS** (short action, duration)
- **NSAID**
- **LOCOREGIONAL ANESTHESIA**

.
High-Surgical Dose Patients can be defined as those undergoing procedures with existing evidence of, or significant risk factors for, hypersensitization, i.e. for post-surgical pain that includes pain exaggerated in scope, severity, duration, character, and field. This maladaptive pain experience can be said to be “Pain with a Neuropathic Component” and contribute significant to patient morbidity, delayed recovery, and in the extreme with patients on the edge, post-op mortality.

Patients with or at risk for maladaptive pain processing include but are not limited to those with:

1. Significant tissue trauma (orthopedic or soft-tissue; pre-existing, surgical, or both)
2. Pre-existing chronic inflammation
3. Nerve injury (pre-existing, surgical i.e. amputation, or both)

[a] https://erassociety.org/

4. Any pre-existing chronic pain syndrome or having risk factors for peripheral neuropathy e.g. diabetes mellitus, vinca alkaloid chemotherapy

Such High Surgical Dose Patients require the same components, albeit somewhat amended, as Low Surgical Dose Patients, but also several more i.e. a 5-, 6-, sometimes 7- or 8-legged stool. These interventions may include one or more of the following:

Alpha-2 agonist: Medetomidine and dexmedetomidine binds opioid-like receptors on C- and A-delta fibers, especially in the central nervous system. Binding pre-synaptically, NE production is reduced and sedation occurs; binding post-synaptically, analgesia is produced, and is profoundly synergistic with opioids. It also blocks NE receptors on blood vessels, resulting in vasoconstriction; the resulting hypertension parasympathetically induces bradycardia, which is extended by a subsequent direct decrease in sympathetic tone. However, central perfusion is maintained and the author has found a wide use for these alpha-2 agonists in acute and peri-operative setting, though only in combination with opioids and at doses much lower than suggested by the manufacturer. One particularly novel and user-friendly utility is IV micro-doses intra- and post-operatively, 0.25 – 1.0 mcg/kg. This may result in intravenous volumes of only 0.01 – 0.03 ml in even the largest of dogs. Alpha-2 agonists can be administered safely in appropriate patients at a Constant Rate Infusion of 1.0 mcg/kg/hr (1.0 ml = 0.5 mg)/L administered at maintenance rate of 2 ml/kg/hr.[2]

Zenalpha® is a new product that combines medetomidine + the peripheral alpha-2 antagonist vatinoxan. The product is labeled for IM sedation as a solo agent in dogs only, and attenuates medetomidine's peripheral vasoconstriction which in turn attenuates the rise in peripheral vascular resistance, reflex bradycardia and drop in cardiac output. Extralabel usage over lower doses in combination with opioids, and administered intraveneously, have been explored but ideal dosing has not been determined. It appears that atipamezole can be safely administered to further reverse the effects of Zenalpha® (but unlike the vatinoxan it includes, will also reverse the central (sedation, analgesic) effects as well.[3]

Sub-anesthetic Ketamine CRI: A phencyclidine dissociative anesthetic, the evidence is building for its pre-emptive and preventive effects when given at subanesthetic doses in an intravenous constant rate infusion. Ketamine binds to a phencyclidine receptor inside the NMDA receptor, i.e. the calcium channel would already have to be open and active for ketamine to exert its effect. However, once bound, it decreases the channel's opening time and frequency, thus reducing Ca+ ion influx and dampening secondary intracellular signaling cascades. Hence it is unlikely (and has not been shown) to be truly analgesic in nature. Rather, it appears to be protective against hyperalgesia and central hypersensitization in the post-operative setting,4 including in the dog.5 Ideal sub-anesthetic ketamine plasma concentrations – eliciting the most benefit with the least adverse effect – has been reported at 2-3 mcg/ml, which can be achieved by administering ketamine IV CRI at 10 mcg/kg/min.[6] This can be accomplished by placing 60 mg (0.6 ml of 100 mg/ml stock) ketamine in 1 L of fluids and administered at customary intra-operative rates of 10 ml/kg/hr. Post-operatively, the rate can be reduced to customary maintenance rates of 2 ml/kg/hr, which administers the ketamine CRI at 2 mcg/kg/min. A loading dose of 0.25 – 0.5 mg/kg ketamine IV is recommended prior to the initiation of the CRI in order to rapidly achieve plasma levels (can be achieved through ketamine itself, a "ketofol" mixture with reduced doses of propofol, ketamine/valium or Telazol™ induction). Human consensus guidelines advise that sub-anesthetic ketamine CRI should be deployed in patients undergoing more painful procedures, guidance that can be extrapolated to both dogs and cats; additionally clinicians should consider utilizing this modality in patients with pre-existing chronic inflammation and known or suspected nerve injury.

Lidocaine CRI: The mechanisms behind a pain-modifying effect of systemic lidocaine remain an area of investigation but appear to include its ability to enter the nociceptor cell body in the dorsal root ganglion. In humans the evidence is strong for safety and the beneficial effects of intravenous lidocaine (IVL) on pain after abdominal surgery in humans (especially for the 1st 24 hours, and less so for other surgeries eliciting somatic pain)[7],[8],[9],[10] and possibly horses, including both pain and return of bowel function. Systemic, intravenous infusion of lidocaine has also been shown to elicit a sustained effect on neuropathic pain in humans.[11] Several systemic lidocaine CRI protocols are described, some combined with other pain-modifying agents. A customary one is described[12]: 300 mg lidocaine 2% (15 ml) is placed in a liter of

crystalloids, and administered at a surgical rate of 5-10 ml/kg/hr, delivering 25-50 mcg/kg/min. Post-operatively the rate may be reduced to maintenance rate of 2 ml/kg/hr, delivering 10 mcg/kg/min. Note: for accurate dosing, 15 ml of the crystalloid should be removed prior to the addition of the lidocaine. Lidocaine should be used with caution in hypovolemic states, and is advised for use in dogs only.

NSAID: Special Considerations.
Suppressing COX enzymes suppresses production of PGE2 and its pro-nociceptive, pro-inflammatory properties, but this molecule also promotes tissue healing through vasodilation and other means.

Fracture repair: Rodent and canine models reveal that NSAIDs elicit a time- and dose-dependent delay in fracture healing.[13] However the effect is reversible upon withdrawal of NSAID[14] and a human Meta-analysis (and FDA FOI data for veterinary-approved NSAIDs) do not support a clinically-relevant affect of delayed- or non-union fracture repair with judicious use of NSAIDs. It is generally considered not only safe, but appropriate to use NSAIDs post-fracture repair (including TPLO), but for a time period of days to weeks rather than months. One canine study showed no difference in radiographic healing between dogs without carprofen and those with 2-week administration of carprofen.[15]

GI surgery: data in humans undergoing intestinal resection/anastomosis reveal a higher rate of leakage from the anastomotic site in cohorts receiving NSAID than those that do not.[16] There is not a clear consensus in veterinary medicine about NSAIDs use post-GI surgery is appropriate in dogs and cats. The author supports the use of NSAIDs in GI surgery as long as the bowel is healthy and patient not otherwise compromised, for the 1st 24-48 hours post-op.

Opioid: Use of extended-duration formulations:
In cats, Simbadol™ (Zoetis) is a 1.8 mg/ml buprenorpine FDA-approved product labeled for 24 hours of post-surgical analgesia in cats labeled for use at 0.24 mg/kg SC; the author utilizes a reduced dose of 0.12 mg/kg to minimize the modest adverse effects of lethargy and diminished appetite (and supported by more recent PK data although with wider range variability than the labeled dose[17]). One recent study in dogs found the off-label use of Simbadol™ in this species at 0.02 mg/kg to be non-inferior to a 0.3 mg/ml product administered SC.[18]

Newer on the market just in 2022 is Zorbium™ (Elanco), a transdermal buprenorphine product for cats. Placed on the skin between the shoulder blades, the product enters into the stratum corneum of the skin, resides there and slowly releases into systemic circulation from there providing 4 days of post-operative analgesia.

Enhanced-duration local anesthetic: Liposome-Encapsulated Bupivacaine
In 2016, an extended-release, LE-encapsulated bupivacaine product was FDA-approved for dogs undergoing stifle surgery (Nocita™, Aratana, since purchased by Elanco), eliciting 3-days of analgesic effect; in 2018 the label was extended to nerve block for digit surgery (onychectomy) in cats. The product has been available for several years in humans under the trade name Experel™. As the liposomes degrade, bupivacaine is released into the surrounding tissue, rendering its local anesthetic effect. The product itself is viscous and does not readily diffuse, therefore the label calls for utilizing an “advancing needle” technique whereby the product is deposited by repeat injections into the affected tissue, at each layer upon closure. A number of extralabel uses have been described. A post-launch study revealed that post-breach, the product has 4 days of stability and 5 days of sterility.[19]

Maropitant (Cerenia®) is a central antiemetic through blockade of Substance-P to the NK-1 receptor, which is also involved in pain processing especially involving central sensitization. The true pain-modifying effect in dogs remains uncertain. A 2020 Systematic Review of its use in dogs and cats revealed that the available evidence supports that it significantly reduces the minimum alveolar concentrations for gas anesthetic for many different surgical procedures, but that it had no clearly proven effect on inflammation and pain.[20] However, these were almost exclusively on ovariohysterectomy models which would generally not be expected to elicit central sensitization. Indeed one study in a population of dogs with risk factors for hypersensitization (undergoing large soft tissue resection i.e. mastectomies), coadministration of maropitantI V (bolus followed by CRI) maropitant with ketamine and lidocaine CRIs had an adjuvant effect with minimal cardiorespiratory effects and effective analgesia,

improving pain management and patient comfort.[21] Maropitant performed poorly in development as pain-modifying agent in humans and was withdrawn as a study target. However the prospect remains it may provide benefit in a subset of patients (e.g. for visceral pain, with central sensitization) or with improved delivery systems (e.g. in a nanoparticle formulation).[22]

Adjunctive drugs:

Tramadol: In humans, tramadol is described as a synthetic opioid with 1/100th of the affinity for the mu receptor as morphine but a much better analgesic effect than this would predict. This is likely due to the combined effect of a highly active M1 metabolite and serotonin- and norepinephrine (inhibitory neurotransmitters) agonism. However, recent work demonstrates that it appears to have a very short half-life (1.7 hours) in the dog,[23] and it appears that dogs produce very little of the M1 opioid metabolite.[24] The unfavorable PK profile of oral tramadol in dogs, and in a Systematic Review and Meta-Analysis the lack of evidence to support a post-surgical pain-modifying effect[25] should lend skepticism about its use as an analgesic in this species. Cats do make the M1 metabolite in similar quantities and PK as humans,[26] and there are data to support its use for post-surgical pain in this species[27]. Its bitter taste may limit its use in cats, but there are case reports and anecdotes of finding palatable versions in beef and marshmallow flavoring.

Gabapentin is labeled for use as an anti-convulsant drug but is in widespread human use for its analgesic properties. While structurally similar to GABA, it is not a direct agonist, although it may have indirect effects on GABA metabolism such as increasing intracellular stores. Another leading hypothesis is that it exerts effect through interaction with the alpha-2-delta subunit of the voltage gated calcium channel.[28] Its utility in chronic, neuropathic pain states is well-established in humans,[29] but more recently its utility in the transoperative setting is supported by a number of systematic reviews.[30],[31],[32],[33],[34],[35] Pharmacokinetic studies in dogs reveal that it may have a half-life of 3-4 hours in the dog[36], suggesting a TID administration schedule. Based on experience in humans, pre-operative doses are recommended in the 10-15mg/kg mg/kg range and post-op 7-10 mg/kg[37]. The primary adverse effect in dogs appears to be somnolescence (as in humans) which usually will spontaneously resolve over a few days acclimation time, but this AE not been a frequent occurrence in the author's experience.

Acetaminophen (paracetamol, APAP) has an unidentified certain mechanism of action although may be predominantly by inhibiting a variant of COX1 in the brain, and bind to cannabinoid receptors. Although anecdotes and older studies may imply a pain-modifying effect, newer studies demonstrate that in the dog, oral (or suppository) APAP does not achieve serum levels generally associated with a pain-modifying effect.[38] However, acceptance of acetaminophen's safety and potential analgesic and anti-pyretic in dogs effect appears to be growing.[39] The clinical benefit of administering a combined acetaminophen + oral opioid in dogs appears to be mixed at best with treatment failures high post-TPLO utilizing APAP+ hydrocodone,[40] and an inferior effect of APAP + codeine to standard NSAD in an model of acute inflammation.[41] This is likely due at least in part to the large first pass effect oral opioid in dogs compared to humans (therefore limiting its bioavailability).
Note that prescribing oral opioid in any formulation puts these tablets into the public sphere, at risk for diversion and thus contributing to the opioid epidemic.

Non-pharmacologic interventions:

Cold-compression: Long known for its pain-modifying effect in humans, recent studies affirm a similar effect in dogs.[42],[43]

Therapeutic Laser: Two studies demonstrate a positive pain-modifying effect pre[44]- and post[45]-operatively, with one not improving better than placebo.[46]

[1] Echeverria-Villalobos M, Stoicea N, Todeschini AB, Fiorda-Diaz J, Uribe AA, Weaver T, Bergese SD. Enhanced Recovery After Surgery (ERAS): A Perspective Review of Postoperative Pain Management Under ERAS Pathways and Its Role on Opioid Crisis in the United States. Clin J Pain. 2020 Mar;36(3):219-226.

[2] Lin GY, Robben JH, Murrell JC, Aspegrén J, McKusick BC, Hellebrekers LJ. Dexmedetomidine constant rate infusion for 24 hours during and after propofol or isoflurane anaesthesia in dogs. Randomized Controlled Trial Vet Anaesth Analg. 2008 Mar;35(2):141-53.

[3] FDA Freedom of Information https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/12187#:~:text=Zenalpha%C2%AE%20%28medetomidine%20and%20vatinoxan%20hydrochlorides%20injection%29%20is%20approved,clinical%20examination%2C%20clinical%20procedures%20and%20minor%20surgical%20procedures.

[4] Ketamine: Does Life Begin at 40? IASP Pain Clinical Updates, Carr DB, ed. XV:3, June 2007

[5] Slingsby LS, Waterman-Pearson AE, The postoperative analgesic effects of ketamine after canine ovariohysterectomy – a comparison between pre- and post-operative administration. Res Vet Sci. 2000 Oct;69(2):147-52

[6] Boscan P, Pypendop BH, Solano AM, Ilkiw JE. Cardiovascular and respiratory effects of ketamine infusions in isoflurane-anesthetized dogs before and during noxious stimulation. Am J Vet Res. 2005 Dec;66(12):2122-9.

[7] McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs. 2010 Jun 18;70(9):1149-63

[8] Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LH, Poepping DM, Weibel S. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev. 2015 Jul 16;(7):CD009642.

[9] Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, Hollmann MW, Poepping DM, Schnabel A, Kranke P. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018 Jun 4;6:CD009642.

[10] Bailey M, Corcoran T, Schug S, Toner A. Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. Pain. 2018 May 1. doi: 10.1097/j.pain.0000000000001273. [Epub ahead of print]

[11] Cahana A, Shvelzon V, et al. Intravenous lignocaine for chronic pain: an 18-month experience. Harefuah. 1998 May 1;134(9):692-4, 751, 750

[12] Muir WW 3rd, Wiese AJ, March PA. Effects of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane. Am J Vet Res. 2003 Sep;64(9):1155-60.

[13] Ochi H, Hara Y, Asou Y, Harada Y, Nezu Y, Yogo T, Shinomiya K, Tagawa M. Effects of long-term administration of carprofen on healing of a tibial osteotomy in dogs. Am J Vet Res. 2011 May;72(5):634-41.

[14] Dodwell ER, Latorre JG, Parisini E, Sweltler E, Chandra D, Mulpuri K, Snyder. NSAID exposure and risk of nonunion: a meta-analysis of case-control and cohort studies. Review Calcif Tissue Int. 2010 Sep;87(3):193-202.

[15] Gallaher HM, Butler JR, Wills RW, Priddy LB, Elder SH, Heller SM, Brinkman E, Baumgartner W. Effects of short- and long-term administration of nonsteroidal anti-inflammatory drugs on osteotomy healing in dogs. Vet Surg. 2019 Oct;48(7):1318-1329.

[16] Rushfeldt CR, Sveinbjørnsson B, Søreide K, Vonen B. Risk of anastomotic leakage with use of NSAIDs after gastrointestinal surgery. Review Int J Colorectal Dis. 2011 Dec;26(12):1501-9.

[17] Taylor PM, Luangdilok CH, Sear JW. Pharmacokinetic and pharmacodynamic evaluation of high doses of buprenorphine delivered via high-concentration formulations in cats. J Feline Med Surg. 2016 Apr;18(4):290-302

[18] Watanabe R, Monteiro BP, Evangelista MC, Castonguay A, Edge D, Steagall PV. The analgesic effects of buprenorphine (Vetergesic or Simbadol) in combination with carprofen in dogs undergoing ovariohysterectomy: a randomized, blinded, clinical trial. BMC Vet Res. 2018 Oct 5;14(1):304.

[19] Carlson AR, Nixon E, Jacob ME, Messenger KM. Sterility and concentration of liposomal bupivacaine single-use vial when used in a multiple-dose manner. Vet Surg. 2020 May;49(4):772-777

[20] Kinobe RT, Miyake Y. Evaluating the anti-inflammatory and analgesic properties of maropitant: A systematic review and meta-analysis. Meta-Analysis Vet J. May-Jun 2020;259-260:105471.

[21] Soares PCLR, Correa JMX, Niella RV, de Oliveria JNS, Costa BA, Silva AC, Sena AS, Pinto TM, Munhoz AD, Martins LAF, Silva EB, Lavor ML. Continuous Infusion of Ketamine and Lidocaine Either with or without Maropitant as an Adjuvant Agent for Analgesia in Female Dogs Undergoing Mastectomy. Vet Med Int. 2021 Jan 26;2021:4747301

[22] Hegron A, Peach CJ, Tonello R, Seemann P, Teng S, Latorre R, Huebner H, Weikert D, Rienties J, Veldhuis NA, Poole DP, Jensen DD, Thomsen ARB, Schmidt BL, Imlach WL, Gmeiner P, Bunnett NW. Therapeutic antagonism of the neurokinin 1 receptor in endosomes provides sustained pain relief. Proc Natl Acad Sci U S A. 2023 May 30;120(22):e2220979120

[23] Kukanich B, Papich MG. Pharmacokinetics of tramadol and the metabolite O-desmethlytramadol in dogs, J. Vet. Pharmacol. Therap. 27, 239–246, 2004

[24] McMillan CJ, Livingston A, Clark CR et al. Pharmacokinetics of intravenous tramadol in dogs. Can J Vet Res. 2008 Jul;72(4):325-31

[25] Donati PA, Tarragona L, Franco JVA, Kreil V, Fravega R, Diaz A, Verdier N, Otero PE. Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis. Vet Anaesth Analg. 2021 May;48(3):283-296.

[26] Pypendop BH, Ilkiw JE. Pharmacokinetics of tramadol, and its metabolite O-desmethyl-tramadol, in cats. J Vet Pharmacol Ther. 2008 Feb;31(1):52-9.

[27] Evangelista MC, Silva RA, Cardozo LB, Kahvegian MA, Rossetto TC, Matera JM, Fantoni DT. Comparison of preoperative tramadol and pethidine on postoperative pain in cats undergoing ovariohysterectomy. BMC Vet Res. 2014 Oct 15;10:252.

[28] Longmire DR, Jay GW, Boswell MV. Neuropathic Pain. In: Weiner's Pain Management, A Practical Guide for Clinicians, 7th ed. Boswell MV, Cole BE ed. Taylor & Francis, Boca Raton FL 2006, p. 305.

[29] Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2011 Mar 16;(3)

[30] Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain--a systematic review of randomized controlled trials.Pain. 2006 Dec 15;126(1-3):91-101

[31] Hurley RW, Coehn SP, Williams KA, et al. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med. 2006 May-Jun;31(3):237-47.

[32] Tippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg. 2007 Jun;104(6):1545-56

[33] Seib RK, Paul JE. Preoperative gabapentin for postoperative analgesia: a meta-analysis. Can J Anaesth. 2006 May;53(5):461-9.

[34]Clivatti J, Sakata RK, Issv AM. Review of the use of gabapentin in the control of postoperative pain. Rev Bras Anestesiol. 2009 Jan-Feb;59(1):87-98

[35]Dauri M, Faria S, Gatti A, et al. Gabapentin and pregabalin for the acute post-operative pain management. A systematic-narrative review of the recent clinical evidences. Curr Drug Targets. 2009 Aug;10(8):716-33

[36] Vollmer KO, von Hodenberg A, Kölle EU. Arzneimittelforschung. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. 1986 May;36(5):830-9.

[37] Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology. 2013 Nov;119(5):1215-21.

[38] Sikina ER, Bach JF, Lin Z, Gehring R, KuKanich B. Bioavailability of suppository acetaminophen in healthy and hospitalized ill dogs. J Vet Pharmacol Ther. 2018 May 13. doi: 10.1111/jvp.12664. [Epub ahead of print]

[39] Bello AM, Dye C. Current perceptions and use of paracetamol in dogs among veterinary surgeons working in the United Kingdom. Vet Med Sci. 2023 Mar;9(2):679-686.

[40] Benitez ME, Roush JK, McMurphy R, KuKanich B, Legallet C. Clinical efficacy of hydrocodone-acetaminophen and tramadol for control of postoperative pain in dogs following tibial plateau leveling osteotomy.

[41] Budsberg SC, Kleine SA, Norton MM, Sandberg GS, Papich MG. Comparison of the effects on lameness of orally administered acetaminophen-codeine and carprofen in dogs with experimentally induced synovitis. Am J Vet Res. 2020 Aug;81(8):627-634.

[42]Drygas KA, McClure SR, Goring L, Pozzi A, Robertson SA, Wang C. Effect of cold compression therapy on postoperative pain, swelling, range of motion, and lameness after tibial plateau leveling osteotomy in dogs. J Am Vet Med Assoc. 2011 May 15;238(10):1284-91.

[43] von Freeden N,, Duerr F, Fehr M, Diekmann C, Mandel C, Harms O. Comparison of two cold compression therapy protocols after tibial plateau leveling osteotomy in dogs. Tierarztl Prax Ausg K Kleintiere Heimtiere. 2017 Aug 10;45(4):226-233.

[44] Rogatko CP Baltzer WI, Tennant R. Preoperative low level laser therapy in dogs undergoing tibial plateau levelling osteotomy: A blinded, prospective, randomized clinical trial. Vet Comp Orthop Traumatol. 2017 Jan 16;30(1):46-53.

[45] Renwick SM, Renwick AI, Brodbelt DC, Ferguson J, Abreu H. nfluence of class IV laser therapy on the outcomes of tibial plateau leveling osteotomy in dogs. Vet Surg..2018 May;47(4):507-515.

[46] Kennedy KC, Martinez SA, Martinez SE, Tucker RL, Davies NM. Effects of low-level laser therapy on bone healing and signs of pain in dogs following tibial plateau leveling osteotomy. Am J Vet Res. 2018 Aug;79(8):893-904

INTRODUCTION TO THE USE OF SGLT2 INHIBITORS IN CATS WITH DIABETES

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SMALL ANIMAL

Introduction to the use of SGLT2 Inhibitors in Cats with Diabetes

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SGLT2 inhibitors are new drugs used to treat hyperglycemia due to diabetes mellitus. Two veterinary products have been recently approved for use in diabetic cats. SGLT2 inhibitors are promising new tools for effective management of feline diabetes. The current label indication for these drugs allows use in newly diagnosed diabetic cats that have not previously received insulin.

The sodium glucose co-transporter (SGLT) proteins family is widely expressed in tissues. These proteins transport sodium and glucose across cell membranes and serve as a cellular uptake mechanism for these substances. Two SGLT proteins, SGLT-1 and SGLT-2, expressed in intestine and renal tubules, have special relevance for glucose homeostasis in health and disease.[1] The intestinal brush border cells express SGLT-1 but not SGLT-2, while the renal proximal tubules express both SGLT-1 and SGLT-2, where both exert important functions. Within the proximal renal tubules, SGLT-2 is expressed exclusively on the apical membrane of epithelial cells lining the S1 and S2 segments while SGLT-1 is expressed only along the S3 segment. Both SGLT-1 and SGLT-2 have similar molecular actions: sodium and glucose in the luminal fluid bind to the SGLT protein located on the epithelial membrane and are co-transported across the membrane and released into the intracellular compartment.

The kidney has an important role in maintaining glucose homeostasis in health but may contribute to persistent hyperglycemia in diabetic individuals. Glucose is freely filtered at the renal glomerulus and is present in high concentration in the glomerular filtrate. In healthy individuals, re-uptake of the filtered glucose load is essentially 100% and effective glucose uptake requires SGLT activity. SGLT-2 activity accounts for 90% of glucose uptake from urine with the remaining uptake mediated by SGLT-1 activity. The importance of SGLT-2 for normal renal glucose handling is illustrated by familial renal glucosuria, a benign condition characterized by persistent and marked glucosuria, that is caused by genetic mutations that inactivate SGLT-2. The activity of SGLTs (primarily SGLT-2) establishes the renal 'threshold' for glucose. In diabetic individuals, hyperglycemia develops when insulin needs are not met and blood glucose may exceed the renal capacity for glucose absorption. When the physiologic threshold is exceeded (i.e. the filtered glucose load exceeds maximal SGLT activity) glucosuria results.

SGLT inhibitors are a family of drugs derived from phlorizin, a non-selective blocker of SGLT-1 and SGLT-2, that interferes with intestinal glucose uptake and produces glucosuria. Newer drugs, such as canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin are highly selective SGLT-2 inhibitors (SGLT-2i) and allow renal glucose handling to be specifically targeted. In diabetics, SGLT-2 inhibitors improve blood glucose and other measures of glycemia and are associated with a very low risk for hypoglycemia. Improved renal and cardiovascular outcomes in patients receiving SGLT-2 inhibitors have expanded the clinical indications for

these drugs.[1] Two SGLT2 inhibitors, bexagliflozin (Bexacat®) and velagliflozin (Senvelgo®. recently received FDA approval for veterinary use in cats as a treatment for newly diagnosed diabetes mellitus. Like other modern SGLT2i drugs, these veterinary SGLT2 inhibitors selectively produce renal glucosuria with minimal SGLT1-mediated gastrointestinal effects.

Initial experience with SGLT2 inhibitors for feline diabetes treatment has been very positive. Several US clinical studies have been reported on recently. [2,3] The SENSATION study included over 250 cats with naturally-occurring diabetes treated for 6 months using velagliflozin as the sole medical therapy (no concurrent insulin was given). The study examined the effect of treatment on relevant clinical and glycemic endpoints, such as improvement, respectively, in diabetes-associate clinical signs and laboratory parameters (fructosamine and mean blood glucose). [3] Velagliflozin treatment successfully lowered blood glucose and reduced clinical signs caused by diabetes in nearly 90% of study cats. The most serious adverse effect associated with velagliflozin use was EDKA[3]. EDKA is similar to the more familiar ketoacidosis of diabetes except the blood glucose is less than 250 mg/dl and may often be near or within the reference range[4,5]. EDKA treatment is identical to that for DKA with one exception. Along with administration of short-acting insulin to inhibit ketone formation, it is necessary to supplement glucose to prevent development of hypoglycemia during insulin treatment. EDKA, like DKA, develops when there is insulin deficiency. For this reason, a cat that develops EDKA while receiving an SGLT2i drug should be immediately taken off the drug and the drug permanently discontinued. After appropriate supportive care to resolve EDKA, the cat should be transitioned to a long-acting insulin and managed as an insulin-treated diabetic.

Overview of SGLT2 inhibitor use in diabetic cats

Indication and patient selection – SGLT2 inhibitors are labeled for once-daily use in diabetic cats that have not been treated with insulin. Contraindications include diabetic cats that have been previously treated with insulin, that have substantial systemic illness (vomiting, diarrhea, dehydration, concurrent morbidities), that have diabetic ketoacidosis (DKA) or signs consistent with DKA should not receive an SGLT2 inhibitor.

Formulations and dose information – Senvelgo (velagliflozin) is an flavored oral solution (15 mg/ml) and is dosed at 1 mg/kg given once daily. Bexacat (bexagliflozin) is a flavored tablet (15 mg) and is dosed at 15 mg (1 tablet) given once daily.

Monitoring – SGLT2 inhibitors are very effective for controlling glycemia in treated patients, so traditional monitoring used for diabetic cats may not provide helpful information. For example, data from bexagliflozin and velagliflozin studies suggests that glucose curves are not helpful for monitoring. Likewise, tests such as fructosamine or hemoglobin A1c, that reflect average glucose concentrations over time are less helpful in SGLT2 treated cats. Ketone monitoring is important since DKA/EDKA is the most serious diabetic complication that develops during SGLT2 use. Recommendations for ketone monitoring vary but regardless of the method used (blood ketometer or urine ketone dipstick) or testing protocol (frequency of testing, at-home vs clinic testing, etc) the goal is to detect significant ketosis as soon as possible to prevent onset of

clinical DKA/EDKA. Ketone testing prior to starting an SGLT2 inhibitor and follow-up testing after several days on the drug is important. Frequent monitoring of overall health, body weight, and ketones is important for the first several weeks after starting an SGLT2 inhibitor. In clinical trials, DKA/EDKA occurred most frequently in the 2 weeks following the initial dose of drug, although DKA/EDKA may occur at anytime during treatment. Like an insulin-treated diabetic, any cat receiving an SGLT2 inhibitor that becomes ill, cannot take oral medication should consult with or be evaluated by a veterinarian.

Summary

Velagliflozin and other SGLT2 inhibitors represent the first significant addition to the feline diabetes toolbox since veterinarians began using insulin to treat the condition decades ago. The introduction of SGLT2 inhibitors to the feline diabetes arena has ushered in exciting days. As we accrue valuable clinical experience with these drugs, we expect to gain additional insights into the biology and management of feline diabetes and envision new applications for these drugs in renal and cardiovascular in our veterinary patients.

References

1. John M, Gopinath D, Jagesh R. Sodium-glucose cotransporter 2 inhibitors with insulin in type 2 diabetes: Clinical perspectives. Indian J Endocrinol Metab. 2016 Jan-Feb;20(1):22-31. doi: 10.4103/2230-8210.172268. Erratum in: Indian J Endocrinol Metab. 2016 Nov-Dec;20(6):894.
2. Hadd MJ, Bienhoff SE, Little SE, Geller S, Ogne-Stevenson J, Dupree TJ, Scott-Moncrieff JC. Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus. J Vet Intern Med. 2023 May-Jun;37(3):915-924.
3. Behrend EN, Ward CR, Chukwu V, Cook AK, Kroh C, Lathan P, Schermerhorn T, Scott-Moncrieff JC, Voth R. Velagliflozin, an SGLT2 Inhibitor, as Once-Daily, Oral Solution, Stand-Alone Therapy for Feline Diabetes Mellitus. 2023 ACVIM Forum [abstract].
4. Nasa P, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: A missed diagnosis. World J Diabetes. 2021 May 15;12(5):514-523.
5. Plewa MC, Bryant M, King-Thiele R. Euglycemic Diabetic Ketoacidosis. [Updated 2023 Jan 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554570/ (accessed 5/1/2024).

TRANSFUSION MEDICINE: PREPARING PRODUCT & TESTING FOR ADMINISTRATION

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SMALL ANIMAL

Transfusion medicine: Preparing product and testing for administration

2024 86th Annual Kansas State College of Veterinary Medicine Conference

Jen Loewen, DVM, DACVECC

Objectives

1. Attendees will be able to describe what some options are for in clinic blood collection of small animals
2. Attendees will be able to justify the use of various blood product selection depending on the disease that is being treated
3. Attendees will be able to develop a transfusion plan including pre-testing, product volumes and monitoring for reactions

Transfusions can be a lifesaving treatment in emergency medicine. However, if done infrequently it can be a daunting task. There are many factors that you must consider when doing a transfusion including acquisition of the product, what product to give, pre-transfusion testing, monitoring during transfusion and identifying transfusion reactions.

While blood products can be purchased, it might not make financial sense to keep blood product on hand due to frequency you administer transfusion. However, often when blood products are needed, they are needed quickly and the patient cannot wait until the product can arrive (depending on your geographical location.

Collection can be done in house through volunteer (clients and the donor) who are ideally screened appropriately. Screening may vary depending on geographical location but recommend you follow the ACVIM consensus statement (Wardrop et al., 2016).

Dog anticoagulant collection reference (non-leukoreduced):

Anticoagulant	Ratio	Additive solution	PRBC shelf life	Whole blood shelf life
CPD	1ml : 7 ml blood	SAGM	42 days	
CPD	1ml : 7 ml blood	AS-1 or AS-5	35 days	
CP2D	1ml : 7 ml blood	AS-3	35 days	
CPDA-1	1ml : 7 ml blood			28 days
CPD	1ml : 7 ml blood			21 days
ACD	1 ml: 7-9 ml blood			21 days
Heparin	5-12.5 U/ml blood			Immediate

Modified from Manual of Veterinary Transfusion and blood banking

Sometimes, the donors require sedation. The use of trazodone and/or gabapentin is fine to use. I generally follow the Canadian Blood Bank for what humans can be on and extrapolate to animals for medications (https://www.blood.ca/en/blood/am-i-eligible-donate-blood/abcs-eligibility#medication). Also see the Red Cross list (https://www.redcrossblood.org/faq.html#eligibility-medications). In general we want them to be overall healthy but there are some medications that are ok. Sometimes dogs need some

butorphanol to lay still for the sedation but ideally the dogs are happy to lay on their sides for the donation.

Cats often need sedation. Again the use of gabapentin is fine to decrease the stress. There are a variety of sedation protocols that have been deemed safe in cats with donation including

- 2 mg/kg alfaxalone + 0.2 mg/kg butorphanol IM
- 2 mg/kg alfaxalone + 0.2 mg/kg butorphanol + 0.2 mg/kg midazolam
- 2-5 mg/kg ketamine + 0.2 mg/kg midazolam IM

See (Taylor S, Spada E, Callan MB, et al. 2021 ISFM Consensus Guidelines on the Collection and Administration of Blood and Blood Products in Cats. Journal of Feline Medicine and Surgery. 2021;23(5):410-432. doi:10.1177/1098612X211007071) for more information.

Component therapy is the separation of whole blood before storage. This is now commonplace in human medicine and very common in veterinary medicine. Whole blood can be separated into several components including plasma, packed red blood cells, cryoprecipitate and platelets to name a few. These can also be further classified depending on the way the product is handled. Component therapy allows us to give the constituents that the patient needs. Below is a chart that includes various blood products, what is in it and how it is stored.

Table 1: Blood products, content and storage

	Content	**Storage conditions**
Fresh whole blood		Room temperature for up to 8 hours
Stored whole blood	Lacking in viable platelets and labile factors (5 and 8)	Refrigerated at 1-6ºC for up to 28 days (pending preservative)
Packed red blood cells	Contains RBC, WBC, non-viable platelets, and small amount of plasma	Refrigerated at 1-6ºC for up to 42 days (pending preservative)
Fresh frozen plasma	All coagulation factors, albumin, globulin	Frozen at ≤–18 ∘C for up to 12 months
Frozen plasma	All coagulation factors (lower concentrations of factor 5, 8 and vWF), albumin, globulin	Frozen at ≤–18 ∘C for up to 5 years
Liquid plasma	All coagulation factors, albumin, globulin	Refrigerated at 1–6 ∘C for up to 14 days
Cryoprecipitate	Factors 8, 13, vWF, fibrinogen and fibronectin	Frozen at≤–18 ∘C for up to 12 months
Lyophilized cryoprecipitate	Factors 8, 13, vWF, fibrinogen and fibronectin	Refrigerated at 1–6 ∘C for up to 18 months
Platelet rich plasma	Platelets, all coagulation factors, albumin, globulin	Room temperature storage under constant gentle agitation for up to 5 days

Platelet concentrate	Platelets, low volume of fresh plasma	Room temperature storage under constant gentle agitation for up to 5 days
DMSO preserved frozen platelet concentrate	Platelets, small volume of plasma, 6% dimethyl sulfoxide	Frozen at≤–18 ∘C for up to 6 months
Lyophilized platelets		Refrigerated at 1–6 ∘C for up to 24 months

Modified from Walker, J. (2016) Component therapy, In Manual of Veterinary Transfusion medicine and blood banking (ed. M. Holowaychuk, K. Yagi) John Wiley & Soms, Inc., Ames, Iowa

Once you determine which product is needed, it is important to know which testing is required before giving the transfusion. Dogs have a universal donor which is DEA 1 negative. Because of this, if you have a canine recipient who is receiving blood and you only stock or have access to DEA 1 negative blood, no testing is required. If you have access to positive and negative blood, the recipient should be blood typed first. No testing is required before giving a plasma transfusion to dogs.

Cats do not have a universal donor. Cats must be typed before receiving ANY blood product (red blood cells or plasma). It is controversial in the literature whether cats should be cross matched before receiving their first transfusion however the one prospective study suggests that it doesn't make a difference. Current recommendations are recommending cross matching.

Cross matches should be performed if the recipient has received a red blood cell transfusion greater than 4 days earlier; if you are within that window from their first transfusion, you do not need to crossmatch. Cross matching should also be considered if the patient is within that window but has had evidence of a reaction on a previous transfusion or if the transfusion history is unknown (a rescue dog). Pregnancy does not appear to cause the formation of alloantibodies.

For more information on cross matching look at (Davidow et al., 2021) and associated open access articles

There have been a variety of calculations that have been used in the past to estimate the amount of blood product to give. Generally you want to increase the PCV by ~10% but this can vary depending on the case. The current recommendations are:

Whole blood: 2 ml/kg to increase the PCV by 1%

Packed red blood cells: 1.5 ml/kg to increase the PCV by 1%

Plasma: 10-20 ml/kg to start

Note: in a study done with cat transfusions, no calculation appeared to work well. Generally an adult cat will get 1 unit (60 ml depending on who is providing the product)(Davidow et al., 2021) *and then reassess to see if more is needed (author's opinion).*

Generally when giving a transfusion we start at a slow rate and slowly increase the rate over the first hour to our maximum rate. The maximum rate is then continued over the next 3 hours to get the blood product into the patient in under 4 hours. The author generally starts at 0.5-1 ml/kg/hr for the starting rate. To determine the final rate the author divides the total volume by 3 hours, as not much product is being delivered over the first hour. During the first hour the rate is slowly increased to get from the starting rate to the maximum rate.

Transfusion reactions can be divided into immunologic and non-immunologic reactions. Non-immunologic reactions can include hypothermia, hypocalcemia (citrate toxicity), sepsis, transfusion associated circulatory overload and embolism. Immunologic reactions can include hemolysis, nonhemolytic febrile reaction, an acute hypersensitivity reaction and transfusion related acute lung injury. Monitoring the patient during the transfusion can lead to early detection of these reactions so they can be addressed quickly. There is no consensus for the ideal monitoring however the author recommends checking temperature, pulse and respiration every 15 minutes for the first hour then hourly during the transfusion. The recipient should also be monitored for facial swelling, tachypnea, vomiting and hives. If there are any concerns for a reaction, the transfusion should first be stopped and the patient should be assessed. For some of the reactions, the transfusion rate is just slowed, however some require treatment. Remember that an acute type one allergic reaction (urticaria, angioedema) is the only IgE mediated reaction and is the only one that will respond to diphenhydramine. Other transfusion reactions require that we treat the symptoms that are seen. For example, if the patient has citrate toxicity from having multiple transfusions and are hypocalcemic, they should receive a 10% calcium bolus over 10-20 minutes IV while monitoring an ECG and possibly a CRI. If the patient has evidence of transfusion associated circulatory overload, the transfusion should be discontinued, and they should be given oxygen therapy and possibly furosemide depending on other comorbidities.

The use of component therapy decreases the amount of antigen that we are giving to the recipient and in theory decreases the risk of a transfusion reaction. Understanding what the recipient needs can help guide the product that you chose to give the patient. Once you know the component, the pretesting can be determined and volume to be administered can be easily calculated. Being familiar with the various reactions can help you monitor for them and intervene if needed.

References:

Yagi, K., Holowaychuk, M. (eds) (2016) Manual of Veterinary Transfusion Medicine and Blood Banking. John Wiley & Soms, Inc., Ames, Iowa

Blais, M.C., Rozanski, E.A., Hale, A.S., *et al*. (2009) Lack of evidence of pregnancy-induced alloantibodies in dogs. J Vet Intern Med 23(3), 462–465.

Sylvane B, Prittie J, Hohenhaus AE, Tozier E. (2018) Effect of cross match on packed cell volume after transfusion of packed red blood cells in transfusion-naïve anemic cats. J Vet Intern Med. 32(3):1077-1083.

Short JL, Diehl S, Seshadri R, Serrano S. (2012) Accuracy of formulas used to predict post-transfusion packed cell volume rise in anemic dogs. J Vet Emerg Crit Care. ;22(4):428-34.

Davidow, E. B., Blois, S. L., Goy-Thollot, I., et al (2021). Association of Veterinary Hematology and Transfusion Medicine (AVHTM) Transfusion Reaction Small Animal Consensus Statement (TRACS) Part 2: Prevention and monitoring. *Journal of Veterinary Emergency and Critical Care*, *31*(2), 167–188. https://doi.org/10.1111/vec.13045

Wardrop, K. J., Birkenheuer, A., Blais, M. C., Callan, M. B., Kohn, B., Lappin, M. R., & Sykes, J. (2016). Update on Canine and Feline Blood Donor Screening for Blood-Borne Pathogens. *Journal of Veterinary Internal Medicine*, *30*(1), 15–35. https://doi.org/10.1111/jvim.13823

Taylor S, Spada E, Callan MB, et al. 2021 ISFM Consensus Guidelines on the Collection and Administration of Blood and Blood Products in Cats. Journal of Feline Medicine and Surgery. 2021;23(5):410-432. doi:10.1177/1098612X211007071

A LITTLE SWEET, A LITTLE SOUR: APPROACH TO DIABETIC KETOACIDOSIS

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SMALL ANIMAL

A little sweet, a little sour: Diabetic Ketoacidosis Management

2024 86th Annual Kansas State College of Veterinary Medicine Conference

Jen Loewen, DVM, DACVECC

Objectives

1. Attendees will be able to list predisposing causes for DKA
2. Attendees will be able to discuss the benefits and limitations of diagnostic tests to recommend to clients.
3. Attendees will be able to develop a treatment plan for DKA including electrolyte monitoring and management and insulin protocols.

Diabetic ketoacidosis should be considered as a differential in any sick patient with a pre-existing diagnosis of diabetes. DKA is also diagnosed in a lot of patients at the time of diagnosis of their diabetes mellitus and quick bed side testing of emergency cases that include a BG can help assist in this.

An important thing to remember in the treatment of patients of DKA, is that not only does the DKA need to be managed but ideally a work up is performed for an underlying cause for the DKA. Some listed causes for pushing a dog or cat with controlled DM into a DKA crisis include:

Dogs	Cats
• Pancreatitis • Cushings • Neoplasia • UTI/pyelonephritis • Hypothyroid • Pneumonia	• Hepatic lipidosis • Cholangiohepatitis • UTI/pyelonephritis • Neoplasia • Pancreatitis

*Note your physical exam may also assist in narrowing down these options

Some specific tests to consider when working up a sick diabetic include:

1. Measurement of Ketones
    a. Urine dipstick
        i. Both serum/plasma or urine can be used
            1. Serum/plasma is more sensitive
        ii. Is most sensitive to measuring **acetoacetate** (less so acetate and doesn't measure Beta Hydroxybutyrate) (Gal & Odunayo, 2023)
    b. Ketometer
        i. Uses whole blood
        ii. Measures **Beta hydroxybutyrate**
            1. Dogs > 3.5 mmol/L (unlikely if < 2.8 mmol/L)
            2. Cats > 2.55 mmol/L
2. Measurement of Acid/base
    a. Evaluation of pH on a blood gas/istat

   b. Evaluation of HCO3- or bicarb
3. Additional tests pending the differentials on the list
   a. CBC/CHEM/UA/URINE CULTURE
   b. Abdominal ultrasound
   c. Chest radiographs

Usually the most important initial treatments for patients in DKA is fluid therapy and correction of electrolytes. While insulin is important, it is not an emergency to start it. Ensuring that the patient is hemodynamically stable should be done first. If the patient is believed to be hypovolemic on PE assessment- fluid boluses should be initiated. This is generally done with a balanced, buffered, isotonic, replacement crystalloid (Plasmalyte, Norm-R, LRS etc). The total shock dose in dogs is 90 ml/kg and the total shock dose in a cat is 60 ml/kg. Shock boluses are typically administered in ¼ shock alliquots (20 ml/kg in dog, 15 ml/kg in cat over 10-15 minutes) unless reason to give less or slower- murmur, history of heart disease for example.

The three main electrolytes that we consider and need to address are:

1. Potassium
   a. Usually the body is deplete of potassium but due to shifting in acidosis, this may not be reflected in the bloodwork (remember potassium is predominantly located inside of the cell) – but monitor closely for it because **once the pH is corrected and the insulin is started it may drop quickly**. I personally prefer a chart similar to the one on the right where the rate is considered rather than choosing the amount to add based on mEq/L because that doesn't take the fluid rate into account. (see below for the equation to use and an example)
   b. Note shouldn't exceed 80 mEq/L in a peripheral vessel

Scott's sliding scale → helpful in a hurry
but not as accurate as it doesn't take fluid rate into account

K concentration (mmol/L)	Potassium supplementation (mEq/ L)
<2	80
2-2.4	60
2.5-2.9	40
3-3.4	30
3.5-5	20

K concentration (mmol/L)	Rate of K+ potassium supplementation (mEq/kg/hr)
<2	0.5
2-2.4	0.3-0.4
2.5-2.9	0.2-0.3
3-3.4	0.1-0.2
3.5-5	0.05-0.1

Don't exceed 0.5 mEq/kg/hr

'- Note if the potassium seems resistant to supplementation- the patient may be deplete in magnesium

2. Phosphorus
   a. Phosphorus can start all over the place depending on additional underlying disease (such as an acute kidney injury due to a pyelonephritis). However,

once insulin therapy is started, it can decrease quickly and require supplementation. Red blood cells are particularly susceptible to hypophosphatemia due to their dependence on ATP and can lyse (phos < 1.5 mg/dL). At time of insulin starting- if the phosphorus is normal, many suggest starting to supplement.

i. Suggested rates of supplementation: 0.03 mmol/kg/hr – 0.12 mmol/kg/hr
    1. Note for author- if phos is mildly low, start at least at 0.06 mmol/kg/hr

3. Sodium
    a. Patients with DKA are often hyponatremic. Not because they are actually deplete of sodium but because the extra glucose is causing osmotic shifts and diluting out the sodium. You can correct for this with
        i. Corrected Sodium= measured sodium +[1.6 (glucose-100)/100]

Fluid math equations

Body weight (kg)x rate of supplementation(mEq/kg.hr) x 1/fluid rate(ml/hr) x final volume(ml/L) = mEq/bag (usually mEq/L)

Note this is written for units for potassium but can be used for other supplements such as CRIs of phosphorus, or medications (pain medications, metoclopramide, lidocaine etc).

Example: Body weight: 10 kg, K+ on bloodwork: 2.8 , fluid rate: 30 ml/hr

Body weight	Rate or supp	Inverted fluid rate	Final bag size		
10 kg	0.2 mEq	hr	1000 ml	=	66.7 mEq
	kg.hr	30 ml	L		L

10 kg x 0.2 mEq/kg/hr x hr/30 ml x 1000 ml/ L = 66.7 mEq/L

Cheat method of calculating Phosphorus and potassium (because phosphorus comes as Potassium Phosphorus)

1) Determine amount of K+ needed (mEq/L)

2) If potassium and phos relatively normal or low normal at starting Insulin → targeting 0.1-0.2 mEq/kg/hr K+

Using the higher end of K+ supplementation compared to a normal patient because going to be adding insulin

3) Do ½ potassium from KCl and ½ from Kphos

Example: if need 66 mEq/L of K → 33 mEq of K from KCl and 33 mEq of K from KPhos

Insulin protocols

Initiation of insulin remains controversial but it appears that it can be started fairly quickly. You should correct electrolytes (Potassium and phosphorus) first to avoid later complications as they will continue to drop with insulin therapy.

IV Humulin R protocol

Blood glucose concentration	Fluid type (250 ml bag)	Rate of admin of insulin solution	*Rate of insulin*
>250 mg/dL	0.9% NaCl	10 ml/hr	*0.09 U/kg/hr*
200-250 mg/dL	0.9% NaCl +2.5% dextrose	7 ml/hr	*0.064 U/kg/hr*
150-199 mg/dL	0.9% NaCl + 2.5% dextrose	5 ml/hr	*0.045 U/kg/hr*
100-149 mg/dL	0.9% NaCl + 5% dextrose	5 ml/hr	*0.045 U/kg/hr*
<100 mg/dL	----	Stop insulin infusion	*0*

Add 2.2 U/kg of Humulin R to 250 ml bag of saline

Note- Author uses the same dose for dogs and cats

The bag is good for 24 hours and you need to run the solution through the fluid bag because it binds to plastic

IM protocol- administered every 2-4 hours

Blood glucose concentration	IM dose of Humulin R	Dextrose supplementation
>250 mg/dL	0.2 U/kg	none
200-250 mg/dL	0.1 U/kg	2.5% administered at maintenance rate
150-199 mg/dL	0.1 U/kg	5% administered at maintenance rate
100-149 mg/dL	----	5% administered at maintenance rate
<100 mg/dL	----	5% administered at maintenance rate

Other protocols

1. Glargine alone protocol(Marshall et al., 2013)
    a. Initial injection: 1-2 U/cat IM + 1-3 U/cat SQ
        i. IM repeated at dose of 1-2 U/cat IM q 2 hours or more often
        ii. SQ repeated at dose of 1-2 U SQ q 12 hours
2. Glargine SQ + Humulin R IM
    a. 0.25 U/kg glargine SQ q 12 hours
    +
    b. 1 U/cat of regular insulin IM q 6 hours if BG > 250 mg/dL
3. Lispro
    a. IV in dogs and cats- Same as the IV Humulin R protocol but used 2.2 U/kg of Lispro into a 250 ml bag of 0.9% NaCl(Sears et al., 2012)
    b. IM in dogs: 0.25 U/kg IM q 1 hour until BG < 10% then 0.125 U/kg IM q 3 hours (Malerba et al., 2020)

References

Gal, A., & Odunayo, A. (2023). Diabetes Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome in Companion Animals. *Veterinary Clinics: Small Animal Practice*, *53*(3), 531–550. https://doi.org/10.1016/j.cvsm.2023.01.005

Malerba, E., Alessandrini, F., Grossi, G., Giunti, M., & Fracassi, F. (2020). Efficacy and Safety of Intramuscular Insulin Lispro vs. Continuous Intravenous Regular Insulin for the Treatment of Dogs With Diabetic Ketoacidosis. *Frontiers in Veterinary Science*, *7*. https://www.frontiersin.org/articles/10.3389/fvets.2020.559008

Marshall, R. D., Rand, J. S., Gunew, M. N., & Menrath, V. H. (2013). Intramuscular glargine with or without concurrent subcutaneous administration for treatment of feline diabetic ketoacidosis. *Journal of Veterinary Emergency and Critical Care*, *23*(3), 286–290. https://doi.org/10.1111/vec.12038

Sears, K. W., Drobatz, K. J., & Hess, R. S. (2012). Use of lispro insulin for treatment of diabetic ketoacidosis in dogs. *Journal of Veterinary Emergency and Critical Care*, *22*(2), 211–218. https://doi.org/10.1111/j.1476-4431.2012.00719.x

PAWING THROUGH POISONS: MANAGEMENT OF SMALL ANIMAL TOXICITY

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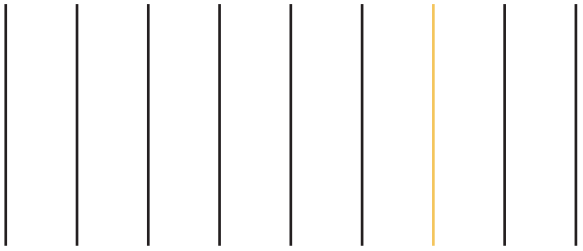

SMALL ANIMAL

Toxicity Management in Small Animals

2024 86th Annual Kansas State College of Veterinary Medicine Conference

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Objectives

1. Attendees will be able to describe the general approach to intoxications
2. Attendees will be able to describe common decontamination strategies
3. Attendees will be able to develop treatment plans (including antidotes when possible) for several common toxicities

Dogs and cats will eat some bizarre toxins. Some of these toxins we see frequently, and we don't need additional information, but sometimes the toxins are ones we rarely deal with or haven't heard of/dealt with before. Having a systematic approach to small animal toxins can be very helpful. The general approach to an intoxication is:

- Gather information about exposure and patient
- Learn about the toxin
- Decontamination
- Provide toxin antidote when possible
- Decrease toxin absorption
- Enhance toxin elimination
- General supportive therapy

There are a lot of resources available to help with toxicities. I have listed some that I have found helpful but there are likely a lot more than this (note I have no affiliation with any of these resources and I like to support my information on a toxin from more than one resource)

- ASPCA pet poison line or Pet poison hotline (note fees apply*)
- Blackwell's 5 minute veterinary consult- Small animal toxicology 2nd edition
- Pet poison app VetCPD 
- American College of Veterinary pharmacists- https://vetmeds.org/pet-poison-control/#
- Plant identification Facebook group: https://www.facebook.com/groups/144798092849300/
- Veterinary Information Network

For most toxins, when it is safe to do so, we want to decontaminate. For the gastrointestinal tract, this could mean inducing emesis and potentially being as aggressive as gastric lavage or endoscopy. In dogs, the dose of apomorphine that I use is 0.03 mg/kg IV or 0.04 IM (can be repeated if needed). In cats I generally use 8 mcg/kg of dexmedetomidine or 0.05 mg/kg hydromorphone SQ. Xylazine can be used in cats, but studies suggest that it doesn't work as well. Hydrogen peroxide should not be used in cats due to the risk of severe hemorrhagic gastroenteritis. Somethings we want to consider before decontaminating include:

- Is the animal alert enough to have a protected airway?

- Could the toxin cause harm being vomited up?
- When was the toxin ingested and do the benefits outweigh the risk on inducing emesis?
- Does the toxin bind to charcoal?

Other areas that we may need to decontaminate are the skin (consider putting an e-collar on to prevent continued grooming and ingestion) or ocular.

Some toxins we can treat with antidotes that either have a direct reaction with the toxicant, interact with the toxicants receptor or alter its metabolism.

To decrease absorption, charcoal can be given. Additionally, some toxins like methylxanthines can be reabsorbed from the bladder and allowing for frequent urination may decrease this risk.

Enhancing elimination decreases the time allowed for absorption. This could include the use of sorbitol in the first dose of charcoal, IV fluids to flush toxins out of the kidneys (may be dogma) may help. Hemodialysis may also be an option but goes beyond the scope of this lecture. Intravenous lipid emulsion can help with if the toxicant if lipid soluble. With the assistance of google, you can often find if the logP of a toxicant is > 1 → this means that lipid emulsion may work. The exact dosing isn't known but often includes 1.5 ml/kg bolus over 1-3 minutes and/or a CRI of 0.25 mg/kg/min over 30-60 minutes. This dose can be repeated in several hours if the serum or plasma is no longer lipemic.

References

- Osweiler GD, et al. 2011. *Blackwell's five-minute veterinary consult clinical companion: Small animal toxicology*. Ames, IA: Wiley-Blackwell.
- Peterson ME, Talcott PA. 2006. *Small Animal Toxicology, 2nd Edition*. St. Louis: Saunders Elsevier.
- Silverstein DC, Hopper K. 2009. *Small Animal Critical Care Medicine.* St. Louis

HIGH VOLUME HIGH QUALITY SPAY NEUTER TECHNIQUES

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SMALL ANIMAL

High Volume High Quality Spay Neuter Techniques

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KSU SSLS PhD Student - Leadership Communication
Professional Interests
- Shelter Medicine/Outreach (Limited Resource Medicine)
- Community Engagement Scholarship of Teaching and Learning

Agenda

6.3.24

- Set Goal
- Why Implement Change?
- Importance of Team
- Resources
- Canine Spay
- Feline Spay
- Canine Castration

Goal

One Technique for Each Procedure

In-depth, hands on training takes 100+ hours.
This is the first step.

Why Implement Change?

Business-side

- Cheaper
- Faster
- Fewer Materials
- Can Serve More Clients

Medicine-side

- Less Time Under Anesthesia
- Fewer Complications
- Overpopulation
- Always Have a Reason

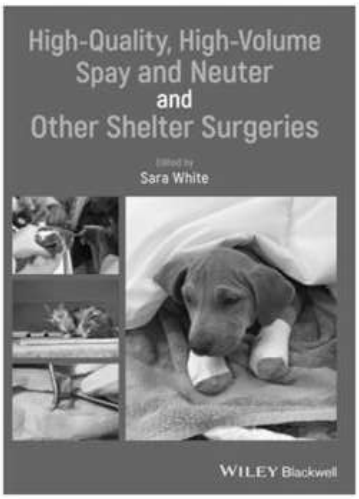
Always Have a Reason

Importance of Team

Veterinarians often not the most important member of that team

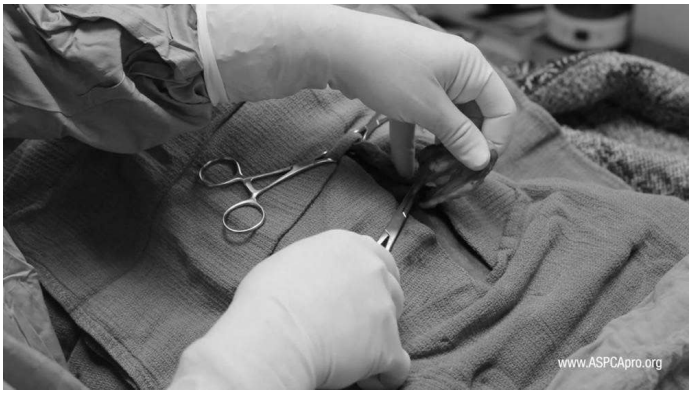
- Scheduling
- Prep
- Drug protocol
- Timing
- Recovery
- Etc.

Resources



Canine Spay - Ovarian Cutaway

After ovary exteriorized and clamps placed but *before* ligature placement.
Transect distal to carmalt to allow greater visualization.



Canine Spay - Ovarian Cutaway Reasons

Pros

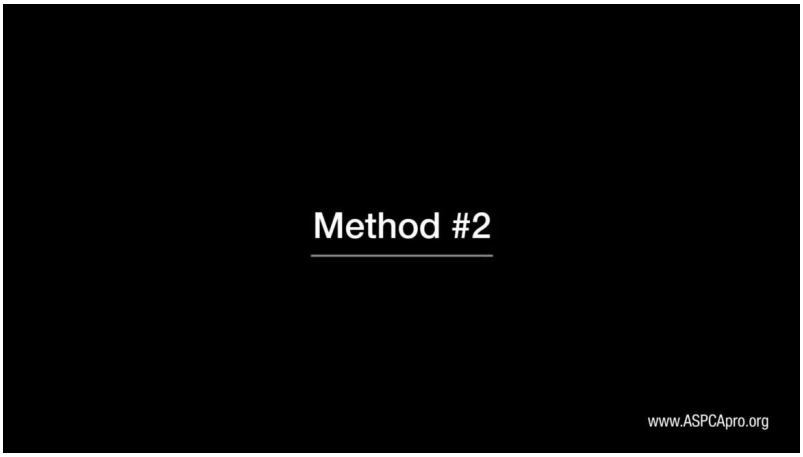
- Ligature can be placed with less manipulation of the tissue.
- Visibility is increased compared to ligating prior to transecting ovary.
- Greater technical efficiency tying over a transected end.

Cons

- Technique
  - Only clamp pedicle, not drape, skin, other tissue
- Instruments
  - Touchy clamp
- Verify all ovarian tissue excised

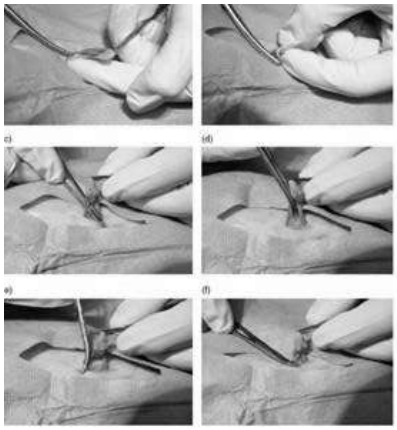
Feline Spay - Ovarian Pedicle Autoligation

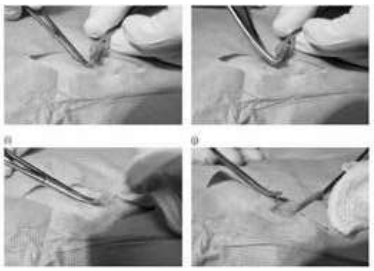
After suspensory ligament ruptured and window in broad ligament but *before* ligature placement. Can use same technique as autoligating feline spermatic cord.



Feline Feline Spay - Ovarian Pedicle Autoligation

Uterine horn and ovary pulled toward surgeon.
With hemostat closed, cross over the vessels and place into the window in the broad ligament behind the ovarian vessels.
With tip of hemostats facing away from surgeon, rotate instrument counterclockwise until tip faces surgeon.
Open hemostat and clamp ovarian vessels.
Transect and gently push the knot off the end of the instrument.





Feline Spay - Pedicle Tie Reasons

Pros

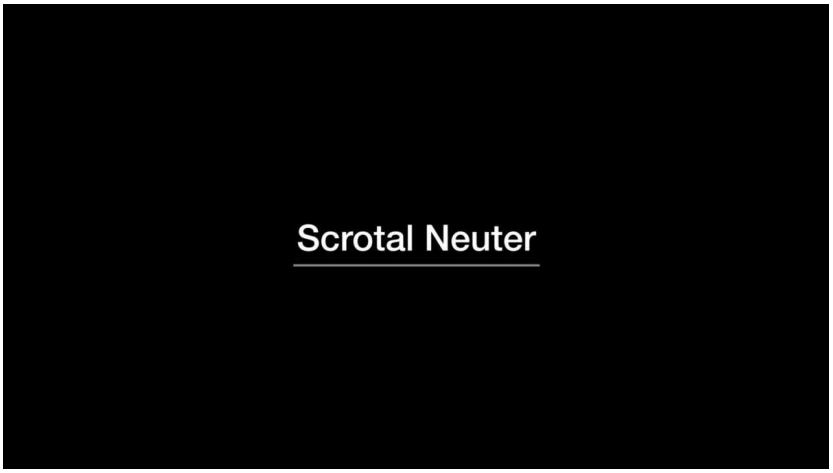
- Efficiency
  - Fast; No instruments impeding view and hands
- Technique
  - As safe as suture ligatures
- Less material
  - No suture needed at this step

Cons

- Technique
  - Inappropriate tension most common complication for new surgeons
- Muscle memory
  - There are other approaches
- Can’t use for every single patient
  - Vascular plexus

Canine Scrotal Castration

Surgical approach on ventral most aspect of scrotum, as opposed to pre-scrotal.
Once testicle is exteriorized, ligation can be surgeon's preference.
Surgeon’s preference on closure; Technically left open
- Single interrupted vs. none



Canine Scrotal Castration

Pros

- Efficiency
  - Fast
- Decreased Complication Rate
  - No instruments impeding view and hands
- Less Material
  - Fewer instruments and less suture needed.

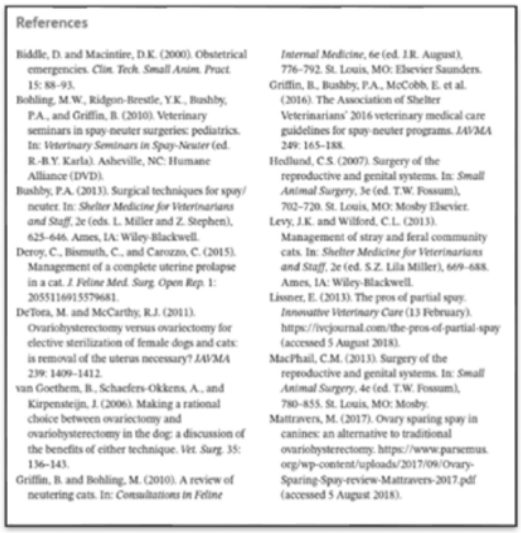
Cons

- Communication
  - Owners must know and consent
- Post-op Drip
  - A feature and a bug
- Colleagues
  - Established practitioners unaware of the evidence

Takeaways

Have a reason for why you do something
These and other HVHQSN techniques can save money and time while reducing complications.
Find quality resources to further evolve your practice.
Making the most out of HVHQSN practices requires the whole team.

References



References

Biddle, D. and Macintire, D.K. (2000). Obstetrical emergencies. *Clin. Tech. Small Anim. Pract.* 15: 88–93.

Bohling, M.W., Ridgon-Brestle, Y.K., Bushby, P.A., and Griffin, B. (2010). Veterinary seminars in spay-neuter surgeries: pediatrics. In: *Veterinary Seminars in Spay-Neuter* (ed. R.-B.Y. Karla). Asheville, NC: Humane Alliance (DVD).

Bushby, P.A. (2013). Surgical techniques for spay/neuter. In: *Shelter Medicine for Veterinarians and Staff*, 2e (eds. L. Miller and Z. Stephen), 625–646. Ames, IA: Wiley-Blackwell.

Deroy, C., Bismuth, C., and Carozzo, C. (2015). Management of a complete uterine prolapse in a cat. *J. Feline Med. Surg. Open Rep.* 1: 2055116915579681.

DeTora, M. and McCarthy, R.J. (2011). Ovariohysterectomy versus ovariectomy for elective sterilization of female dogs and cats: is removal of the uterus necessary? *JAVMA* 239: 1409–1412.

van Goethem, B., Schaefers-Okkens, A., and Kirpensteijn, J. (2006). Making a rational choice between ovariectomy and ovariohysterectomy in the dog: a discussion of the benefits of either technique. *Vet. Surg.* 35: 136–143.

Griffin, B. and Bohling, M. (2010). A review of neutering cats. In: *Consultations in Feline Internal Medicine*, 6e (ed. J.R. August), 776–792. St. Louis, MO: Elsevier Saunders.

Griffin, B., Bushby, P.A., McCobb, E. et al. (2016). The Association of Shelter Veterinarians' 2016 veterinary medical care guidelines for spay-neuter programs. *JAVMA* 249: 165–188.

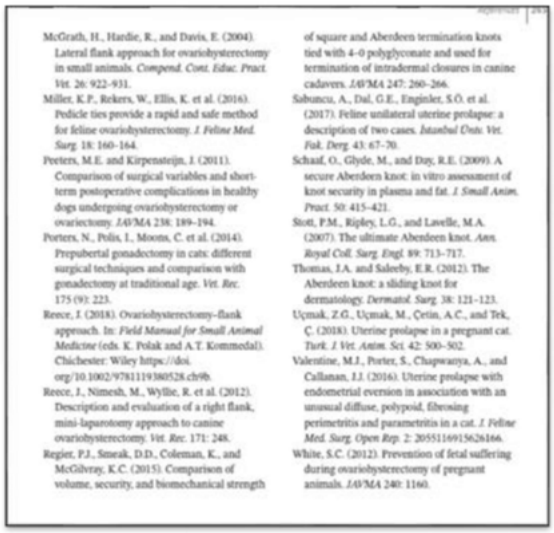
Hedlund, C.S. (2007). Surgery of the reproductive and genital systems. In: *Small Animal Surgery*, 3e (ed. T.W. Fossum), 702–720. St. Louis, MO: Mosby Elsevier.

Levy, J.K. and Wilford, C.L. (2013). Management of stray and feral community cats. In: *Shelter Medicine for Veterinarians and Staff*, 2e (ed. S.Z. Lila Miller), 669–688. Ames, IA: Wiley-Blackwell.

Lissner, E. (2013). The pros of partial spay. *Innovative Veterinary Care* (13 February). https://ivcjournal.com/the-pros-of-partial-spay (accessed 5 August 2018).

MacPhail, C.M. (2013). Surgery of the reproductive and genital systems. In: *Small Animal Surgery*, 4e (ed. T.W. Fossum), 780–855. St. Louis, MO: Mosby.

Mattravers, M. (2017). Ovary sparing spay in canines: an alternative to traditional ovariohysterectomy. https://www.parsemus.org/wp-content/uploads/2017/09/Ovary-Sparing-Spay-review-Mattravers-2017.pdf (accessed 5 August 2018).



McGrath, H., Hardie, R., and Davis, E. (2004). Lateral flank approach for ovariohysterectomy in small animals. *Compend. Cont. Educ. Pract. Vet.* 26: 922–931.

Miller, K.P., Rekers, W., Ellis, K. et al. (2016). Pedicle ties provide a rapid and safe method for feline ovariohysterectomy. *J. Feline Med. Surg.* 18: 160–164.

Peeters, M.E. and Kirpensteijn, J. (2011). Comparison of surgical variables and short-term postoperative complications in healthy dogs undergoing ovariohysterectomy or ovariectomy. *JAVMA* 238: 189–194.

Porters, N., Polis, I., Moons, C. et al. (2014). Prepubertal gonadectomy in cats: different surgical techniques and comparison with gonadectomy at traditional age. *Vet. Rec.* 175 (9): 223.

Reece, J. (2018). Ovariohysterectomy–flank approach. In: *Field Manual for Small Animal Medicine* (eds. K. Polak and A.T. Kommedal). Chichester: Wiley https://doi.org/10.1002/9781119380528.ch9b.

Reece, J., Nimesh, M., Wyllie, R. et al. (2012). Description and evaluation of a right flank, mini-laparotomy approach to canine ovariohysterectomy. *Vet. Rec.* 171: 248.

Regier, P.J., Smeak, D.D., Coleman, K., and McGilvray, K.C. (2015). Comparison of volume, security, and biomechanical strength of square and Aberdeen termination knots tied with 4–0 polyglyconate and used for termination of intradermal closures in canine cadavers. *JAVMA* 247: 260–266.

Sabuncu, A., Dal, G.E., Enginler, S.Ö. et al. (2017). Feline unilateral uterine prolapse: a description of two cases. *Istanbul Univ. Vet. Fak. Derg.* 43: 67–70.

Schaaf, O., Glyde, M., and Day, R.E. (2009). A secure Aberdeen knot: in vitro assessment of knot security in plasma and fat. *J. Small Anim. Pract.* 50: 415–421.

Stott, P.M., Ripley, L.G., and Lavelle, M.A. (2007). The ultimate Aberdeen knot. *Ann. Royal Coll. Surg. Engl.* 89: 713–717.

Thomas, J.A. and Saleeby, E.R. (2012). The Aberdeen knot: a sliding knot for dermatology. *Dermatol. Surg.* 38: 121–123.

Uçmak, Z.G., Uçmak, M., Çetin, A.C., and Tek, Ç. (2018). Uterine prolapse in a pregnant cat. *Turk. J. Vet. Anim. Sci.* 42: 500–502.

Valentine, M.J., Porter, S., Chapwanya, A., and Callanan, J.J. (2016). Uterine prolapse with endometrial eversion in association with an unusual diffuse, polypoid, fibrosing perimetritis and parametritis in a cat. *J. Feline Med. Surg. Open Rep.* 2: 2055116915626166.

White, S.C. (2012). Prevention of fetal suffering during ovariohysterectomy of pregnant animals. *JAVMA* 240: 1160.

Questions

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POINT-OF-CARE ULTRASONOGRAPHY

MACKENZIE HALLMAN
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SMALL ANIMAL

Point-of-Care Veterinary Ultrasonography

Kansas State University Annual Conference for Veterinarians

June 3, 2024

Manhattan, Kansas

Speaker: Mackenzie Hallman, DVM, DACVR. Assistant Clinical Professor of diagnostic imaging at Kansas State University.

Lecture Hours: 2

Reference: The format of this session is based on proceedings provided by Dr. Søren Boysen, DVM, DACVECC, Faculty of Veterinary Medicine, University of Calgary (srboysen@ucalgary.ca, https://vet.ucalgary.ca/vcds/podcasts). Additional references are provided to attendees upon request.

Introduction:

Ultrasonography (US) has become a widely available diagnostic tool in most small animal veterinary practices. US provides rapid information, is non-invasive especially in unstable patients, and can be learned by all levels of staff. However, a full systematic ultrasound examination can be daunting for the general practice clinician, or unfeasible in the emergency setting. In these instances, Point-of-Care Ultrasound (POCUS) can provide focused information to support and guide the clinical decision-making process.

Point-of-Care Ultrasound, also referred to as bedside/cageside ultrasound, focused ultrasound, or FAST scanning, is most useful in the following situations:

- **Triage** of the traumatized or unstable patient in the emergency setting
- **Monitoring** of the unstable patient in the hospitalized setting
- **Therapeutic** guidance or intervention in both these scenarios

The key to successful POCUS examination is for the scan to be guided by specific clinical questions (most helpfully binary YES/NO questions) and not an unguided perusal to see what 'shows up'. Most importantly, POCUS cannot replace physical exam and auscultation, and in fact these important findings will often guide the binary clinical questions that POCUS hopes to answer.

For example, instead of asking "Why is this cat dyspneic?" we instead ask YES/NO questions such as "Does this dyspneic cat have pleural fluid?" "Does this dyspneic cat have a big left atrium?"

It is also important to remember that ultrasonography cannot replace radiography in every scenario (especially GI, the thorax, and musculoskeletal), and should instead guide and be guided by these additional imaging options.

Basic machine settings, imaging planes, and transducer movements:

Every ultrasound machine available has a large array and slightly different arrangement of buttons, knobs, and settings. When encountering a new piece of equipment, the following five buttons/settings should be identified and manipulated first:

1. Depth: the region of interest should be centered in the screen.
2. Frequency: this may be a number or a range, and should be adjusted after the depth is set. If the image is too dark in the far field, the frequency should be reduced.
3. Focal zone: this allows the computer to maximize your image resolution at a particular level, and should be adjusted to just deep to the region of interest
4. Time-Gain Compensation: this automated setting has different names on different pieces of equipment, and creates a uniform 'grayness' to the image from top to bottom
5. Gain: this artificially increases or decreases the overall brightness on the screen.

Other settings (such as dynamic range/power, frame rate, precision, harmonics, etc) are more difficult to adjust 'on the fly' and should be adjusted as part of 'Presets' that can be set up by your sales rep or applications tech.

Options to freeze, label, and store images and videos are available on most machines.

In order to achieve efficient muscle memory, the imager and patient should be positioned in a standard set up each time. To achieve uniform images and aid in pattern recognition, ultrasound images should be obtained in two standard planes: sagittal/long-axis, and transverse/short-axis. Images should always be oriented with cranial toward the left of the screen while in sagittal plane, and with the patient's right toward the left of the screen while in transverse plane. This allows standardized image acquisition and prevents 'getting lost.'

Transducer or probe movements are described as a combination of: sliding, fanning, rotating, and rocking. Movements should be slow, and coordinated to obtain as many 'slices' or views of the area of interest, with the area of interest squared and centered and in the middle of the screen.

POCUS Abdomen

Indications: Triage and Monitoring POCUS scans are indicated in patients with a history of trauma, systemically unstable or critical patients, and in post-surgical patients with complications or lack of clinical improvement.

Positioning and Quadrants:

POCUS exams of the abdomen are generally performed in lateral recumbency. Hair can be clipped if thick, or a large amount of alcohol can be used to contact the skin.

Images should be obtained at each of the four quadrants of the abdomen:

1. Cranial/xyphoid/hepatic
2. Non-dependent kidney region
3. Bladder

4. Central and dependent region

YES/NO questions:

- Is there free fluid? Where? How much?
- Is there free gas?
- Is there SI ileus?
- Is there renal pelvic dilation?
- Is the patient producing urine?
- Is there a large mass lesion?

Potential pitfalls of abdominal POCUS:

Large amounts of GI gas may inhibit imaging or may mimic free gas. In large patients, a lack of depth may hide significant findings. Important artifacts may mimic clinically serious findings, such as mirror artifact mimicking diaphragmatic hernia, or edge shadowing mimicking free fluid or gas.

POCUS Thorax part 1- Pleural space and lungs

Indications: Triage and Monitoring POCUS exams can be performed on all patients that present with respiratory distress, tachypnea, or muffled or crackling lung sounds.

POCUS exam of the pleural space and lungs can help differentiate pulmonary vs cardiac sources of respiratory distress.

Positioning and Quadrants: As these patients usually present with respiratory difficulty, exams are often performed in sternal recumbency or standing, and can be performed while the patient receives supplemental oxygen therapy.

Hair can be clipped if thick, or a large amount of alcohol can be used to contact the skin. Images should be obtained at four general quadrants of the thorax, on both the left and right side:

1. Craniodorsal (caudal to scapula)
2. Caudodorsal
3. Cranioventral (level of heart)
4. Caudoventral (level of xyphoid)

YES/NO questions:

- Is there pleural space fluid?
- Is there pleural space gas?
- Are there normal lung surface A lines?
- Is there normal lung surface glide sign?
- Are there abnormal lung surface B lines? Where? How many?
- Is there lung consolidation?

The location of free pleural gas and free pleural fluid will shift with gravity depending on how the patient is positioned.

B-lines are referred to by several names including ring down, lung rockets, and comet tails. These are a type of reverberation artifact created by an irregular pleural surface and increased density/loss of aeration of the lung periphery. These are non-specific findings that are created by any pathology that results in loss of aeration (such as atelectasis), and/or infiltration of normally-aerated lung with any type of fluid or cells (ie cardiogenic or non-cardiogenic edema, hemorrhage, infection, neoplasia, fibrosis, other interstitial lung disease, etc).

Potential pitfalls of thoracic POCUS:

Glide sign can be difficult to identify in normal patients, especially in patients who are panting or not taking deep breaths, making identification of pneumothorax challenging. A gas-filled stomach may mimic free gas near the diaphragm.

B-lines are non-specific and can be identified with many diseases; B-lines are also present in small numbers in healthy animals, in older animals, and can be due to atelectasis caused by sedation, anesthesia, or recumbency.

Disease deep within the lung parenchyma that does not affect the subpleural tissue will not create visible changes on ultrasound.

Consolidated lung can look like liver, and mirror-image artifacts at the diaphragm can mimic diaphragmatic hernia.

POCUS Thorax part 2- Heart

Indications: Triage and Monitoring POCUS exams can be performed on all patients that present systemically unstable or in respiratory distress, especially those with a history of heart disease, an ausculted heart murmur, muffled heart sounds, pulse deficits, or pale mucus membranes.

POCUS exam of the heart can help differentiate pulmonary vs cardiac sources of respiratory distress.

Positioning and Quadrants: As these patients may present with respiratory difficulty, exams are often performed in sternal recumbency or standing, and can be performed while the patient receives supplemental oxygen therapy. Better views of the heart may be obtained with the patient in lateral recumbency, either from the 'up' side of the thorax, or from the 'down'/recumbent side.

Hair can be clipped if thick, or a large amount of alcohol can be used to contact the skin. Images should be obtained at four planes of the heart, from either the left and right side:

1. Apical view (level of the xyphoid)
2. Short axis at the base
3. Short axis at the apex
4. Long axis of the ventricles

YES/NO questions:

- Is there pericardial effusion?
- Is there decreased contractility?

- Is the ventricle wall thickened?
- Is there decreased ventricle volume?
- Is there increased ventricle and atrial volume?
- Is the left atrium significantly larger than the aortic root?

Potential pitfalls of cardiac POCUS:

Patient positioning and thoracic conformation (particularly deep chested and brachycephalic-breed conformations), and tachycardia can make standard views of the heart challenging to obtain.

Animals with normally-aerated lungs and no pericardial or cardiac enlargement may not allow visualization of the heart without a table designed for cardiac imaging from underneath the patient.

Heart wall thickness and lumen volumes will be influenced by fluid administration and volume overloading, or conversely by severe dehydration/hypovolemia.

Specific cardiac measurements should be repeated multiple times and averaged, and patient sedation, heart rate, hydration status, and body weight should all be taken into consideration when comparing measurements to normal. Coordinated timing with ECG tracings should be performed to ensure measurements are taken at systole vs diastole.

Ultrasound-guided Diagnostic and Therapeutic techniques:

Ultrasound can be used to guide a variety of both diagnostic and therapeutic interventions, including:

- Sampling of fluids for cytology and culture, and needle sampling (for cytology) or core biopsy sampling (for histopathology) of tissues.
- Removal of fluid or free gas for therapeutic stabilization of the patient.
- Placement of intravenous catheters, chest tubes, and urinary catheters.

CONFERENCE EVALUATION

Thank you for joining us!